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Esterase-mediated synthesis of optically active GABA analogues containing a stereogenic all-carbon quaternary carbon atom

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ABSTRACT

Esterase from Horse Liver (HLAP) was able to hydrolyze a series of linear and cyclic β,β-dialkyl-γ-nitroesters, in spite of the well-known reluctance of hydrolytic enzymes to recognize and transform hindered substrates, such as those possessing a stereogenic quaternary carbon atom next to the reaction site. The resulting optically active γ-nitroesters gave access to optically active β,β-disubstituted γ-aminoacids as well as α,α-disubstituted succinic acids, both being biologically relevant compounds.

1. Introduction

The stereoselective synthesis of optically active substituted γ-amino acids has received considerable attention in recent years.[1] These compounds are structurally related to γ-aminobutyric acid **1** (GABA), which is the main Central Nervous System (CNS) inhibitory neurotransmitter.[2] Many non-natural γ-amino acids have been designed and synthesized for the therapeutic treatment of the diseases arising from a deficiency in the GABA system.[3] Some examples of commercial β-aryl- and β-alkyl GABA are (*R*)-Baclofen **2** (Fig. 1),[4,5] a muscle relaxant and antispastic agent, and (*S*)-Pregabalin **3**[6,7] [(3-aminomethyl-5-methylhexanoic acid)], having anticonvulsant, anxiolytic-like and analgesic properties. Gabapentine **4**[3a,8] [1-(aminomethyl)cyclohexylacetic acid] is an achiral β,β-disubstituted GABA analogue, commercialized as Neurontin® for the treatment of epilepsy, faintness, hypokinesis and cranial traumas. It is also the only drug specifically licensed for the treatment of neuropathic pain.

Although these compounds have been shown to act with very different mechanisms, they were all designed as lipophilic GABA analogues.

The ability to exert their action is in fact strictly related to their lipophilicity and the consequent capacity to cross the Blood–Brain Barrier (BBB),[9] which is prohibited for the highly hydrophilic GABA itself, whose direct administration is not therapeutically useful for this reason.

The chirality of non-racemic synthetic GABA analogues is very important, as their activity is recognized to reside only in a single enantiomer, as indicated in Figure 1.[4,6]

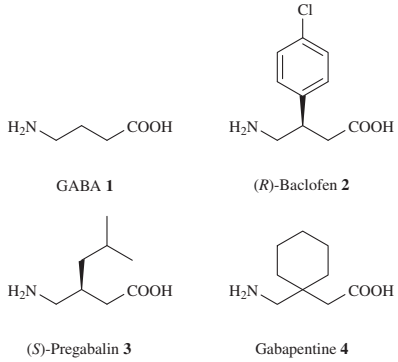

Figure 1. GABA and commercially available GABA derivatives.

It is worth noting that in addition to having a biological activity in the CNS, chiral γ-aminoacids are also present in the structure of natural antitumor compounds,[10] some of which are known to form helicoidal γ-peptidomimetics,[11] conformationally stable both in solution and in solid state, even for oligopeptides consisting of as few as four residues.

For all these reasons, the enantioselective synthesis, as well as the biological activity evaluation and practical applications of new chiral linear and cyclic γ-aminoacids, has been the subject of many publications,[4,5,7,12–14] However, whereas β-monosubstituted γ-aminobutyric acid derivatives, including β-alkyl,[7,13,14] β-aryl[4,5] and β-heteroaryl[12a] substituted systems, have been extensively described, very little has been reported on the synthesis of β,β-disubstituted GABA analogues, structurally related to Gabapentin.

A single example is present in the literature[12b] on the synthesis of an acyclic optically active β,β-dialkylated γ-aminobutyric acid,

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namely (*R*)-β-benzyl-β-methylGABA, obtained from stereoselective α-benzylation of a chiral ester derived from 2-cyanopropanoic acid and (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisoborneol (Oppolzer's alcohol),[15] used as a chiral auxiliary. Using this six-step route, the final compound was obtained with 82% ee and in 65% total yield.

Among the cyclic Gabapentin-related analogues, *cis*-(1*S*,3*R*)-(1-aminomethyl)-3-methylcyclohexaneacetic acid[16] was shown to be one of the most active compounds among a series of mono- and polymethylsubstituted Gabapentin analogues, exhibiting a higher affinity for the Gabapentin receptor binding site with respect to the parent unsubstituted achiral aminoacid. It also showed a higher activity than its enantiomer and its diastereomeric *trans*-isomer. It was obtained as a pure enantiomer by preparative HPLC separation of its racemic form,[16] prepared in turn by a route involving the diastereoselective addition of nitromethane to ethyl (*E*,*Z*)-2-(3-methylcyclohexylidene)acetate as the key step.

Finally, a bicyclic derivative, namely (1*S*,5*S*,6*R*)-(−)-(6-(aminomethyl)bicyclo[3.2.0]heptane-6-acetic acid,[17–19] is a therapeutic agent used against a variety of neurodegenerative and neuropathological disorders. Its synthesis is based on commercially available (1*R*,5*S*)-(+)-*cis*-bicyclo[3.2.0]hept-2-en-6-one.[19–21]

In the frame of our research, involving the use of hydrolytic enzymes in the synthesis of chiral compounds of biological and pharmaceutical interest, and in particular of γ-aminobutyric acid analogues, we developed a short and inexpensive route to a series of acyclic and cyclic β,β-disubstituted-γ-aminobutyric acids using commercial esterases in the enantiodifferentiating step. This work is of interest not only for the biological potential relevance of these compounds but also for the synthetic problem associated with the obtainment of chiral compounds with a quaternary asymmetric carbon atom.[22] The method presented here also gives access to α,α-disubstituted chiral non-racemic succinic acids, which are potentially of great relevance as valuable building blocks.

In fact, monosubstituted succinic acids have been reported in their enantiomerically pure forms since 1960[23] as important synthetic intermediates to homochiral building blocks, such as β-lactams, β-and γ-lactones and to chiral subunits of pseudopeptides, which have been proven to be effective inhibitors of various zinc-enzymes,[24] and to have different biological activities. Only a few examples of carboxylic acids possessing an all-carbon α-quaternary centre which can be obtained by catalytic methods are known so far.[25,26] Recently, one example has been published[27] concerning the asymmetric synthesis of α-alkyl-α-aryl substituted succinate derivatives, through the Cu-catalyzed 1,4-addition of dialkylzinc reagents to β-arylacetates.

To the best of our knowledge, no other examples of chiral non-racemic α,α-disubstituted succinic acids have been reported as yet in the literature.

2. Results and discussion

2.1. Synthesis and characterization of racemic γ-nitroesters

The general strategy used for the synthesis of β,β-disubstituted GABA analogues **9a**–**e** is reported in Scheme 1. It is based on the Horner–Wadsworth–Emmons homologation reaction carried out on the substrates **5a**–**e** which furnished the corresponding α,β-unsaturated esters **6a**–**e**[28] as mixtures of *E* and *Z* diastereomers. The subsequent conjugate addition reaction between nitromethane and the Michael acceptors **6a**–**e**, carried out under basic conditions, afforded the corresponding γ-nitroesters **7a**–**e** as racemates. The base used in this step was DBU for **6a**–**c**[28a] and tetrabutylammonium fluoride in refluxing THF for **6d**,**e**.[28b]

It should be noted that the formation of the γ-nitroesters **7d** and **7e** occurred with complete diastereoselectivity, as a single stereoisomer was isolated in each case. The assignment of the relative configuration had already been made for **7d**,[28] while for **7e** it was made by means of DIFNOE experiments, whose results are presented in Figure 2 for both compounds. A complete assignment for all proton and carbon resonances was previously made through 2D experiments. As expected, the addition of the nitromethane carbanion to the corresponding α,β-unsaturated esters **6d** and **6e** took place from the less hindered side of the molecules, namely that containing the equatorial position for **6d** and the bridge hydrogen atom for **6e**. As a consequence, the nitromethyl group in **7d** is *cis* to the methyl group at C-3, while in **7e** the same substituent is *cis* to the junction hydrogen atoms. Reduction of the nitro group in **7a**–**e** gave the corresponding γ-lactams **8a**–**e**, which were hydrolyzed to the desired GABA analogues **9a**–**e**, which were separated as hydrochlorides. In the reaction sequence presented here, the enantiodifferentiating step was the enzymatic resolution of the chiral racemic γ-nitroesters **7a**–**e** to the corresponding optically active γ-nitroacids **10a**–**e**, with recovery of unreacted, enantioenriched γ-nitroesters **7a**–**e**. All intermediates and products, presented in Scheme 1, were isolated as pure compounds and were fully characterized.

2.2. Kinetic resolution of γ-nitroesters 7a–e

Chiral racemic γ-nitroesters **7a**–**e** were treated for kinetic resolution with a series of commercially available hydrolytic enzymes, such as esterases, lipases and proteases. Among them, only the crude esterases from horse liver (HLAP, Horse Liver Acetone Powder) and from porcine liver (PLAP, Porcine Liver Acetone Powder) proved active towards the substrates, affording their respective carboxylic acids **10a**–**e**. For PLAP, however, the *E* value was generally too low to be useful for preparative purposes.

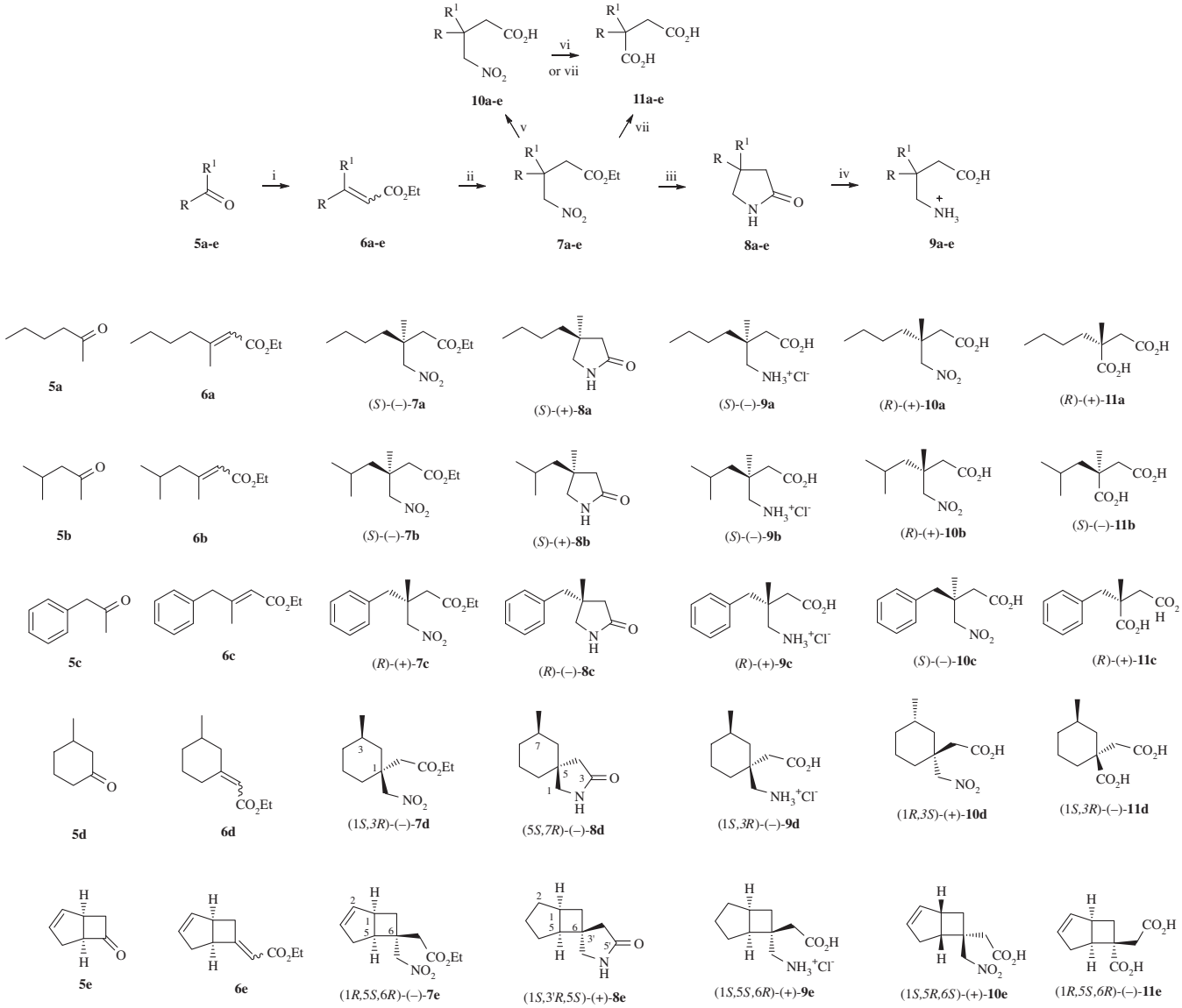
Other enzymes, such as proteases (α-chymotrypsin, Subtilisin) and Lipases (*Aspergillus niger* lipase, *Pseudomonas* sp. Lipase, *Pseudomonas fluorescens* lipase, Novozyme 435), were completely ineffective and the substrates were recovered unaltered after 48 h.

The results for kinetic enzymatic resolutions are summarized in Table 1, which lists the ee values, enantiomeric ratios[29] and yields for the isolated acids **10a**–**e**, and for the recovered unreacted esters **7a**–**e**.

The reactions were stopped at approximately 20% conversions, in order to calculate the enantiomeric ratio *E*[29] for all enzymes. All resolutions were run up to the conversions indicated in Table 1, in order to isolate the carboxylic acid products and the unreacted esters with the highest possible ee's. Since in all cases the enantioselectivity was moderate, the reactions were allowed to exceed 50% conversion, until the ee's of the unreacted nitroesters were satisfactory.

The enantioselectivities observed were quite low in the case of the enzymatic resolutions of **7a**,**b**,**c** and, accordingly, the resulting carboxylic acids **10a**,**b**,**c** were isolated with ee's lower than 75%, at low conversion values. Moreover, hydrolyses of 7**a** and **7c** did not proceed over 39% and 42% conversion, respectively, where the unreacted nitroesters **7a** and **7c** had 39% and 63% ee, respectively. Both compounds were therefore recycled and, after three consecutive hydrolysis procedures, they could be recovered with 62% ee in the former case and with 91% ee in the latter. The enantioselectivity was found to increase with the complexity of the substrate structure, reaching its maximum value with the bicyclic system **7e** ($E = 40$), which could be isolated as an almost enantiomerically pure compound at 60% conversion.

The last steps in this reaction sequence were the conversion of the chiral non-racemic γ-nitroesters **7a**–**e** into their corresponding aminoacids **9a**–**e**, through reduction of their nitro group to an amino group, cyclization into the corresponding γ-lactams **8a**–**e** and subsequent acidic hydrolysis. In the reduction step, carried out with H_2 under catalytic conditions, the ring double bond in **7e** was also reduced, so that both (+)-**8e** and (+)-**9e** were saturated systems.



Scheme 1. General strategy for the synthesis of the β,β-disubstituted GABA analogues **9a**–**e**. Reagents and conditions: (i) triethylphosphonoacetate, *tert*-BuOK, refluxing THF, 20 min; (ii) CH_3NO_2, DBU, rt, overnight; or equimolar CH_3NO_2, TBAF, refluxing THF; (iii) H_2, Ra–Ni; (iv) 6 M HCl; (v) enzymatic resolution; (vi) spontaneous, 2 weeks; (vii) 1:1 6 N HCl/glacial AcOH under reflux, 2 h. Compounds **7**–**11** are given with the correct stereochemistry for the enantiomer shown, after enzymatic procedures.

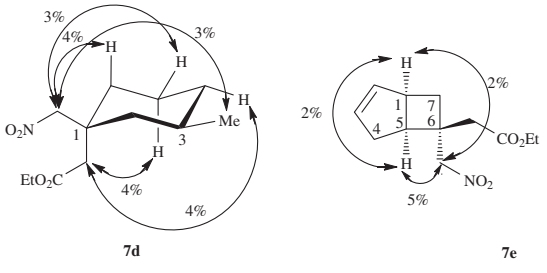


Figure 2. The main results of DIFNOE measurements for compounds **7d** and **7e**.

In all cases examined, when the hydrolysis was prolonged to very high conversion values, the corresponding succinic acids **11a**–**e** were isolated instead of the expected γ-nitroacids **10a**–**e**. Evidently, long reaction times favour the spontaneous oxidative Nef reaction occurring on the γ-nitroacids **10a**–**e** leading to **11a**–**e**. It is noteworthy that the transformation of a nitroalkane to an alkanoic acid usually requires prolonged heating in a mineral acid.[30]

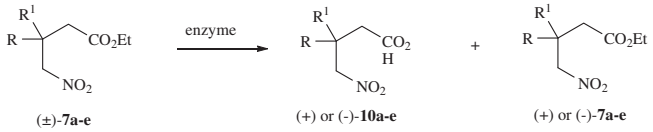
A similar Nef reaction occurring under the mild conditions of an enzymatic hydrolysis, that is room temperature and a pH near neutrality, was first observed in the enzymatic resolution of ethyl (±)-5,5-dimethyl-3-nitromethylhexanoate.[7a]

The α,α-disubstituted succinic acids **11a**–**e** could also be obtained from the corresponding optically active γ-nitroesters **7a**–**e** and from the γ-nitroacids **10a**–**e**, under acidic treatment with a 1:1 solution of glacial AcOH and 6 M HCl, at reflux. The reaction was very rapid and went to completion within two hours with no loss of chirality observed in the products.

2.3. Determination of the absolute configurations of the chiral non-racemic γ-nitroesters and γ-nitroacids

First, the absolute configuration was determined for (−)-**9d**[16] and for (+)-**9e**.[17] Although their syntheses had already been

Table 1
Enzymatic hydrolysis of the racemic nitroesters **7a–e**[a]



(±)-**7a-e** (+) or (-)-**10a-e** (+) or (-)-**7a-e**

Substrate	*E*	γ-Nitroacid			Unreacted γ-Nitroester		
		Acid [yield, %][b]	Conv.[c] (%) [time, h]	ee (%)	Ester [yield, %][b]	Conv.[c] (%) [time, h]	ee (%)
7a	8	(+)-**10a** [15]	20 [7]	74[d,e]	(−)-**7a** [35]	39 [24]	39[d,f]
7b	9	(+)-**10b** [18]	23 [24]	75[d,e]	(−)-**7b** [22]	75 [72]	88[d]
7c	11	(−)-**10c** [15]	20 [24]	71[g,e]	(+)-**7c** [40]	42 [72]	63[g,h]
7d	10	(+)-**10d** [20]	24 [24]	78[d,e]	(−)-**7d** [24]	75 [72]	>99[d]
7e	41	(+)-**10e** [18]	21 [16]	94[i]	(−)-**7e** [30]	60 [26]	>99[i,j]

[a] Reaction conditions: 1.0 g substrate, 0.5 g enzyme, 0.1 phosphate buffer, pH 7.4 (5 mL/mmol), rt.
[b] Yields of isolated products.
[c] Calculated conversion.
[d] Determined by chiral HRGC.
[e] After esterification of the carboxylic group.
[f] 62% after three hydrolyses.
[g] Determined by chiral HPLC.
[h] 91% after three hydrolyses.
[i] Determined by ^{1}H NMR after coupling the carboxylic function with (*S*)-(−)-1-phenylethylamine, followed by integration of the corresponding nitromethylene proton signals.
[j] After hydrolysis of the CO_2Et (1 M NaOH, followed by 1 M HCl, rt).

described in the literature, no data on their chiroptical properties were given and their absolute configurations were uncertain.

This assignment was made unambiguously for the precursors of (−)-**9d**, namely the γ-nitroester (−)-**7d**, recovered from the enzymatic resolution. For this purpose, an authentic sample of (−)-**7d** was prepared, starting from the commercially available parent homochiral ketone (3*R*)-(+)-**5d**. The absolute configuration of the asymmetric quaternary carbon atom, assigned as (*S*), followed from the knowledge of its relative configuration, established by DIFNOE experiments, as seen above.

By the same procedure the (1*S*,5*S*,6*R*)-absolute configuration was attributed to (−)-**7e**, recovered from the enzymatic hydrolysis, which was compared with a sample of (−)-**7e** prepared from the commercially available ketone (1*R*,5*S*)-(+)-**5e**.

The opposite configuration was consequently assigned to their related γ-nitroacids (+)-**10d** and (+)-**10e**, isolated from enzymatic hydrolyses.

The GABA analogue β-benzyl-β-methyl-γ-aminobutyric acid (+)-**9c**, derived from (+)-**7c**, was assigned the (*R*)-configuration, by comparison with the specific rotation value reported in the literature for the same enantiomer.[12b]

As for the other two acyclic β,β-dialkyl-GABA analogues **9a** and **9b**, their absolute configurations were only tentatively assigned as (*S*) by comparison of the CD spectra of their γ-lactam precursors **8a** and **8b** with those of similar γ-lactams bearing no methyl group at C-4. In fact, the γ-lactams **8a** and **8b** showed a negative Cotton effect associated with the n–π^* transition of the lactam group at 220 nm, while (*R*)-(+)-4-butyl-2-pyrrolidinone and (*R*)-(+)-isobutyl-2-pyrrolidinone showed a positive Cotton effect associated with the same band.[7a] Further support of this hypothesis can be found in the CD spectrum of (−)-**8d**, whose absolute configuration at the quaternary carbon atom is (*S*), and which exhibited a strong negative Cotton effect at 219 nm.

Finally, succinic acids **11a–e** were given the same configurations as their γ-nitroacid precursors **10a–e**, as epimerization at the fully substituted chiral carbon atom is not possible. The same can be said for succinic acids **11a–e** derived directly from their γ-nitroester precursors **7a–e**.

3. Conclusion

In conclusion, an easy and short enantioselective synthesis of a series of potentially useful β,β-disubstituted GABA analogues has been developed, starting from the readily available racemic γ-nitro ester precursors **7**, through their enzymatic kinetic resolution. Their ee's ranged from 71 to 94 for acids and from 39 to >99 for esters.

Although enantioselectivities observed may look modest, at least for **7a–c**, the results obtained are of interest. In fact, it is well known that, because of steric repulsions, the most common hydrolases are unable to accept substrates in which the chiral centre close to the hydrolyzable function is fully substituted, as is the case of esters of tertiary alcohols,[22] or esters of α,α-disubstituted carboxylic acids. In this latter case, for instance, resolution is known to occur only when at least one of the α-substituents exerts electron-withdrawing effects.[31]

This procedure gives also access to unknown optically active 2,2-dialkylsuccinic acids, whose monosubstituted analogues are extensively studied compounds.

4. Experimental

IR spectra were recorded on a Jasco FT-IR 200 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were run on a Jeol EX-400 (400 MHz for proton, 100.1 MHz for carbon), using deuteriochloroform as the solvent and tetramethylsilane as the internal standard. Chemical shifts are expressed in parts per million (δ). Coupling constants are given in hertz. Optical rotations were determined on a Perkin Elmer Model 241 polarimeter, at 25 °C. CD spectra were recorded on a Jasco J-710 spectropolarimeter. ESI-MS were run on a Bruker Esquire 4000 instrument. Enzymatic hydrolyses were performed using a pH-stat Controller PHM290 Radiometer, Copenhagen. Chiral HRGC analyses were run on a Shimadzu GC-14B instrument, the capillary columns being Chiraldex™ type G-TA, γ-cyclodextrin (40 m × 0.25 mm) (carrier gas He, 180 kPa, split 1:100), or DiMePe β-cyclodextrin (25 m × 0.25 mm) (carrier gas He, 110 kPa, split 1:50); Chiral HPLC analyses were run on a Hewlett Packard series 1100 instrument, the capillary column being Daicel OD20 (250 L.

mm × 4.6 I.D. mm); TLCs were performed on Polygram® Sil G/UV_{254} silica gel pre-coated plastic sheets (eluent: light petroleum 40–70 °C/ethyl acetate mixtures). Flash chromatography was run on silica gel, 230–400 mesh ASTM (Kieselgel 60, Merck), using light petroleum 40–70 °C/ethyl acetate mixtures as the eluent. Elemental analyses (C, H, N) were carried out with a Carlo Erba 1106 elemental analyzer, at the Department of Chemical Sciences and Technologies of the University of Udine, Italy. Liver acetone powder equine (HLAP), Liver acetone powder porcine (PLAP), (*R*)-(+)-3-methylcyclohexanone and (+)-(1*R*,5*S*)-*cis*-bicyclo[3.2.0]hept-2-en-6-one were purchased from Sigma–Aldrich.

4.1. Synthesis of the α,β-unsaturated esters. General procedure

To a solution of the appropriate ketone **5a**–**e** (36 mmol) and triethyl phosphonoacetate (30 mmol) in anhydrous THF, *t*-BuOK (30 mmol) was added portionwise and the mixture was heated at gentle reflux for 20 min. After cooling to rt, the organic solution was washed with 5% HCl, then with brine, dried over Na_2SO_4 and the solvent was removed in vacuo to give a clear oil. The oily residue was purified by flash chromatography (eluent: petroleum ether 40–70 °C, ethyl acetate 98:2).

4.1.1. Ethyl (*E*,*Z*)-3-methylhept-2-enoate 6a

E/*Z* mixture in 2:1 ratio, 73% yield from **5a**; IR (neat) 1717 (CO_2Et), 1649 (C=C) cm^{-1}; ^1H NMR δ 5.64 (m, H-2, *Z*-isomer), 5.62 (m, H-2, *E*-isomer), 4.14 (2q, 2H, CH_2O), 2.13 (d, *J* 1.1, CH_3C, *E*-isomer), 2.11 (m, H-4, *E*-isomer), 2.00 (m, H-4, *Z*-isomer), 1.85 (d, *J* 1.1, CH_3C, *Z*-isomer), 1.42 (m, 2H, H-5), 1.34–1.27 (t and m, 5H, CH_3CH_2O and H-6), 0.93–0.85 (2t, 3H, H-7); $^{13}C\{^1H\}$ NMR δ 166.9 (s, C-1, *E* isomer), 166.3 (s, C-1, *Z* isomer), 160.7 (s, C-3, *Z*-isomer), 160.3 (s, C-3, *E*-isomer), 115.9 (d, C-2, *Z*-isomer), 115.4 (d, C-2, *E*-isomer), 60.4 (t, CH_3CH_2O, *Z*-isomer), 59.5 (t, CH_3CH_2O, *E*-isomer), 40.7 (2t, C-4), 29.7 (2t), 25.2 (q, CH_3C=), 22.2 (2t), 14.4 (2q, CH_3CH_2O), 13.9 (2q, C-7); ESI-MS 171.2 ($M+H^+$), 193.1 (M+Na).

4.1.2. Ethyl (*E*,*Z*)-3,5-dimethylhex-2-enoate 6b

E/*Z* mixture in 6:1 ratio, 80% yield from **5b**; IR (neat) 1717 (CO_2Et), 1648 (C=C) cm^{-1}; ^1H NMR δ 5.65 (br s, H-2, *Z*-isomer), 5.58 (br s, H-2, *E*-isomer), 4.10 (q, 2H, CH_2O), 2.54 (d, *J* 7.7, H-4, *Z*-isomer), 2.09 (d, *J* 7.3, H-4, *E*-isomer), 2.11 (br s, CH_3C, *E*-isomer), 1.85 (br s, CH_3C, *Z*-isomer), 1.85 (m, 1H, H-5), 1.25 (t, CH_3CH_2O, *E*-isomer), 1.24 (t, CH_3CH_2O, *Z*-isomer), 0.89 (d, *J* 6.6, $(CH_3)_2CH$, *Z*-isomer), 0.85 (d, *J* 6.6, $(CH_3)_2CH$, *E*-isomer); $^{13}C\{^1H\}$ δ 166.8 (s, C-1, *E*-isomer), 166.5 (s, C-1, *Z*-isomer), 159.5 (s, C-3, *Z*-isomer), 159.3 (s, C-3, *E*-isomer), 117.1 (d, C-2, *Z*-isomer), 116.7 (d, C-2 *E*-isomer), 59.4 (2t, CH_2O), 50.6 (t, C-4, *E*-isomer), 41.7 (t, C-4, *Z*-isomer), 27.4 (d, C-5, *Z*-isomer), 26.2 (d, C-5, *E*-isomer), 22.4 (4q, $(CH_3)_2CH$), 18.6 (2q, CH_3C=), 14.3 (2q, CH_3CH_2O); ESI-MS 171.0 [$M+H^+$], 193.0 [$M+Na^+$].

4.1.3. Ethyl (*E*,*Z*)-3-methyl-4-phenylbut-2-enoate 6c

E/*Z* mixture in 4:1 ratio, 77% yield from **5c**; IR (neat) 3063, 3028, 1602, 1495, 1453, 740, 700 (Ph), 1716 (CO_2Et), 1650 (C=C) cm^{-1}; ^1H NMR δ 7.28 (m, 3H, ArH), 7.15 (d, 2H, ArH), 5.78 (s, H-2, *Z*-isomer), 5.68 (s, H-2, *E*-isomer), 4.14 (q, 2H, CH_2O), 4.02 (s, H-4, *Z*-isomer), 3.42 (s, H-4, *E*-isomer), 2.12 (s, CH_3C, *E*-isomer), 1.78 (s, CH_3C, *E*-isomer), 1.26 (t, 3H, CH_3CH_2O); $^{13}C\{^1H\}$ δ 166.8 (s, C-1, *E*-isomer), 166.7 (s, C-1, *Z*-isomer), 158.4 (s, C-3, *Z*-isomer), 157.6 (s, C-3, *E*-isomer), 137.8 (s, Ph), 129.2 (d, Ph), 128.6 (d, Ph), 126.7 (d, Ph) 117.3 (d, C-2, *E*-isomer), 117.2 (d, C-2, *Z*-isomer), 59.7 (t, CH_2O), 47.1 (t, C-4, *E*-isomer), 38.9 (t, C-4, *Z*-isomer), 24.5 (q, CH_3C=, *Z*-isomer), 18.7 (q, CH_3C=, *E*-isomer), 14.4 (q, CH_3CH_2O); ESI-MS 205.1 [$M+H^+$].

4.1.4. Ethyl (*E*,*Z*)-(±)-2-(3-methylcyclohexylidene)acetate 6d[28b]

E/*Z* mixture in 1:1 ratio, 82% yield from (±)-**5d**, IR (neat) 1716 (CO_2Et), 1650 (C=C) cm^{-1}; ^1H NMR δ 5.61, 5.59 (2s, 1H, H-2), 4.14 (q, 2H, CH_2O), 3.64 (br t, 1H), 2.23 (br t, 1H), 2.0–1.5 (m, 5H), 1.41 (1H), 1.28 (t, 3H, CH_3CH_2O), 1.14 (tq, 1H), 0.98, 0.94 (2d, *J* 6.4, 3H, CH_3CH); $^{13}C\{^1H\}$ δ 166.8 (2s), 162.8, 162.4 (2s, C=), 113.2 113.1 (d, C-2), 59.40, 59.35 (2q), 46.1 (t), 37.7 (t), 37.4 (t), 34.8 (d), 34.6 (t), 34.5 (t), 34.1 (d), 29.1 (t), 27.3 (t), 26.5 (t), 22.2, 22.1 (2q), 14.2, 14.0 (2q); ESI-MS 183.1 [$M+H^+$], 205.2 [$M+Na^+$].

The enantiomer (3*R*)-(−)-**6d** obtained from (*R*)-(+)-**5d** had $[\alpha]_D^{25} = -48.3$ (*c* 1, $CHCl_3$).

4.1.5. Ethyl (*E*,*Z*)-(±)-bicyclo[3.2.0]hept-2-en-6-ylidene acetate[18a,b] 6e

E/*Z* mixture in 2:1 ratio, 78% yield from **5e**; IR (neat) 1714 (CO_2Et), 1673 (C=C) cm^{-1}; ^1H NMR δ 5.87, 5.86 (m, 3H, C*H*=C*H* and C*H*=CO_2Et), 4.11, 4.09 (2q, 2H, CH_2O), 3.85 and 3.60 (2 br signals, 1H, H-5) 3.42 (br signal, 1H, H-1), 3.25 (ddd, *J* 18.0, 8.0, 2.6, 1H, H-7, *E*-isomer), 3.03 (ddm, H-7, *Z*-isomer), 2.85 (dq, *J* 5.8 and 2.9, 1 H, H-7, *E*-isomer), 2.74 (dd, *J* 6.0 and 8.9, 1H, H-4, *Z*-isomer), 2.62 (2 m, 2H, H-4), 2.45 (dq, *J* 11.7 and 3.3, H-7, *Z*-isomer), 2.39 (br d, *J* 16.6, H-4, *E*-isomer), 1.25, 1.24 (2t, 3H, CH_3CH_2O); $^{13}C\{^1H\}$ δ 172.5, 172.0 (2s, CO), 166.2, 166.0 (2s, C-2, *E* and *Z*-isomers), 133.5, 132.7 (2d, C-2, *E* and *Z*-isomers), 131.8, 130.0 (2d, C-3, *Z* and *E*-isomers), 115.0, 114.6 (2d, $CHCO_2Et$, *Z* and *E*-isomers), 59.5 (t, CH_2O), 47.0, 45.9 (2d, C-1, *Z* and *E*-isomers), 43.6 and 42.3 (2d, C-4, *E* and *Z*-isomers), 40.3, 39.3 (t, C-5, *E* and *Z*-isomers), 39.2 and 39.0 (2t, C-7, *Z* and *E*-isomers), 14.2 (q, CH_3CH_2O). ESI-MS 179.2 ($M+H^+$), 201.0 ($M+Na^+$).

The enantiomer (1*R*,5*S*)-(+)-**6e** obtained from commercial (1*R*,5*S*)-(+)-**5e**, had $[\alpha]_D^{25} = +58.2$ (*c* 1.1, $CHCl_3$).

4.2. General procedure for the synthesis of racemic γ-nitroesters 7a–e

To a solution of the α,β-unsaturated esters **6a**–**c** (100 mmol) in nitromethane (25 mL), DBU (100 mmol) was added dropwise and the solution was stirred overnight at room temperature. In the synthesis of **7d**,**e**, nitromethane was used in an equimolar amount and TBAF (1 M solution in THF, 1 mmol) was used as a base, and the solution refluxed overnight. After evaporation of the solvent in vacuo, the residue was dissolved in diethyl ether and washed with 5% HCl followed by brine; then the organic phase was dried over anhydrous Na_2SO_4 and concentrated to give a dark brown oil, which was purified by flash chromatography (eluent petroleum ether/ethyl acetate 98:2).

4.2.1. Ethyl (±)-3-methyl-3-(nitromethyl)heptanoate 7a

Oil, 69% yield, after purification; IR (neat) 1732 (CO_2Et), 1551, 1376 (NO_2) cm^{-1}; ^1H NMR δ 4.58, 4.50 (AB system, J_{AB} 11.0, 2H, CH_2NO_2), 4.10 (q, 2H, CH_2O), 2.42, 2.37 (AB system, J_{AB} 15.9, 2H, H-2), 1.38 (m, 2H, H-4), 1.25, 1.24 (m and t, 7H, H-5, H-6, CH_3CH_2O), 1.08 (s, 3H, CH_3C), 0.86 (t, 3H, CH_3CH_2). $^{13}C\{^1H\}$ δ 171.1 (s, C-1), 82.4 (t, CH_2NO_2), 60.4 (t, CH_2O), 40.9 (t, C-2), 37.6 (t, C-4), 36.9 (s, C-3), 25.4 (t, C-5), 23.1 (t, C-6), 22.9 (q, CH_3C), 14.2 (q, CH_3CH_2O), 13.9 (q, C-7). ESI-MS 254.0 [$M+Na^+$]. Anal. Calcd for $C_{11}H_{21}NO_4$: C, 57.12; H, 9.15; N, 6.06. Found: C, 57.05; H, 9.18; N, 6.06.

4.2.2. Ethyl (±)-3,5-dimethyl-3-(nitromethyl)hexanoate 7b

Oil, 74% yield, after purification, IR (neat) 1732 (CO_2Et), 1550, 1375 (NO_2) cm^{-1}; ^1H NMR δ 4.66 (part A of an AB system, J_{AB} 11.0, 1H, CH_2NO_2), 4.55 (part B of an AB system, J_{AB} 11.0, 1H, CH_2NO_2), 4.15 (q, 2H, CH_2O), 2.50, 2.46 (AB system, J_{AB} 16.3, 2H, H-2), 1.70 (sept, *J* 6.6, 1H, $CH(CH_3)_2$), 1.41 (dq, J_1 14.7, J_2 5.5, 2H, H-4), 1.27 (t, 3H, CH_3CH_2O), 1.16 (s, 3H, CH_3C), 0.96, 0.95 (2d, *J* 6.6, 6H, $(CH_3)_2CH$); $^{13}C\{^1H\}$ δ 171.0 (s, CO), 82.7 (t, CH_2NO_2), 60.5 (t, CH_2O), 46.3 (t, C-2), 41.0 (t, C-4), 37.6 (s, C-3), 25.2 (q, $(CH_3)_2CH$), 23.8 (q, CH_3C), 23.2 (d, C-5), 14.2 (q, CH_3CH_2O); ESI-MS 186.0

[M−NO_2], 232 [MH^+], 254.0 [M+Na^+]. Anal. Calcd for $C_{11}H_{21}NO_4$: C, 57.12; H, 9.15; N, 6.06. Found: C, 57.15; H, 9.10; N, 6.17.

4.2.3. Ethyl (±)-3-benzyl-3-methyl-4-nitrobutanoate 7c

Oil, 72% yield, after purification; IR (neat) 3030, 1649, 1495, 1455, 764, 703 (Ph), 1731 (CO_2Et), 1549, 1376 (NO_2) cm^{-1}. ^{1}H NMR δ 7.29 (m, 3H, Ph), 7.17 (d, 2H, Ph), 4.68 (part A of an AB system, J_{AB} 11.3, 1H, CH_2NO_2), 4.64 (part B of an AB system, J_{AB} 11.3, 1H, CH_2NO_2), 4.16 (q, 2H, CH_2O), 2.87 (part A of an AB system, J_{AB} 13.4, 1H, CH_2Ph), 2.82 (part B of an AB system, J_{AB} 13.4, 1H, CH_2Ph), 2.43 (part A of an AB system, J_{AB} 16.3, 1H, H-2), 2.38 (part B of an AB system, J_{AB} 16.3, 1H, H-2), 1.29 (t, 3H, C$H_3$$CH_2O$), 1.11 (s, 3H, C$H_3$C); ^{13}C{^{1}H} δ 171.0 (s, CO), 135.7 (s, Ph), 130.7, 128.3, 127.0 (d, Ph), 81.7 (t, CH_2NO_2), 60.5 (t, CH_2O), 43.4 (t, CH_2Ph), 40.3 (t, C-2), 37.7 (s, C-3), 22.8 (q, CH_3C), 14.3 (q, C$H_3$$CH_2O$); ESI-MS 266.1 [M+$H^+$], 288.1 [M+$Na^+$]. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.42; H, 7.30; N, 5.19.

4.2.4. Ethyl (±)-3-methyl-1-(nitromethyl)cyclohexaneacetate 7d

Oil, 75% yield, after purification IR (neat) 1732 (CO_2Et), 1548, 1377 (NO_2) cm^{-1}; ^{1}H NMR δ 4.53 (s, 2H, CH_2NO_2), 4.16 (q, 2H, CH_2O), 2.53 (AB system, J_{AB} 17.5, 2H, CH_2CO_2Et), 1.64 (m, 4H), 1.59 (m, 2H), 1.42 (qt, 1H, H-5_{ax}), 1.24 (t, 3H, C$H_3$$CH_2O$), 1.17 (qt, 1H, H-$6_{ax}$), 0.89 (m, 1H), 0.88 (d, J 4.8, CH_3CH), 0.78 (qd, 1H, H-4_{ax}); ^{13}C{^{1}H} δ 171.3 (s, CO), 84.6 (t, CH_2NO_2), 60.4 (t, CH_3CH_2O), 41.7 (t, CH_2CO_2Et), 37.7 (s, C-1 of the ring), 35.7 (t), 34.2 (t), 32.7 (t), 27.1 (d, C$H$$CH_3$), 22.4 (q, C$H_3$CH), 21.0 (t), 14.1 (q, C$H_3$$CH_2O$). Irradiation of the signal at 0.88 (CH_3CH) enhanced the signal at 4.53 (CH_2NO_2, 3%); irradiation of the signal at 2.53 (CH_2CO_2Et) enhanced the signals at 1.42 (H-5_{ax}, 4%) and at 1.64 (H-6_{eq}, 5%); irradiation of the signal at 1.17 (H-6_{ax}) enhanced the signal at 4.53 (CH_2NO_2, 4%); irradiation of the signal at 4.53 (CH_2NO_2) enhanced the signals at 0.78 (H-4_{ax}, 1%), at 0.84 (CH_3CH, 3%), and at 1.59 (H-5_{eq}, 2%). ESI-MS 244.2 [M+H^+], 266.0 [M+Na^+]; Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.20; H, 8.63; N, 5.90.

4.2.5. Ethyl (±)-6-(nitromethyl)bicyclo[3.2.0]hept-2-ene-6-acetate 7e

Oil, 68% yield, after purification, IR (neat) 1731 (CO_2Et), 1548, 1376 (NO_2) cm^{-1}; ^{1}H NMR δ 5.82 (m, 1H, H-2), 5.79 (m, 1H, H-3), 4.81, 4.75 (AB system, J_{AB} 12.1, 2H, CH_2NO_2), 4.11 (q, 2H, CH_2O), 3.26 (br s, 1H, H-1), 2.99 (br dd, J_1 8.8, J_2 8.0, 1H, H-5), 2.72, 2.67 (AB system, J_{AB} 17.5, 2H, CH_2CO_2Et), 2.54 (ddd, ^3J 7.3, ^3J 8.8, ^2J 16.1, 1H, H-4 *trans* to CH_2COOEt), 2.36 (br d, ^2J 16.1, 1H, H-4 *cis* to CH_2COOEt), 2.30 (dd, ^3J 8.8, ^2J 12.9, 1H, H-7 *cis* to H-1), 1.73 (dd, ^3J 4.4, ^2J 12.9, 1H, H-7 *trans* to H-1), 1.24 (t, 3H, C$H_3$$CH_2O$); ^{13}C {^{1}H} NMR δ 171.4 (s, CO), 135.0 (d, C-2), 131.7 (d, C-3), 82.5 (t, CH_2NO_2), 60.6 (t, CH_3CH_2O), 42.4 (d, C-1), 40.4 (d, C-5), 39.4 (s, C-6), 36.8 (t, CH_2CO_2Et), 36.5 (t, C-4), 34.5 (t, C-7), 14.2 (q, C$H_3$$CH_2O$). DIFNOE measurements: irradiation of the signal at 2.70 (CH_2COOEt) enhanced the signals at 1.73 (H-7 *trans* to H-1, 3%) and at 2.36 (H-4 *cis* to CH_2COOEt, 5%); irradiation of the signal at 3.29 (H-1) enhanced the signals at 2.30 (H-7 *cis* to H-1, 3%), at 2.99 (H-5, 2%), at 4.78 (CH_2NO_2, 2%); irradiation of the signal at 2.99 (H-5) enhanced the signal at 4.78 (CH_2NO_2, 5%); ESI-MS 240.2 [M+H^+], 262.0 [M+Na^+]. Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.30; H, 7.22; N, 5.73.

4.3. General procedure for enzymatic hydrolyses

A suspension of the appropriate γ-nitroester **7a**–**e** (1.0 g), in 0.1 M KH_2PO_4/Na_3PO_4 buffer (pH 7.4), was hydrolyzed with HLAP (0.5 g), or with PLAP (0.5 g), at room temperature under vigorous stirring. The pH was kept at the initial value by continuous addition of 1 M NaOH. At the desired conversion value, the unreacted γ-nitroester was extracted from the suspension with ethyl acetate (3 × 10 ml) using a centrifuge for the separation of the layers. For the isolation of the γ-nitroacids **10a**–**e**, the aqueous layer was acidified to pH 2 with 2 M HCl and extracted with $CHCl_3$ (3 × 10 ml).

4.3.1. Ethyl (*S*)-(−)-3-methyl-3-(nitromethyl)heptanoate 7a

The title compound was obtained with 39% ee at 39% conversion (35% yield). Under the conditions used, hydrolysis did not proceed any further. After two consecutive hydrolyses, the product was isolated with 62% ee (12% isolated yield); $[\alpha]_D^{25} = -0.8$ (*c* 0.65, $CHCl_3$).

4.3.2. (*R*)-(+)-3-Methyl-3-(nitromethyl)heptanoic acid 10a

The title compound was obtained with 74% ee by stopping the enzymatic hydrolysis with HLAP at 20% conversion (15% isolated yield); $[\alpha]_D^{25} = +2.1$ (*c* 0.5, $CHCl_3$); IR (neat) 3400–2400 (br, OH), 1711 (CO), 1551, 1379 (NO_2) cm^{-1}; ^{1}H NMR δ 8.95 (broad, 1H, CO_2H), 4.52 (AB system, J 11.0, CH_2NO_2), 2.51 (AB system, J_{AB} 16.0, CH_2CO_2H), 1.35 (m, 2H), 1.29 (m, 6H, H-4), 1.13 (s, 3H, CH_3–C), 0.89 (t, 3H, C$H_3$$CH_2$); ^{13}C NMR δ 177.0 (s, CO), 82.0 (t, CH_2NO_2), 40.5 (t, CH_2CO_2H), 37.5 (t, C-4), 36.7 (s, C-3), 25.3 (t, C-5), 23.0 (t, C-6), 22.7 (q, CH_3–C), 13.8 (q, C-7). ESI-MS (negative ion polarity) 202.0 [M−H]$^-$. Anal. Calcd for $C_9H_{17}NO_4$: C, 53.19; H, 8.43; N, 6.89. Found: C, 53.24; H, 8.27; N, 6.80.

4.3.3. Ethyl (*S*)-(−)-3,5-dimethyl-3-(nitromethyl)hexanoate 7b

The title compound was obtained with 88% ee stopping the enzymatic hydrolysis at 75% conversion (22% isolated yield), $[\alpha]_D^{25} = -1.3$ (*c* 1.9, $CHCl_3$).

4.3.4. (*R*)-(+)-3,5-Dimethyl-3-(nitromethyl)hexanoic acid 10b

The title compound was obtained with 75% ee by stopping the enzymatic hydrolysis at 23% conversion (18% isolated yield), $[\alpha]_D^{25} = +3.7$ (*c* 0.35, $CHCl_3$); IR (neat) 3500–2500 (br, OH), 1710 (CO), 1550, 1375 (NO_2) cm^{-1}; ^{1}H NMR δ 8.70 (broad, CO_2H), 4.65 (d, part A of an AB system, J_{AB} 11.2, 1H, CH_2NO_2), 4.55 (d, part B of an AB system, J_{AB} 11.2, 1H, CH_2NO_2), 2.56 (AB system, J_{AB} 17.1, 2H, H-2), 1.72 (m, 1H, CH(CH_3)$_2$), 1.41 (dd, J_1 5.9, J_2 11.5, 2H, H-4), 1.17 (s, 3H, CH_3C), 0.96, 0.87 (2d, J 6.8, 6H, (CH_3)$_2$CH); δ 175.9 (s, CO), 82.5 (t, CH_2NO_2), 46.4 (t, C-2), 40.7 (t, C-4), 37.4 (s, C-3), 25.2 (2q, (CH_3)$_2$CH), 23.8 (s, CH_3C), 23.2 (d, C-5); ESI-MS 226.1 (M+Na^+); ESI-MS (negative ion polarity) 202.0 [M−H]$^-$. Anal. Calcd for $C_9H_{17}NO_4$: C, 53.19; H, 8.43; N, 6.89. Found: C, 53.31; H, 8.38; N, 6.75.

4.3.5. Ethyl (*R*)-(+)-3-benzyl-3-methyl-4-nitrobutanoate 7c

The title compound was obtained with 63% ee at 42% conversion (40% isolated yield). Under these conditions the hydrolysis did not proceed any further. After two more hydrolyses a 91% ee was reached $[\alpha]_D^{25} = +36.0$ (*c* 1.8, CH_3OH). Enantiomeric excess was determined by HPLC using a chiral column Daicel OD20, t_R = 7.95 and 9.97 min for (+)- and (−)-**7c**, respectively (10:1 hexane: *i*-PrOH; flow rate 0.5 ml/min).

4.3.6. (*S*)-(−)-3-Benzyl-3-methyl-4-nitrobutanoic acid 10c

The title compound was obtained with 71% ee by stopping the enzymatic hydrolysis at 20% conversion (15% isolated yield), $[\alpha]_D^{25} = -4.4$ (*c* 0.5, $CHCl_3$); IR (neat) 3700–2500 (br, OH), 3030, 1642, 1495, 1454, 754, 703 (Ph), 1705 (CO), 1549, 1378 (NO_2) cm^{-1}; ^{1}H NMR δ 8.42 (broad, CO_2H), 7.32 (m, 3H, Ph), 7.18 (d, 2H, Ph), 4.67 (d, part A of an AB system, J_{AB} 11.3, 1H, $CHNO_2$), 4.48 (d, part B of an AB system, J_{AB} 11.3, 1H, $CHNO_2$), 2.86 (AB system, J 13.2, 2H, CH_2Ph), 2.51 (AB system, J_{AB} 16.8, 2H, H-2), 1.13 (s, 3H, CH_3C); ^{13}C NMR δ 177.2 (s, CO), 135.5 (s, Ph), 130.8 (d, Ph), 128.7 (d, Ph), 127.2 (d, Ph), 81.6 (t, CH_2NO_2), 43.4 (t, CH_2Ph), 40.2 (t, C-2), 37.6 (s, C-3), 22.9 (s, CH_3C); ESI-MS: 260.1 [M+Na^+]; ESI-MS (negative ion polarity) 236.0 [M−H]$^-$; Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.80; H, 6.24; N, 6.03.

4.3.7. Ethyl (1*S*,3*R*)-(−)-3-methyl-1-(nitromethyl)cyclohexaneacetate 7d

The title compound was obtained with >99% ee by stopping the enzymatic hydrolysis at 75% conversion (24% isolated yield), $[\alpha]_D^{25} = -2.5$ (*c* 1, $CHCl_3$). The same compound (−)-**7d**, prepared from (*R*)-(+)-**5e**, had $[\alpha]^{25} = -2.5$ (*c* 1.8, $CHCl_3$).

4.3.8. Ethyl (1*R*,3*S*)-(+)-3-methyl-1-(nitromethyl)cyclohexaneacetic acid 10d

The title compound was obtained with 78% ee by stopping the enzymatic hydrolysis at 24% conversion (20% isolated yield), $[\alpha]_D^{25} = +3.2$ (*c* 0.35, $CHCl_3$); IR (neat) 3500–3246 (br, OH), 1732 (CO), 1548, 1378 (NO_2) cm^{-1}; ^1H NMR δ 9.90 (broad, 1H, CO_2H), 4.58 (AB system, J_{AB} 11.0, 2H, CH_2NO_2), 2.69 (s, 2H, CH_2CO_2H), 1.78–1.40 (m, 7H), 0.97–0.84 (m, 5H); ^{13}C NMR δ 177.6 (s, CO), 84.3 (t, CH_2NO_2), 41.7 (t, CH_2CO_2H), 37.4 (s, C-1 of the ring), 35.3 (t), 34.2 (t), 32.7 (t), 27.1 (d, C-3 of the ring), 22.5 (q, CH_3CH), 21.0 (t); ESI-MS 238.2 ($M+Na^+$); ESI-MS (negative ion polarity) 214.0 $[M-H]^-$; Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.80; H, 7.85; N, 6.60.

4.3.9. Ethyl (1*R*,5*S*,6*R*)-(−)-6-(nitromethyl)bicyclo[3.2.0]hept-2-ene-6-acetate 7e

The title compound was obtained with >99% ee by stopping the enzymatic hydrolysis at 60% conversion (30% isolated yield), $[\alpha]_D^{25} = -18.8$ (*c* 1.0, $CHCl_3$). The same compound (−)-**7e**, synthesized from (+)-(1*R*,5*S*)-**5d**, had $[\alpha]_D^{25} = -18.8$ (*c* 1.0, $CHCl_3$).

4.3.10. (1*S*,5*R*,6*S*)-(+)-[6-(Nitromethyl)bicyclo[3.2.0]hept-2-ene-6-acetic acid 10e

The title compound was obtained with 94% ee by stopping the enzymatic hydrolysis at 21% conversion (18% yield), $[\alpha]_D^{25} = +25.1$ (*c* 1, $CHCl_3$); IR (neat) 3500–2700 (broad, CO_2H), 1709 (C=O), 1547, 1379 (NO_2) cm^{-1}; ^1H NMR δ 9.80 (broad, CO_2H), 5.84 (br m, 1H, H-2), 5.80 (br m, 1H, H-3), 4.75 (AB system, J_{AB} 12.2, 2H, CH_2NO_2), 3.26 (br m, 1H, H-1), 2.99 (dd, J_1 8.3, J_2 8.0, 1H, H-5), 2.76 (AB system, J_{AB} 19.4, 2H, CH_2CO_2H), 2.54 (m, 1H, H-4), 2.36 (br d, $^2J_1$ 18.3, 1H, H-4) 2.30 (dd, ^3J 9.3, ^2J 11.2, 1H, H-7 *cis* to H-1), 1.73 (dd, ^3J 3.5, ^2J 12.9, 1H, H-7 *trans* to H-1); $^{13}C\{^1H\}$ δ 177.5 (s, CO), 135.0 (d, C-2), 131.8 (d, C-3), 82.4 (t, CH_2NO_2), 42.3 (d, C-1), 40.4 (d, C-5), 39.1 (s, C-6), 36.45 (t, CH_2CO_2H), 36.4 (t, C-4), 34.5 (t, C-7); ESI-MS 234.1 ($M+Na^+$); ESI-MS (negative ion polarity) 210.0 $[M-H]^-$. Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63. Found: C, 56.87; H, 6.32; N, 6.51.

4.4. General procedure for the transformation of the nitroesters 7a–e into the corresponding γ-lactams 8a–e

The nitroesters **7a**–**e** (2.0 mmol) were dissolved in a solution of ethyl acetate/ethanol in 1:1 ratio (10 mL), and Ra–Ni (Aldrich) was added. The mixture was hydrogenated at room temperature and atmospheric pressure until the disappearance of the starting material (TLC, eluent: methanol). The catalyst was filtered off on a pad of Celite and washed with ethanol and dichloromethane. The filtrate was evaporated to dryness in vacuo, then the residue was dissolved in toluene and the solution was heated at reflux to assure complete cyclization. After removal of the solvent, the residue was chromatographed on column (eluent: ethyl acetate), to give the pure γ-lactams **8a**–**e**.

4.4.1. (*S*)-(+)-4-Butyl-4-methylpyrrolidin-2-one 8a

White solid, mp 67–8 °C, 74% yield from **7a**; 63% ee, $[\alpha]_D^{25} = +8.0$ (*c* 1, $CHCl_3$); $\Delta\varepsilon_{219}$ −2.0 (MeOH); IR (Nujol) 3237 (NH), 1699 (CO) cm^{-1}; ^1H NMR δ 6.43 (br s, 1H, NH), 3.08 (AB system, J_{AB} 9.5, 2H, 2 H-5), 2.11 (AB system, J_{AB} 16.8, 2H, 2 H-3), 1.43 (m, 2H), 1.25 (m, 4H), 1.12–1.10 (s, 3H, CH_3C), 0.89 (t, 3H, CH_3CH_2); ^{13}C NMR δ 178.5 (s, CO), 54.4 (t, C-5), 44.1 (t, C-3), 40.7 (t), 38.8 (s, C-4), 26.9 (t), 25.6 (q, CH_3C), 23.3 (t), 14.1 (q, CH_3CH_2); ESI-MS 156.0 $[M+H^+]$, 178.0 $[M+Na^+]$; Anal. Calcd for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.75; H, 11.00; N, 9.12.

4.4.2. (*S*)-(+)-4-Isobutyl-4-methylpyrrolidin-2-one 8b

White solid, mp 54–56 °C, 90% yield from **7b**; 88% ee, $[\alpha]_D^{25} = +11.4$ (*c* 1, $CHCl_3$); $\Delta\varepsilon_{219}$ −2.0 (MeOH); IR (Nujol) 3175 (NH), 1693 (CO) cm^{-1}; ^1H NMR δ 6.68 (br s, 1H, NH), 3.15, 3.01 (AB system, J_{AB} 9.9, 2H, 2 H-5), 2.22, 2.03 (AB system, J_{AB} 16.5, 2H, 2 H-3), 1.70 (m, 1H, $CH(CH_3)_2$), 1.35 (d, *J* 6.2, CH_2CH), 1.13 (s, 3H, CH_3C), 0.90, 0.89 (2d, *J* 6.6, 6H, $(CH_3)_2CH$); ^{13}C NMR δ 178.2 (s, CO), 55.3 (t, C-5), 49.6 (t, C-3), 45.1 (t, CH_2CH), 39.1 (s, C-4), 25.3 (q, CH_3C), 25.0 (d, $CH(CH_3)_2$), 24.4, 24.2 (2q, $CH(CH_3)_2$); ESI-MS 156.1 $[M+H^+]$, 178.1 $[M+Na^+]$; Anal. Calcd for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.80; H, 10.96; N, 9.08.

4.4.3. (*R*)-(−)-4-Benzyl-4-methylpyrrolidin-2-one 8c

White solid, mp 110 °C, 82% yield from (+)-**7c**; (91% ee), $[\alpha]_D^{25} = -10.0$ (*c* 0.8, $CHCl_3$) [lit.[12b] −12.7 (*c* 2, $CHCl_3$), 82% ee]. Spectroscopic and analytical data were in accordance with those reported in the literature.

4.4.4. (5*S*,7*R*)-(−)-7-Methyl-2-azaspiro[4.5]decan-3-one 8d

White solid, mp 70–75 °C, 88% yield from **7d**, >99% ee, $[\alpha]_D^{25} = -11.8$ (*c* 1.15, $CHCl_3$); $\Delta\varepsilon_{220}$ −2.0 (MeOH). The same compound, obtained from (*R*)-(−)-**5d**, had $[\alpha]_D^{25} = -11.8$ (*c* 0.85, $CHCl_3$); IR (Nujol) 3177 (NH), 1702 (CO) cm^{-1}; ^1H NMR δ 6.87 (br s, 1H, NH), 3.03 (s, 2H, 2 H-5), 2.16 (s, 2H, 2 H-3), 1.62 (m, 4H), 1.40 (m, 1H, $CHCH_3$), 1.32 (m, 1H), 1.12 (m, 1H), 0.90 (m, 1H), 0.83 (d, *J* 6.4, CH_3CH), 0.78 (m, 1H). $^{13}C\{^1H\}$ δ 178.0 (s, CO), 56.0 (t, CH_2N), 45.2 (t), 40.9 (t, CH_2CO), 39.5 (s), 36.0 (t), 34.2 (t), 28.7 (d, CH), 22.4 (t), 22.2 (q, CH_3CH). Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.37. Found: C, 72.0; H, 10.3; N, 8.4. ESI-MS 168.0 $(M+H^+)$, 190.0 $(M+Na^+)$, 205.9 $[M+K^+]$; Anal. Calcd. for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.37. Found: C, 71.72; H, 10.32; N, 8.40.

4.4.5. (1*S*,3′*R*,5*S*)-(+)-Spiro[bicyclo[3.2.0]heptane-6-pyrrolidin]-5′-one 8e

White solid, mp 85–86 °C, 84% yield from **7e**; >99% ee, $[\alpha]_D^{25} = +28.5$ (*c* 1, $CHCl_3$); $\Delta\varepsilon_{215}$ −0.8 (MeOH). An enantiomerically pure sample obtained from (+)-(1*R*,5*S*)-**5d** had mp 85–86 °C, $[\alpha]_D^{25} = +28.6$ (*c* 2, $CHCl_3$). IR (neat) 3235 (NH), 1695 (CO) cm^{-1}; ^1H NMR δ 6.59 (br s, 1H, NH), 3.36 (AB system, J_{AB} 9.7, 2H, CH_2NH), 2.74 (quint, 1H, H-1), 2.50 (dd, *J* 6.7 and 6.2, 1H, H-5), 2.32 (d, part A of an AB system, *J* 15.6, 1H, CH_2CO), 2.13 (ddd, *J* 12.5, 9.4, 2.3, 1H), 1.99 (d, part B of an AB system, *J* 15.6, 1H, CH_2CO), 1.79 (m, 1H), 1.74–1.59 (m, 2H), 1.52–1.36 (m, 4H); ^{13}C NMR δ 178.0 (s, CO), 57.6 (t, CH_2N), 45.7 (d, C-1), 40.7 (s, C-3′), 39.1 (t, CH_2CO), 37.8 (t), 33.2 (d, C-5), 32.4 (t), 28.5 (t), 25.3 (t). ESI-MS 166.1 $[M+H^+]$, 198.1 $[M+Na^+]$. Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.78; H, 9.05; N, 8.57.

4.5. Transformation of the chiral non-racemic γ-lactams 8a–e into the corresponding γ-amino acid hydrochlorides 9a–e

The γ-amino acids **9a**–**e** were obtained by hydrolysis of the corresponding enantiomerically active γ-lactams **8a**–**e** carried out in 6 M HCl at reflux for 4 h.

4.5.1. (*S*)-(−)-3-(Aminomethyl)-3-methylheptanoic acid hydrochloride 9a

The title compound was isolated with 63% ee from (+)-**8a**, $[\alpha]_D^{25} = -2.0$ (*c* 1, H_2O), IR (neat) 3650–2380 (broad), 1710, 1465; ^1H NMR (D_2O) δ 3.06, 3.02 (AB system, *J* 13.5, 2H, $CH_2NH_3^+$), 2.46, 2.41 (AB system, *J* 16.0, 2H, 2 H-2), 1.35 (m, 2H), 1.22 (m,

4H), 1.02 (s, 3H, CH_3C), 0.82 (t, 3H, CH_3CH_2); ^{13}C NMR (D_2O) δ 176.9 (s), 47.9 (t, $CH_2NH_3^+$), 42.3 (t, CH_2CO_2H), 37.5 (t, C-4), 35.3 (s, C-3), 25.4 (t), 23.2 (t), 22.6 (q, CH_3C), 13.9 (q, CH_3CH_2); ESI-MS 174.1 [M^+].

4.5.2. (*S*)-(−)-3-(Aminomethyl)-3,5-dimethylhexanoic acid hydrochloride 9b

The title compound was isolated with 88% ee from (+)-**8b**; $[\alpha]_D^{25} = -2.4$ (*c* 1.25, CH_3OH); IR (neat) 3500–2958 (br, OH), 1710 (CO) 1467 (NH), cm^{-1}; ^1H NMR (CD_3OD) δ 2.92 (AB system, J_{AB} 13.1, 2H, $CH_2NH_3^+$), 2.35 (AB system, J_{AB} 16.1, 2H, 2 H-2), 1.64 (m, 1H, H-5), 1.34–1.16 (ddd, part AB of an ABX system, ^3J 4.9, ^3J 5.5, ^2J 13.7, 2H, 2 H-4), 1.01 (s, 3H, CH_3C), 0.89 (2d, 6H, $(CH_3)_2CH$); ^{13}C NMR (CD_3OD) δ 175.4 (s, CO_2H), 49.1 (t, $CH_2NH_3^+$), 47.5 (t, C-4), 42.5 (t, C-2), 36.5 (s, C-3), 26.6, 26.5 (2q), 25.6 (d, C-5), 24.2 (q, CH_3C); ESI-MS 174.2 [M^+], 197.1 [M+Na^+].

4.5.3. (*R*)-(+)-4-Amino-3-benzyl-3-methylbutanoic acid hydrochloride 9c

The title compound was isolated with 91% ee from (−)-**8c**; $[\alpha]_D^{25} = +13.0$ (*c* 0.5, H_2O) [lit[12b] = +13.6 (*c* 1, H_2O, 82% ee)]. Other spectroscopic and analytical data were in accordance with the literature.[15]

4.5.4. (1*S*,3*R*)-(−)-1-(Aminomethyl)-3-methylcyclohexaneacetic acid hydrochloride 9d

The title compound was isolated with >99% ee from (−)-**8d**, mp 172–174 °C; $[\alpha]_D^{25} = -1.5$ (*c* 0.9, H_2O). The same compound, obtained from (*R*)-(+)-**5a**, had $[\alpha]_D^{25} = -1.5$ (*c* 0.5, H_2O); IR (neat) 3500–3246 (br, OH), 2927, 2070, 1478 (NH), 1670 (CO) cm^{-1}; ^1H NMR (D_2O) δ 2.97 (br s, 2H, $CH_2NH_3^+$), 2.58 (AB system, J_{AB} 15.4, 2H, CH_2CO), 1.71 (br d, 1H), 1.59 (m, 4H), 1.48 (tq, 1H, $CHCH_3$), 1.17 (dt, 1H), 0.86 (d *J* 6.2, 3H, CH_3CH), 0.84 (m, 2H); ^{13}C NMR (D_2O) δ 177.2 (s, CO_2H), 50.4 (t, $CH_2NH_3^+$), 41.8 (t, CH_2CO), 36.2 (s), 34.6 (t), 33.0 (t), 27.4 (d), 22.7 (q), 21.4 (t); ESI-MS 186.1 [M^+], 209.1 [M+Na^+].

4.5.5. (1*S*,5*S*,6*R*)-(+)-6-(Aminomethyl)bicyclo[3.2.0]heptane-6-acetic acid hydrochloride 9e

The title compound was isolated with >99% ee from (−)-**8e**, mp 158–160 °C; $[\alpha]_D^{25} = +8.0$ (*c* 1.5, H_2O). The enantiomerically pure form, synthesized from commercial (+)-(1*R*,5*S*)-**5e**, had $[\alpha]_D^{25} = +8.0$ (*c* 1.0, H_2O) {lit.[17] $[\alpha]_D$ = +13.0 (*c* 0.35, MeOH)}; IR (neat): 3500–2470 (broad), 1720 (CO), 1407 (NH); ^1H NMR (CD_3OD) δ 3.28 (AB system, *J* 13.6, 2H, $CH_2NH_3^+$), 2.78 (quint, 1H), 2.56 (d, part A of an AB system, *J* 22.0, 1H, CH_2CO_2H), 2.46 (m, 1H), 2.45 (d, part B of an AB system, *J* 22.0, CH_2CO_2H), 1.92 (ddd, ^2J 12.4, 9.4, 2.3, 1H), 1.78, 1.71, 1.63 (3 m, 1H each), 1.48, 1.39 (2 m, 2H each); ^{13}C NMR (CD_3OD) δ 175.1 (s, CO_2H), 49.5 (t, $CH_2NH_3^+$), 46.1 (d, C-5), 37.9 (s, C-6), 37.3 (t, CH_2CO_2H), 35.3 (d, C-1), 35.1 (t), 33.4 (t), 29.3 (t), 27.5 (t). ESI-MS 184.2 [M^+].

4.6. Transformations of chiral non-racemic γ-nitroesters 7a–e and γ-nitro acids 10a–e into the corresponding succinic acids 11a–e

A solution of the optically active γ-nitroacids **10a–e**, isolated from enzymatic resolutions, was refluxed in a 1:1 solution of HCl/AcOH for 2 h to give, after elimination of the solvents, the corresponding succinic acids **11a–e.** The same compounds also formed spontaneously from the isolated γ-nitroacids **10a–e** on standing for months at room temperature. The opposite enantiomers of **11a–e** were obtained from the corresponding optically active γ-nitroesters **7a–e** when treated under the same acidic conditions.

The data given for the succinic acid derivatives **11a–e** are relative to the products obtained with the best enantiomeric excesses.

4.6.1. (*R*)-(+)-2-Butyl-2-methylsuccinic acid 11a

The title compound was obtained with 74% ee from (*R*)-(+)-**10a**, $[\alpha]_D^{25} = +2.2$ (*c* 0.5, $CHCl_3$); IR (nujol) 3500–2500 (broad, CO_2H), 1730, 1711 (C=O); ^1H NMR δ 8.00 (broad, CO_2H), 2.59 (d, part A of an AB system, J_{AB} 18.1, 1H, $CHCO_2H$), 2.40 (d, part B of an AB system, J_{AB} 18.1, 1H, $CHCO_2H$), 1.53 (m, 2H), 1.16 (s, 3H, CH_3), 1.14 (m, 4H), 0.83 (t, *J* 6.8, 3H, CH_3CH_2); ^{13}C NMR δ 178.6 (s, CO_2H), 171.8 (s, CO_2H), 41.1 (s, C-3), 38.2 (t, CH_2CO_2H), 37.7 (t, C-4), 26.0 (t), 23.9 (q, CH_3C), 22.6 (t), 13.6 (q, CH_3CH_2); ESI-MS (negative ion polarity) 186.9 [M−H]$^-$. Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.50; H, 8.40.

4.6.2. (*S*)-(−)-2-Isobutyl-2-methylsuccinic acid 11b

The title compound was isolated with 88% ee from (*S*)-(−)-**7b**, $[\alpha]_D^{25} = -6.1$ (*c* 0.25, $CHCl_3$); IR (neat) 3400–2500 (broad, CO_2H), 1720, 1715 (CO) cm^{-1}; ^1H NMR δ 5.13 (broad, CO_2H), 2.73 (d, part A of an AB system, J_{AB} 18.1, 1H, H-3), 2.44 (d, part B of an AB system, J_{AB} 18.1, 1H, H-3), 1.65–1.58 (2 m, 3H, $CHCH_2$), 1.24 (s, 3H, CH_3C), 0.85, 0.78 (2d, *J* 6.0, 6H, $(CH_3)_2CH$); ^{13}C NMR δ 178.7 (s, CO_2H), 171.7 (s, CO_2H), 45.9 (t, CH_2CO_2H), 41.1 (t, CH_2 isobutyl), 38.6 (s, C-3), 25.1, 24.9 (2q, $(CH_3)_2CH$), 24.7 (q, CH_3C), 23.0 (d, $(CH_3)_2CH$); ESI-MS (negative ion polarity) 188.1 [M−H]$^-$; Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.50; H, 8.50.

4.6.3. (*R*)-(+)-2-Benzyl-2-methylsuccinic acid 11c

White solid, mp >180 °C, 91% ee from (*R*)-(+)-**7c**, $[\alpha]_D^{25} = +3.3$ (*c* 1 MeOH); IR (neat) 3600–2500 (broad, CO_2H), 1732, 1712 (C=O), 1495, 1454, 745, 701 (Ph); ^1H NMR (CD_3OD) δ 7.20 (m, 3H, Ph); 7.09 (d, 2H, Ph), 2.90 (s, 2H, CH_2Ph), 2.64 (d, part A of an AB system, J_{AB} 16.8, 1H, $CHCO_2H$), 2.34 (d, part B of an AB system, J_{AB} 16.8, 1H, $CHCO_2H$), 1.17 (s, 3H, CH_3); ^{13}C NMR (CD_3OD) δ 180.5 (s, CO_2H), 175.6 (s, CO_2H), 138.8 (s, Ph), 131.9 (d, Ph), 129.6 (d, Ph), 128.3 (d, Ph), 46.5 (s, C-3), 46.0 (t, CH_2CO_2H), 43.3 (t, CH_2Ph), 22.9 (q, CH_3); ESI-MS (negative ion polarity) 206.9 [M−H]$^-$; Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.95; H, 6.28.

4.6.4. (1*S*,3*R*)-(−)-1-Carboxy-3-methylcyclohexaneacetic acid 11d

White solid, mp 152–154 °C, 99% ee from (1*S*,3*R*)-(−)-**7d**, $[\alpha]_D^{25} = -2.6$ (*c* 0.8, $CHCl_3$), IR (neat) 3500–2500 (broad, CO_2H), 1721, 1710 (C=O); ^1H NMR δ 2.54 (AB system, J_{AB} 12.5, 2H, CH_2CO_2H), 1.54 (m, 3H), 1.49–1.20 (m, 5H), 0.94–0.85 (m and d, 4H, CH_3CH and CH); ^{13}C NMR δ 178.5 (s, CO_2H), 171.9 (s, CO_2H), 42.8 (s, C-1), 41.8 (t), 37.4 (t), 33.4 (t), 32.6 (t), 28.1 (d), 22.3 (q), 21.7 (t); ESI-MS (negative ion polarity) 199.1 [M−H]$^-$; Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.12; H, 7.98.

4.6.5. (1*R*,5*S*,6*R*)-(−)-6-Carboxybicyclo[3.2.0]hept-2-en-6-acetic acid 11e

The title compound was isolated with >99% ee from (1*R*,5*S*,6*R*)-(−)-**7e**, $[\alpha]_D^{25} = -14.9$ (*c* 0.5, $CHCl_3$); IR (nujol) 3500–2500 (broad, CO_2H), 1721, 1710 (C=O); ^1H NMR δ 5.84 (m, 2H, CH=CH), 3.32 (br dd, J_1 6.4, J_2 6.6, 1H, H-1), 3.19 (br s, 1H, H-5), 2.89 (m, 1H, H-4), 2.81 (d, part A of an AB system, J_{AB} 18.3, 1H, $CHCO_2H$), 2.51 (m, 1H, H-4), 2.48 (d, part B of an AB system, J_{AB} 18.3, 1H, $CHCO_2H$), 2.20 (m, 1H, H-7), 1.72 (m, 1H, H-7); ^{13}C NMR δ 177.9 (s, CO_2H), 171.9 (s, CO_2H), 134.4 (d), 130.8 (d), 42.2 (s, C-6), 41.6 (d, C-1, 41.1 (d, C-5), 38.1 (t, CH_2CO_2H), 35.4 (t), 34.5 (2t); ESI-MS (negative ion polarity) 195.2 [M−H]$^-$. Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.34; H, 6.46.

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