Synthesis A. P. Maximiano et al. Feature

Functionalized Cyclopropanes as Versatile Intermediates for the Diversity-Oriented Synthesis of γ-Lactones, γ-Lactams and δ-Lactams

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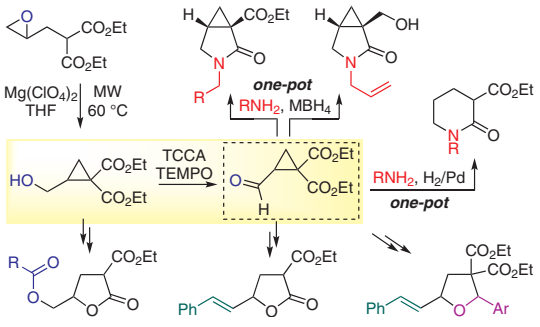
To Professor Albert J. Kascheres, *in memoriam*



Received: 30.11.2020
Accepted after revision: 11.02.2021
Published online: 11.02.2021
DOI: 10.1055/a-1389-1203; Art ID: ss-2020-z0612-fa

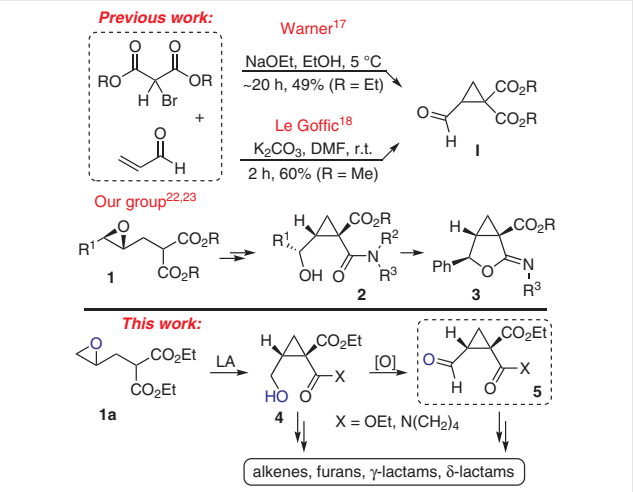
Abstract A two-step procedure for the preparation of cyclopropanecarboxaldehyde-1,1-diester from a γ,δ-epoxyester and its synthetic versatility are described herein. The epoxide ring-opening/cyclopropanation process occurs in the presence of $Mg(ClO_4)_2$ under heating, resulting in cyclopropanemethanol-1,1-diester in 65% yield. A mild TEMPO-mediated oxidation of this substrate readily generated the corresponding aldehyde in 75% yield, which was applied in the one-pot synthesis of four cyclopropylidene-γ-lactams and three δ-lactams. In addition, vinylcyclopropanes were obtained through the Wittig reaction of the aldehyde with phosphonium salts and used as precursors for tetrahydrofurans.

Key words γ,δ-epoxyester, cyclopropanecarboxaldehyde, lactonization, cyclopropylidene-γ-lactams, δ-lactams, one-pot process, structural diversity

Functionalized cyclopropanes are widely used in organic synthesis as versatile building blocks due to their distinct reactivity modes as a C3 unit in a series of inter- or intramolecular transformations.[1–7] Despite its unique reactivity, the cyclopropyl fragment is commonly found in natural products and pharmacologically active compounds, making this strained ring a highly attractive synthetic target.[8–10]

Cyclopropanecarboxaldehydes are among the most commonly employed functionalized cyclopropanes in synthesis.[11] They are interesting synthetic intermediates that have found application in several transformations such as ring-opening reactions,[12] rearrangements,[13] and annulations/cyclizations,[14] among others,[15] resulting in a diversity of products that include functionalized carbocycles, heterocycles and polycyclic structures of molecular complexity.

Cyclopropane-1,1-diesters containing the carboxaldehyde group (**I**, Scheme 1) have been known for decades and are of particular interest due to their distinct uses in synthesis.[16] Warner was a pioneer in the synthesis of a substituted cyclopropane-1,1-diester containing the carboxaldehyde group **I**, using acrolein and ethyl bromomalonate as the precursors in the presence of a strong base[17] (Scheme 1). Later, Le Goffic and co-workers reported a method for the preparation of an analogue of **I** in 60% yield, from acrolein and methyl bromomalonate, by replacing NaOEt with K_2CO_3 as the base.[18] More recently, methodologies involving the use of organocatalysis for the enantioselective cyclopropanation of α,β-unsaturated aldehydes have been described.[19–21]



Scheme 1 Synthesis of functionalized cyclopropane-1,1-diesters

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We have recently been conducting research on the chemistry of functionalized cyclopropanes, developing a cooperative acid/base catalysis for the stereoselective synthesis of cyclopropanecarboxamides **2** from γ,δ-epoxyesters **1** through a domino cyclopropanation/lactonization/aminolysis process.[22] These cyclopropanecarboxamides **2** were further employed in a novel acid-mediated diastereoselective cyclization reaction as a simple and reliable method to

Biographical Sketches

Adrielle Patricio Maximiano received her master's degree in organic chemistry from the Federal University of Santa Catarina (UFSC) in 2013. After two years as a fellow of the RHAE-CNPq program (Human Resources in Strategic Areas - researcher in the company), she returned to UFSC and joined MESOLab. In 2020, she obtained her PhD in organic chemistry under the guidance of Prof. Marcus Mandolesi Sá. Her work was focused on the development of efficient methods for the diastereoselective synthesis of carbo- and heterocycles employing functionalized epoxides and cyclopropanes.

Marcelo Volpatto Marques received his bachelor's degree in chemistry from the Universidade Luterana do Brasil in 2007 and his master's degree from the Federal University of Rio Grande do Sul in 2010. In 2014, he received his PhD from UFSC under the guidance of Prof. Marcus Mandolesi Sá. His PhD research focused on the preparation of γ,δ-epoxymalonates and their application in the synthesis of cyclopropane carboxamides and γ-arylmethyl lactones. He is currently the coordinator of the Postgraduate Program at the Instituto Federal Catarinense (IFC).

Giovana da Silva Ramos earned her BSc degree in chemistry in 2018 at the State University of Londrina (UEL), Brazil. During that period, she also studied chemistry at Purdue University – Calumet (IN, USA) for a year, as a Science Without Borders exchange student. She obtained her master's degree also at UEL in 2020, and is currently a graduate student under the mentoring of Prof. Marcus Mandolesi Sá at UFSC. Her main research interests include organic synthesis, with emphasis on the synthesis of bioactive molecules.

Marcus Mandolesi Sá is a Full Professor of Organic Chemistry at the Federal University of Santa Catarina (UFSC), in Florianópolis, Brazil. He received his diploma (1989) and his doctoral (1995) degrees in organic chemistry from the State University of Campinas (UNICAMP) under the guidance of Prof. Albert Kascheres, studying the chemistry of vinyl azides and azirines. He then spent two years as a postdoctoral fellow in the group of Prof. Albert Padwa at Emory University (Atlanta, USA) working on the reactivity of diazo compounds. In 1997, he returned to Brazil and joined the group of Prof. José Tércio Ferreira at the Federal University of São Carlos as a postdoctoral researcher in medicinal chemistry for one year. He then moved to UFSC in 1998 to start his independent academic career. After being promoted to Associate Professor, he was awarded Full Professor of Organic Chemistry in 2019 at UFSC. He has been granted research scholarships from CNPq (Brazilian Research Council, 2007–2022) and is currently the Coordinator of the Chemistry Postgraduate Program at UFSC. His research group focuses on the development of sustainable synthetic methods, the synthesis of heterocycles and bioactive substances, and the reactivity of three-membered rings and multifunctionalized compounds.

access cyclopropylidene iminolactones **3**, which were found to be versatile building blocks for the construction of cyclopropanes decorated with a variety of functional groups[23] (Scheme 1).

Herein, we describe the straightforward isomerization of epoxide **1a** to give cyclopropanemethanol **4a**, mediated by a Lewis acid, and also address its mild oxidation to cyclopropanecarboxaldehyde **5a**, which was able to participate in further synthetic transformations to give a diversity of O- and N-heterocycles.

During the studies involved in the Lewis acid mediated preparation of cyclopropanecarboxamides **2** from γ,δ-epoxyesters **1** and amines through the domino process described previously,[22] we found that the transformation is catalyst-dependent. For the particular case of the terminal epoxide **1a**, employing LiCl as the catalyst (as in the original method)[22] under microwave conditions, in the absence of an added amine or any other external base, led to the exclusive formation of the known cyclopropylidenelactone **6** (Table 1, entry 1). However, replacing LiCl with $Mg(ClO_4)_2$ furnished cyclopropanemethanol **4a** in 65% yield, with no detectable presence of lactone **6** (entry 2). Conducting the $Mg(ClO_4)_2$-mediated transformation under conventional heating (oil bath, entry 3) also led to the exclusive formation of alcohol **4a**, although the reaction time was longer than that observed under microwave-assisted conditions (compare with entry 2).

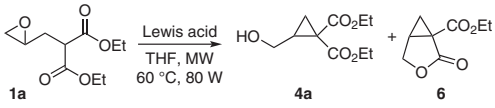
This somewhat unexpected chemoselectivity led us to investigate other possible conditions for this epoxide-to-cyclopropane isomerization. It was found that the addition of an external base hinders the formation of **4a**, as lactone **6** was the sole product detected in the crude mixture (Table 1, entry 4). Similarly, decreasing the amount of $Mg(ClO_4)_2$ had a negative effect on the selective formation of **4a**, furnishing lactone **6** competitively in nonnegligible amounts (entry 5). Other Lewis acids tested proved to be either inefficient (entries 6, 10–12) or nonselective (entries 7–9) for the formation of alcohol **4a**.

Having established the appropriate conditions for the $Mg(ClO_4)_2$-mediated isomerization of epoxide **1a** to cyclopropanemethanol **4a** (Table 1, entries 2 and 3), the synthetic application of **4a** was investigated. Firstly, the acylation of the primary hydroxyl group was readily achieved with functionalized carboxylic acids through the Steglich esterification reaction.[24] This simple strategy generates potential precursors **7** for the Lewis acid mediated intramolecular [3+2] cycloaddition attempted in this study (Scheme 2). However, no bicyclic framework, such as **8**, was detected under the various conditions applied. Instead, cyclopropanes **7** underwent ring expansion in the presence of scandium(III) triflate, employed as the catalyst, to give exclusively γ-lactones **9**. The Lewis acid catalyzed unimolecular formation of γ-lactones from cyclopropane-1,1-diesters has some precedents in the literature as an alternative pathway to other previously designed transformations.[25] For the particular case of fumaric ester **7a**, the corresponding lactone **9a** was isolated in excellent yield as a diastereomeric mixture (1:1 *syn*/*anti*, Scheme 2). The α,β-unsaturated ester **7b** was also tested and, as anticipated, led to γ-lactone **9b** in moderate yield. On the other hand, the isomeric β,γ-unsaturated ester **7c** underwent extensive isomerization of the C=C double bond during the ring expansion, giving rise to a complex mixture of diastereoisomers **9b** and **9c** (*syn* versus *anti* as well as α,β- versus β,γ-unsaturation) that could not be properly separated by chromatography. For the malonyl derivative **7d**, slow consume of the starting material was observed and the expected lactone was not formed in significant amounts after 72 hours.

It is also important to note that cyclopropanemethanol **4a** was unable to generate the corresponding γ-lactone under reaction conditions similar to those used for esters **7** [$Sc(OTf)_3$, CH_2Cl_2, r.t.] or even more vigorous conditions (heating for prolonged periods), suggesting that the presence of the free hydroxyl group in **4a** hinders the ring expansion process.

Another interesting application of cyclopropanemethanol **4a** was found in the straightforward oxidation to the corresponding cyclopropanecarboxaldehyde **5a** through a combination of trichloroisocyanuric acid (TCCA) and cata-

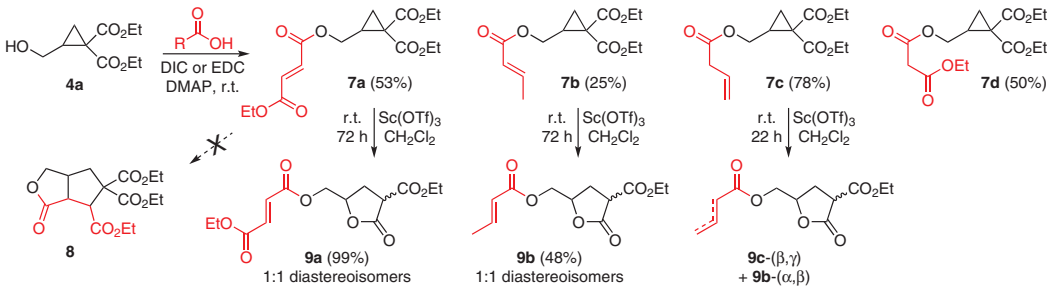
Table 1 Synthesis of Cyclopropanemethanol **4a** and Cyclopropylidenelactone **6** from γ,δ-Epoxyester **1a**



1a **4a** **6**

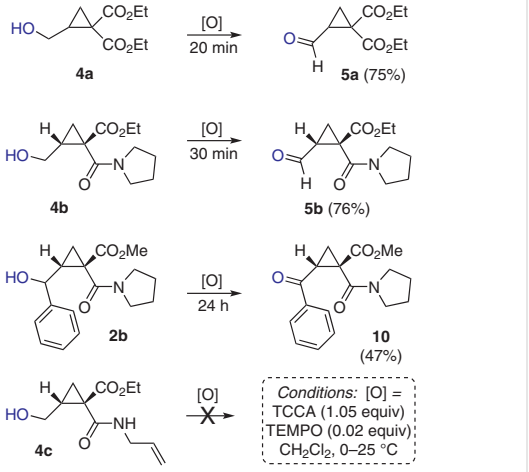
Entry	Lewis acid (equiv)	Time (h)	Conv. (%)[a]	Ratio **4a**/**6** (%)[a][Yield (%)][b]
1	LiCl (1.0)	0.75	48	0:100
2	$Mg(ClO_4)_2$ (1.0)	0.75	100	100:0 [65]
3	$Mg(ClO_4)_2$ (1.0)[c]	2	100	100:0 [58]
4	$Mg(ClO_4)_2$ (1.0)[d]	0.75	100	0:100
5	$Mg(ClO_4)_2$ (0.2)	2	100	73:27
6	$MgSO_4$ (1.0)	0.75	0	–
7	$Yb(OTf)_3$ (0.2)	0.75	100	0:100
8	$Yb(OTf)_3$ (0.2)[e]	24	100	50:50
9	$Cu(OTf)_2$ (0.2)	0.75	100	0:100[f]
10	$Fe(OTf)_3$ (0.2)	0.75	100	–[f]
11	$Zn(OAc)_2$ (0.2)	0.75	0	–
12	$SrCl_2$ (0.2)	0.75	0	–

[a] Conversion (%) and ratio (%) were determined by ^1H NMR integration of the crude reaction mixture.
[b] Yield of isolated cyclopropanemethanol **4a** after column chromatography.
[c] Reaction carried out at 60 °C under conventional heating (oil bath).
[d] Addition of triethylamine (1 equiv).
[e] Reaction carried out at r.t.
[f] Presence of unidentified products.



Scheme 2 Preparation of γ-lactones **9** from O-acylated cyclopropanes **7**

lytic 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), at room temperature, according to the method described by De Luca and co-workers[26] (Scheme 3).

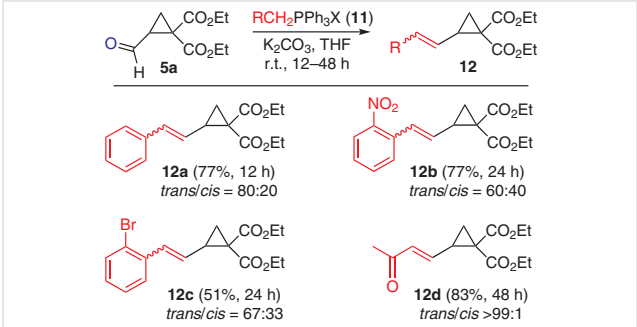


Scheme 3 Oxidation of cyclopropanemethanol **4a** and carboxamides **4b** and **2b**

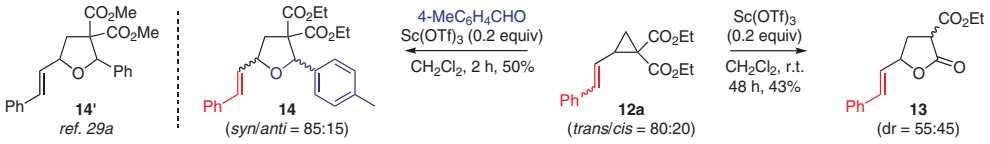
With these simple reaction conditions, it was possible to obtain cyclopropanecarboxaldehyde **5a** in a short reaction time of 20 minutes. Aldehyde **5a** was obtained in 75% yield after a workup which consisted of simple filtration through Celite followed by washing the filtrate with aqueous saturated Na_2CO_3 and 1 M HCl. No additional purification step was necessary due to the high purity of the product, as determined by ^{1}H NMR analysis (see the Supporting Information). The fact that the oxidation is carried out at room temperature with readily accessible reagents compares favorably to the existing methods described in the literature for the oxidation of related cyclopropanemethanols to cyclopropanecarboxaldehydes, which involve the use of toxic chromium-based oxidizing agents[15c,27] or the Swern oxidation under cryogenic conditions (–78 °C).[28]

Given the facility with which aldehyde **5a** could be obtained from alcohol **4a**, this oxidation method with TCCA/TEMPO was also extended to the hydroxy-substituted cyclopropanecarboxamides **4b** and **2b** (Scheme 3). In the case of cyclopropanecarboxaldehyde monoamide **5b**, it was obtained from **4b** after 30 minutes in 76% yield. The less reactive secondary alcohol in the phenyl-substituted cyclopropanecarboxamide **2b** was also conveniently oxidized to the ketonic derivative **10**, although a more prolonged reaction time was required to achieve a reasonable isolated yield. In contrast, cyclopropanecarboxamide **4c** underwent extensive decomposition under similar oxidation conditions and did not result in the expected aldehyde. This could be explained by the presence of a free N–H amidic bond in **4c**, which might be competitively oxidized to give reactive N–O and N–Cl intermediates that decompose under the reaction conditions employed.

With the straightforward preparation of cyclopropanecarboxaldehyde **5a** in hand, it was attractive to employ this functionalized building block in a variety of reactions using different nucleophiles. Firstly, a mild Wittig reaction with phosphonium salts **11** in the presence of a weak base, such as K_2CO_3, was developed to give vinylcyclopropanes **12** with varied *trans*/*cis* diastereoselectivity depending on the structure of the starting phosphonium (Scheme 4). Thus, benzyl-derived semistabilized ylides originating from salts **11a–c** gave alkenes **12a–c** in *trans*/*cis* ratios ranging from 80:20 to 60:40, while the stabilized ylide obtained from α-keto phosphonium **11d** furnished exclusively the *trans*-alkene **12d** in high yield.



Scheme 4 Preparation of vinylcyclopropanes **12** through the Wittig reaction from aldehyde **5a** and phosphonium salts **11** ($RPPh_3X$; X = Br, Cl)

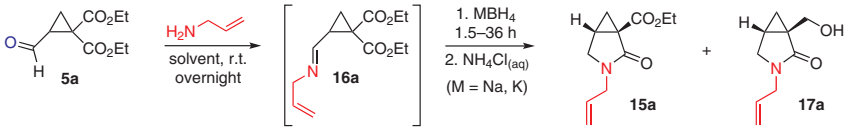


Scheme 5 Synthesis of O-heterocycles **13** and **14** from vinylcyclopropane **12a**

Vinylcyclopropanes, such as **12a**, have been applied in the synthesis of several compounds, serving as a 1,3-dipolar synthon due to the donor–acceptor substitution pattern attached to the ring.[29,30] We explored the synthetic versatility of **12a** for the preparation of O-heterocycles such as γ-lactone **13** and tetrahydrofuran **14** (Scheme 5). Vinylcyclopropane **12a** was treated with catalytic $Sc(OTf)_3$ to give the corresponding γ-lactone **13** in 43% yield (55:45 mixture of *anti*/*syn* diastereoisomers) through ring expansion, as observed previously for the O-acylated cyclopropanes **7** (see Scheme 2). On the other hand, a different reaction outcome was observed in the presence of tolualdehyde as an external dipolarophile.[29] The spectroscopic data for the cycloaddition adduct **14** are in agreement with those found for the analogue **14′** (Scheme 5), which was previously prepared by Pohlhaus and Johnson.[29a] On the basis of these previous studies,[29a] the relative stereochemistry of the major isomer was assigned as being *syn*.

The synthetic versatility of cyclopropanecarboxaldehyde **5a** was also addressed through a one-pot imination/reductive cyclization as a direct strategy to access cyclopropylidene-γ-lactams **15** and an iminosugar analogue. Initially, allylamine was employed as the model amine and the reaction conditions were evaluated, including the type and stoichiometry of reducing agent, the solvent and the reaction time (Table 2). As observed in entry 1, treating **5a** with allylamine for 16–18 hours followed by the addition of 1.0 equivalent of $NaBH_4$ to the pre-formed imine **16a** produced cyclopropylidene-γ-lactam **15a** (58% yield), which was obtained in reasonable purity from the organic extracts after aqueous workup with NH_4Cl. The relatively low percentage of recovered mass for **15a** was correlated to the competitive formation of hydroxylated cyclopropylidene-γ-lactam **17a**, which was recovered from the aqueous layer after basification of the acidic aqueous phase and subsequent back-extraction with ethyl acetate. This interesting bicycle **17a** possesses a structural motif related to pyrrolidine iminosugars[31] and may originate from the selective overreduction of the carboxylate group in the main product **15a** or in the various intermediates postulated for this one-pot process. Indeed, a control reaction partially supported the formation of **17a** from the direct reduction of **15a** with $NaBH_4$,

Table 2 Reaction Conditions Used in the Preparation of Cyclopropylidene-γ-lactam **15a**[a]



Entry	Reducing agent (equiv)	Solvent	Time (h)[b]	Yield (%)[c] of **15a**	Yield (%)[c] of **17a**
1	$NaBH_4$ (1.0)	2-propanol	21	58	40
2	$NaBH_4$ (0.5)	2-propanol	26	64[c]	25
3	$NaBH_4$ (2.0)	2-propanol	26	37	30
4	$NaBH_4$ (1.0)	2-propanol	1.5	40	15
5	$NaBH_4$ (1.0)	ethanol	36	25	25
6	$NaBH_4$ (1.0)[d]	2-propanol	24	32	20
7	KBH_4 (1.0)	2-propanol	28	21[e]	0
8	KBH_4 (1.0)	ethanol	23	24[e]	–[f]
9	$NaBH_3CN$ (1.0)	ethanol	24	35[e]	–[f]

[a] One-pot reaction conditions: 1. aldehyde **5a**, amine (1.0 equiv), solvent, r.t., 16–18 h; 2. reducing agent, r.t.
[b] Time refers to the reduction step.
[c] Yields after aqueous workup; products were of satisfactory purity, as verified by ^1H NMR analysis of the crude reaction mixtures.
[d] LiCl (1.0 equiv) was added to the reaction medium.
[e] Yield of cyclopropylidene-γ-lactam **15a** after column chromatography.
[f] The aqueous phase was not recovered.

although the conversion was not selective and secondary byproducts were also detected in the NMR analysis of the crude reaction mixture.

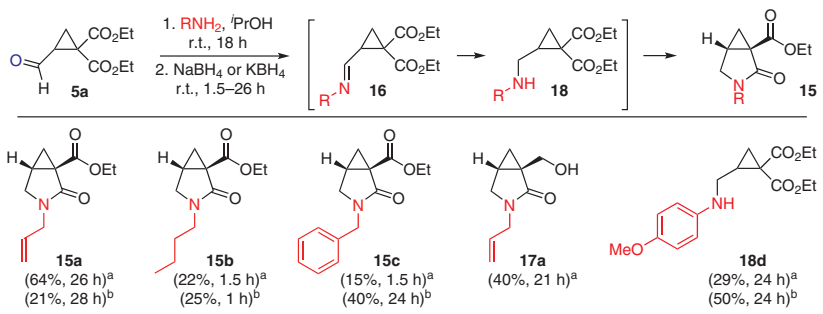
We were unable to improve the formation of alcohol **17a** from the one-pot imination/reductive cyclization and the protocol described in entry 1 of Table 2 was found to be the best approach (see the experimental section). On the other hand, the formation of cyclopropylidene-γ-lactam **15a** could be slightly improved by decreasing the amount of $NaBH_4$ and adding molecular sieves to act as a water scavenger (entry 2). In this case, **15a** was cleanly obtained in 64% yield without requiring any further purification. Other variations in the reaction conditions, such as increasing the amount of reducing agent (entry 3), decreasing the reaction time (entry 4), changing the solvent (entry 5) or adding lithium chloride as an additive (entry 6), all led to inferior results compared to entries 1 and 2.

The replacement of $NaBH_4$ with a milder hydride, such as KBH_4 (Table 2, entry 7), promoted the expected formation of **15a**, but in this case the conversion was not complete and the imine intermediate **16a** as well as the starting aldehyde **5a** were both detected in the ^1H NMR analysis of the crude reaction mixture. The complete consumption of intermediates and starting materials was achieved when KBH_4 was used in the presence of ethanol as the solvent (entry 8) instead of 2-propanol, but the isolated yield obtained for **15a** after purification by chromatography (24%) was not as significant as that observed with the use of $NaBH_4$. Nevertheless, the recovered mass of the crude product **15a** originating from the one-pot imination/reductive cyclization process with KBH_4 was higher than with $NaBH_4$, indicating that the potassium-derived reducing agent could be employed with other substrates (see below). On the other hand, the use of a more harmful reducing agent ($NaBH_3CN$, entry 9) furnished lactam **15a** together with unidentified byproducts, resulting in a low isolated yield of **15a**.

Cyclopropanes fused to pyrrolidine rings represent a privileged class of organic compounds in view of their recognized pharmacological properties, including antiviral, antibiotic and anxiolytic activity.[32] Nevertheless, accessing these bicyclic structures represents a synthetic challenge due to the intrinsic conformational constraints. To the best of our knowledge, there have been only two reports related to the one-pot imination/reductive cyclization from cyclopropanecarboxaldehydes to give cyclopropylidene-γ-lactams.[16e,33] However, both transformations are very particular cases and do not constitute a general method for the preparation of bicyclic lactams due to the absence of a broader study to determine the proper reaction conditions that would be applied to structurally diverse substrates. Considering these limitations together with our results, we extended the one-pot imination/reductive cyclization strategy to other representative amines, namely *n*-butylamine, benzylamine and *p*-anisidine (Scheme 6).

The data collected indicate that the one-pot imination/reductive cyclization process is substrate-dependent and none of the reducing agents under study were found to be suitable for general application in terms of furnishing the expected cyclopropylidene-γ-lactams **15** in acceptable yield for each amine studied. However, employing either $NaBH_4$ or KBH_4 led to satisfactory results depending on the aliphatic amine employed. The use of KBH_4 as the reducing agent resulted in slightly better yields for γ-lactams **15b** and **15c** when compared with $NaBH_4$. Surprisingly, the generation of the elusive hydroxylated cyclopropylidene-γ-lactam **17b** or **17c** that would arise from the overreduction of the carboxylate group, as observed previously for allylamine (see the formation of **17a** in Table 2), was not detected in the crude reaction mixture for the other amines under study. In the case of a less nucleophilic aromatic amine (*p*-anisidine), the formation of the expected bicyclic lactam **15** was not observed, possibly due to the low propensity of the cyclopropylamine intermediate **18d** to undergo cyclization, being isolated as the single product in varying yields depending on the hydride source (Scheme 6).

Besides the use of metal hydrides in the imination/reductive cyclization from aldehyde **5a** and amines, a one-pot process employing catalytic hydrogenation was also evaluated, and the main results are compiled in Table 3. While the imination/reductive cyclization mediated by metal borohydrides furnished cyclopropylidene-γ-lactams **15**, the use of H_2 in the presence of a Pd-supported catalyst promoted the lactamization with concomitant ring opening of



Scheme 6 One-pot synthesis of cyclopropylidene-γ-lactams **15** from aldehyde **5a**. [a] $NaBH_4$; [b] KBH_4.

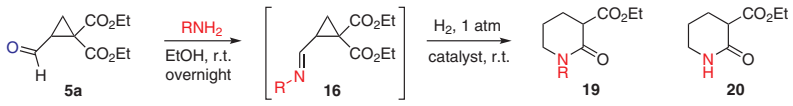
the cyclopropyl moiety to give δ-lactams (2-piperidinones) **19**. The piperidine ring is one of the most prevalent heterocycles among the US-FDA approved pharmaceuticals.[34] Therefore, the simple preparation of substituted δ-lactams would provide convenient access to advanced building blocks of synthetic relevance for the chemistry of piperidines.

For the hydrogenation involving aldehyde **5a** and *n*-butylamine, the corresponding δ-lactam **19b** was obtained using $Pd(OH)_2/C$ as the catalyst for 1 hour (Table 3, entry 1). Replacing $Pd(OH)_2/C$ with Pd/C did not lead to the formation of the expected δ-lactam **19b** under the same reaction conditions and only the intermediate imine **16b** was detected in the crude reaction mixture (entry 2). Treating imine **16b** with H_2–Pd/C for more prolonged periods led to a mixture of unidentified products (entry 3). On the other hand, when benzylamine was employed in the one-pot process, with Pd/C as the catalyst and a reaction time of 1 hour, the corresponding *N*-benzyl-δ-lactam **19c** was obtained in 15% yield together with the N-unsubstituted δ-lactam **20** in 60% yield, which would arise from the hydrogenolysis of the *N*-benzyl group (entry 4). The selective formation of debenzylated δ-lactam **20** was achieved through the use of $Pd(OH)_2/C$ for an extended time (entry 5). Interestingly, an attempt to convert cyclopropylidene-γ-lactam **15c** into δ-lactam **19c** or **20** under catalytic hydrogenation conditions [H_2, $Pd(OH)_2/C$, EtOH, 24 h] was not successful and only the starting material was recovered from the reaction medium after workup (results not shown). This control reaction indicates that γ-lactam **15** is not involved in the generation of δ-lactam **19** or **20** and the ring opening of the cyclopropyl moiety should occur before the cyclization to the six-membered ring. Finally, the use of the less reactive *p*-anisidine under the catalytic hydrogenation conditions tested did not lead to the expected δ-lactam **19d** (entries 6 and 7), while attempts to hydrogenate the intermediate imine **16d** gave mixtures of unidentified products (entry 8).

In summary, we developed a simple and mild procedure for the synthesis of diethyl 2-(hydroxymethyl)cyclopropane-1,1-dicarboxylate (**4a**) from γ,δ-epoxyester **1a** promoted by $Mg(ClO_4)_2$. Acylation of alcohol **4a** followed by scandium(III)-catalyzed ring expansion gave γ-lactones **9** in good yields but poor *syn*/*anti* diastereoselectivity. Alcohol **4a** was readily oxidized to the corresponding aldehyde **5a** in high yield through a facile protocol based on the combination of TCCA/catalytic TEMPO. This method was successfully extended to two tertiary cyclopropanecarboxamides **2b** and **4b**, although the oxidation of the secondary amide **4c** did not result in the expected carbonyl compound due to the uncontrolled reactivity of the free N–H amidic bond.

The synthetic versatility of cyclopropanecarboxaldehyde-1,1-diester **5a** was revealed in a series of transformations. The preparation of vinylcyclopropanes **12** through the Wittig reaction with phosphonium salts in a mild alkaline medium gave access to functionalized O-heterocycles, either through scandium-catalyzed ring expansion to give γ-lactone **13** or a formal [3+2] cycloaddition with tolualdehyde to furnish tetrahydrofuran **14**. Furthermore, aldehyde **5a** was employed in the one-pot synthesis of cyclopropylidene-γ-lactams **15** (as well as the overreduced lactam **17**) through an imination/reductive cyclization process in the presence of a primary amine and a metal borohydride. Although the yields vary depending on the amine and borohydride used, the conditions are simple and the resulting bicyclic γ-lactams **15** and **17** can be considered as advanced building blocks for the chemistry of iminosugars. Finally,

Table 3 Catalytic Hydrogenation in the One-Pot Protocol from Aldehyde **5a** and Amines[a]



Entry	R	Catalyst	Time (h)[b]	Product	Yield (%)[c]
1	^{n}Bu	$Pd(OH)_2/C$	1	**19b**	20
2	^{n}Bu	Pd/C	1	**16b**	–
3	^{n}Bu	Pd/C[d]	4	–[e]	–
4	Bn	Pd/C	1	**19c**/**20**	15/60
5	Bn	$Pd(OH)_2/C$	24	**20**	99
6	4-$MeOC_6H_4$	Pd/C	0.5	**16d**	–
7	4-$MeOC_6H_4$	Pd/C	24	–[e]	–
8	4-$MeOC_6H_4$	$Pd(OH)_2/C$[d]	12	–[e]	–

[a] One-pot reaction conditions: 1. aldehyde **5a**, amine (1.0 equiv), EtOH, r.t., 23 h; 2. catalyst (0.1 equiv), H_2, 1 atm, r.t.
[b] Time refers to the catalytic hydrogenation reaction.
[c] Isolated yield after purification by column chromatography, except for lactam **20** (entry 5), which was obtained in high purity without any further purification step.
[d] The hydrogenation reaction was carried out directly with the imine intermediate **16**.
[e] Cyclopropane ring opening and formation of unidentified products.

the one-pot reduction carried out under catalytic hydrogenation [H_2–Pd/C or $Pd(OH)_2$/C] led to δ-lactams **19** or **20** as a result of the cyclopropane ring opening before lactamization. The results described herein demonstrate the potential of alcohol **4a** and aldehyde **5a** as versatile intermediates for the diversity-oriented synthesis of O- and N-heterocycles of biological interest.

All chemicals were of reagent grade and used as received. Phosphonium salt **11d** (acetonyltriphenylphosphonium chloride) was purchased from Sigma-Aldrich. Phosphonium salts **11a–c** were prepared by reacting triphenylphosphine and the corresponding benzyl bromide in acetonitrile under microwave irradiation at 100 °C (80 W) for 30 min. Their physical and spectroscopic data were consistent with the expected structures and the related literature.[35] Infrared spectra were acquired with an FT-IR spectrometer (FT Alpha, Bruker) using KBr pellets. TLC analysis was performed on silica gel plates supported on aluminum with fluorescent indicator and visualized by irradiation with UV light. Phosphomolybdic acid in EtOH was used as TLC staining solution. Column chromatographic purifications were performed using silica gel (70–230 mesh) as the stationary phase and hexane/EtOAc as the eluent. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-200F (200 MHz and 50 MHz, respectively) or Varian AS-400 (400 MHz and 100 MHz, respectively) spectrometer. Chemical shifts were recorded in parts per million (ppm, δ), relative to $CDCl_3$ (δ = 7.26 ppm for ^{1}H NMR and δ = 77.16 ppm for ^{13}C NMR) or TMS (0.00 ppm) as the internal standard. Splitting patterns are designated as s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublet), ddd (doublet of doublet of doublet), dt (doublet of triplet), app dt (apparent douplet of triplet), t (triplet), q (quartet), m (multiplet). Coupling constants (*J*) are given in hertz (Hz). The ESI-QTOF mass spectrometer (micrOTOF Q-II, Bruker Daltonics) was operated in the positive ion mode at 4.5 kV and at a desolvation temperature of 180 °C. A standard electrospray ion (ESI) source was used to generate the ions. The instrument was calibrated in the range of *m*/*z* 50–3000 using a calibration standard (low concentration tuning mix solution) and data were processed with the aid of computer software. Microwave-assisted reactions were performed in 10 mL sealed tubes in a monomode microwave CEM Explorer reactor instrument with infrared temperature monitoring and a noninvasive pressure transducer.

Ethyl (±)-4,5-Epoxy-2-(ethoxycarbonyl)pentanoate[22] (1a)

To a stirred solution of commercially available diethyl 2-allylmalonate (0.88 mL, 4.5 mmol) in EtOAc (30 mL), acetone (17 mL) and phosphate buffer (K_2HPO_4/KH_2PO_4, 1.0 mol·L^{-1}, pH 8, 40 mL), at r.t., was added dropwise a solution of Oxone (5.53 g, 9.0 mmol) in H_2O (40 mL). The reaction was stirred overnight (16–18 h). The insoluble solid was filtered off under reduced pressure and washed with EtOAc. The filtrate was washed with 1.0 M $Na_2S_2O_3$ and brine, dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude oil. Purification by column chromatography (silica gel; hexane/EtOAc, 3:2) provided epoxide **1a** as a light yellow oil in 86% yield (0.84 g).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.21–4.09 (m, 4 H, OCH_2), 3.47 (dd, *J* = 8.4, 6.3 Hz, 1 H, CH), 3.00–2.91 (m, 1 H, CH), 2.71 (t, *J* = 4.7 Hz, 1 H, CH_2), 2.46 (dd, *J* = 4.7, 2.5 Hz, 1 H, CH_2), 2.20 (ddd, *J* = 14.2, 8.4, 4.7 Hz, 1 H, CH_2), 1.93 (dt, *J* = 14.2, 6.3 Hz, 1 H, CH_2), 1.25–1.17 (m, 6 H, CH_3).

Diethyl 2-(Hydroxymethyl)cyclopropane-1,1-dicarboxylate (4a)

To a stirred solution of ethyl (±)-4,5-epoxy-2-(ethoxycarbonyl)pentanoate (**1a**; 0.54 g, 2.5 mmol) in THF (6 mL), at r.t., was added $Mg(ClO_4)_2$ (0.56 g, 2.5 mmol). The resulting suspension was submitted to microwave irradiation at 60 °C (80 W) for 45 min. Next, H_2O (50 mL) was added to the reaction medium. The reaction mixture was extracted with EtOAc (6 × 20 mL). The organic extract was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude oil. Purification by column chromatography (silica gel; hexane/EtOAc, 3:2) resulted in **4a** as a light yellow oil in 65% yield (0.35 g). The reaction also takes place under conventional heating at 60 °C, but with a longer time of 2 h.

IR (KBr): 3523, 2984, 2878, 1728, 1371, 1205, 1132, 1028 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.32–4.14 (m, 4 H, OCH_2), 3.91 (dd, *J* = 12.4, 5.0 Hz, 1 H, CH_2OH), 3.31 (dd, *J* = 12.4, 9.0 Hz, 1 H, CH_2OH), 2.21–2.06 (m, 1 H, CH), 1.52 (dd, *J* = 9.0, 5.0 Hz, 1 H, CH_2), 1.38–1.23 (m, 7 H, CH_2 + CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.0 (C), 168.8 (C), 62.4 (CH_2), 62.0 (CH_2), 61.9 (CH_2), 34.0 (C), 29.9 (CH), 18.2 (CH_2), 14.14 (CH_3), 14.12 (CH_3).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{16}O_5Na$: 239.08899; found: 239.08902.

Esters 7 by O-Acylation of Diethyl 2-(Hydroxymethyl)cyclopropane-1,1-dicarboxylate (4a); General Procedure

To a stirred solution of diethyl 2-(hydroxymethyl)cyclopropane-1,1-dicarboxylate (**4a**; 216.2 mg, 1.0 mmol) and the corresponding carboxylic acid (1.2 mmol) in CH_2Cl_2 (2 mL), at 0 °C (in an ice bath), was added *N*,*N*′-diisopropylcarbodiimide (187.8 μL, 1.2 mmol) for **7a**,**c**,**d** or *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (230.0 mg, 1.2 mmol; previously diluted in 1 equiv of 4-(dimethylamino)pyridine and 1 mL of CH_2Cl_2) for **7b**. After 5 min, 4-(dimethylamino)pyridine (146.6 mg, 1.2 mmol) was added and the ice bath was removed so that the reaction mixture reached r.t. The reaction was stirred for 2–72 h, then the insoluble solid formed was filtered off under reduced pressure and washed with CH_2Cl_2. The filtrate was washed successively with 1.0 M HCl, satd $NaHCO_3$ and brine. The organic phase was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure, providing the crude product. Purification by column chromatography (silica gel; hexane/EtOAc, 3:2) gave ester **7**.

Diethyl 2-{[(*E*)-4-Ethoxy-4-oxobutenoyloxy]methyl}cyclopropane-1,1-dicarboxylate (7a)

Yield: 53% (181.4 mg); 2 h; yellow oil.

IR (KBr): 2984, 1726, 1646, 1467, 1297, 1026, 775 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.84 (d, *J* = 16.0 Hz, 1 H, =CH), 6.80 (d, *J* = 16.0 Hz, 1 H, =CH), 4.34 (dd, *J* = 12.0, 6.4 Hz, 1 H, OCH_2), 4.26–4.11 (m, 6 H, OCH_2), 4.07 (dd, *J* = 12.0, 8.4 Hz, 1 H, OCH_2), 2.33–2.25 (m, 1 H, CH), 1.54 (dd, *J* = 7.6, 5.2 Hz, 1 H, CH_2), 1.46 (dd, *J* = 9.0, 5.2 Hz, 1 H, CH_2), 1.30 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.27–1.23 (m, 6 H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 169.3 (C), 167.4 (C), 164.8 (C), 164.5 (C), 134.2 (CH), 132.9 (CH), 63.4 (CH_2), 61.8 (2 × CH_2), 61.4 (CH_2), 33.4 (C), 25.3 (CH), 18.6 (CH_2), 14.1 (CH_3), 14.03 (CH_3), 13.98 (CH_3).

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{23}O_8$: 343.1387; found: 343.1389.

Diethyl 2-{[(*E*)-But-2-enoyloxy]methyl}cyclopropane-1,1-dicarboxylate (7b)

Yield: 25% (71.1 mg); 72 h; light yellow oil.

IR (KBr): 3098, 2982, 1726, 1658, 1446, 1371, 1179, 1134, 971 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.03–6.85 (m, 1 H, =CH), 5.83–5.74 (m, 1 H, =CH), 4.27–4.07 (m, 5 H, OCH_2), 4.00 (dd, *J* = 12.1, 8.1 Hz, 1 H, OCH_2), 2.33–2.17 (m, 1 H, CH), 1.86–1.82 (m, 3 H, CH_3), 1.51 (dd, *J* = 7.4, 4.6 Hz, 1 H, CH_2), 1.41 (dd, *J* = 9.1, 4.6 Hz, 1 H, CH_2), 1.22 (t, *J* = 7.3 Hz, 6 H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 169.6 (C), 167.5 (C), 166.0 (C), 145.2 (CH), 122.3 (CH), 62.2 (CH_2), 61.7 (2 × CH_2), 33.4 (C), 25.7 (CH), 18.7 (CH_2), 18.0 (CH_3), 14.08 (CH_3), 14.06 (CH_3).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{20}O_6Na$: 307.1152; found: 307.1151.

Diethyl 2-[(But-3-enoyloxy)methyl]cyclopropane-1,1-dicarboxylate (7c)

Yield: 78% (221.8 mg); 19 h; colorless oil.

IR (KBr): 3084, 2984, 1732, 1644, 1467, 1322, 1207, 1134, 997 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 5.94–5.73 (m, 1 H, =CH), 5.13–5.03 (m, 2 H, $=CH_2$), 4.27–4.04 (m, 5 H, OCH_2), 3.95 (dd, *J* = 11.9, 7.9 Hz, 1 H, OCH_2), 3.02 (d, *J* = 6.6 Hz, 2 H, $COCH_2$), 2.28–2.12 (m, 1 H, CH), 1.50–1.35 (m, 2 H, CH_2), 1.21 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.20 (t, *J* = 7.3 Hz, 3 H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.1 (C), 169.5 (C), 167.4 (C), 130.1 (CH), 118.6 (CH_2), 62.8 (CH_2), 61.72 (CH_2), 61.71 (CH_2), 38.9 (CH_2), 33.4 (C), 25.6 (CH), 18.7 (CH_2), 14.10 (CH_3), 14.06 (CH_3).

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{21}O_6$: 285.1333; found: 285.1334.

Diethyl 2-[(3-Ethoxy-3-oxopropanoyloxy)methyl]cyclopropane-1,1-dicarboxylate (7d)

Yield: 50% (165.2 mg); 24 h; yellow oil.

IR (KBr): 3100, 2984, 1752, 1726, 1467, 1132, 1028, 863 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.27–4.11 (m, 7 H, OCH_2), 4.06 (dd, *J* = 12.0, 8.0 Hz, 1 H, OCH_2), 3.34 (s, 2 H, CH_2), 2.28–2.20 (m, 1 H, CH), 1.51 (dd, *J* = 7.4, 5.0 Hz, 1 H, CH_2), 1.43 (dd, *J* = 9.4, 5.0 Hz, 1 H, CH_2), 1.27–1.22 (m, 9 H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 169.3 (C), 167.3 (C), 166.2 (C), 63.4 (CH_2), 61.7 (CH_2), 61.5 (CH_2), 41.3 (CH_2), 33.4 (C), 25.2 (CH), 18.6 (CH_2), 13.98 (CH_3), 13.96 (2 × CH_3).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{22}O_8Na$: 353.1207; found: 353.1209.

3-(Ethoxycarbonyl)-5-{[(*E*)-4-ethoxy-4-oxobutenoyloxy]methyl}-γ-lactone (9a)

To a stirred solution of **7a** (342.3 mg, 1.0 mmol) in CH_2Cl_2 (3.5 mL), at r.t., was added $Sc(OTf)_3$ (98.4 mg, 0.2 mmol). After 72 h, the reaction mixture was filtered through a pad of silica gel. The filtrate was concentrated under reduced pressure to give a yellow oil.

Yield: 99% (311.1 mg); mixture of diastereoisomers (1:1).

IR (KBr): 2984, 1781, 1726, 1301, 1263, 1157, 1030, 977 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 6.80 (bs, 2 H, =CH), 4.95–4.83 (m, 0.5 H, CH), 4.78–4.64 (m, 0.5 H, CH), 4.45 (dd, *J* = 4.6, 3.2 Hz, 0.5 H, CH_2), 4.39 (dd, *J* = 4.6, 3.2 Hz, 0.5 H, CH_2), 4.32–4.14 (m, 5 H, CH_2 + OCH_2), 3.68–3.58 (m, 1 H, CH), 2.79–2.19 (m, 2 H, CH_2), 1.25 (t, *J* = 7.1 Hz, 6 H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.1 (C), 170.9 (C), 167.5 (C), 167.3 (C), 164.7 (C), 164.6 (C), 164.5 (C), 164.4 (C), 135.1 (CH), 134.9 (CH), 132.4 (CH), 132.2 (CH), 76.3 (CH), 75.9 (CH), 65.6 (CH_2), 65.4 (CH_2), 62.6 (CH_2), 62.5 (CH_2), 61.6 (CH_2), 61.5 (CH_2), 46.51 (CH), 46.48 (CH), 28.1 (CH_2), 27.8 (CH_2), 14.13 (2 × CH_3), 14.10 (2 × CH_3).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{18}O_8Na$: 337.0894; found: 337.0895.

5-{[(*E*)-But-2-enoyloxy]methyl}-3-(ethoxycarbonyl)-γ-lactone (9b)

To a stirred solution of **7b** (284.3 mg, 1.0 mmol) in CH_2Cl_2 (3.5 mL), at r.t., was added $Sc(OTf)_3$ (98.4 mg, 0.2 mmol). After 72 h, the reaction mixture was filtered through a pad of silica gel. The filtrate was concentrated under reduced pressure to give a colorless oil.

Yield: 48% (123.0 mg); mixture of diastereoisomers (1:1).

IR (KBr): 2923, 1779, 1724, 1656, 1446, 1261, 1157, 967 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.13–6.93 (m, 1 H, =CH), 5.92–5.81 (m, 1 H, =CH), 4.97–4.85 (m, 0.5 H, CH), 4.79–4.65 (m, 0.5 H, CH), 4.46–4.20 (m, 4 H, OCH_2), 3.70–3.60 (m, 1 H, CH), 2.84–2.24 (m, 2 H, CH_2), 1.92–1.87 (m, 3 H, CH_3), 1.32 (t, *J* = 7.0 Hz, 3 H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.4 (C), 171.1 (C), 167.7 (C), 167.4 (C), 166.0 (C), 165.9 (C), 146.6 (CH), 146.4 (CH), 121.9 (CH), 121.8 (CH), 76.7 (CH), 76.4 (CH), 64.8 (CH_2), 64.5 (CH_2), 62.6 (CH_2), 62.5 (CH_2), 46.7 (CH), 46.6 (CH), 28.3 (CH_2), 28.0 (CH_2), 18.24 (CH_3), 18.21 (CH_3), 14.2 (2 × CH_3).

Oxidation of Cyclopropane-1,1-diester 4a and Cyclopropanecarboxamides; General Procedure

To a stirred solution of cyclopropane-1,1-diester **4a** (0.86 g, 4.0 mmol) or cyclopropanecarboxamide **4b** or **2b** (4.0 mmol) in CH_2Cl_2 (8 mL), at 0 °C (in an ice bath), was added TCCA (0.97 g, 4.2 mmol) followed by TEMPO (12.5 mg, 0.08 mmol). The ice bath was removed so that the reaction mixture reached r.t. The reaction was monitored by TLC until the total consumption of the starting material (20 min to 24 h). Next, the mixture was filtered through Celite and the filtrate was washed with satd Na_2CO_3 (3 × 20 mL) and 1 M HCl. Then, the organic extract was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to give the expected product in high purity without any further purification step.

Diethyl 2-Formylcyclopropane-1,1-dicarboxylate[17] (5a)

Yield: 75% (0.64 g); 20 min; yellow oil.

IR (KBr): 3104, 2984, 2874, 1783, 1732, 1448, 1373, 1269, 1201, 1022, 865 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.31 (d, *J* = 4.4 Hz, 1 H, CHO), 4.29–4.15 (m, 4 H, OCH_2), 2.73 (ddd, *J* = 8.8, 7.0, 4.4 Hz, 1 H, CH), 2.06 (dd, *J* = 7.0, 5.2 Hz, 1 H, CH_2), 1.80 (dd, *J* = 8.8, 5.2 Hz, 1 H, CH_2), 1.27 (t, *J* = 7.2 Hz, 6 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.4 (CH), 168.0 (C), 166.0 (C), 62.5 (CH_2), 62.3 (CH_2), 34.9 (CH + C), 19.3 (CH_2), 14.1 (2 × CH_3).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{14}O_5Na$: 237.0733; found: 237.0732.

Ethyl 2-Formyl-1-(pyrrolidin-1-ylcarbonyl)cyclopropane-1-carboxylate (5b)

Yield: 76% (0.73 g); 30 min; brown oil.

IR (KBr): 2978, 2878, 1779, 1722, 1636, 1444, 1254, 1146 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.91 (d, *J* = 6.0 Hz, 1 H, CHO), 4.16 (q, *J* = 7.2 Hz, 2 H, OCH_2), 3.48–3.21 (m, 4 H, NCH_2), 2.61 (ddd, *J* = 6.4, 6.0, 4.0 Hz, 1 H, CH), 2.06 (dd, *J* = 6.4, 4.8 Hz, 1 H, CH_2), 1.95–1.80 (m, 5 H, CH_2), 1.20 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.5 (CH), 168.3 (C), 162.7 (C), 62.2 (CH_2), 46.4 (CH_2), 46.2 (CH_2), 38.1 (C), 35.6 (CH), 25.7 (CH_2), 23.9 (CH_2), 19.5 (CH_2), 13.9 (CH_3).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{17}NO_4Na$: 262.1050; found: 262.1051.

Methyl 2-Benzoyl-1-(pyrrolidin-1-ylcarbonyl)cyclopropane-1-carboxylate (10)

Purified by column chromatography (silica gel; hexane/EtOAc, 2:3).

Yield: 47% (0.57 g); 24 h; yellow oil.

IR (KBr): 3062, 2956, 2878, 1730, 1677, 1646, 1446, 1273, 1148, 702 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.01–7.96 (m, 2 H, CH_{Ar}), 7.59–7.39 (m, 3 H, CH_{Ar}), 3.76 (s, 3 H, OCH_3), 3.56 (dd, *J* = 8.6, 7.0 Hz, 1 H, CH), 3.44 (t, *J* = 6.8 Hz, 2 H, NCH_2), 3.35–3.11 (m, 2 H, NCH_2), 2.25 (dd, *J* = 7.0, 4.0 Hz, 1 H, CH_2), 1.82–1.60 (m, 5 H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.7 (C), 170.4 (C), 163.1 (C), 137.3 (C), 133.4 (CH), 128.7 (2 × CH), 128.4 (2 × CH), 53.3 (CH_3), 46.8 (CH_2), 46.2 (CH_2), 40.7 (C), 31.6 (CH), 25.9 (CH_2), 24.0 (CH_2), 22.0 (CH_2).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{19}NO_4Na$: 324.1206; found: 324.1205.

Alkenes 12; General Procedure

To a stirred solution of cyclopropanecarboxaldehyde **5a** (214.2 mg, 1.0 mmol) in THF (4 mL), at r.t., were added the corresponding phosphonium salt **11** (1.2 mmol) and K_2CO_3 (207.3 mg, 1.5 mmol). After stirring the suspension for 12–48 h, the solvent was evaporated and the residue was diluted with EtOAc (15 mL). The resulting organic solution was washed with H_2O and brine. The organic phase was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to provide the crude product. Purification by column chromatography (silica gel; hexane/EtOAc, 3:2) gave alkene **12**.

Diethyl 2-Styrylcyclopropane-1,1-dicarboxylate[36] (12a)

Mixture of isomers (80:20 *trans*/*cis*).

Yield: 77% (222 mg); 12 h; yellow oil.

IR (KBr): 3082, 2982, 2872, 1724, 1448, 1371, 1201, 1026, 694 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (*trans* isomer) = 7.33–7.12 (m, 5 H, CH_{Ar}), 6.57 (d, *J* = 16.0 Hz, 1 H, =CH), 5.74 (dd, *J* = 16.0, 8.8 Hz, 1 H, =CH), 4.22–4.06 (m, 4 H, OCH_2), 2.70–2.64 (m, 1 H, CH), 1.75 (dd, *J* = 7.6, 4.8 Hz, 1 H, CH_2), 1.59 (dd, *J* = 9.2, 4.8 Hz, 1 H, CH_2), 1.22 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.15 (t, *J* = 7.4 Hz, 3 H, CH_3).

^{1}H NMR (400 MHz, $CDCl_3$): δ (*cis* isomer) = 7.33–7.12 (m, 5 H, CH_{Ar}), 6.52 (d, *J* = 11.6 Hz, 1 H, =CH), 5.17 (dd, *J* = 11.6, 9.6 Hz, 1 H, =CH), 4.22–4.06 (m, 4 H, OCH_2), 2.91–2.85 (m, 1 H, CH), 1.66 (dd, *J* = 7.6, 4.8 Hz, 1 H, CH_2), 1.61–1.55 (m, 1 H, CH_2), 1.23–1.13 (m, 6 H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 169.7 (C), 167.7 (C), 136.9 (C), 136.8 (C), 133.7 (CH), 133.6 (CH), 129.0 (2 × CH), 128.7 (2 × CH), 128.4 (2 × CH), 127.7 (CH), 127.4 (CH), 126.9 (CH), 126.2 (2 × CH), 125.0 (CH), 61.8 (CH_2), 61.7 (CH_2), 61.6 (2 × CH_2), 36.8 (C), 36.5 (C), 31.3 (CH), 27.9 (CH), 22.6 (CH_2), 21.2 (CH_2), 14.4 (CH_3), 14.34 (CH_3), 14.27 (CH_3), 14.2 (CH_3).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{20}O_4Na$: 311.1254; found: 311.1252.

Diethyl 2-(2-Nitrostyryl)cyclopropane-1,1-dicarboxylate (12b)

Mixture of isomers (60:40 *trans*/*cis*).

Yield: 77% (256 mg); 24 h; yellow oil.

IR (KBr): 3070, 2984, 1726, 1526, 1444, 1346, 1203, 1132, 1024, 787 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (*trans* isomer) = 7.92 (dd, *J* = 8.2, 1.0 Hz, 1 H, CH_{Ar}), 7.64–7.36 (m, 3 H, CH_{Ar}), 7.15 (d, *J* = 15.6 Hz, 1 H, =CH), 5.84 (dd, *J* = 15.6, 8.8 Hz, 1 H, =CH), 4.32–4.14 (m, 4 H, OCH_2), 2.65–2.58 (m, 1 H, CH), 1.82 (dd, *J* = 7.2, 5.2 Hz, 1 H, CH_2), 1.72 (dd, *J* = 9.0, 5.2 Hz, 1 H, CH_2), 1.30 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.26 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{1}H NMR (400 MHz, $CDCl_3$): δ (*cis* isomer) = 8.08 (dd, *J* = 8.2, 1.0 Hz, 1 H, CH_{Ar}), 7.64–7.36 (m, 3 H, CH_{Ar}), 6.92 (d, *J* = 11.2 Hz, 1 H, =CH), 5.39 (dd, *J* = 11.2, 10.0 Hz, 1 H, =CH), 4.32–4.14 (m, 4 H, OCH_2), 2.82–2.76 (m, 1 H, CH), 1.76 (dd, *J* = 7.4, 4.8 Hz, 1 H, CH_2), 1.60 (dd, *J* = 9.0, 4.8 Hz, 1 H, CH_2), 1.31 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.26 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.3 (C), 169.2 (C), 167.6 (C), 167.5 (C), 148.1 (C), 147.6 (C), 133.1 (2 × CH), 132.4 (C), 132.2 (C), 132.1 (CH), 131.0 (CH), 129.6 (CH), 129.1 (CH), 128.6 (CH), 128.49 (CH), 128.47 (CH), 128.2 (CH), 124.9 (CH), 124.7 (CH), 61.9 (CH_2), 61.83 (2 × CH_2), 61.77 (CH_2), 36.7 (C), 36.5 (C), 31.0 (CH), 27.4 (CH), 22.3 (CH_2), 21.3 (CH_2), 14.33 (CH_3), 14.29 (CH_3), 14.2 (2 × CH_3).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{19}NO_6Na$: 356.1105; found: 356.1107.

Diethyl 2-(2-Bromostyryl)cyclopropane-1,1-dicarboxylate (12c)

Mixture of isomers (67:33 *trans*/*cis*).

Yield: 51% (187 mg); 24 h; yellow oil.

IR (KBr): 3056, 2982, 1726, 1469, 1371, 1201, 1132, 1024, 753 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (*trans* isomer) = 7.44 (dd, *J* = 8.0, 1.2 Hz, 1 H, CH_{Ar}), 7.30 (dd, *J* = 8.0, 1.6 Hz, 1 H, CH_{Ar}), 7.16–7.12 (m, 1 H, CH_{Ar}), 6.99 (dt, *J* = 8.0, 1.6 Hz, 1 H, CH_{Ar}), 6.91 (d, *J* = 15.6 Hz, 1 H, =CH), 5.70 (dd, *J* = 15.6, 8.8 Hz, 1 H, =CH), 4.22–4.07 (m, 4 H, OCH_2), 2.75–2.66 (m, 1 H, CH), 1.75 (dd, *J* = 7.4, 4.8 Hz, 1 H, CH_2), 1.61 (dd, *J* = 9.0, 4.8 Hz, 1 H, CH_2), 1.22 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.17 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{1}H NMR (400 MHz, $CDCl_3$): δ (*cis* isomer) = 7.51 (dd, *J* = 7.8, 1.2 Hz, 1 H, CH_{Ar}), 7.41 (dd, *J* = 7.8, 1.8 Hz, 1 H, CH_{Ar}), 7.22 (dt, *J* = 7.8, 1.2 Hz, 1 H, CH_{Ar}), 7.05 (dt, *J* = 7.8, 1.8 Hz, 1 H, CH_{Ar}), 6.58 (d, *J* = 11.6 Hz, 1 H, =CH), 5.25 (dd, *J* = 11.6, 9.8 Hz, 1 H, =CH), 4.22–4.07 (m, 4 H, OCH_2), 2.75–2.64 (m, 1 H, CH), 1.67 (dd, *J* = 7.4, 4.8 Hz, 1 H, CH_2), 1.53 (dd, *J* = 8.8, 4.8 Hz, 1 H, CH_2), 1.21 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.18 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.5 (C), 169.3 (C), 167.7 (C), 167.6 (C), 136.65 (C), 136.62 (C), 133.0 (CH), 132.8 (CH), 132.7 (CH), 132.3 (CH), 130.8 (CH), 128.95 (CH), 128.89 (CH), 128.3 (CH), 128.1 (CH), 127.5 (CH), 127.1 (CH), 126.8 (CH), 124.1 (C), 123.3 (C), 61.8 (CH_2), 61.70 (CH_2), 61.69 (CH_2), 61.67 (CH_2), 36.6 (C), 36.4 (C), 31.1 (CH), 27.6 (CH), 22.3 (CH_2), 21.2 (CH_2), 14.33 (CH_3), 14.30 (CH_3), 14.20 (CH_3), 14.17 (CH_3).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{19}BrO_4Na$: 389.0359; found: 389.0360.

Diethyl 2-[(*E*)-3-Oxobut-1-en-1-yl]cyclopropane-1,1-dicarboxylate (12d)

Yield: 83% (211 mg); 48 h; yellow oil.

IR (KBr): 2984, 2876, 1728, 1677, 1626, 1371, 1252, 1205, 1132, 1022, 971 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.37–6.29 (m, 2 H, =CH), 4.30–4.15 (m, 4 H, OCH_2), 2.72–2.59 (m, 1 H, CH), 2.21 (s, 3 H, $COCH_3$), 1.81 (dd, *J* = 7.4, 5.2 Hz, 1 H, CH_2), 1.74 (dd, *J* = 8.8, 5.2 Hz, 1 H, CH_2), 1.29 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.28 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 197.2 (C), 168.9 (C), 167.1 (C), 142.7 (CH), 133.4 (CH), 62.1 (CH_2), 62.0 (CH_2), 37.1 (C), 29.8 (CH), 27.2 (CH_3), 21.6 (CH_2), 14.3 (CH_3), 14.2 (CH_3).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{18}O_5Na$: 277.1046; found: 277.1047.

3-(Ethoxycarbonyl)-5-[(*E*)-styryl]-γ-lactone[37] (13)

To a stirred solution of **12a** (57.6 mg, 0.20 mmol) in CH_2Cl_2 (1 mL), at r.t., was added $Sc(OTf)_3$ (19.7 mg, 0.04 mmol). After 48 h, the reaction mixture was filtered through a pad of Celite and silica gel. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel; hexane/EtOAc, 3:2) to give lactone **13** as a yellow oil.

Yield: 43% (22.4 mg); mixture of diastereoisomers (55:45).

IR (KBr): 3082, 2990, 1771, 1740, 1452, 1373, 1171, 967, 761, 694 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.26 (m, 5 H, CH_{Ar}), 6.72 (d, *J* = 16.0 Hz, 0.55 H, =CH), 6.71 (d, *J* = 16.0 Hz, 0.45 H, =CH), 6.25 (dd, *J* = 16.0, 7.2 Hz, 0.55 H, =CH), 6.17 (dd, *J* = 16.0, 7.2 Hz, 0.45 H, =CH), 5.34–5.29 (m, 0.45 H, OCH), 5.09–5.03 (m, 0.55 H, OCH), 4.28 (q, *J* = 7.2 Hz, 2 H, OCH_2), 3.71–3.65 (m, 1 H, CH), 2.89–2.83 (m, 0.45 H, CH_2), 2.74–2.67 (m, 0.55 H, CH_2), 2.62–2.54 (m, 0.55 H, CH_2), 2.38–2.30 (m, 0.45 H, CH_2), 1.33 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.61 (C), 171.56 (C), 167.8 (C), 167.7 (C), 135.6 (C), 134.5 (CH), 133.7 (CH), 128.9 (2 × CH), 128.8 (2 × CH), 128.7 (2 × CH), 127.0 (2 × CH), 126.9 (2 × CH), 125.7 (CH), 125.6 (CH), 80.1 (CH), 79.8 (CH), 62.5 (CH_2), 62.4 (CH_2), 47.4 (CH), 46.8 (CH), 33.1 (CH_2), 33.0 (CH_2), 14.2 (2 × CH_3).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{16}O_4Na$: 283.0941; found: 283.0938.

Diethyl 5-Styryl-2-(4-tolyl)tetrahydrofuran-3,3-dicarboxylate (14)

To a stirred solution of **12a** (57.6 mg, 0.20 mmol) in CH_2Cl_2 (2 mL), at r.t., were added tolualdehyde (70.7 μL, 0.6 mmol) and $Sc(OTf)_3$ (19.7 mg, 0.04 mmol). After 2 h, the reaction mixture was filtered through a pad of silica gel. The filtrate was concentrated under reduced pressure and diluted with EtOH (2 mL). Next, a solution of sodium bisulfite (62 mg) in H_2O (1 mL) was added to the reaction medium and the resulting mixture was stirred for 4 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (5 × 10 mL). The organic phase was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to furnish **14** as a yellow oil.

Yield: 50% (40.8 mg); mixture of diastereoisomers (85:15 major *trans*/minor *trans*).

IR (KBr): 3027, 2982, 1730, 1448, 1369, 1263, 1181, 1048, 694 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ (major *trans* isomer) = 7.39–7.15 (m, 7 H, CH_{Ar}), 7.02 (d, *J* = 7.6 Hz, 2 H, CH_{Ar}), 6.64 (d, *J* = 15.8 Hz, 1 H, =CH), 6.36 (dd, *J* = 15.8, 7.2 Hz, 1 H, =CH), 5.62 (s, 1 H, OCH), 4.49 (app dt, *J* = 10.6, 6.5 Hz, 1 H, OCH), 4.30–4.06 (m, 2 H, OCH_2), 3.77–3.31 (m, 2 H, OCH_2), 2.78 (dd, *J* = 13.2, 10.6 Hz, 1 H, CH_2), 2.46 (dd, *J* = 13.2, 6.0 Hz, 1 H, CH_2), 2.23 (s, 3 H, CH_3), 1.20 (t, *J* = 7.2 Hz, 3 H, CH_3), 0.74 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{1}H NMR (200 MHz, $CDCl_3$): δ (minor *trans* isomer) = 7.39–7.15 (m, 7 H, CH_{Ar}), 7.02 (d, *J* = 7.6 Hz, 2 H, CH_{Ar}), 6.60 (d, *J* = 16.2 Hz, 1 H, =CH), 6.18 (dd, *J* = 16.2, 6.5 Hz, 1 H, =CH), 5.76 (s, 1 H, OCH), 5.16 (q, *J* = 6.5 Hz, 1 H, OCH), 4.30–4.06 (m, 2 H, OCH_2), 3.77–3.31 (m, 2 H, OCH_2), 3.00 (dd, *J* = 13.2, 6.5 Hz, 1 H, CH_2), 2.23 (s, 3 H, CH_3), 2.22–2.14 (m, 1 H, CH_2), 1.16 (t, *J* = 7.2 Hz, 3 H, CH_3), 0.74 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ (major *trans* isomer) = 170.9 (C), 168.8 (C), 137.8 (C), 136.6 (C), 135.0 (C), 132.8 (CH), 128.7 (2 × CH), 128.58 (CH), 128.55 (2 × CH), 128.0 (CH), 127.2 (2 × CH), 126.8 (2 × CH), 84.2 (CH), 79.0 (CH), 61.9 (CH_2), 61.5 (CH_2), 40.9 (CH_2), 21.2 (CH_3), 14.1 (CH_3), 13.5 (CH_3).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{28}O_5Na$: 431.1829; found: 431.1832.

Cyclopropylidene-γ-lactams 15; General Procedure

To a stirred solution of cyclopropanecarboxaldehyde **5a** (214.2 mg, 1.0 mmol) in 2-propanol (2 mL), at r.t., was added the corresponding amine (1.0 mmol). The reaction mixture was stirred overnight (16–18 h). Next, the corresponding reducing agent ($NaBH_4$ or KBH_4, 0.5–1.0 mmol) was added (for allylamine and benzylamine, 190 mg of 3 Å molecular sieves were also added to the reaction mixture). After a certain time (1–26 h), the solvent was removed under reduced pressure and the residue was dissolved in EtOAc (10 mL). The resulting organic solution was washed with H_2O and 6 M NH_4Cl. The organic extract was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to provide a crude residue, which was purified by column chromatography (silica gel; hexane/EtOAc, 3:2) to give the expected γ-lactam.

Ethyl 3-Allyl-2-oxo-3-azabicyclo[3.1.0]hexane-1-carboxylate[38] (15a)

$NaBH_4$ (18.9 mg, 0.5 mmol) was used for 26 h.

Yield: 64% (134 mg); yellow oil (obtained in high purity without any further purification step).

IR (KBr): 3082, 2982, 1722, 1695, 1448, 1277, 1179, 1006, 934, 761 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.71–5.51 (m, 1 H, =CH), 5.14–5.03 (m, 2 H, $=CH_2$), 4.17 (q, *J* = 7.0 Hz, 2 H, OCH_2), 3.87–3.63 (m, 2 H, CH_2), 3.46 (dd, *J* = 10.6, 6.0 Hz, 1 H, NCH_2), 3.14 (d, *J* = 10.6 Hz, 1 H, NCH_2), 2.27 (dt, *J* = 8.0, 6.0 Hz, 1 H, CH), 1.86 (dd, *J* = 8.0, 5.0 Hz, 1 H, CH_2), 1.23 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.02 (t, *J* = 5.0 Hz, 1 H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2 (C), 168.8 (C), 132.4 (CH), 118.4 (CH_2), 61.5 (CH_2), 46.8 (CH_2), 45.2 (CH_2), 31.9 (C), 22.9 (CH), 21.0 (CH_2), 14.3 (CH_3).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{15}NO_3Na$: 232.0944; found: 232.0944.

Ethyl 3-Butyl-2-oxo-3-azabicyclo[3.1.0]hexane-1-carboxylate (15b)

KBH_4 (54.0 mg, 1.0 mmol) was used for 1 h.

Yield: 25% (56.3 mg); yellow oil.

IR (KBr): 2960, 2874, 1722, 1693, 1452, 1379, 1279, 1181, 1057 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.16 (q, *J* = 7.2 Hz, 2 H, OCH_2), 3.49 (dd, *J* = 10.4, 6.0 Hz, 1 H, NCH_2), 3.22–3.05 (m, 3 H, NCH_2), 2.27 (dt, *J* = 8.0, 6.0 Hz, 1 H, CH), 1.84 (dd, *J* = 8.0, 4.6 Hz, 1 H, CH_2), 1.41–1.34 (m, 2 H, CH_2), 1.26–1.17 (m, 2 H, CH_2), 1.23 (t, *J* = 7.2 Hz, 3 H, CH_3), 0.98 (t, *J* = 4.6 Hz, 1 H, CH_2), 0.84 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.3 (C), 168.9 (C), 61.5 (CH_2), 47.1 (CH_2), 42.1 (CH_2), 31.9 (C), 29.4 (CH_2), 22.8 (CH), 20.9 (CH_2), 20.0 (CH_2), 14.2 (CH_3), 13.8 (CH_3).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{19}NO_3Na$: 248.1257; found: 248.1260.

Ethyl 3-Benzyl-2-oxo-3-azabicyclo[3.1.0]hexane-1-carboxylate[39] (15c)

KBH_4 (53.9 mg, 1.0 mmol) was used for 24 h.

Yield: 40% (104 mg); yellow oil.

IR (KBr): 3064, 2982, 1720, 1693, 1448, 1379, 1277, 1185, 702 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.18 (m, 3 H, CH_{Ar}), 7.13–7.11 (m, 2 H, CH_{Ar}), 4.43 (d, *J* = 14.4 Hz, 1 H, CH_2Ph), 4.20–4.15 (m, 3 H, CH_2Ph + OCH_2), 3.36 (dd, *J* = 10.4, 5.6 Hz, 1 H, NCH_2), 3.02 (d, *J* = 10.4 Hz, 1 H, NCH_2), 2.23 (dt, *J* = 8.0, 5.6 Hz, 1 H, CH), 1.83 (dd, *J* = 8.0, 4.6 Hz, 1 H, CH_2), 1.24 (t, *J* = 7.0 Hz, 3 H, CH_3), 0.98 (t, *J* = 4.6 Hz, 1 H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.4 (C), 168.8 (C), 136.4 (C), 128.8 (2 × CH), 128.3 (2 × CH), 127.8 (CH), 61.6 (CH_2), 46.6 (CH_2), 46.5 (CH_2), 31.7 (C), 22.8 (CH), 20.8 (CH_2), 14.3 (CH_3).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{17}NO_3Na$: 282.1101; found: 282.1103.

3-Allyl-1-(hydroxymethyl)-3-azabicyclo[3.1.0]hexan-2-one (17a)

To a stirred solution of cyclopropanecarboxaldehyde **5a** (214.2 mg, 1.0 mmol) in 2-propanol (2 mL), at r.t., was added allylamine (75.0 µL, 1.0 mmol). After 20 h, $NaBH_4$ (37.8 mg, 1.0 mmol) was added and the stirring was continued for another 21 h. The solvent was removed under reduced pressure and the residue was dissolved in EtOAc (10 mL). The resulting organic solution was washed with H_2O (10 mL) and 6 M NH_4Cl (10 mL). The combined aqueous phases were basified with a few drops of 6 M NaOH and extracted with EtOAc (5 × 10 mL) and CH_2Cl_2 (10 mL). The combined organic extracts were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to give **17a** as a yellow oil in 40% yield (66.8 mg).

IR (KBr): 3392, 2923, 2872, 1664, 1463, 1254, 1026, 930 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.64–5.54 (m, 1 H, =CH), 5.12–5.05 (m, 2 H, $=CH_2$), 3.85 (d, *J* = 12.0 Hz, 1 H, CH_2O), 3.82–3.76 (m, 1 H, CH_2), 3.70–3.64 (m, 2 H, CH_2 + CH_2O), 3.40 (dd, *J* = 10.4, 6.0 Hz, 1 H, NCH_2), 3.16 (d, *J* = 10.4 Hz, 1 H, NCH_2), 1.85 (ddd, *J* = 8.0, 6.0, 4.4 Hz, 1 H, CH), 1.07 (dd, *J* = 8.0, 4.4 Hz, 1 H, CH_2), 0.68 (t, *J* = 4.4 Hz, 1 H, CH_2).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 175.3 (C), 132.6 (CH), 118.1 (CH_2), 62.3 (CH_2), 48.2 (CH_2), 44.9 (CH_2), 32.5 (C), 17.2 (CH_2), 16.9 (CH).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_9H_{13}NO_2Na$: 190.0838; found: 190.0839.

Diethyl 2-{[(4-Methoxyphenyl)imino]methyl}cyclopropane-1,1-dicarboxylate (16d)

To a stirred solution of cyclopropanecarboxaldehyde **5a** (214.2 mg, 1.0 mmol) in CH_2Cl_2 (2 mL), at r.t., was added 4-methoxyaniline (123.2 mg, 1.0 mmol). After 19 h, the solvent was evaporated to give the crude product as a brown oil.

Yield: 63% (236 mg, contains ~15% of 4-methoxyaniline).

IR (KBr): 2982, 2837, 1728, 1511, 1246, 1032, 832 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 7.2 Hz, 1 H, CHN), 7.02 (d, *J* = 9.0 Hz, 2 H, CH_{Ar}), 6.86 (d, *J* = 9.0 Hz, 2 H, CH_{Ar}), 4.28–4.14 (m, 4 H, OCH_2), 3.81 (s, 3 H, OCH_3), 2.88 (ddd, *J* = 9.2, 7.2, 5.0 Hz, 1 H, CH), 2.05 (dd, *J* = 7.2, 5.0 Hz, 1 H, CH_2), 1.83 (dd, *J* = 9.2, 5.0 Hz, 1 H, CH_2), 1.29 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.25 (t, *J* = 7.2 Hz, 3 H, CH_3).

Diethyl 2-{[(4-Methoxyphenyl)amino]methyl}cyclopropane-1,1-dicarboxylate (18d)

To a stirred solution of imine **16d** (319.3 mg, 1.0 mmol) in EtOH (2 mL), at 0 °C (in an ice bath), was added KBH_4 (53.9 mg, 1.0 mmol). After 5 min, the ice bath was removed so that the reaction mixture reached r.t. After 23 h, the solvent was evaporated under reduced pressure and the residue was diluted with EtOAc (10 mL). The resulting organic solution was washed with H_2O and 6 M NH_4Cl. Next, the organic extract was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude oil. The product was purified by column chromatography (silica gel; hexane/EtOAc, 7:3) and isolated as a brown oil in 50% yield (160 mg).

IR (KBr): 3390, 2982, 2833, 1724, 1514, 1283, 1036, 822 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.78 (d, *J* = 9.0 Hz, 2 H, CH_{Ar}), 6.60 (d, *J* = 9.0 Hz, 2 H, CH_{Ar}), 4.28–4.13 (m, 4 H, OCH_2), 3.75 (s, 3 H, OCH_3), 3.36 (dd, *J* = 13.2, 5.6 Hz, 1 H, NCH_2), 2.88 (dd, *J* = 13.2, 8.0 Hz, 1 H, NCH_2), 2.26–2.19 (m, 1 H, CH), 1.51–1.45 (m, 2 H, CH_2), 1.28 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.26 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.1 (C), 168.1 (C), 152.6 (C), 142.2 (C), 115.1 (2 × CH), 114.6 (2 × CH), 61.85 (CH_2), 61.79 (CH_2), 55.9 (CH_3), 44.9 (CH_2), 34.0 (C), 27.5 (CH), 19.3 (CH_2), 14.3 (CH_3), 14.2 (CH_3).

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{24}NO_5$: 322.1649; found: 322.1650.

Ethyl 1-Butyl-2-oxopiperidine-3-carboxylate (19b)

To a stirred solution of cyclopropanecarboxaldehyde **5a** (214.2 mg, 1.0 mmol) in EtOH (2 mL), at r.t., was added *n*-butylamine (98.8 µL, 1.0 mmol). After 23 h, palladium(II) hydroxide on carbon 20 wt % (70.2 mg, 0.1 mmol) was added to the reaction. Next, a balloon containing hydrogen gas was connected to the reaction mixture and the stirring was continued at r.t. for 1 h. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The product was purified by column chromatography (silica gel; hexane/EtOAc, 3:2) to provide δ-lactam **19b** as a yellow oil in 20% yield (45.5 mg).

IR (KBr): 2960, 2872, 1736, 1646, 1493, 1371, 1179, 1032, 861 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.24–4.14 (m, 2 H, OCH_2), 3.47–3.23 (m, 5 H, CH + NCH_2), 2.14–1.87 (m, 3 H, CH_2), 1.80–1.71 (m, 1 H, CH_2), 1.56–1.49 (m, 2 H, CH_2), 1.34–1.24 (m, 5 H, CH_2 + CH_3), 0.91 (t, *J* = 7.4 Hz, 3 H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.4 (C), 165.7 (C), 61.4 (CH_2), 49.3 (CH), 47.7 (CH_2), 47.4 (CH_2), 29.2 (CH_2), 25.3 (CH_2), 21.3 (CH_2), 20.2 (CH_2), 14.2 (CH_3), 14.0 (CH_3).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{21}NO_3Na$: 250.1414; found: 250.1412.

Ethyl 1-Benzyl-2-oxopiperidine-3-carboxylate[40] (19c)

To a stirred solution of cyclopropanecarboxaldehyde **5a** (214.2 mg, 1.0 mmol) in EtOH (2 mL), at r.t., was added benzylamine (109.2 µL, 1.0 mmol). After 23 h, palladium on carbon 10 wt % (106 mg, 0.1 mmol) was added. Next, a balloon containing hydrogen gas was connected to the reaction mixture and the stirring was continued at r.t. for 1 h. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The product was purified by column chromatography (silica gel; hexane/EtOAc, 3:2) to provide δ-lactam **19c** as a yellow oil in 15% yield (39.2 mg).

IR (KBr): 3062, 2939, 1734, 1646, 1493, 1356, 1163, 1030, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.25 (m, 5 H, CH_{Ar}), 4.74 (d, *J* = 14.4 Hz, 1 H, CH_2Ph), 4.51 (d, *J* = 14.4 Hz, 1 H, CH_2Ph), 4.28–4.20 (m, 2 H, OCH_2), 3.50 (t, *J* = 7.0 Hz, 1 H, CH), 3.31–3.18 (m, 2 H, NCH_2), 2.19–2.03 (m, 2 H, CH_2), 1.96–1.87 (m, 1 H, CH_2), 1.80–1.69 (m, 1 H, CH_2), 1.32 (t, *J* = 7.0 Hz, 3 H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.3 (C), 166.1 (C), 137.0 (C), 128.7 (2 × CH), 128.1 (2 × CH), 127.5 (CH), 61.5 (CH_2), 50.4 (CH_2), 49.4 (CH), 47.1 (CH_2), 25.3 (CH_2), 21.0 (CH_2), 14.2 (CH_3).

HRMS (ESI+): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{19}NO_3Na$: 284.1257; found: 284.1259.

Ethyl 2-Oxopiperidine-3-carboxylate (20)

[CAS Reg. No. 3731-16-6]

To a stirred solution of cyclopropanecarboxaldehyde **5a** (128.5 mg, 0.60 mmol) in EtOH (2 mL), at r.t., was added benzylamine (65.5 µL, 0.60 mmol). After 23 h, palladium(II) hydroxide on carbon 20 wt % (70.2 mg, 0.1 mmol) was added to the reaction. Next, a balloon containing hydrogen gas was connected to the reaction mixture and the stirring was continued at r.t. for 24 h. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to give **20** as a yellow oil in 99% yield (101 mg).

IR (KBr): 3225, 2980, 2874, 1734, 1671, 1493, 1371, 1265, 1173, 1032 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.72 (bs, 1 H, NH), 4.22–4.15 (m, 2 H, OCH_2), 3.43–3.24 (m, 3 H, CH + NCH_2), 2.14–2.01 (m, 2 H, CH_2), 1.95–1.83 (m, 1 H, CH_2), 1.76–1.67 (m, 1 H, CH_2), 1.26 (t, *J* = 7.0 Hz, 3 H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.9 (C), 168.2 (C), 61.5 (CH_2), 48.7 (CH), 42.3 (CH_2), 24.9 (CH_2), 20.4 (CH_2), 14.2 (CH_3).

HRMS (ESI+): *m*/*z* $[M + Na]^+$ calcd for $C_8H_{13}NO_3Na$: 194.0788; found:194.0785.

Conflict of Interest

The authors declare no conflict of interest.

Funding Information

The authors are grateful to the Brazilian governmental agencies CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior), CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico) and FAPESC (Fundação de Amparo à Pesquisa do Estado de Santa Catarina) for fellowships. Support from INCT-Catálise/FAPESC/CNPq/CAPES (Instituto Nacional de Ciência e Tecnologia Catálise em Sistemas Moleculares e Nanoestruturados) is also gratefully acknowledged.

Acknowledgment

The authors would like to thank the Central de Análises (Departamento de Química, Universidade Federal de Santa Catarina) for the spectroscopic analysis. Special thanks are due to CEBIME (Laboratório Central de Biologia Molecular e Estrutural, UFSC) for providing the mass spectra.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1389-1203.

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