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Asymmetric synthesis of glutamate derivatives

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Dedicated to the memory of Professor Jean d'Angelo

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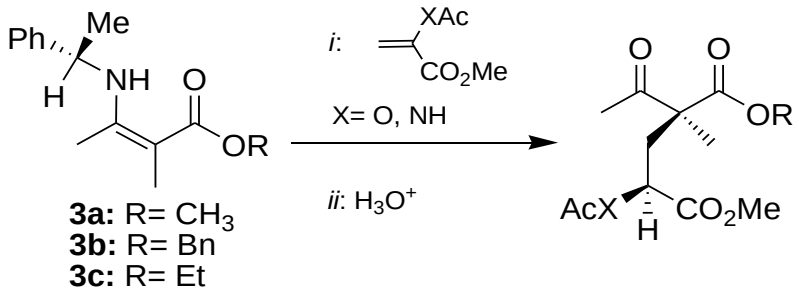
Abstract

Analogs of glutamic acid were synthesized through the asymmetric Michael reaction using chiral acyclic β-enaminoesters and various Michael acceptors. The influence of the alkoxy group of the enaminoesters and also the nature of the olefins in the presence or not of zinc chloride on yield and enantioselectivity are explored.



3a: R= CH_3
3b: R= Bn
3c: R= Et

Keywords: Glutamic acid, Michael addition, symmetric synthesis, β-enaminoesters, zinc chloride

Introduction

Glutamic acid (**1**) (Glu, Figure **1**) is the major excitatory neurotransmitter in the central nervous system where it is involved in many biological processes by means of two types of receptors: the ionotropic ones (iGluR) and metabotropic ones (mGluR). Those receptors, in particular mGluR, are thought to interesting targets for the treatment of different pathologies such as Parkinson's disease[1,2] or epilepsy.[3] So developing synthesis of non natural analogs of glutamic acid appears to be of interest to access new ligands of mGluR. Asymmetric Michael reaction involving acyclic chiral β-enaminoesters appears to be a tool of choice and can easily afford new precursors of glutamic acid analogs like compound **2** (Figure 1).

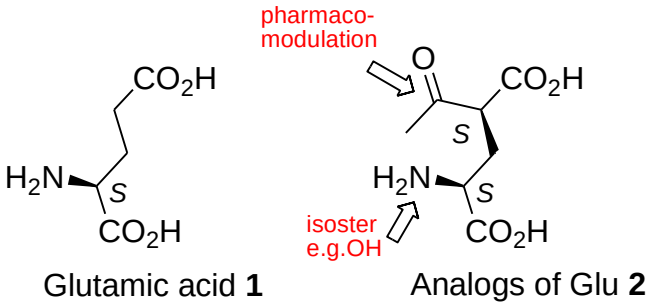


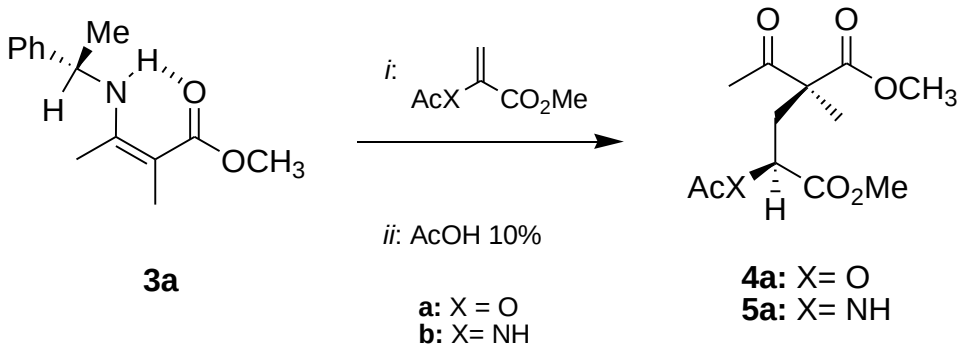
Figure 1

Indeed, the Michael reaction is known to be one of the simplest and most efficient methods for the construction of quaternary carbon centers. Use of an asymmetric variant of this reaction with chiral imines/enamines is proved to give an easy access to molecules presenting an asymmetric quaternary center, generally with a high degree of regio- and enantio- selectivity. Since its discovery in 1985, this methodology as generally been applied to various cyclic systems notably for the synthesis of natural products such as terpenes and steroids,[4-11] but only rarely to acyclic ones.[12-18]

In this paper, we explore the Michael reaction between acyclic chiral β-enaminoesters exhibiting various alkoxy groups and various olefins, the effect of Lewis acid on the reactivity and the enantioselectivity of this reaction will be explored.

Results and Discussion

In a previous study, acyclic chiral α,β-dimethyl-β-enaminoester **3a** was condensed to methyl acetoxy- and methyl acetamidoacrylate to furnished, after hydrolytic work-up, Michael adducts in satisfying yields (~ 55%) and excellent optical purities (ee's and de's ≥ 95%) (Scheme 1).[19,20] Ketodiesters **4a** and **5a** constitute attractive chiral blocks for the elaboration of new non-natural analogs of glutamate.



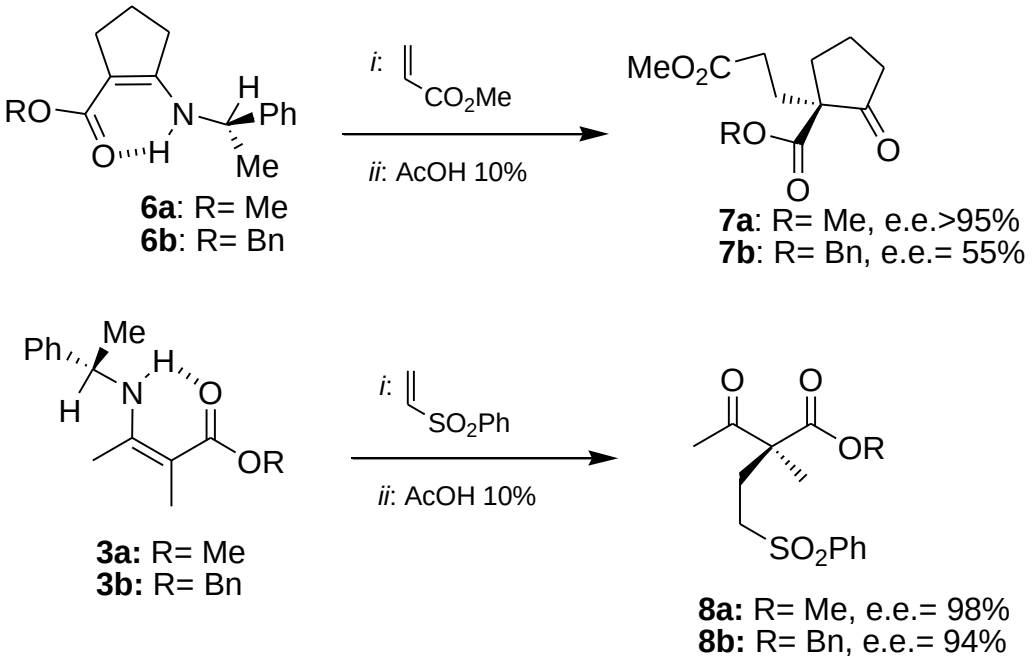
3a

a: X = O
b: X= NH

4a: X= O
5a: X= NH

Scheme 1

Synthesis of ketoesters of types **4** and **5** bearing differentiated ester groups, e.g. an easily cleavable benzylic, appears to be of interest in the elaboration of a new variety of molecules with acid functions. In previous works, we observed that the nature of the ester group carried by the quaternary carbon center could induce a decrease of the enantioselectivity **into** the final Michael compounds.[21] Indeed, the asymmetric Michael reaction between cyclic benzyl β-enaminoester **6b** and methyl acrylate furnished the corresponding adduct **7b** with a disappointing ee (55%) compared to the ee of its methyl analog **7a** which was ≥ 95%. Firstly, the erosion of the enantioselectivity was attributed to the presence of benzyl ester group, but compared to the result obtained with Michael adduct **8b** (ee = 94%) formed by condensation of the acyclic benzyl enaminoester **3b** with phenyl vinyl sulfone, other factors should be implicated (Scheme 2).



6a: R= Me
6b: R= Bn

7a: R= Me, e.e.>95%
7b: R= Bn, e.e.= 55%

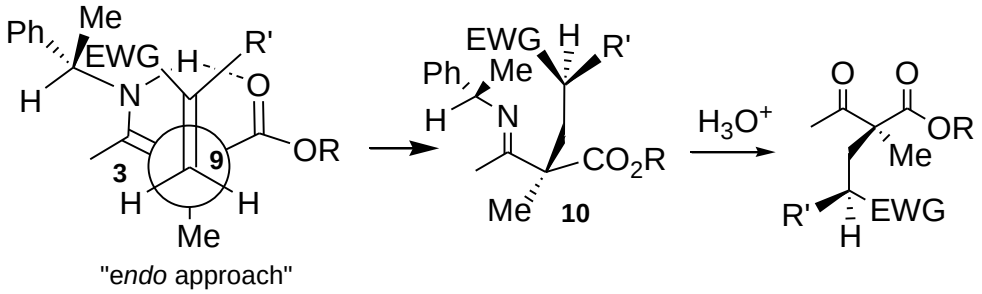
3a: R= Me
3b: R= Bn

8a: R= Me, e.e.= 98%
8b: R= Bn, e.e.= 94%

Scheme 2

In the asymmetric Michael reaction, the acrylate **9** approaches on the less hindered π-face of enamino-ester **3** (*anti* to the bulky phenyl group of the chiral amine moiety) with an *endo*-arrangement in which the electron withdrawing group of the olefin faces the nitrogen atom of enaminoester **3**. Besides the related six

membered aza-ene-synthesis-like transition state, the transfer of the proton of the enaminoester to the α–vinylic centre of acceptor **9**, induced the control of the tertiary stereogenic centre in intermediate imines **10**. It could be considered that using a benzylic enaminoester can modify the usual approach of the two reactants due to the steric hindrance caused by the benzylic group (Scheme 3).

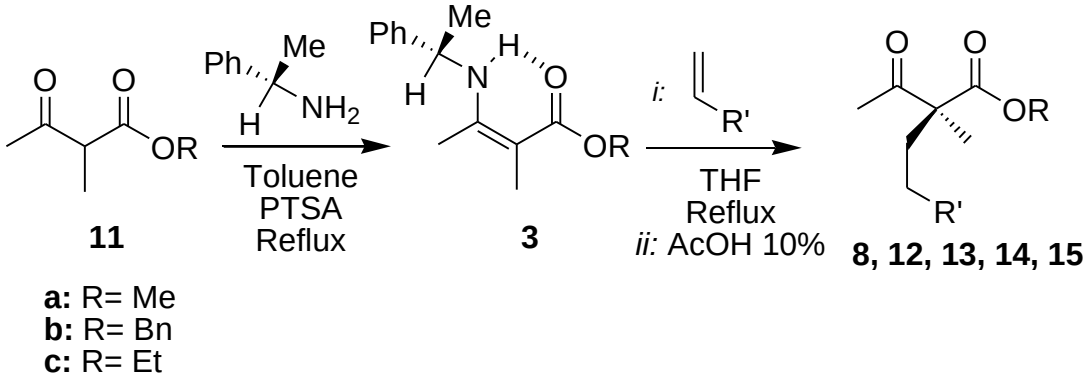


Scheme 3

In order to know the role of the benzyloxy group of the enaminoester in the asymmetric Michael issue, the enthalpies of formation of the two more stable transition states of the *Re* and the *Si* approaches of the enaminoester **6b** and methyl acrylate were calculated.[22-24] The energy difference is in favour of the *Re*-approach in which the benzyl group of **6b** is pushed away from the methyl acrylate face approach. Consequently, using a benzyl enaminoester does not disturb the asymmetric Michael mechanism.

In our aim to synthetize final chiral compounds with differentiated ester functions and to understand the influence of the alkoxy groups of the enaminoesters in the asymmetric Michael reaction, acyclic methyl and benzyl enamines **3a** and **3b** were condensed to various mono-substitued acrylates in neutral conditions and with the presence of zinc chloride as activator.

At first, it can be noted that β-ketoester **11c** is commercially available and inexpensive, contrary to **11a** and **11b** which must be prepared by methylation of their corresponding acetoacetates, and separation of the methylate adducts from the starting materials is demanding due to very close polarity. In a first step, in order to have sufficient material available, we proved equivalence between methylic enamine **3a** and ethylic enamine **3c** toward certain monosubstituted Michael acceptors. (Scheme 4)



Scheme 4

Chiral β-enaminoesters **3a-c** were easily and quantitatively prepared by condensation between pure (*S*)-1-phenylethylamine and respectively methyl, ethyl and benzyl 2-methylacetoacetates **11**, in refluxing toluene in the presence of a catalytic quantity of *p*-toluenesulfonic acid. These enaminoesters were of pure *Z* geometry secured by an intramolecular hydrogen bonding between the hydrogen atom carrying by nitrogen of the enaminoesters and the carbonyl group of the ester. **3a-c** can be used as it is and no further purification is necessary. These crude enamines were first condensed, under neutral condition in refluxing THF, to various monosubstitued olefins. Thus, addition of **3a** and **3c**, in refluxing anhydrous THF, to methylacrylate, acrylonitrile and phenyl vinyl sulfone furnished, after hydrolytic work-up, the expected compounds. In all cases, the Michael adducts were obtained with similar yields and excellent ee's (Table 1; entries 1, 2, 4, 5, 7 and 8) and demonstrated the equal reactivity of methyl and ethyl enaminoesters. Then, all these results were compared with those obtained with benzylic enaminoester **1b**, and to extend our comparative study the *t*-butyl and benzyl acrylates were also used. All the results are summarized in Table 1.

The ethyl β-enaminoester **3c** is able to react with all olefins, as the expected yield is higher with phenyl vinyl sulfone (Table 1, entry 8); and acrylonitrile (Table 1, Entry 5) or acrylate with an ester function (Table 1, entries 10 and 12), yields are around 40%. Generally, ee's are at least equal to 95% except for **15c** derived from benzyl acrylate which was obtained with 85% ee. Concerning benzylic enaminoester **3b**, this revealed another intrinsic reactivity. Indeed, **3b** exhibited a great reactivity with phenylvinylsulfone and benzylic acrylate (Table 1, entries 9 and 13) which furnished corresponding adducts with 80% yield over three steps,but very poor results were obtained with other acrylates (Table 1, entries 3, 6 and 11). Enaminoester **3b** seems to be reactive only with acrylates bearing a phenyl group, these results could implicate interactions between the aromatic groups of both partners. In case of the other acceptors, even after several days of reaction, considerable starting ketoester **11b** was recovered after the hydrolytic work-up, showing the lack of reactivity of **3b** toward them.

Table 1. Asymmetric Michael reaction in neutral conditions

Entry	Enaminoester	R'	Product	Yield	e.e.
1	**3a**	CO_2Me	**12a**	46%	95% [a]
2	**3c**		**12c**	46%	95% [a]
3	**3b**		**12b**	30%	95% [a]
4	**3a**	CN	**13a**	37%	95% [a]
5	**3c**		**13c**	34%	≥ 95% [a]
6	**3b**		**13b**	7%	n.d.
7[c]	**3a**	SO_2Ph	**8a**	63%	95% [b]
8	**3c**		**8c**	61%	≥ 95% [b]
9[c]	**3b**		**8b**	80%	94% [b]
10	**3c**	$CO_2{}^tBu$	**14c**	37%	94% [a]
11	**3b**		**14b**	5%	n.d.
12	**3c**	CO_2Bn	**15c**	41%	85% [a]
13	**3b**		**15b**	80%	84% [a]

(a) determined by ^1H NMR with $Eu(hfc)_3$ as chiral shift reagent; (b) determined by chiral HPLC;
(c) reaction already published (entries 7 and 9)[21], mentioned for comparison .

Even if the Michael adduct **8b**, formed by the condensation of **3b** with phenyl vinyl sulfone, was obtained with 94% ee's (Table 1, entry 9); a reduction in the stereoselectivity was however observed when benzylic acrylate was used (84%; Table 1, Entry 13).

In the first part of our study, we have thus confirmed that the asymmetric Michael reaction could be extended to ethylic and benzylic β-enaminoesters and various electrophilic mono-substituted alkenes. Final adducts were generally obtained in three steps with good stereocontrol of the quaternary carbon center. A decrease of the e.e. was observed when using benzyl acrylate.

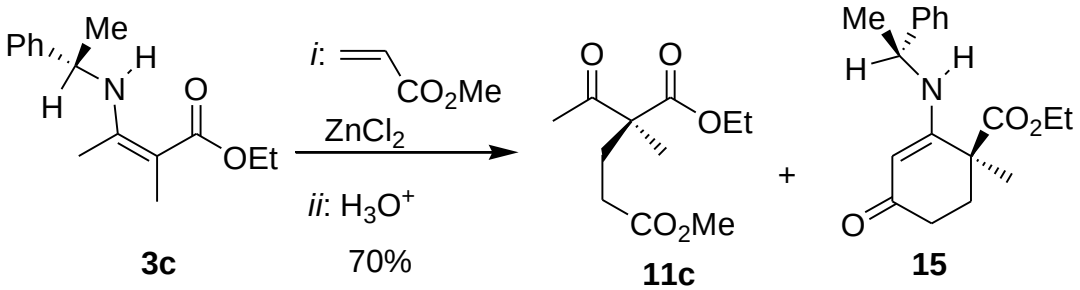
Asymmetric Michael reactions using β-enaminoesters are generally performed with Lewis acid as Michael acceptor activator,[4-11] so the preceding reactions were repeated in the presence of zinc chloride (1.4 equivalents) in order to study the influence of this catalyst on both reactivity and selectivity. The results are summarized in Table 2.

Table 2. Asymmetric Michael reaction in presence of zinc chloride

Entry	Enaminoester	R'	Product	Yield	e.e.
1	**3c**	CO_2Me	**12c**	20%	95% [a]
2	**3c**	CN	**13c**	42%	≥ 95% [a]
3	**3b**		**13b**	53%	76% [b]
4[c]	**3c**	SO_2Ph	**8c**	80%	≥ 95% [b]
5[c]	**3b**		**8b**	≥ 98%	55%[b]
6	**3c**	$CO_2{}^tBu$	**14c**	85%	94% [a]
7	**3b**		**14b**	80%	92% [b]

(a) determined by ^1H NMR with $Eu(hfc)_3$ as chiral shift reagent; (b) determined by chiral HPLC;
(c) reaction already published (entries 4 and 5)[21], mentioned for comparison.

We observed that the addition of zinc chloride caused, in general, an improvement in term of yields. However, an exception was noted in the case of the reaction between β-enaminoester **3c** and methyl acrylate, in which the expected Michael adduct **12c** was isolated in lower yield when using zinc chloride (Table 2, entry 1 versus table 1, entry 1). In fact, the overall yield is good, but in this case a by-product was formed in 50% yield and was characterized as the cyclohexenone **15** (ee and de ≥ 95%) (Scheme 5).[3] This process was not observed when *t*-butyl acrylate was used instead of methyl acrylate (Table 2, entries 6 and 7). It implied that this cyclization is dependent on the steric hindrance of the ester function in the acrylate.



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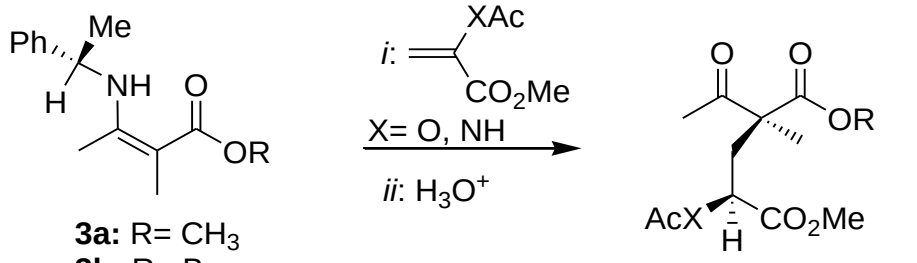
Scheme 5

In the presence of zinc chloride, reactivity of acrylonitrile and *ter*-butyl acrylate are enhanced and can react with benzylic enamine **3b**. With *t*-butyl acrylate, **3c** and **3b** furnished the corresponding adducts **14c** and **14b** with excellent yield and ee's (Table 2, entries 6 and 7). If the addition of ethylic enaminoester **3c** with acrylonitrile furnished adduct **13c** with good optical purity, an erosion was observed using **3b** (Table 2, entries 2 and 3). Similarly, both enamines react very well with phenyl vinyl sulfone but a great decrease of enantioselectivity is observed in the case of the benzyl enamine: ee = 55% (Table 2, entries 4 and 5).

In order to have access to precursors of functionalized analogs of glutamic acid, β-enaminoesters used previously were condensed with different α-substituted acrylates (Scheme 6). Thin layer chromatographies of crude reactions using methyl acetoxy- and methyl acetamido-acrylate in presence of zinc chloride showed the formation of many side-products. Performed without catalyst, the Michael reaction led to expected adducts with good overall yields. When the Michael acceptor is methyl acetoxyacrylate, optical purities are over 95%, but with methyl acetamidoacrylate, a reduction of the d.e. was observed with enaminoester **3b** and even more with **3c** (Table 3).



3a: R= CH_3
3b: R= Bn
3c: R= Et

4a: R= CH_3, X= O
4b: R= Bn, X= O
4c: R= Et, X= O
5a: R=CH_3, X= NH
5b: R= Et, X= NH
5c: R= Bn, X= NH

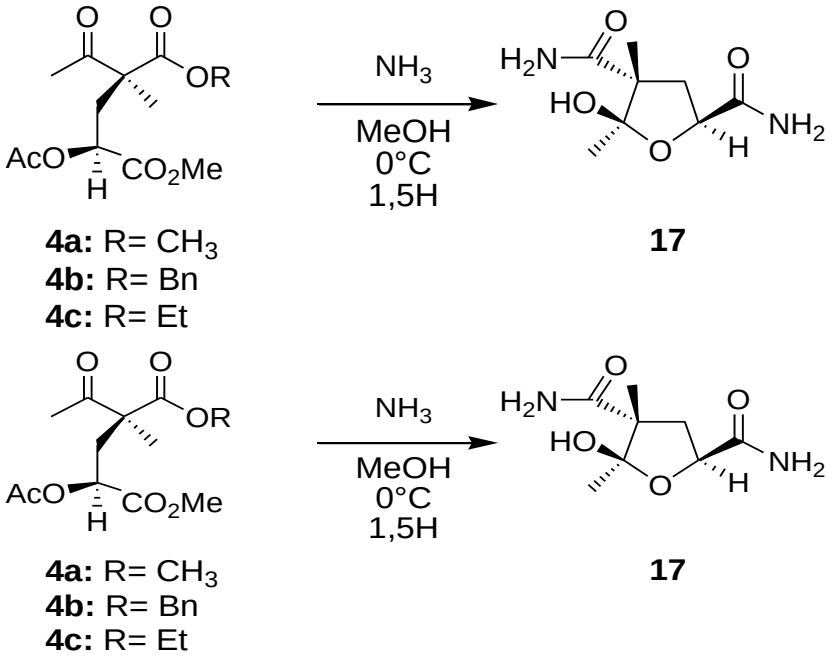
Scheme 6

Table 3. Asymmetric Michael reaction in neutral conditions

Entry	Enamine	XAc	Product	Yield	e.e.	d.e.
1[c]	**3a**		**4a**	50%	95%	95%[a]
2	**3b**	OAc	**4b**	50%	95%	95%[a]
3	**3c**		**4c**	50%	95%	95%[b]
4[c]	**3a**		**5a**	55%	95%	95%[a]
5	**3b**	NHAc	**5b**	30%	95%	90%[a]
6	**3c**		**5c**	55%	n.d.	70%[b]

(a) determined by ^{1}H NMR with Eu(hfc)$_3$ as chiral shift reagent; (b) determined by chiral HPLC;
(c) reaction already published (entries 1 and 4)[19,20], mentioned for comparison.

In order to determine relative configurations, compounds **4a-c** and **5a-c** were cyclised in the presence of ammonia. All ketoesters **4** lead in quantitative yield to the hemiacetal **17**, and compounds **5** furnish the pyrrolidine **18** in quantitative yields (Scheme 7). Both cyclic adducts were crystallized.[19]



Scheme 7

Conclusions

In conclusion, we have demonstrated that the asymmetric Michael reaction can be successfully extended to acyclic β-enaminoesters leading to β-ketoesters with different ester groups.

The ethyl enaminoester **3c** reacted with monosubstitued olefins and furnished Michael adducts with excellent optical purity and good global yields with or without the use of a Lewis acid. The intrinsic reactivity of the benzyl analogue **3b** is different. Indeed, in neutral conditions, enaminoester **3b** reacted very well with Michael acceptor bearing a phenyl group and poor results were obtained with acrylonitrile or *ter*-butyl acrylate; an activation with zinc chloride is necessary. When using benzyl acrylate, final compounds were obtained with low ee.

Moreover, a decrease of the enantioselectivity was observed with benzyl enaminoester **3b** depending of the nature of the acrylate and the presence or absence of zinc chloride.

The Michael adducts obtained by the condensation between the acyclic β-enaminoesters and methyl acetoxy- and methyl acetamidoacrylate are polyfunctionalized and bear differentiated ester functions. Their transformation into diacid and pharmacomodulation are in process.

Experimental Section

General. Commercial reagents were used without purification. Prior to use, THF was freshly distilled from sodium-benzophenone, Methanol was dried over magnesium and distilled under a nitrogen atmosphere. All anhydrous reactions were carried out under nitrogen atmosphere. Analytical thin layer chromatography was performed on SDS silica gel 60F_{254} aluminium plates (0.2 mm layer) and was revealed by UV-light or Kägi-Misher reagent. All flash chromatography separations were performed with SDS silica gel 60. Melting points

were recorded on a Kofler bench and were uncorrected. Infrared (IR) spectra were obtained as neat films and were recorded on Bruker Vector 22 spectrophotometer. ^{1}H and ^{13}C spectra were recorded respectively either on a Bruker AC 200 P or a Bruker Avance 300 at 200 or 300 MHz and 50 or 75 MHz, respectively. $CDCl_3$ was used as internal reference. Specific rotations $[\alpha]_D$ were measured on a Optical Activity Limited AA-10R polarimeter with sodium (589 nm) lamp at specified temperature in a 1 dm-cell. Elemental analyses were performed by the Service de Microanalyse, Centre d'Etudes Pharmaceutiques, Châtenay-Malabry, France, with a Perkin-Elmer 2400 analyser. Enantiomeric excesses (ee's) were evaluated either by ^{1}H NMR spectroscopy using $Eu(hfc)_3$ as chiral shift reagent or by chiral HPLC on a Spectrasystem P1000XR with a Spectraseries UV100 spectrophotometer and a chiral column Chiralcel AD. HPLC spectra were obtained by using Azur program.

General procedure for the addition of acrylates to the enamino esters 3a-c. In neutral condition: a mixture of enamine 3 (21.4 mmol), olefin (28 mmol) and hydroquinone (2 mg) in anhydrous THF (20 mL) was heated at 70 °C under nitrogen until disappearence of starting material, after which 5mL of 10% aqueous acetic acid solution were added. The mixture was stirred for an additional 2 h at 20 °C. The solvents were removed under reduced pressure and 1M hydrochloric acid (10 mL) then added. The mixture was extracted with ethyl acetate (3 x 10 mL) and the combined organic layers were washed with brine, dried over sodium sulfate and concentrated. The crude was purified over silica gel. In presence of Lewis acid, 1.4 eq. of freshly dried zinc chloride was previously dissolved in 5 mL of anhydrous THF before addition of the reactants.

(2*S*)-2-Acetyl-2-methyl-pentanedioic acid dimethyl ester (12a). Oil, 46% (hexane/AcOEt 8:2); $[\alpha]_D^{26}$ = -7.33 (*c* 1.5, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.75 (s, 3H), 3.67 (s, 3H), 2.32-2.21 (m, 3H), 2.17 (s, 3H), 2.13-2.04 (m, 1H), 1.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 204.76, 173.04, 172.75, 58.55, 52.39, 51.57, 29.52, 29.11, 25.94, 18.82. IR (ν_{max}, cm^{-1}): 1742, 1718. Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46. Found: C, 55.48; H, 7.51 %.

(2*S*)-2-Acetyl-2-methylpentanedioic acid 1-benzyl ester 5-methyl ester (12b). Oil, 3% (hexane/AcOEt 8.5:1.5); $[\alpha]_D^{26}$ = -8.1 (*c* 0.61, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.35 (s, 3H), 2.07 (s, 3H), 2.28-2.08 (m, 4H), 3.65 (s, 3H), 5.16 (s, 2H), 7.35-7.30 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 204.70, 173.17, 172.21, 135.17, 128.63, 128.51, 128.33, 67.21, 58,90, 51.70, 29.71, 29.25, 26,09, 18.91. IR(max, cm^{-1}): 1742, 1712. Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.71; H, 6.85 %.

(2*S*)-2-Acetyl-2-methylpentanedioic acid 1-ethyl ester 5-methyl ester (12c). Oil, 46% (hexane/AcOEt 8.5:1.5); $[\alpha]_D^{26}$ = -0.0023 (*c* 21;09, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = (ppm) 4.20 (q, *J* = 7.16 Hz, 2H), 3.67 (s, 3H), 2.32-2.27 (m, 2H), 2.16 (s, 3H), 2.26-2.18 (m, 1H), 2.14-2.04 (m, 1H), 1.35 (s, 3H), 1.27 (t, *J* = 7.16 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 204.8, 173.1, 172.2, 61.3, 58.6, 51.6, 29.5, 29.1, 25.9, 18.8, 13.9. IR (ν_{max}, cm^{-1}): 1741, 1714. Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.90; H, 7.98 %.

(2*S*)-2-Acetyl-4-cyano-2-methyl-butyric acid methyl ester (13a). Oil, 37% (hexane/AcOEt 7.5:2.5); $[\alpha]_D^{26}$ = -26.1 (*c* 2.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.79 (s, 3H), 2.41-2.35 (m, 2H), 2.33-2.26 (m, 1H), 2.18 (s, 3H), 2.13-2.03 (m, 1H), 1.42 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = (ppm) 203.8, 171.8, 118.9, 58.2, 52.6, 30.36, 25.8, 19.0, 12.7. IR (ν_{max}, cm^{-1}): 2240, 1730, 1714. Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.78; H, 7.00; N, 7.46 %.

(2*S*)-2-Acetyl-4-cyano-2-methyl-butyric acid benzyl ester (13b). Oil, 53% (hexane/AcOEt 8.5:1.5); $[\alpha]_D^{26}$ = -26.9 (*c* 1.37, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = (ppm) 7.39-7.32 (m, 5H), 5.20 (s, 2H), 2.33-2.21 (m, 3H), 2.14-2.02 (m, 1H), 2.08 (s, 3H), 1.40 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = (ppm) 203.82, 171.31, 134.31, 128.75, 128,71, 128,51, 118.89, 67.64, 58,46, 30.56, 26, 04, 19.12, 12,83. IR (ν_{max}, cm^{-1}): 2174, 1742, 1708. Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.51; H, 6.63; N, 5.44 %.

(2*S*)-2-Acetyl-4-cyano-2-methyl-butyric acid ethyl ester (13c). Oil, 34% (hexane/AcOEt 8.5:1.5); $[\alpha]_D^{26}$ = -41.6 (*c* 1.2, $CDCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = (ppm) 4.24 (q, *J* = 7.16 Hz, 2H), 2.40-2.22 (m, 3H), 2.18 (s, 3H), 2.13-2.03 (m, 1H), 1.40 (s, 3H, CH_3), 1.29 (t, *J* = 7.16 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = (ppm) 204.0, 171.4, 119.0, 61.8, 58.3, 30.4, 26.0, 19.0, 13.8, 12.8. IR (ν_{max}, cm^{-1}): 2248, 1740, 1714.Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.77; H, 7.79; N, 6.99 %.

(*S*)-2-(2-Benzenesulfonylethyl)-2-methyl-3-oxobutyric acid ethyl ester (8c). Solid, without $ZnCl_2$: 61%, with $ZnCl_2$: 80% (hexane/AcOEt 6.5:3.5); $[\alpha]_D^{26}$ = -15.2 (*c* 2.83, $CDCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.93-7.90 (m, 2H), 7.71-7.66 (m, 1H), 7.62-7.56 (m, 2H), 4.17 (q, *J* = 7.16 Hz, 2H), 3.18-3.00 (m, 2H), 2.27-2.05 (m, 2H), 2.11 (s, 3H), 1.32 (s, 3H), 1.23 (t, *J* = 7.16 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = (ppm) 204.1, 171.5, 138.4, 133.8, 129.2, 127.9, 61.7, 58.0, 51.8, 27.5, 25.9, 19.2 13.8. IR (ν_{max}, cm^{-1}): 1738, 1714, 1447. Calcd for $C_{15}H_{20}O_5S$: C, 57.67; H, 6.45. Found: C, 57.47; H, 6.56 %.

(*S*)-3-(*S*)-phenylethylamino-4-ethoxycarbonyl-4-methylcyclohex-2-enone (16). Solid, 50% (hexane/AcOEt 8:2 then AcOEt 100%); P_F = 96-98°C. $[\alpha]_D^{26}$ = -220 (*c* 0.64, MeOH). ^1H NMR (300 MHz, CD_4O): δ = (ppm) 7.30-7.14 (m, 5H), 4.93 (s, 1H), 4.50 (q, *J* = 6.97 Hz, 1H), 4.17 (q, *J* = 7.16 Hz, 2H), 2.80-2.14 (m, 3H), 1.91-1.83 (m, 1H), 1.55 (s, 3H), 1.46 (d, *J* = 6.97 Hz, 3H), 1.23 (t, *J* = 7.16 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = (ppm) 198.8, 174.9, 167.6, 144.6, 129.9, 128.4, 126.8, 98.6, 62.9, 54.6, 48.0, 35.2, 33.3, 23.5, 23.3, 14.5. IR (ν_{max}, cm^{-1}): 3283, 3063, 1733, 1530. Anal. Calcd for $C_{18}H_{23}NO_3$: C,71.73; H, 7.69; N, 4.65. Found: C, 71.90; H, 7.58; N, 4.49 %.

(*S*)-2-Acetyl-2-methylpentanedioic acid 1-benzyl ester 5-tert-butyl ester (14b). Oil, with $ZnCl_2$: 80% (hexane/AcOEt 9:1); $[\alpha]_D^{26}$ = -5.0 (*c* 2.96, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = (ppm) 7.27-7.15 (m, 5H), 5.16 (s, 2H), 2.22-2.03 (m, 4H), 2.07 (s, 3H), 1.42 (s, 9H), 1.23 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = (ppm) 204.86, 172.33, 172.03, 135.26, 128.61, 128.46, 128.30, 80.53, 67.13, 58.97, 30.60, 29.74, 28.05, 26.10, 18.85. IR (ν_{max}, cm^{-1}): 1712, 1710, 1150, 1098. Calcd for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 68.31; H, 7.80 %.

(*S*)-2-Acetyl-2-methylpentanedioic acid 5-tert-butyl ester 1-ethyl ester (14c). Oil, without $ZnCl_2$: 37%, with $ZnCl_2$: 85% (hexane/AcOEt 9:1); $[\alpha]_D^{26}$ = -5.6 (*c* 1.25, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = (ppm) 4.20 (q, *J* =7.16 Hz, 2H), 2.24-2.17 (m, 2H), 2.16 (s, 3H, CH_3), 2.15-2.03 (m, 2H), 1.44 (s, 9H), 1.33 (s, 3H), 1.27 (t, *J* =7.16 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = (ppm) 205.0, 172.4, 172.0, 80.4, 61.3, 58.7, 30.5, 29.6, 27.9, 26.0, 18.7, 13.9. IR (ν_{max}, cm^{-1}): 1735, 1717. Calcd for $C_{14}H_{24}O_5$: C, 61.74; H, 8.88. Found: C, 61.67; H, 8.80 %.

(*S*)-2-Acetyl-2-methyl-pentanedioic acid dibenzyl ester (15b). Oil, 80% (hexane/AcOEt 7.5:2.5); $[\alpha]_D^{26}$ = -12.7 (*c* 1.18, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = (ppm) 7.36-7.28 (m, 10H), 5.15 (s, 2H), 5.10 (s, 2H), 2.31-2.10 (m, 4H), 2.06 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = (ppm) 204.7, 172.5, 172.2, 135.7, 135.1, 128.6, 128.5, 128.4, 128.3, 128.2, 128.2, 67.1, 66.7, 58.8, 29.5, 29.4, 26.1, 18.9. IR (ν_{max}, cm^{-1}): 1738, 1715, 1455. Calcd for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57. Found: C, 71.51; H, 6.52 %.

(*S*)-2-Acetyl-2-methylpentanedioic acid 5-benzyl ester 1-ethyl ester (15c). Oil, 41% (hexane/AcOEt 8:2); $[\alpha]_D^{26}$ = -7.8 (*c* 0.64, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = (ppm) 7.36-7.31 (m, 5H), 5.10 (s, 2H), 4.17 (q, *J* = 7.16 Hz, 2H), 2.36-2.05 (m, 4H), 2.15 (s, 3H), 1.33 (s, 3H), 1.25 (t, *J* = 7.16 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = (ppm) 204.80, 172.50, 172.27, 135.7, 135.72, 128.43, 128.32, 66.30, 61.37, 29.51, 29.40, 25.97, 18.86, 12.88. IR (ν_{max}, cm^{-1}): 1734, 1712, 1155. Calcd for $C_{22}H_{24}O_5$: C, 61.74; H, 8.88. Found: C, 61.70; H, 8.92 %.

(*S*,*S*)-4-Acetoxy-2-acetyl-2-methylpentanedioic acid 1-benzyl ester 5-methyl ester (4b). Oil, 50% (hexane/AcOEt 7.5:2.5); $[\alpha]_D^{26}$ = 1.82 (c = 0.55, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = (ppm) 7.39-7.31 (m, 5H), 5.17 (s, 2H), 5.04 (dd, *J* = 4.14 Hz, 1H), 3.74 (s, 3H), 2.57-2.43 (m, 2H), 2.09 (s, 3H), 2.03 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = (ppm) 203.40, 171.73, 169.98, 169.60, 134.81, 128.58, 128.54, 128.29, 68.65, 67.42, 57.75, 52.50, 35.37, 25.94, 20.08, 18.31. IR (ν_{max}, cm^{-1}): 2960, 1750, 1717, 1450, 1418. Anal. Calcd for $C_{18}H_{22}O_7$: C, 61.71; H, 6.33. Found C, 62.03; H 6.29 %.

(*S*,*S*)-4-Acetoxy-2-acetyl-2-methylpentanedioic acid 1-ethyl ester 5-methyl ester (4c). Oil, 50% (hexane/AcOEt 7.5:2.5); $[\alpha]_D^{26}$ = 7.89 (c = 1.14, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$,): δ = (ppm) 5.03 (dd, *J* = 3.96 Hz, 1H), 4.21 (q, *J* = 7.16 Hz, 2H), 4.76 (s, 3H), 2.56-2.41 (m, 2H), 2.19 (s, 3H), 2.05 (s, 3H), 1.38 (s, 3 H), 1.27 (t, *J* = 7.163, 3H); ^{13}C NMR (75 MHz , $CDCl_3$): δ = (ppm) 203.69, 171.95, 170.06, 169.66, 68.70, 61.80 , 57.66, 52.54, 35.37, 25.96, 20.13, 18.36, 13.87. IR (ν_{max}, cm^{-1}): 1751, 1715. Anal. Calcd for $C_{13}H_{20}O_7$: C, 54.16; H, 6.99. Found C, 54.01; H, 7.09 %.

(2*S*,4*S*)-2-Acetyl-4-acetylamino-2-methylpentanedioic acid 1-benzyl ester 5-methyl ester (5b). Oil, 30% (hexane/AcOEt 2.5:7.5); $[\alpha]_D^{26}$ = -3.33 (c= 1.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = (ppm) 7.40-7.30 (m, 5H), 6.17 (d, *J* = 8.29 Hz, 1H, NH,), 5.19 (d, *J* = 12.24 Hz, 1H), 5.11 (d, *J* = 12.24 Hz, 1H), 4.61 (m, 1H), 3.69 (s, 3H), 2.37 (m, 2H), 2.10 (s, 3H), 1.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = (ppm) 205.36, 172.34, 171.84, 169.80, 134.90, 128.59, 128.51, 128.21, 67.45, 58.08, 52.39, 49.00, 35.92, 26.23, 22.85, 18.52. IR (ν_{max}, cm^{-1}): 3050, 1751, 1714, 1661, 1534, 1438, 1420. Anal. Calcd for $C_{18}H_{23}NO_6$: C, 61.88; H, 6.64; N, 4.01. Found: C, 62.18; H, 6.84; N 3.76 %.

(*S*,*S*)-2-Acetyl-4-acetylamino-2-methylpentanedioic acid 1-ethyl ester 5-methyl ester (5c). Oil, 55% (hexane/AcOEt 2.5:7.5); $[\alpha]_D^{26}$ = -2.86 (c= 4.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = (ppm) 6.34 (s, 1H, NH), 4.65-4.57 (m, 1H), 4.20 (q, *J* = 7.16 Hz, 2H), 3.72 (s, 3H), 2.37-2.34 (m, 2H), 2.19 (s, 3H), 1.97 (s, 3H), 1.49 (s, 3H), 1.27 (t, *J* = 7.16 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = (ppm) 205.62, 172.45, 172.02, 169.85, 61.77, 57.96, 52.35, 48.98, 35.84, 26.20, 27.79, 18.47, 13.79. IR (ν_{max}, cm^{-1}): 3278, 1740, 1714, 1662, 1536. Anal. Calcd for $C_{13}H_{21}NO_6$: C, 54.35; H, 7.37; N, 4.88. Found: C, 54.66; H, 7.55; N, 4.80 %.

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