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Efficient Access to Virtually Enantiopure α-Dialkyl-, α-Acetoxy-, and α-Acetamido esters

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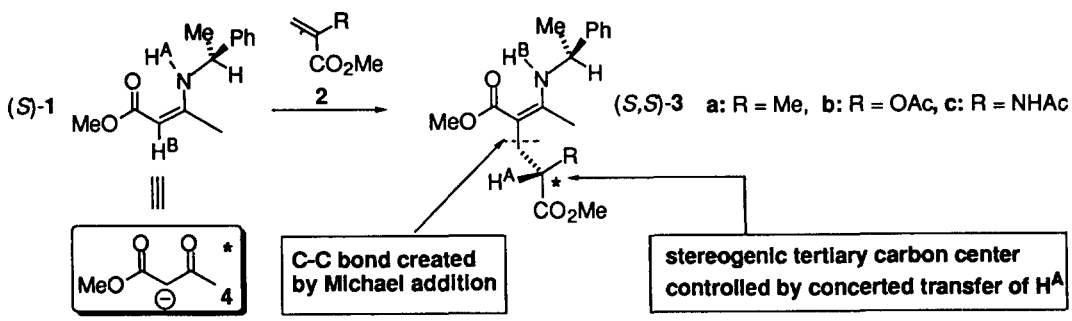
Abstract : Addition of acyclic chiral β-enamino ester (*S*)-**1** to α-methyl-, α-acetoxy-, and α-acetamido acrylates **2** gave with good yields, and with de≥ 95 % the corresponding Michael adducts (*S*, S)-**3**.

In 1986, Koga *et al* have investigated the asymmetric Michael addition of cyclic β-keto esters, as their valine lithium enamides. The lithium derivative added directly to methylene malonic esters without further activation,[1] but was not reactive enough to add to methyl vinyl ketone or ethyl acrylate, unless trimethylsilyl chloride was also added.[2] In all cases the Michael adducts were isolated in fair to excellent yields (50-90 %), and with *ee* up to 97 %. Later on, Brunner,[3] Guingant,[4] and ourselves,[5] have demonstrated that addition of β-enamino esters, derived from *cyclic* β-keto esters and the chiral auxiliary 1-phenylethylamine, to Michael acceptors can be achieved *under neutral conditions*, in the presence of cobalt (II) acetylacetonate,[3] magnesium bromide,[4,5] zinc chloride,[4] or diethylaluminum chloride.[4] A variety of electrophilic alkenes was used (methylene malonic esters, acrylic esters, α,β-ethylenic ketones, acrylonitrile), and the enantioselectivities were up to 95 % in optimized cases.



In this paper, we show that chiral β-enamino ester (*S*)-**1**, derived from the *acyclic* β-keto ester methyl acetoacetate and (*S*)-1-phenylethylamine, condenses with α-methyl-, α-acetoxy-, and α-acetamido acrylates **2** to furnish Michael adducts (*S-S*)-**3** in 65-75 % yield and with *de* ≥ 95 %. Incidentally, it should be noted that enamino ester **1** thus acts as a formal equivalent of the chiral enolate ion **4**.

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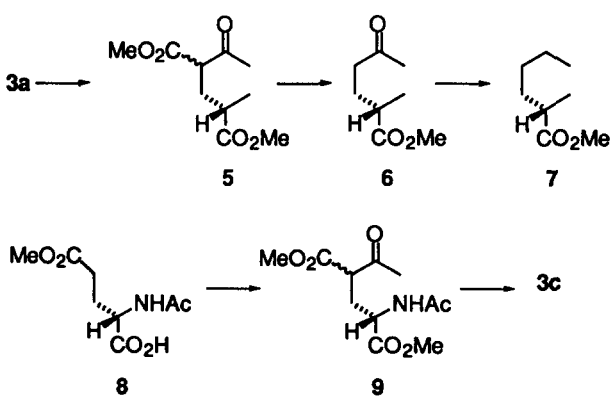
Addition of enamino ester (*S*)-**1**, *of pure Z geometry* (secured by the intramolecular hydrogen bonding H^A...O=C), prepared from methyl acetoacetate and (*S*)-1-phenylethylamine (12 h in toluene at reflux, with a catalytic amount of *p*-toluenesulfonic acid, 82 % yield), to methyl methacrylate **2a** required the presence of 1 eq. of zinc chloride. In contrast, additions of **1** to the more reactive Michael acceptors methyl 2-acetoxyacrylate **2b** or methyl 2-acetamidoacrylate **2c** were performed under purely thermal conditions. In all cases the Michael adducts were isolated in satisfying yields, and with excellent *de* (Table 1).

(*S*,*S*)-**3**	R	Yield [%]	*de* [%]	$[\alpha]_D^{20}$ (c, MeOH)
a	Me	74	94 [a]	+355 (4.6)
b	OAc	66	≥ 95 [b]	+336 (5.0)
c	NHAc	67	≥ 95 [b]	+267 (1.4)

Table 1. Yields, diastereomeric excesses and rotational values of the Michael adducts (*S*,*S*)-**3**.
[a] Determined on the corresponding keto ester derivative **6** by ^1H NMR spectroscopy, after adding Eu(hfc)3.
[b] Determined by ^1H and ^{13}C NMR spectroscopy on the Michael adducts.

The *S* configuration at the newly created stereogenic center in adducts **3a** and **3c** was established through the following chemical correlations. Hydrolysis of **3a** (10 % aqueous AcOH, 24 h at 20 °C) gave with a 70 % yield an equimolar mixture of diastereomeric keto esters **5** which, upon saponification (LiOH in MeOH), acidification, spontaneous decarboxylation, and esterification with diazomethane, furnished with a 75 % yield δ-keto ester (*S*)-**6**. The latter derivative was then converted in two steps, through the corresponding 1,3-dithiolane derivative, into (*S*)-(+)-methyl methyl-2-hexanoate **7**, of known configuration[6] (*i*: 1,2-ethanedithiol, boron trifluoride diethyl etherate; *ii*: Raney nickel). An authentic sample of **3c** was synthetized as follows. Acetylation[7] of (*S*)-*N*-acetylglutamic acid 5-methyl ester **8**[8] (*i*: 10 eq. of LDA, THF, 0 °C; *ii*: MeCOCl, 0 °C; *iii*: acidification with 2 *N* HCl; *iv*: CH_2N_2) gave with a 32 % yield β-keto ester **9**, as an equimolar mixture of diastereomers. Treatment of **9** with (*S*)-1-phenylethylamine (24 h in toluene at reflux) finally led with a 70 % yield to enamino ester (*S*,*S*)-**3c**, undistinguishable in all respects with the Michael adduct resulting from the condensation of **1** with **2c**. Structure of adduct (*S*,*S*)-**3b** was unambiguously determined through an X-ray crystallographic analysis (Figure 1).



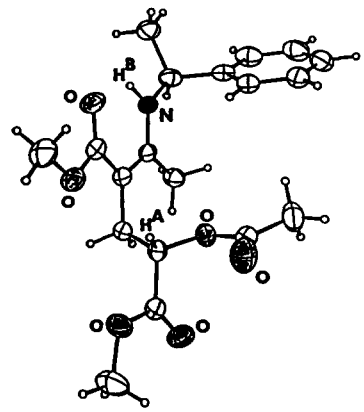
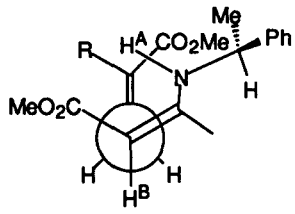


Figure 1

The remarkable remote transfer of chirality observed in the previous Michael additions can be interpreted by invoking the *syn*-approach of the two reactants **1** and **2**, with the "*endo*-arrangement" of the ester part of the acrylate partner **2** (the carbomethoxy group facing the nitrogen atom of enamino ester **1**, Newman projection **10**), and the related six-membered "aza-ene-synthesis-like" transition state structure **11**.[9] According to such a model, the alkylation took place predominantly on the less hindered π-face of enamino ester **1** (*anti* to the bulky phenyl group of the chiral amine moiety, portrayed in its energetically preferred conformation minimizing the $A^{(1,3)}$ allylic-type interactions). The transfer of proton H^A of the enamino ester to the α–vinylic center of acceptor **2**, *more or less concerted with the creation of the C-C bond*, then secured the control of the asteriked stereogenic center in putative intermediates **12**. Imine → enamine tautomerization of **12** finally delivered the observed Michael adducts **3**.



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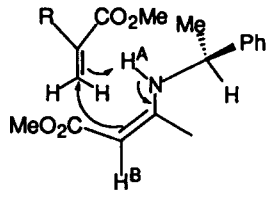

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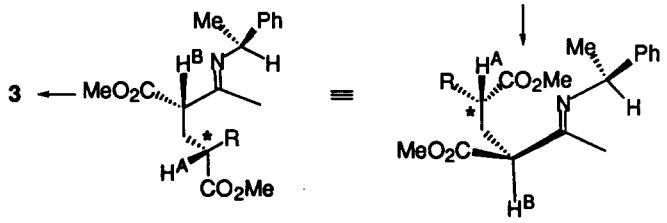

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To conclude, the asymmetric Michael addition of acyclic chiral β-enamino esters to α-substituted acrylates described here opens a new, simple and efficient entry to virtually enantiopure α-dialkyl-, α-acetoxy-, and α-acetamido esters. Since the used chiral auxiliary 1-phenylethylamine is commercially available in both optically pure forms at a moderate price, it is possible to readily synthetize both enantiomers of such α-substituted esters, and to extend thus the scope of application of these important chiral synthons.

References and Notes

1 Tomioka, K;. Ando, K.; Yasuda, K.; Koga, K. *Tetrahedron Lett.* **1986**, *27*, 715-716.

2 Tomioka, K.; Seo, W.; Ando, K.; Koga, K. *Tetrahedron Lett.* **1987**, *28* , 6637-6640.

3 Brunner, H.; Kraus, J.; Lautenschlager, H.-J. *Monatsh. Chem.* **1988**, *119* , 1161-1167.

4 a) Guingant, A.; Hammami, H. *Tetrahedron: Asymmetry* **1991**, *2*, 411-414; b) Guingant, A. *ibid.* **1991**, *2*, 415-418; c) Guingant, A.; Hammami, H. *ibid.* **1993**, *4*, 25-26.

5 a) Cavé, C.; Daley, V.; d'Angelo, J.; Guingant, A. *Tetrahedron: Asymmetry* **1995**, *6*, 79-82; b) Cavé, C.; Desmaële, D.; d'Angelo, J.; Riche, C.; Chiaroni, A. *J. Org. Chem.* **1996**, *61*, 4361-4368; c) Cavé, C.;

Gassama, A.; Mahuteau, J.; d'Angelo, J.; Riche, C. *Tetrahedron Lett.* **1997**, *38* , 4773-4776; d) d'Angelo, J.; Cavé, C.; Desmaële, D.; Gassama, A.; Thominiaux, C.; Riche, C. *Heterocycles* **1998**, *47*, in press.

6 Goering, H. L.; Chung Chyi Tseng *J. Org. Chem.* **1983**, *48*, 3986-3990.

7 Beausoleil, E.; L'Archevêque, B.; Bélec, L.; Aftani, M.; Lubell, W. D. *J. Org. Chem.* **1996**, *61*, 9447-9454.

8 Prepared through *N*-acetylation of commercially available (*S*)-glutamic acid 5-methyl ester (acetic anhydride, 12 h at 20 °C, 70 % yield).

9 Ambroise, L.; Desmaële, D.; Mahuteau, J.; d'Angelo, J. *Tetrahedron Lett.* **1994**, *35* , 9705-9708.

Experimental Procedures

(*S,S*)-(+)-**3a**: A solution of enamino ester **1** (5 g, 23 mmol) in diethyl ether (20 mL), and methyl methacrylate (5 mL, 46 mmol) were added to a solution of $ZnCl_2$ (23 mmol) in diethyl ether (23 mL). The mixture was stirred at 20 °C under nitrogen for 9 days. During this period, additional portions of methyl methacrylate (0.15 mL, 4.7 mmol) were added to this mixture each 3 days. The solvent was removed and the crude oil was purified by flash chromatography (SiO_2, ethyl acetate/hexane 1/2) to give **3a**, as a colorless oil in 74 % yield; IR (neat): ν = 3242, 1734, 1648, 1597 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 9.86 (d, ^3J (H, H) = 7 Hz, 1H), 7.48-7.33 (m, 5H), 4.63 (dq, ^3J (H, H) = 7 Hz, 7 Hz, 1H), 3.68 (s, 3H), 3.61 (s, 3H), 2.77-2.22 (m, 3H), 1.80 (s, 3H), 1.48 (d, ^3J (H, H) = 7 Hz, 3H), 1.03 (d, ^3J (H, H) = 7 Hz, 3H).

(*S,S*)-(+)-**3b**: A mixture of enamino ester **1** (2.2 g, 10 mmol), freshly distilled methyl 2-acetoxyacrylate (2.1 g, 14 mmol) and hydroquinone (10 mg) in THF (10 mL) was stirred at 60 °C under nitrogen for 4 days. The solvent was removed and the crude oil was purified by flash chromatography (SiO_2, ethyl acetate/hexane 20/1) to give, after recrystallization in hexane/ether 4/1, **3b**, as a solid in 66 % yield. Slow evaporation of a solution of (+)-**3b** in hexane/ether 4/1 gave small monocrystals, suitable for an X-ray crystallographic analysis; Mp 110 °C; IR (neat): ν = 3294, 1742, 1652, 1608 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 9.92 (d, ^3J (H, H) = 7 Hz, 1H), 7.33-7.19 (m, 5H), 4.99 (dd, ^3J (H, H) = 9.5 Hz, 4.9 Hz, 1H), 4.65 (dq, ^3J (H, H) = 7 Hz, 7 Hz, 1H, CH), 3.71 (s, 3H), 3.70 (s, 3H), 2.86 (dd, ^3J (H, H) = 15.1 Hz, 4.9 Hz, 1H), 2.63 (dd, ^3J (H, H) = 15.1 Hz, 9.5 Hz, 1H), 1.84 (s, 3H), 1.83 (s, 3H), 1.50 (d, ^3J (H, H) = 7 Hz, 3H); Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.81; H, 6.89; N, 3.86. Found: C, 62.63; H, 7.08; N, 3.78.

(*S,S*)-(+)-**3c**: A mixture of enamino ester **1** (0.55 g, 2.5 mmol), methyl 2-acetamidoacrylate (0.43 g, 3.0 mmol) and hydroquinone (10 mg) in THF (5 mL) was stirred at 60 °C under nitrogen for 3 days. The solvent was removed and the crude oil was purified by flash chromatography (SiO_2, hexane/ethyl acetate 2/1) to give **3c**, as an amorphous solid in 67 % yield; IR (neat): ν = 3321, 1746, 1660, 1597 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 9.90 (d, ^3J (H, H) = 7 Hz, 1H), 7.34-7.12 (m, 5H), 6.26 (d, ^3J (H, H) = 7 Hz, 1H), 4.64 (dq, ^3J (H, H) = 7 Hz, 7 Hz, 1H), 4.36 (dd, ^3J (H, H) = 14.5 Hz, 7.1 Hz, 1H) 3.69 (s, 3H), 3.65 (s, 3H), 2.64 (m, 2H), 1.91 (s, 3H), 1.84 (s, 3H), 1.50 (d, ^3J (H, H) = 7 Hz, 3H).

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