Tetrahedron 70 (2014) 75–82

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Catalytic asymmetric one-pot synthesis of α-methylene-γ-lactams

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ARTICLE INFO

Article history:
Received 4 August 2013
Received in revised form 29 October 2013
Accepted 12 November 2013
Available online 16 November 2013

Keywords:
Organocatalysis
Lactams
Asymmetric synthesis
One-pot reaction
Morita–Baylis–Hillman

ABSTRACT

An organocatalytic enantioselective synthesis of α-methylene-γ-lactams has been developed. The reaction between protected 2-aminomalonates and Morita–Baylis–Hillman carbonates is catalyzed by chiral Lewis bases to afford the corresponding lactams in excellent yields and moderate to good enantioselectivities, after work-up.

1. Introduction

α-Methylene-γ-lactams show interesting biological properties, and hence, their synthesis has attracted much attention from the chemical community. The aforementioned interest in α-methylene-γ-lactams relies in the fact that these compounds show bioactivities similar to those of α-methylene-γ-lactones but with much lower toxic side effects. However, α-methylene-γ-lactams are less abundant in nature than are α-methyl-γ-lactones.[1]

α-Methylene-γ-lactams found in plants are often used in traditional medicine for the treatment of inflammatory diseases. Examples of a few naturally occurring compounds having this structure include pukeleimid E, isolated from *Lyngbya majuscula*,[1b] and two imidazole alkaloids, anatin and isoanatin, found in the leaves of *Cynometra* (Fig. 1), and they show a broad spectrum of biological activities.[1d]

The high bioactivity of these compounds is most often due to the presence of the highly electrophilic α-*exo*-methylene-γ-lactam moiety, which can react with nucleophilic sites on enzyme targets (for instance with mercapto groups in cysteine residues) via Michael addition. α-Methylene-γ-lactams have been found to be active as cellular steroidal inhibitors, blockers of tumor necrosis factor-a production, DNA polymerase inhibitors, etc.[2] These

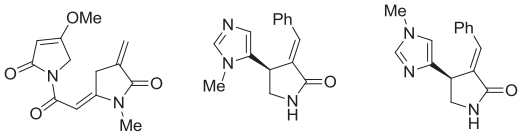

Fig. 1. Natural compounds with an α-methylene-γ-lactam moiety.

inhibitory properties, and the consequent allergenic, phytotoxic, cytotoxic, and antimicrobial properties of α-methylene-γ-lactams make them potential drug candidates.[3] However, an important drawback of α-methylene-γ-lactams is their multitarget nature resulting from their chemical properties, which can lead to diminished therapeutic value.

More importantly, in recent years, the abovementioned type of compounds have been extensively studied because of their anticancer properties.[4] Some of the mechanisms involved in the anticancer activity of α-methylene-γ-lactams are as follows: inhibition of transcription factors and gene expression, inhibition of the MAPK signaling pathway, microtubule-interfering activity, modulation of DNA methylation, induction of apoptosis, cell cycle arrest, and inhibition of proliferation and suppression of metastasis.

In spite of the interest in the synthesis of these privileged compounds, only a few methodologies allowing for their preparation in optically active form have been reported. There are some organometallic asymmetric synthesis methods for α-methylene-γ-

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http://dx.doi.org/10.1016/j.tet.2013.11.028

lactams, but all of them rely on the use of chiral auxiliaries.[5] Recently, Wang and co-workers reported the asymmetric construction of a couple of spirocyclic α-methylene-γ-lactams through sequential reactions of cyclic iminoesters with Morita–Baylis–Hillman (MBH) bromides, catalyzed by chiral copper complexes.[6]

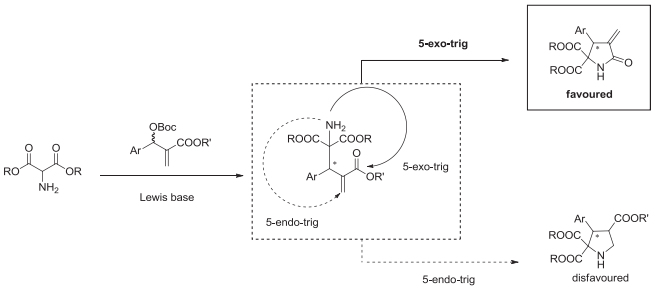
In the field of organocatalysis, in 2008, Jørgensen and co-workers reported an elegant multistep asymmetric approach to α-methylene-δ-lactones and δ-lactams, based on the enantioselective Michael addition of aldehydes to α-(diethoxyphosphoryl) acrylates.[7] In 2012, Liao and co-workers reported the racemic syntheses of α-methylene-γ-lactams via both a tandem allylic alkylation/amination protocol[8] and a multicomponent tandem organocatalytic reaction.[9] In 2013, Zhu and co-workers reported the addition of diazo compounds to MBH carbonates promoted by chiral Lewis bases. After further functionalization they reported a single example of the synthesis of an α-methylene-γ-lactam with good yield and enantioselectivity.[10] Almost at the same time Krawczyk and co-workers reported the racemic synthesis of α-methylene-γ-lactams via conjugate addition of acetamido malonates to unsaturated phosphonates.[11]

Very recently, our research group has disclosed the direct asymmetric synthesis of α-methylene-γ-lactones by the base-catalyzed substitution of MBH carbonates with 2-hydroxy malonates, with good yields and enantioselectivities.[12]

Remarkably, a general catalytic asymmetric strategy for the synthesis of α-*exo*-methylene-γ-lactams remains an unmet challenge in organocatalysis.[13] Herein, we report the first enantioselective organocatalytic one-pot synthesis of α-methylene-γ-lactams, which can be achieved directly from the substitution of MBH carbonates[14] by 2-aminomalonates.

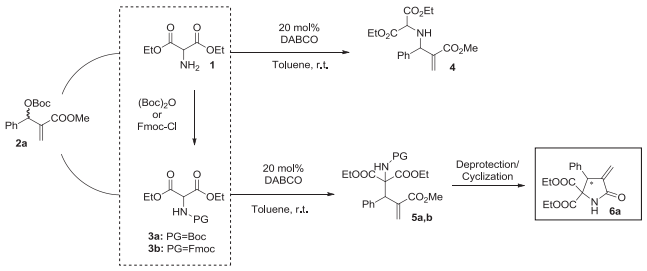
2. Results and discussion

Based on our previous research in organocatalysis[15] and taking into account the excellent results obtained in our MBH carbonate substitution approach to α-methylene-γ-lactones,[12] we envisioned an easy protocol for the asymmetric synthesis of α-methylene-γ-lactams via the nucleophilic substitution of MBH carbonates by 2-aminomalonates, followed by intramolecular lactamization (Scheme 1). Notably, the possible intramolecular Michael reaction between the amine with the conjugated double bond would be disfavored (5-*endo-trig* cyclization according to Baldwin rules) in preference to the lactamization (5-*exo-trig* cyclization).



Scheme 1. Proposed reaction pathway for the catalytic asymmetric synthesis of α-methylene-γ-lactams.

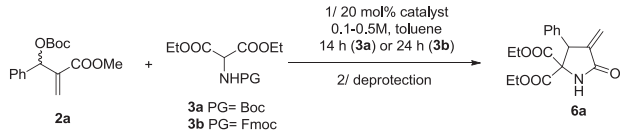
In preliminary experiments, the reaction of 2-amino-diethyl malonate **1** with MBH carbonate **2a** was explored using DABCO as catalyst. Unfortunately, all of the reactions resulted in substitution of the MBH carbonate by the amine, affording the allylic aminoester **4**. For this reason, we turned our attention to the use of *N*-protected malonates (**3a** and **3b**). This time, the C_2 carbon of the malonate acted as a nucleophile, and subsequent in situ deprotection of the nitrogen substitution adduct **5a** (TFA) or **5b** (piperidine/DMF) afforded the desired α-methylene-γ-lactam **6a** (Scheme 2).



Scheme 2. Modified strategy for the synthesis of α-methylene-γ-lactams.

Next, we proceeded to evaluate different chiral Lewis bases as catalysts. As shown in Table 1, the best results with *N*-Boc-protected malonate **3a** were obtained when using β-isocupreidine (β-ICPD)[16] as the catalyst, and the final product was obtained in full conversion and with 75% ee after 14 h of stirring at room temperature in toluene (entry 1). Cinchona alkaloids or dimeric catalysts, such as Sharpless ligands resulted in lower reaction rates and enantioselectivities (entries 2–6). Use of additives, such as $FeCl_2$ or $Ti(^iOPr)_4$, which had been previously used by Shibata and co-workers[17] in the substitution of MBH carbonates by fluorobis(phenylsulfonyl) methane with excellent results, did not improve the previous

Table 1
Reaction screening[a]



Entry	3	Catalyst	*T*	[3] (M)	Conv.[b]	ee[c]
1	3a	β-ICPD	rt	0.1	100%	+75%
2	3a	Quinine	50 °C	0.1	Traces	—
3	3a	Cinchonine	50 °C	0.1	Traces	—
4	3a	$(DHQ)_2AQN$	50 °C	0.1	Traces	+16%
5	3a	$(DHQD)_2PHAL$	50 °C	0.1	Traces	−65%
6	3a	β-ICPD	50 °C	0.1	Traces	+48%
7[d]	3a	β-ICPD	rt	0.5	n.r.	Nd
8[e]	3a	β-ICPD	rt	0.5	92%	+60%
9	3a	β-ICPD	4 °C	0.5	78%[f]	+74%
10	3a	β-ICPD	−5 °C	0.5	n.r.[f]	—
11	3b	$(DHQ)_2PYR$	rt	0.5	13%	+65%
12	3b	$(DHQ)_2AQN$	rt	0.5	25%	+50%
13	3b	$(DHQD)_2PHAL$	rt	0.5	17%	−88%
14	3b	β-ICPD	rt	0.5	100%	+86%
15[d]	3b	β-ICPD	rt	0.5	Traces	—
16[g]	3b	β-ICPD	rt	0.5	100%	+50%
17	3b	β-ICPD	4 °C	0.5	100%	+81%

[a] In a vial equipped with a magnetic stirring bar, the MBH carbonate **2a** (0.1 mmol, 2 equiv), *N*-Boc-aminomalonate (0.05 mmol, 1 equiv) and catalyst (0.01 mmol, 0.2 equiv) were added in toluene and the reaction was stirred at room temperature for 14 h (for **3a**) or 24 h (for **3b**). Next, the reaction crude was diluted with 1.0 mL of CH_2Cl_2, 0.1 mL of TFA was added in one portion and the mixture was stirred overnight (with compound **3a**) or 1.0 mL of DMF/piperidine (20% w/w) was added in one portion and the mixture was stirred overnight (with compound **3b**). Then, 1.0 mL H_2O was added at the reaction crude and neutralized until pH=7, extracted three times with EtOAc.

[b] Conversion of product **6a** determined by ^1H NMR analysis of the reaction crude.

[c] Enantiomeric excess of **6a**, determined by chiral HPLC.

[d] 0.2 equiv of $FeCl_2$ were used as catalyst additive in the substitution step.

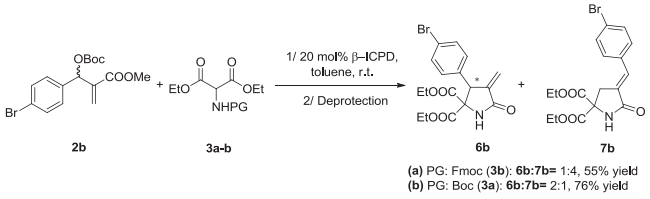
[e] 0.2 equiv of $Ti(O^iPr)_4$ were used as catalyst additive in the substitution step.

[f] Conversion after 3 days.

[g] 0.1 equiv of Schreiner thiourea were used as additive.

results (entries 7, 8). Decreasing the temperature did not increase the ee of the reaction (entries 9, 10). Then, we turned our attention to Fmoc-protected aminomalonates **3b**; in this case, both the yield and enantioselectivity of the product α-methylene-γ-lactam **6a** were improved, albeit with longer reaction times (entries 11–17). Again, the best catalyst was β-ICPD, affording **6a** with full conversion and in 86% ee after 14 h (entry 14). When Sharpless ligands were tested with **3b**, the reaction proceeded with very low conversions (entries 11–13). The use of additives or decreasing the temperature did not improve the outcome of the reaction (entries 14–16). Other solvents, such as dichloromethane, xylene, THF, and CF_3–Ph were also investigated, but the yields and enantioselectivities were not better than those obtained with toluene.

With the optimized conditions on hand, we proceeded to study the scope of the reaction. Unfortunately the β-ICPD-catalyzed reaction of *N*-Fmoc-protected malonate **3b** with MBH carbonate **2b**, having a *p*-bromophenyl substituent, gave a 1:4 nonseparable mixture of products **6b** and **7b** in 55% global yield (Scheme 3). When the same reaction was run with the *N*-Boc-protected malonate **3a**, the formation of **7b** was diminished, and hence, we decided to use **3a** in the β-ICPD-catalyzed reaction with a series of MBH carbonates **2a**–**i**, although the enantioselectivity was poorer than that with **3b** in our screening experiments.



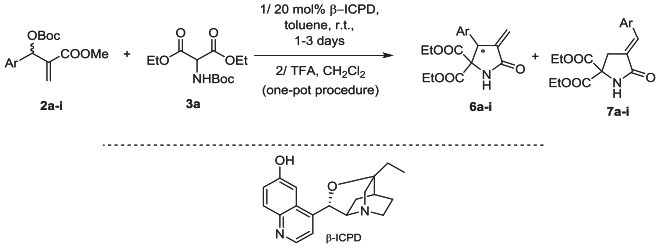
Scheme 3. Reaction of **2b** with **3a** and **3b**.

Complete conversion of the starting MBH carbonates **2a**–**i** to the products **6a**–**i** and/or **7a**–**i** was achieved after 1–3 days (monitored by ^{1}H NMR) at room temperature. As shown in Table 2, the yield of byproduct **7** depends on the nature of the aromatic moiety of **2**, and **7** is observed to be the sole product when a substituent is present at the *ortho* position (compound **2c**, entry 3) and in the case of the α-naphthyl derivative **2f** (entry 6). Remarkably, the racemic reactions using DABCO as catalyst only rendered products **6a**–**i** with moderate to good yields. Therefore, steric hindrance in the aryl moiety of the MBH carbonate appears to be an important factor in the β-ICPD catalyzed reaction. The enantioselectivity for the formation of the chiral α-methylene-γ-lactams **6** varies from moderate to good. Strongly electronegative substituents at the 4-position of the phenyl ring (entries 4,7, and 8) decrease the enantioselectivity of the reaction. On the other hand, the highest enantioselectivities were obtained with the *p*-Br derivative **2b** (entry 2) and the *p*-tolyl derivative **2i** (entry 9). The β-naphthyl derivative **2e** gave similar results as did **2a** (entry 5).

In order to explain the formation of the achiral lactams **7**, we postulate that the reaction can take place via two possible competing pathways: an S_N2'–S_N2' pathway (Scheme 4, left) and an S_N2' pathway (Scheme 4, right).

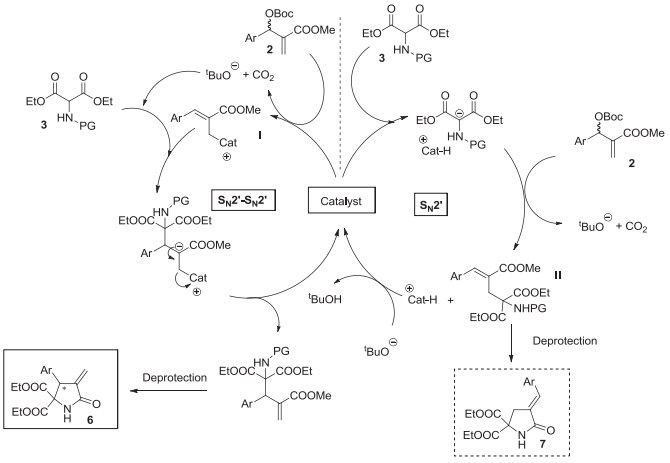
In the S_N2'–S_N2' pathway, the Lewis base catalyst first substitutes the carbonate to give a cationic chiral intermediate **I** that undergoes enantioselective allylic substitution by the carbanion derived from the *N*-protected malonate **3**. In the S_N2' pathway, the malonate carbanion directly substitutes the MBH carbonate, affording an achiral intermediate II that after N-deprotection, cyclizes to form lactam **7**. Steric hindrance in the aryl substituent of the MBH carbonate **2** will slow down the S_N2'–S_N2' pathway, driving the reaction toward the achiral S_N2' pathway. The higher

Table 2
Reaction scope[a]



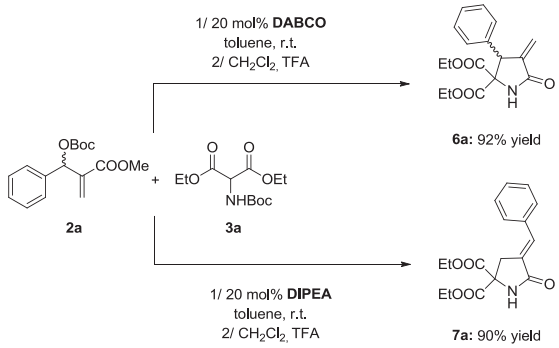
Entry	Ar	2	t[b]	6:7 ratio[c]	Yield[d]	ee[e]
1		**2a**	14 h	1:0	79%	73%
2	Br	**2b**	2 d	2:1	76%	83%
3	Br	**2c**	3 d	0:1	97%	—
4	F	**2d**	2 d	1:0	90%	53%
5		**2e**	3 d	3:1	83%	74%
6		**2f**	3 d	0:1	83%	—
7	MeO	**2g**	3 d	1:0	87%	61%
8	Cl	**2h**	2 d	7:1	95%	58%
9	Me	**2i**	3 d	1:0	90%	78%

[a] In a vial equipped with a magnetic stirring bar, the corresponding MBH carbonate (0.05 mmol, 2 equiv), *N*-Boc-aminomalonate (0.025 mmol, 1 equiv) and catalyst (0.001 mmol, 20 mol %) were added in 1.0 mL of toluene (C=0.1 M) and the reaction was stirred at room temperature for 14 h. Next, the reaction crude was diluted with 1.0 mL of CH_2Cl_2, 0.1 mL of TFA was added in one portion and the mixture was stirred overnight. Then, 1.0 mL H_2O was added at the reaction crude and neutralized until pH=7 with Na_2CO_3, extracted three times with EtOAc.
[b] Allylic substitution reaction time.
[c] Determined by ^{1}H NMR of the crude reaction.
[d] Isolated combined (**6**+**7**) yield after column chromatography.
[e] Determined by chiral HPLC.



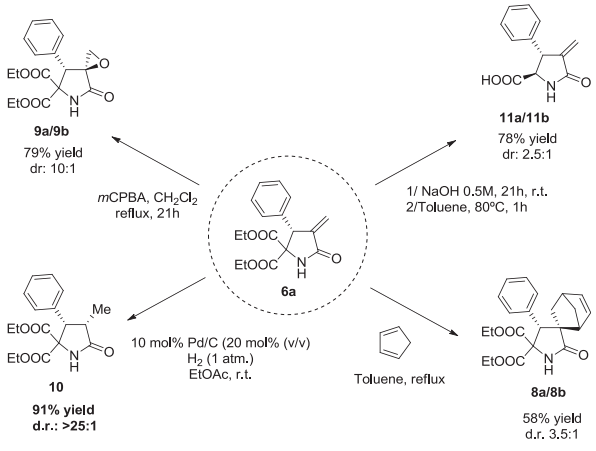
Scheme 4. Mechanistic scheme for the competing formation of lactams **6** and **7**.

steric bulk of the Fmoc moiety could also explain the predominance of **7** when **3b** was used. Finally, the nature of the Lewis base is also a key factor in the process, since a sterically hindered Lewis base (such as β-ICPD) would slow down the formation of intermediate **I** and favor direct S_N2' substitution of the MBH carbonate by the malonate carbanion. To confirm this hypothesis (two possible reaction pathways, one catalyzed by Brønsted base and another catalyzed by Lewis base), we ran additional experiments (Scheme 5). When we used a tertiary hindered amine, such as Hünig's base (a rather poor Lewis base and a good Brønsted base) the only product obtained from **2a** and **3a** was the achiral compound **7a** in 90% yield. When DABCO was used, the only product observed was **6a** in 92% yield.



Scheme 5. Influence in the base catalyst in the competing formation of products **6** and **7**.

The synthetic usefulness of this methodology was exemplified by the transformation of **6a** into different products. For example, **6a** reacted with cyclopentadiene to afford a 3.5:1 mixture of the Diels–Alder adducts **8a**/**8b**.[18] The *exo*-methylene double bond of **6a** could be epoxidised by mCPBA in good yield and high diastereoselectivity (**9a**/**9b**=10:1) or hydrogenated by catalysis with Pd/C to afford the reduced product **10** in satisfactory yields and as a single diastereoisomer, to which a *cis* configuration was tentatively assigned.[19] Finally, **6a** underwent sequential saponification and decarboxylation to afford **11a**/**11b** in good yields and moderate diastereoselectivities (Scheme 6).



Scheme 6. Synthetic transformations of compound **6a**.

The absolute configuration of α-methylene-γ-lactams **6** was assigned by means of TD-DFT calculations of the electronic circular dichroism (ECD) spectra.[20] Four different methods (functionals) and two different basis sets were used to ascertain if different theoretical levels provided consistent shapes of the simulated spectra. Simulations were performed using BH&HLYP, M06-2X, ωB97XD and CAM-B3LYP, together with the 6-311++G(2d,p) or the def2-TZVP basis sets. As shown in Fig. 2, the spectra calculated assuming the (*R*) configuration match very well the experimental spectra of **6b** (using β-ICPD as catalyst.) The full conformational analysis and further details can be found in S.D.

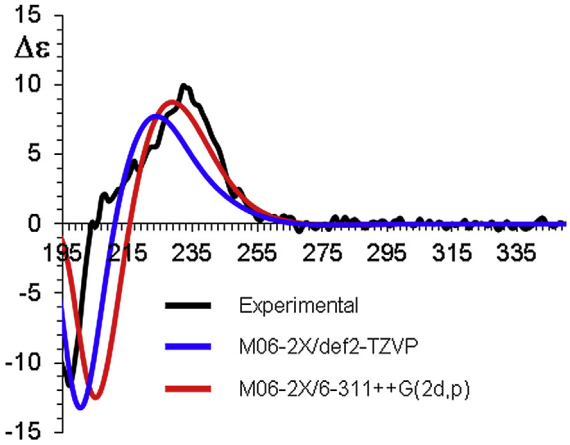


Fig. 2. TD-DFT Simulations of the ECD spectrum of **6b** (red and blue traces). The experimental spectrum (black trace) was obtained of acetonitrile solution ($1.0\ 10^{-4}$ M, 0.2 cm path length). $\Delta\varepsilon$ are expressed in mol L^{-1} cm^{-1}.

3. Conclusions

In summary, we have developed a new enantioselective one-pot methodology for the synthesis of α-methylene-γ-lactams. Starting from MBH carbonates, the reaction affords α-methylene-γ-lactams in satisfactory yields and moderate to good enantioselectivities when commercially available chiral Lewis bases are used as catalysts. Remarkably, this is the first report on the asymmetric organocatalytic synthesis of α-*exo*-methylene-γ-lactams by a one-pot procedure. These results allow for more compounds to be synthesized and evaluated, which could lead to the discovery of new drug candidates.

4. Experimental section

4.1. General methods

Chemicals and solvents were either purchased *puriss p.A.* from commercial suppliers or purified by standard techniques. For thin-layer chromatography (TLC), silica gel plates Merck 60 F_{254} were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (25.0 g), $Ce(SO_4)_2 \cdot H_2O$ (10.0 g), concd H_2SO_4 (60.0 mL), and H_2O (940.0 mL) followed by heating or by treatment with a solution of *p*-anisaldehyde (23.0 mL), concd H_2SO_4 (35.0 mL), acetic acid (10.0 mL), and ethanol (900 mL) followed by heating. Flash chromatography was performed using silica gel Merck 60 (particle size 0.040–0.063 mm), ^1H NMR, ^{19}F NMR and ^{13}C NMR spectra were recorded on Varian AS 400. Chemical shifts are given in parts per million relative to tetramethylsilane (TMS) and the coupling constants *J* are given in Hertz. The spectra were recorded in $CDCl_3$ as solvent at room temperature. TMS served as internal standard (δ=0 ppm) for ^1H NMR, $CDCl_3$ was used as internal standard (δ=77.0 ppm) for ^{13}C NMR and TFA was used as external standard for ^{19}F NMR. High-resolution mass spectra were recorded on a Bruker MicroTOF spectrometer.

4.2. Procedure for the preparation of the MBH-alcohols

To a round bottom flask charged with MeOH (0.75 equiv) was added the arylaldehyde (1.0 equiv) and methyl acrylate (1.2 equiv). After was added 1,4-diaza-bicyclo[2.2.2]octane (0.5 equiv) and the solution was stirred for 48–96 h until consumption of the starting material. The crude reaction mixture was purified directly by flash column chromatography (Hexane/EtOAc mixtures).

4.3. Procedure for the preparation of MBH-carbonates

To a solution of 1.0 equiv of the Morita–Baylis–Hillman alcohol in CH_2Cl_2 (0.5 M), 1.05 equiv of $(Boc)_2O$ and 0.1 equiv of 4-dimethylaminopyridine were added. The solution was stirred until consumption of starting material, the solvent was removed by rotary evaporation and the reaction mixture was purified directly by flash column chromatography (Hexane/EtOAc mixtures).

*4.3.1. Diethyl 2-(tert-butoxycarbonylamino)malonate (**3a**).* This compound was synthetized according to the procedure described by Berner and co-workers.[21] To a solution of 10.0 g of diethyl aminomalonate hydrochloride (47.3 mmol, 1.008 equiv) in 80.0 mL of dioxane, 1.89 g of NaOH in water (1.01 equiv, 47.4 mmol, 1.0 M) were added. After complete dissolution of the salt, a solution of 10.3 g of $(Boc)_2O$ (1.0 equiv, 46.8 mmol) in 20.0 mL of dioxane was added dropwise and reacted overnight. Once the reaction was finished the solvents were removed at reduced pressure, the crude solid was redissolved with EtOAc, washed with solutions of 1 N HCl and saturated NaCl, dried over $MgSO_4$ anhyd and the solvent of the combined organic phases was removed at reduced pressure. Finally, the crude product was purified by flash column chromatography (Hexane/EtOAc 3:1) to afford the desired product as a white solid in 91% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ=5.54 (br s, 1H), 4.93 (d, J=7.8 Hz, 1H), 4.35–4.15 (m, 4H), 1.44 (s, 9H), 1.29 (t, J=7.1 Hz, 6H).

*4.3.2. Diethyl 2-(((9H-fluoren-9-yl)methoxy)carbonylamino)malonate (**3b**).* 8.0 g of diethyl aminomalonate hydrochloride (1.0 equiv, 18.9 mmol) were dissolved in 30.0 mL of THF and 50.0 mL of $NaHCO_3$ 10% (w/v). After the complete dissolution of the salt, a solution of 5.4 g of Fmoc-Cl (1.1 equiv, 20.8 mmol) in 60.0 mL of THF was added dropwise and reacted overnight. After complete consumption of the starting material, the solution was extracted three times with EtOAc, dried over anhydrous $MgSO_4$ and the solvent was removed at reduced pressure. Finally, the crude product was purified by flash column chromatography (Hexane/EtOAc 3:1) to afford the desired product as a white solid in 83% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm)=7.76 (d, J=7.6 Hz, 2H), 7.61 (d, J=7.2 Hz, 2H), 7.41 (t, J=7.2 Hz, 2H), 7.31 (t, J=7.3 Hz, 2H), 5.85 (br s, 1H), 5.03 (d, J=8.3 Hz, 1H), 4.40 (d, J=7.8 Hz, 2H), 4.34–4.20 (m, 4H), 1.31 (t, J=7.3 Hz, 6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm)=166.3, 155.4, 143.6, 141.2, 127.7, 127.0, 125.0, 119.9, 67.5, 62.6, 57.7, 46.9, 13.9. IR (ν_{max}, cm^{-1}): 539, 585, 620, 759, 1023, 1053, 1087, 1176, 1224, 1282, 1447, 1464, 1687, 1737, 2976, 3309. HRMS (ESI) calcd for $C_{22}H_{24}NO_6$ $(M+H)^+$ 398.1598, found 398.1600.

4.4. General procedure for the synthesis of racemic α-methylene-γ-lactams 6 from diethyl 2-(*tert*-butoxycarbonylamino) malonate (*N*-Boc-aminomalonate) catalyzed by DABCO

In a vial equipped with a magnetic stirring bar, 0.2 mmol of the corresponding MBH carbonate (2.0 equiv), 0.1 mmol of *N*-Boc-aminomalonate **3a** (1.0 equiv) and 0.02 mmol of DABCO (0.2 equiv) were dissolved in 1.0 mL of toluene (C=0.1 M) and the reaction was stirred at room temperature. After consumption of starting material (monitored by ^{1}H NMR) the reaction crude was diluted with 1.0 mL of CH_2Cl_2, 0.1 mL of TFA were added in one portion and the mixture was stirred overnight. Then, the solution was diluted with 1.0 mL H_2O and neutralized until pH=7 with solid Na_2CO_3. The reaction mixture was extracted three times with EtOAc, the combined organic layers were dried over anhydrous $MgSO_4$ and the organic solvent eliminated at reduced pressure. Finally, the crude product was purified by flash column chromatography to afford the desired α-methylene-γ-lactam in racemic form. Spectral data for racemic compounds **6g**, **6h**, **6i** coincided with those reported in Ref. 11.

4.5. General procedure for the asymmetric synthesis of α-methylene-γ-lactams from diethyl 2-(*tert*-butoxycarbonyl amino)malonate (*N*-Boc-aminomalonate)

In a vial equipped with a magnetic stirring bar, 0.2 mmol of the corresponding MBH carbonate (2.0 equiv), 0.1 mmol of *N*-Boc-aminomalonate **3a** (1.0 equiv) and 0.02 mmol of β-ICPD (0.2 equiv) were dissolved in 1.0 mL of toluene (C=0.1 M) and the reaction was stirred at room temperature over 1–5 days. After consumption of starting material (monitored by ^{1}H NMR) the reaction crude was diluted with 1.0 mL of CH_2Cl_2, 0.1 mL of TFA was added in one portion and the mixture was stirred overnight. Then, the solution was diluted with 1.0 mL H_2O and neutralized until pH=7 with solid Na_2CO_3. The reaction mixture was extracted three times with EtOAc, the combined organic layers were dried with $MgSO_4$ anhyd and the organic solvent eliminated at reduced pressure. Finally, the crude product was purified by flash column chromatography to afford the desired α-methylene-γ-lactam.

4.6. General procedure for the asymmetric synthesis of α-methylene-γ-lactams from diethyl 2-(((9*H*-fluoren-9-yl)methoxy)carbonylamino) malonate (*N*-Fmoc-aminomalonate)

In a vial equipped with a magnetic stirring bar, 0.2 mmol of the corresponding MBH carbonate (2.0 equiv), 0.1 mmol of *N*-Fmoc-aminomalonate **3b** (1.0 equiv) and 0.02 mmol of β-ICPD (0.2 equiv) were added in 1.0 mL of toluene (C=0.1 M) and the reaction was stirred at room temperature over 1–5 days. After consumption of starting material (monitored by ^{1}H NMR) 1.0 mL of DMF/piperidine (20% w/w) was added in one portion and the mixture was stirred overnight. Then, the reaction was quenched with 1.0 mL H_2O, treated with HCl 1 M until pH=6 and extracted three times with EtOAc. The combined organic layers were dried with $MgSO_4$ and the organic solvent eliminated to afford the crude product that was purified by flash column chromatography to afford the desired α-methylene-γ-lactam.

*4.6.1. Diethyl 2-(2-(methoxycarbonyl)-1-phenylallylamino)malonate (**4**).* White foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm)=7.32–7.15 (m, 5H), 6.33 (s, 1H), 6.08 (s, 1H), 4.69 (s, 1H), 4.20–4.10 (m, 4H), 3.87 (s, 1H), 3.59 (s, 3H), 1.22–1.15 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm)=168.5, 168.3, 166.4, 141.1, 140.1, 127.9, 128.4, 127.7, 125.6, 62.9, 61.8, 60.3, 61.7, 51.7, 14.1, 14.0. IR (ν_{max}, cm^{-1}): 668, 966, 1080, 1219, 1263, 1462, 1721, 1747, 2858, 2961 HRMS (ESI): calcd for $C_{18}H_{24}NO_6$ $(M+H)^+$ 350.1598, found 350.1600.

*4.6.2. (R)-Diethyl 4-methylene-5-oxo-3-phenylpyrrolidine-2,2-dicarboxylate (**6a**).* White foam (25 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm)=7.29–7.26 (m, 5H), 6.68 (br s, 1H), 6.27 (d, J=2.7 Hz, 1H), 5.34 (d, J=2.7 Hz, 1H), 5.0 (t, J=2.7 Hz, 1H), 4.31–4.21 (m, 2H), 3.81–3.69 (m, 1H), 3.58–3.47 (m, 1H), 1.28 (t, J=7.1 Hz, 3H), 0.79 (t, J=7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm)=168.2, 167.7, 167.3, 140.9, 137.7, 129.5, 128.4, 128.0, 120.5, 71.2, 62.8, 62.3, 49.9, 13.9, 13.4. IR (ν_{max}, cm^{-1}): 668, 966, 1081, 1209, 1263, 1461, 1725, 1742, 2852, 2956. HRMS (ESI) calcd for $C_{17}H_{20}NO_5$ $(M+H)^+$ 318.1336, found 318.1340. $[\alpha]_D$ +40.6 (c 0.8, $CHCl_3$). HPLC (Daicel

Chiralpak IA, *i*-PrOH/Hexane=20:80, 220 nm, 1 mL/min): major 7.3 min, minor 8.8 min. Enantiomeric excess: 73%.

*4.6.3. (R)-Diethyl 3-(4-bromophenyl)-4-methylene-5-oxopyrroli dine-2,2-dicarboxylate (**6b**).* Yellowish foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm)=7.43 (d, *J*=8.6 Hz, 2H), 7.17 (d, *J*=8.6 Hz, 2H), 6.65 (br s, 1H), 6.28 (d, *J*=2.9 Hz, 1H), 5.33 (dd, *J*=0.9 Hz, 2.5 Hz, 1H), 4.96 (t, 2.9 Hz, 1H), 4.35–4.25 (m, 2H), 3.86–3.77 (m, 1H), 3.65–3.57 (m, 1H), 1.30 (t, *J*=7.4 Hz, 3H), 0.87 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm)=168.3, 167.5, 167.1, 140.4, 136.6, 132.2, 131.5, 131.3, 131.2, 122.2, 120.7, 70.9, 63.0, 62.5, 49.4, 13.9, 13.4. IR (ν_{max}, cm^{-1}): 672, 829, 891, 940, 1009, 1149, 1189, 1205, 1406, 1709, 1736, 2850, 2923, 2979, 3085, 3177. HRMS (ESI) calcd for $C_{17}H_{19}BrNO_5$ $(M+H)^+$ 396.0441, found 396.0437. HPLC (Daicel Chiralpak IC, *i*-PrOH/Hexane=10:90, 220 nm, 1 mL/min): major 65.9 min, minor 39.3. Enantiomeric excess: 82%.

*4.6.4. Diethyl 3-(2-bromophenyl)-4-methylene-5-oxopyrrolidine-2,2-dicarboxylate (**6c**).* White foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm)=7.56 (dd, *J*=1.2 Hz, *J′*=8.0 Hz 1H), 7.20 (td, *J*=1.1 Hz, 7.6 Hz, 1H), 7.13–7.03 (m, 2H), 6.70 (br s, 1H), 6.22 (d, *J*=2.7 Hz, 1H), 5.76 (t, *J*=2.1 Hz, 1H), 5.40 (dd, *J*=1.1 Hz, 2.1 Hz, 1H), 4.35–4.24 (m, 2H), 3.86–3.77 (m, 1H), 3.66–3.60 (m, 1H), 1.29 (t, *J*=7.0 Hz, 3H), 0.86 (t, *J*=7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm)=168.0, 167.2, 166.6, 141.7, 139.6, 132.7, 129.4, 129.2, 127.9, 125.4, 121.2, 70.7, 63.1, 62.3, 47.7, 13.9, 13.4. IR (ν_{max}, cm^{-1}): 685, 832, 878, 940, 1013, 1167, 1213, 1376, 1422, 1717, 1735, 2856, 2974, 3087, 3188. HRMS (ESI) calcd for $C_{17}H_{19}BrNO_5$ $(M+H)^+$ 396.0441, found 396.0442.

*4.6.5. (R)-Diethyl 3-(4-fluorophenyl)-4-methylene-5-oxopyrrolidine-2,2-dicarboxylate (**6d**).* White foam (30 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm)=7.30–7.25 (m, 2H), 7.01 (t, *J*=8.5 Hz, 2H), 6.66 (br s, 1H), 6.29 (d, *J*=2.9 Hz, 1H), 5.34 (dd, *J*=1.0 Hz, 2.9 Hz, 1H), 5.00 (t, *J*=2.9 Hz), 4.37–4.23 (m, 2H), 3.86–3.76 (m, 1H), 3.64–3.55 (m, 1H), 1.30 (t, *J*=6.8 Hz, 3H), 0.91 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm)=168.4, 167.6, 167.2, 162.4 (d, *J*=256 Hz), 140.7, 133.3, 131.3, 131.2, 120.6, 115.4, 115.2, 71.1, 62.9, 62.4, 49.2, 13.9, 13.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ(ppm)=−113.8. IR (ν_{max}, cm^{-1}): 546, 738, 818, 845, 1014, 1079, 1209, 1195, 1299, 1419, 1507, 1713, 1745, 2983, 3080, 3183. HRMS (ESI) calcd for $C_{17}H_{19}FNO_5$ $(M+H)^+$ 336.1214, found 336.1245. $[\alpha]_D$ +29.7 (*c* 1, $CHCl_3$) HPLC (Daicel Chiralpak IA, *i*-PrOH/Hexane=10:90, 250 nm, 1 mL/min): major 12.6 min, minor 13.7 min. Enantiomeric excess: 53%.

*4.6.6. (R)-Diethyl 4-methylene-3-(naphthalen-2-yl)-5-oxopyrroli dine-2,2-dicarboxylate (**6e**).* White foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm)=7.82–7.74 (m, 4H), 7.50–7.45 (m, 2H), 7.38–7.35 (m, 1H), 6.66 (br s, 1H), 6.32 (d, *J*=2.7 Hz, 1H), 5.37 (dd, *J*=0.9 Hz, 2.5 Hz, 1H), 5.19 (t, *J*=2.7 Hz, 1H), 4.36–4.26 (m, 2H), 3.29–3.18 (m, 1H), 2.84–2.76 (m, 1H), 1.07 (t, *J*=7.0 Hz, 3H), 0.60 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm)=168.6, 168.0, 166.9, 142.6, 136.2, 133.4, 132.7, 128.6, 128.4, 127.1, 126.5, 125.8, 125.3, 123.8, 121.2, 71.3, 63.0, 61.9, 43.6, 13.9, 12.6. IR (ν_{max}, cm^{-1}): 647, 744, 857, 1011, 1038, 1077, 1260, 1394, 1507, 1600, 1729, 1746, 2980, 3056, 3184. HRMS (ESI) calcd for $C_{21}H_{22}NO_5$ $(M+H)^+$ 368.1492, found 368.1496. HPLC (Daicel Chiralpak IA, *i*-PrOH/Hexane=10:90, 220 nm, 1 mL/min): major 14.4 min, minor 18.2 min. Enantiomeric excess: 74%.

*4.6.7. Diethyl 4-methylene-3-(naphthalen-1-yl)-5-oxopyrrolidine-2,2-dicarboxylate (**6f**).* White foam ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm)=8.27 (d, *J*=9.1 Hz, 1H), 7.62 (d, *J*=8.4 Hz, 1H), 7.53 (d, *J*=8.4 Hz, 1H), 7.41–7.28 (m, 2H), 7.15 (t, *J*=7.4 Hz, 1H), 6.98 (dd, *J*=7.4 Hz, 1.4 Hz 1H), 6.64 (br s, 1H), 6.08 (d, *J*=2.5 Hz, 1H), 5.82 (t, *J*=2.3 Hz, 1H), 5.11 (dd, *J*=0.9 Hz, *J*=2.1 Hz, 1H), 4.14–4.01 (m, 2H), 3.70–3.66 (m, 1H), 3.45–3.35 (m, 1H), 1.30 (t, *J*=7.0 Hz, 3H), 0.60 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm)=167.9, 167.2, 166.9, 143.0, 139.9, 132.2, 130.4, 121.2, 118.3, 112.1, 70.8, 63.2, 62.6, 49.7, 13.9, 13.5. IR (ν_{max}, cm^{-1}): 599, 748, 845, 1023, 1037, 1065, 1245, 1396, 1613, 1723, 1754, 2982, 3045, 3170. HRMS (ESI) calcd for $C_{21}H_{22}NO_5$ $(M+H)^+$ 368.1492, found 368.1492.

*4.6.8. (R)-Diethyl 3-(4-methoxyphenyl)-4-methylene-5-oxopyrroli dine-2,2-dicarboxylate (**6g**).* Colorless crystals mp 140–143 °C (30 mg, 87%) ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm)=7.19 (d, *J*=9.2 Hz, 2H), 6.81 (d, *J*=9.2 Hz, 2H), 6.63 (br s, 1H), 6.26 (d, *J*=2.9 Hz, 1H), 5.33 (dd, *J*=0.9 Hz, 2.5 Hz, 1H), 4.95 (t, *J*=2.9 Hz, 1H), 4.34–4.22 (m, 2H), 3.84–3.75 (m, 1H), 3.77 (s, 3H), 3.64–3.54 (m, 1H), 1.29 (t, *J*=7.0 Hz, 3H), 0.86 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm)=168.7, 167.7, 167.4, 159.3, 141.1, 130.7, 129.5, 120.3, 113.7, 71.2, 62.8, 62.3, 55.3, 49.4, 13.9, 13.5. IR (ν_{max}, cm^{-1}): 553, 656, 808, 834, 892, 1032, 1144, 1464, 1511, 1583, 1610, 1658, 1734, 1756, 2838, 2935, 2980, 3074, 3183. HRMS (ESI) calcd for $C_{18}H_{22}NO_6$ $(M+H)^+$ 348.1442, found 348.1449. $[\alpha]_D$ +41.0 (*c* 0.2, $CHCl_3$) HPLC (Daicel Chiralpak IA, *i*-PrOH/Hexane=10:90, 220 nm, 1 mL/min): major 15.0 min, minor 16.3 min. Enantiomeric excess: 61%.

*4.6.9. (R)-Diethyl 3-(4-chlorophenyl)-4-methylene-5-oxopyrroli dine-2,2-dicarboxylate (**6h**).* Colorless crystals mp 154–156 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm)=7.30–7.12 (m, 4H), 6.73 (br s, 1H), 6.29 (d, *J*=2.9 Hz, 1H), 5.34–5.32 (m, 1H), 4.98 (t, *J*=2.7 Hz, 1H), 4.36–4.22 (m, 2H), 3.87–3.78 (m, 1H), 3.66–3.58 (m, 1H), 1.29 (t, *J*=7.0 Hz, 3H), 0.87 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm)=168.4, 167.5, 167.2, 140.5, 136.1, 134.0, 130.9, 128.6, 120.7, 71.0, 62.9, 62.4, 49.3, 13.9, 13.4. IR (ν_{max}, cm^{-1}): 645, 709, 833, 1014, 1090, 1148, 1209, 1260, 1410, 1445, 1491, 1655, 1725, 1756, 2982, 3197. HRMS (ESI) calcd for $C_{17}H_{19}ClNO_5$ $(M+H)^+$ 352.0946, found 352.0943. HPLC (Daicel Chiralpak IC, *i*-PrOH/Hexane=20:80, 220 nm, 1 mL/min): major 58.7 min, minor 36.9 min. Enantiomeric excess: 58%.

*4.6.10. (R)-Diethyl 3-(4-methylphenyl)-4-methylene-5-oxopyrroli dine-2,2-dicarboxylate (**6i**).* Colorless crystals mp 109–113 °C (30 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm)=7.18–7.06 (m, 4H), 6.48 (br s, 1H), 6.26 (d, *J*=2.9 Hz, 1H), 5.34 (dd, *J*=0.9 Hz, 2.5 Hz, 1H), 4.96 (t, *J*=2.9 Hz, 1H), 4.34–4.22 (m, 2H), 3.83–3.74 (m, 1H), 3.62–3.54 (m, 1H), 2.31 (s, 3H),1.28 (t, *J*=7.0 Hz, 3H), 0.83 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm)=168.6, 167.7, 167.3, 141.0, 137.8, 137.7, 128.7, 128.2, 126.5, 71.2, 62.8, 62.3, 49.7, 21.0, 13.9, 13.3. IR (ν_{max}, cm^{-1}): 717, 808, 935, 1012, 1040, 1113, 1145, 1207, 1261, 1391, 1444, 1514, 1659, 1709, 1740, 2924, 3081. HRMS (ESI) calcd for $C_{18}H_{22}NO_5$ $(M+H)^+$ 332.1492, found 332.1495. $[\alpha]_D$ +42.1 (*c* 0.5, $CHCl_3$) HPLC (Daicel Chiralpak IA, *i*-PrOH/Hexane=10:90, 220 nm, 1 mL/min): major 11.8 min, minor 13.5 min. Enantiomeric excess: 78%.

*4.6.11. Diethyl 4-(2-bromobenzylidene)-5-oxopyrrolidine-2,2-dicarboxylate (**7c**).* White foam (38 mg, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm)=7.65 (t, *J*=2.7 Hz, 1H), 7.67–7.63 (m, 1H), 7.48–7.43 (m, 1H), 7.40–7.33 (m, 1H), 7.24–7.18 (m, 1H), 6.60 (br s, 1H), 4.32–4.23 (m, 4H), 3.53 (d, *J*=2.7 Hz, 2H), 1.29 (t, *J*=7.1 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm)=169.3, 168.2, 133.4, 132.6, 131.6, 130.2, 129.3, 127.3, 121.1, 65.6, 63.0, 33.1, 13.9. IR (ν_{max}, cm^{-1}): 756, 1026, 1095, 1162, 1188, 1466, 1707, 1745, 2853, 2924,m 2980, 3197. HRMS (ESI) calcd for $C_{17}H_{19}BrNO_5$ $(M+H)^+$ 396.0441, found 396.0444.

*4.6.12. Diethyl 4-(naphthalen-1-ylmethylene)-5-oxopyrrolidine-2,2-dicarboxylate (**7f**).* White foam (31 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm)=8.15–8.10 (m, 2H), 7.91–7.85 (m, 1H), 7.64–7.48 (m, 5H), 6.51 (br s, 1H), 4.27 (m, 4H), 3.57 (d, *J*=2.5 Hz, 2H), 1.28 (t, *J*=7.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm)=187.2, 169.7,

168.4, 133.6, 131.8, 131.7, 130.0, 129.6, 128.9, 128.7, 126.7, 126.3, 126.2, 125.1, 124.0, 65.7, 62.9, 33.5, 13.9. IR (ν_{max}, cm^{-1}): 631, 726, 777, 796, 1011, 1076, 1161, 1188, 1238, 1342, 1443, 1517, 1701, 1740, 2924, 2980. HRMS (ESI) calcd for $C_{21}H_{22}NO_5$ $(M+H)^+$ 368.1492, found 368.1489.

*4.6.13. Diethyl 2′-oxo-4′-phenylspiro[bicyclo[2.2.1]hept[5]ene-2,3′-pyrrolidine]-5′,5′-dicarboxylate (**8a**).* A solution of 50.0 mg of compound **6a** (0.16 mmol, 1.0 equiv) and 100.0 mg of freshly distilled cyclopentadiene (1.6 mmol, 10.0 equiv) in 5.0 mL of toluene was refluxed overnight. Then, the organic solvent was removed at reduced pressure and the crude product was directly purified by flash column chromatography (Hexane/EtOAc=3:1) to afford the desired product (35 mg, 58% yield, 3.5:1 *d.r.*). ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm)=7.23–7.15 (m, 3H), 7.07–6.95 (m, 2H), 6.50 (br s, 1H), 6.41–6.36 (m, 1H), 6.31–6.26 (m, 1H), 4.38–4.28 (m, 2H), 4.03 (s, 1H), 3.76–3.64 (m, 2H), 2.79–2.72 (m, 2H), 2.08–1.98 (m, 2H), 1.34 (t, J=7.8 Hz, 3H), 0.77 (t, J=7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm)=171.2, 167.2, 166.9, 140.7, 134.7, 130.9, 128.6, 127.5, 71.4, 62.8, 62.1, 56.1, 55.6, 52.3, 46.3, 42.4, 35.0, 14.0, 13.3. HRMS (ESI) calcd for $C_{22}H_{28}NO_5$ $(M+H)^+$ 386.1962, found 386.1966.

*4.6.14. Diethyl 4-oxo-7-phenyl-1-oxa-5-azaspiro[2.4]heptane-6,6-dicarboxylate (**9a**).* To a stirred solution of 0.1 mmol of **6a** (1.0 equiv) in 3 mL of CH_2Cl_2, were added 35.0 mg of *m*CPBA (0.2 mmol, 2.0 equiv) and the solution was refluxed for 21 h. After cooling the solution, the solvent was evaporated and the crude product treated with 2.0 mL of acetone and 2.0 mL of a saturated solution of $NaHCO_3$ for 30 min. Then 5.0 mL of water were added and the mixture was extracted three times with Et_2O. The organic layers were dried and evaporated and the crude product was purified by flash column chromatography (Hexane/EtOAC=1:1) to furnish the desired final product (26 mg, 79% yield, 10:1 *d.r.*). ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm)=7.31–7.27 (m, 3H), 7.21–7.18 (m, 2H), 4.40 (s, 1H), 4.37–4.24 (m, 2H), 3.89–3.79 (m, 1H), 3.68–3.60 (m, 1H), 3.29 (d, J=5.6 Hz, 1H), 2.68 (d, J=5.6 Hz, 1H), 1.30 (t, J=7.3 Hz, 3H), 0.81 (t, J=7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm)=171.2, 167.2, 166.9, 135.5, 129.2, 128.6, 128.4, 128.3, 126.3, 63.2 62.6, 61.6, 50.6, 48.3, 29.6, 13.9, 13.3. HRMS (ESI) calcd for $C_{17}H_{20}NO_6$ $(M+H)^+$ 334.1285, found 334.1288.

*4.6.15. Diethyl 4-methyl-5-oxo-3-phenylpyrrolidine-2,2-dicarboxylate (**10**).* To a solution of 0.2 mmol of **6a** in 2.0 mL EtOAc was added 10 mol % Pd/C (0.1 equiv). Hydrogenation was carried out under hydrogen atmosphere at room temperature and atmospheric pressure for 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. Purification of the residue by flash column chromatography (Hexane/EtOAC=3:1) afforded the desired reduced product (62 mg, 93% yield, >25:1 *d.r.*). ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm)=7.40–7.25 (m, 5H), 6.17 (br s, 1H), 4.37–4.21 (m, 2H), 3.95–3.75 (m, 2H), 3.67–3.57 (m, 1H), 2.94 (m, 1H), 1.28 (t, J=7.0 Hz, 3H), 1.20 (d, J=7.4 Hz, 3H), 0.81 (t, J=7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ(ppm)=177.8, 168.7, 168.2, 136.4, 129.2, 128.7, 128.1, 71.4, 62.2, 61.9, 53.3, 14.5, 14.1, 13.7. HRMS (ESI) calcd for $C_{17}H_{22}NO_5$ $(M+H)^+$ 320.1492, found 320.1495.

*4.6.16. 4-Methylene-5-oxo-3-phenylpyrrolidine-2-carboxylic acid (**11a**/**11b**).* This compound was synthetized adapting the procedure reported by Rios and Cordova for a related compound.[22] 50 mg of compound **4a** (0.15 mmol, 1.0 equiv) was stirred for 21 h with 2.0 mL of NaOH 0.5 M at room temperature. Then, the solution was extracted with 5.0 mL of EtOAc, the aqueous fraction was acidified to pH=2 with HCl, extracted three times with CH_2Cl_2, the combined organic layers were dried over $MgSO_4$ anhyd and the solvent was eliminated at reduced pressure. Afterward, the corresponding crude product was suspended in toluene and heated at 80 °C for 1 h. Finally, the solution was directly purified by flash column chromatography (EtOAC/MeOH=15:1) to furnish the desired product as a mixture of diastereomers (25 mg, 78% yield, 2.5:1 *d.r.*). **11a** (Major diastereoisomer) ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm)=8.51 (br s, 1H), 7.38–7.13 (m, 5H), 5.86 (d, J=2.54 Hz, 1H), 5.04 (d, J=2.54 Hz, 1H), 4.52 (dt, J=8.4 Hz, 2.5, 1H), 4.37 (dd, J=8.4 Hz, 0.97 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ(ppm)= 171.9, 169.3, 143.7, 138.3, 129.0, 128.2, 127.2, 115.8, 58.7, 47.0. **11b** (Minor diastereomer) ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm)=8.65 (br s, 1H), 7.38–7.13 (m, 5H), 5.82 (d, J=2.5 Hz, 1H), 5.07 (d, J=2.5 Hz, 1H),4.13–4.09 (m, 1H), 4.07 (dd, J=4.2 Hz, 1.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ(ppm)=172.9, 168.2, 144.2, 142.1, 128.8, 127.4, 127.0, 116.7, 60.3, 47.9. HRMS (ESI) calcd for $C_{12}H_{12}NO_3$ $(M+H)^+$ 218.0812, found 218.0814.

Acknowledgements

Financial support from the University of Southampton (to R.R.) and from the Universitat de Barcelona (to A.M.) is gratefully acknowledged. X.C. is grateful to MICINN for a PFU pre-doctoral fellowship. A.M. thanks the University of Bologna (RFO funds 2008). This work has been done under the auspices of COST Action CM0905 (ORCA). Financial support from European Regional Development Fund (ERDF) (AI-Chem & InterReg IVb) is gratefully acknowledged (R.R.).

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.11.028.

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