Tetrahedron: *Asymmetry* 26 (2015) 230–246

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

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

Functionalized α-oximinoketones as building blocks for the construction of imidazoline-based potential chiral auxiliaries

Rsuini U. Gutiérrez [a,†], Araceli Rebollar [a,†], Rafael Bautista [a,b], Vanessa Pelayo [a], José Luis Várgas [a], Mabel M. Montenegro [a], Carlos Espinoza-Hicks [a], Francisco Ayala [a], Pablo M. Bernal [b], Cuauhtemoc Carrasco [b], L. Gerardo Zepeda [a], Francisco Delgado [a], Joaquín Tamariz [a,*]

[a] *Departamento de Química Orgánica, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Prol. Carpio y Plan de Ayala, 11340 México, D.F., Mexico*
[b] *Departamento de Investigación y Desarrollo, Signa, S.A. de C.V., Av. Industria Automotriz No. 301, Zona Industrial Toluca, 50200 Toluca, Edo. de México, Mexico*

ARTICLE INFO

Article history:
Received 27 December 2014
Accepted 6 January 2015

ABSTRACT

Functionalized α-oximinoketones with β-alkoxy, β-alkyl, and β-sulfenyl groups were used as efficient synthons for the preparation of chiral 1-acyl-4-imidazolin-2-ones and 1-acylimidazolidin-2-ones. For the preparation of the former heterocycles, α-oximinoketones were transformed into their respective imidazole *N*-oxides by neutral treatment with a chiral triazine, followed by reaction with acetic or propionic anhydrides to furnish the desired chiral 1-acetyl- or 1-propionyl-4-imidazolin-2-ones in moderate overall yields. Upon palladium hydroxide-catalyzed hydrogenation, these series were converted into their corresponding 1-acylimidazolidin-2-ones in high diastereoisomeric ratios. Thus, these novel chiral 1-acetyl- and 1-propionyl-imidazolidin-2-ones were obtained with a variety of alkyl groups at the C-4 and C-5 positions of the heterocycle, through a three-step methodology, and can be applied as new potential chiral auxiliaries.

1. Introduction

Imidazole is a five-membered aromatic heterocycle constituted by two nitrogen atoms at the 1,3-positions.[1] One of them is substituted and shares its lone pair of electrons with two conjugated double bonds to stabilize the ring by aromaticity. The other bears a lone pair of electrons in the plane of the ring providing a basic character to that center of the heterocycle. This electron-density distribution renders unique biological properties to imidazoles among the vast number of nitrogen containing heterocycles.[2] Imidazole-containing compounds have been used as reagents for various synthetic transformations,[3] while natural and synthetic imidazole derivatives show a broad range of pharmacological activities,[4] such as histamine-based receptors,[5] antifungal (clotrimazole, miconazole, sulconazole, tioconazole, luliconazole, and ketoconazole),[6] antimicrobial,[7] anticonvulsant,[8] and antiparasitic drugs,[9] as well as anti-tumor and anticancer agents.[10]

Recently, the development of 1*H*-imidazole *N*-oxide derivatives has enhanced the antitumoral, antiparasitic, antiviral, and antimicrobial activities of the imidazole and benzimidazole parent systems.[11] 1*H*-Imidazole *N*-oxides have also been revealed to be attractive synthetic building blocks,[12] and as new achiral and chiral ionic liquids.[13] Among the preparation methods of chiral and racemic 1*H*-imidazole *N*-oxides,[14] the reaction of α-oximinoketones with hexahydro-1,3,5-triazines is an easy and efficient procedure.[15] The resulting *N*-oxides display a diverse reactivity that allows this skeleton to be transformed into a variety of imidazole derivatives,[16] including their isomerization into imidazolin-2-ones.[17]

The great interest in the preparation of imidazol-2-ones is due to their broad range of uses, including analogues inhibiting the MurB enzyme,[18] anti-tumor potential agents,[19] and anti-oxidants.[20] Recently, imidazol-2-ones have been used as key-fragments for successfully designing new drugs through a fragment-based drug discovery.[21] Consequently, the synthesis of such heterocycles has been reported through many procedures, which consist of the condensation of carbonylic compounds with substituted ureas[22] or isocyanates,[23] intramolecular cyclization of imino salts,[24] or transition metal-catalyzed transformations.[25]

In spite of the growing interest in the design and preparation of modern chiral transition-metal complex catalysts[26] and organocatalysts,[27] and their efficiency for improving asymmetric synthesis, the use of chiral auxiliaries still represents a highly selective and

* Corresponding author. Fax: +52 (55) 5396 3503.
E-mail addresses: jtamarizm@gmail.com, jtamariz@woodward.encb.ipn.mx (J. Tamariz).
† Equivalent contribution.

http://dx.doi.org/10.1016/j.tetasy.2015.01.011
0957-4166/

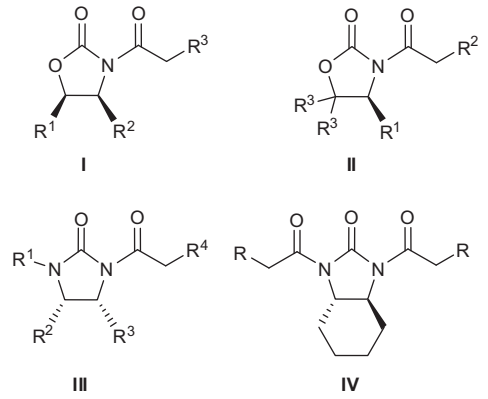


Figure 1. Oxazolidin-2-one-based chiral auxiliaries **I** (Evans) and **II** (Davies, Seebach) and imidazolidin-2-one-based chiral auxiliaries **III** (Helmchen, Cardillo) and **IV** (Davies).

easy methodology for the construction of desired non-racemic chiral compounds (Fig. 1).[28] In particular, oxazolidin-2-one- [e.g., **I** (Evans) and **II** (Davies, Seebach)] or imidazolidin-2-one-based [e.g., **III** (Helmchen, Cardillo) and **IV** (Davies)] chiral auxiliaries, which are also associated with chiral 1,2-amino alcohols and 1,2-diamino compounds and ligands,[29] have proven to be efficient in carrying out diverse reactions with high diastereoselectivities while not being susceptible to nucleophilic ring opening on cleavage. Under conditions that do not cause racemization of the product, the auxiliary is removed and recovered for future inductions.[30]

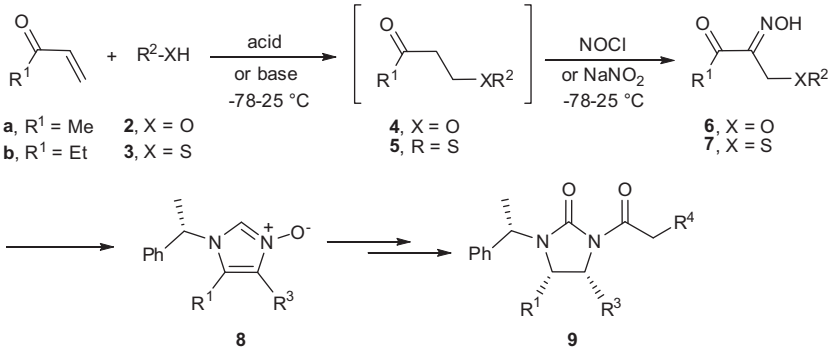
We previously reported the direct conversion of enones **1a–b** into β-alkoxy and β-sulfenyl α-oximinoketones **6–7** through a cascade reaction or a sequential one-pot two-step process involving an acid- (Brønsted or Lewis) or base-promoted 1,4-addition of alcohols or thiols **2–3** to enones **1a–b** in the presence of or by the consecutive addition of nitrosyl chloride (Scheme 1).[31] Herein we report a study of synthetic applications of these functionalized α-oximinoketones for the preparation of imidazole *N*-oxides **8** and novel chiral 4-imidazolidin-2-ones **9**.

2. Results and discussion

2.1. Preparation of α-oximinoketones 6a–c, 7a–c, and 12a–f

A series of β-alkoxy α-oximinoketones **6a–c** were prepared through the optimized procedure by using $BF_3{\cdot}Et_2O$ as the Lewis acid catalyst in the presence of the desired alkyl alcohol **2a–c** and bubbling dry NOCl to carry out the oxa-Michael addition reactions to methyl vinyl ketone **1a**, followed by electrophilic addition (Scheme 1) (Table 1, entries 1–3).[31] We found that the efficiency of the process did not significantly decrease when shortening the reaction time from that previously reported[31] (lasting for days) to 4 h (at −78 °C for 2 h, then at room temperature for 2 h).

Table 1 also summarizes the preparation of 4-arylthio-3-(hydroxyimino)butan-2-ones **7a–c** via a one-pot two-step reaction in good overall yields (entries 4–6).[31] In some cases this procedure resulted in the formation of both (*Z*)- and (*E*)-stereoisomers, although the former was generally the major one. The synthesis of **7a–c** through the two-step procedure increased selectivity,



Scheme 1.

Table 1
Acid-catalyzed hetero-Michael additions of alcohols **2a–c** or base-catalyzed hetero-Michael additions of thiophenols **3a–c** to enone **1a**, followed by nitrosation of either the in situ formation of **4a–c** or **5a–c** or of β-thioketones **5a–c**

Entry	**2** or **3** or **5** (R^2)	Acid or base[a]	Solvent	*T* (°C)	*t* (h)	Product[b] (%)
1	**2a** (Me)[c]	$BF_3{\cdot}OEt_2$	—	−78 (25)[d]	2 (2)[d]	**6a** (65)
2	**2b** (Et)[c]	$BF_3{\cdot}OEt_2$	—	−78 (25)[d]	2 (2)[d]	**6b** (51)
3	**2c** (*i*-Pr)[c]	$BF_3{\cdot}OEt_2$	—	−78 (25)[d]	2 (2)[d]	**6c** (46)
4	**3a** (Ph)	DABCO	THF	65 (25)[e]	4 (12)[e]	**7a** (90)
5	**3b** (C_6H_4-4-Cl)	DABCO	THF	65 (25)[e]	4 (12)[e]	**7b** (65)
6	**3c** (C_6H_4-4-Br)	DABCO	THF	65 (25)[e]	4 (12)[e]	**7c** (55)
7	**5a** (Ph)	HCl	THF	0 (25)[f]	2 (12)[f]	**7a** (92)
8	**5b** (C_6H_4-4-Cl)	HCl	THF	0 (25)[f]	2 (12)[f]	**7b** (62)
9	**5c** (C_6H_4-4-Br)	HCl	THF	0 (25)[f]	2 (12)[f]	**7c** (60)

[a] Under an N_2 atmosphere, with $BF_3{\cdot}Et_2O$ (0.16 mol equiv), or DABCO (0.2 mol equiv), or concd HCl (6.0 mol equiv).
[b] Yields after column chromatography.
[c] Nitrosation ($HCl/NaNO_2$) of a mixture of **1a** with the alcohol **2**.
[d] Addition of reagents at −78 °C for 2 h, then the mixture was left at 25 °C for 2 h.
[e] The reaction was carried out with thiol **3** at 65 °C for 4 h, followed by the addition of $HCl/NaNO_2$ at 0 °C; the mixture was then left at 25 °C for 12 h.
[f] The addition of HCl to a mixture of ketone **5** and $NaNO_2$ was carried out at 0 °C, followed by stirring for 2 h, then the mixture was left at 25 °C for 12 h.

and also mainly furnishing the (*Z*)-isomer. Thus, the DMAP-catalyzed addition to **1a** with the same series of substituted thiophenols **3a–c** gave Michael adducts **5a–c**, respectively, in high yields (83–90%). The latter were then treated with sodium nitrite and hydrochloric acid at room temperature to afford the corresponding 4-arylthio-3-(hydroxyimino)butan-2-ones **7a–c** in good overall yields (entries 7–9).

The X-ray diffraction crystallography of **7a** shows that the (*Z*)-configuration and the *s-trans* conformation are preferred in the crystalline state (Fig. 2). It is noteworthy that the oximino proton does not form a hydrogen bond with the sulfur atom, whose group adopts an orthogonal conformation with respect to the plane formed by the conjugated hetero-atom double bonds.

Alkyl α-oximinoketones **12a–e** were prepared by the addition of hydroxylamine to α-diketones **10a–b** or by direct nitrosation of the corresponding dialkyl ketones **11a–d** (Scheme 2) (Table 2). α-Oximinoketones **12a–b** were efficiently prepared from **10a–b** (Table 2, entries 1 and 2), although **10a** is also commercially available. Non-symmetrical ketones 2-pentanone **11a** and 2-hexanone **11c** afforded a single chemoisomer, **12c** and **12e**, respectively (entries 3 and 5). This can be accounted for by the fact that the slowest step of the reaction mechanism is the acid-promoted enol formation of the ketone.[32] Hence, the thermodynamic enol is preferentially formed, leading to nitrosation in the secondary carbon adjacent to the carbonyl group.

The synthesis of aryl methyl α-oximinoketone **12f** started from the Lewis acid-promoted propionylation of anisole to yield ketone **11d** in 45% yield, which was then submitted to nitrosation conditions to give the desired product (Table 2, entry 6). The modest yield of the latter was due to the formation of α-diketone **10c** as a side-product, which resulted from a further conversion of the firstly obtained α-oximinoketone **12f** into **10c** under the same nitrosation conditions.[33] Therefore, we decided to optimize the formation of **10c** and to carry out treatment with hydroxylamine. Although α-diketone **10c** was prepared in moderate yield (43%) and its conversion into **12f** (entry 7) did not improve the overall yield (31%), purification of the product was easier than when using the direct nitrosation of **11d**.

Table 2
Preparation of α-oximinoketones **12a–12f** via addition of hydroxylamine to α-diketones **10a–10c** or via nitrosation of ketones **11a–11d**[a]

Entry	Ketone	Reagents	Solvent	*t* (h)	Product[b] (%)
1	**10a**	$HONH_2{\cdot}HCl$[c]	MeOH	2	**12a** (95)
2	**10b**	$HONH_2{\cdot}HCl$[c]	MeOH	2	**12b** (92)
3	**11a**	NOCl[d]	Et_2O/MeOH/HCl[e]	2	**12c** (63)
4	**11b**	NOCl[d]	Et_2O/MeOH/HCl[e]	2	**12d** (65)
5	**11c**	NOCl[d]	Et_2O/MeOH/HCl[e]	2	**12e** (57)
6	**11d**	NOCl[f]	MeOH	192	**12f** (52)
7	**10c**	$HONH_2{\cdot}HCl$[c]	MeOH	2	**12f** (71)

[a] All reactions were carried out at room temperature.
[b] After purification by column chromatography.
[c] In the presence of pyridine (1.1 mol equiv).
[d] Generated as gas ($NaNO_2/H_2SO_4$), which was bubbled it in the substrate solution.
[e] In a 2:3:1 ratio; HCl (37%).
[f] HCl (37%) in MeOH was added to the substrate solution containing $NaNO_2$ (3.0 mol equiv) at 25 °C. $NaNO_2$ (3.0 mol equiv) was added three times each 24 h after the first addition.

2.2. Preparation of chiral 1*H*-imidazole *N*-oxides 8a–l and their conversion into 1-acyl 4-oxazolin-2-ones 14d–p

Previously, Heimgartner et al. described the efficient synthesis of a series of 1*H*-imidazole *N*-oxide derivatives by reacting α-oximinoketones with hexahydrotriazines.[12a,13,15] We applied this methodology using our α-oximinoketones **6a–c**, **7a–c**, and

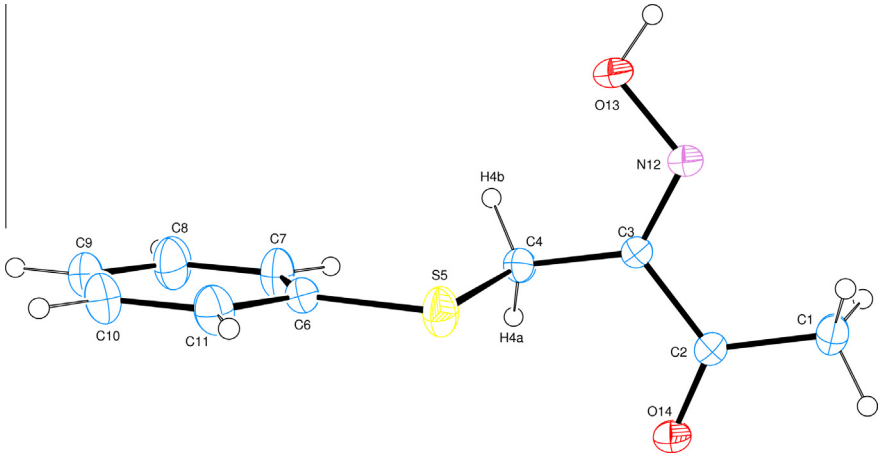
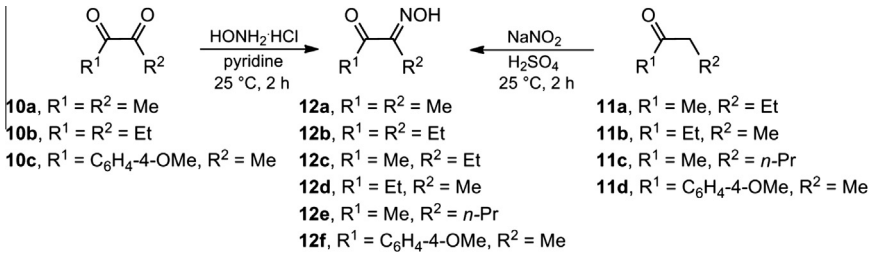
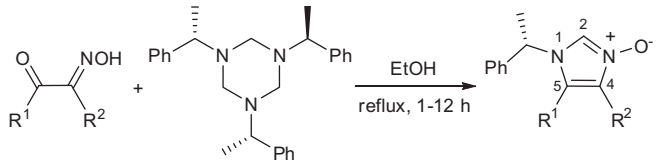


Figure 2. X-ray structure of α-oximinoketone **7a** (ellipsoids at the 30% probability level).



Scheme 2.

Table 3
Preparation of 1*H*-imidazole *N*-oxides **8a–l** by reacting α-oximinoketones **6a–c**, **7a–c**, and **12a–f** and the chiral hexahydrotriazine **13**



6a-c, **7a-c**, **12a-f** **13** **8a-l**

Entry	α-Oximinoketone	R^1	R^2	Product[a] (%)
1	**6a**	Me	CH_2OMe	**8a** (82)
2	**6b**	Me	CH_2OEt	**8b** (81)
3	**6c**	Me	CH_2Oi-Pr	**8c** (75)
4	**7a**	Me	CH_2SPh	**8d** (85)
5	**7b**	Me	$CH_2SC_6H_4$-4-Cl	**8e** (80)
6	**7c**	Me	$CH_2SC_6H_4$-4-Br	**8f** (79)
7	**12a**	Me	Me	**8g** (98)
8	**12b**	Et	Et	**8h** (93)
9	**12c**	Me	Et	**8i** (96)
10	**12d**	Et	Me	**8j** (91)
11	**12e**	Me	*n*-Pr	**8k** (90)
12	**12f**	C_6H_4-4-OMe	Me	**8l** (96)

[a] Yields after column chromatography.

12a–f and the chiral hexahydrotriazine **13** (Table 3).[13,34] Although these described α-oximinoketones have quite different structures than those previously reported, the procedure was found to be highly efficient for our substrates, thereby providing a series of 1*H*-imidazole *N*-oxides **8a–l** in good to excellent yields.

For example, the α-oximinoketones **6a–c** that bear alkoxy methyl ethers as substituents at C-4 of the heterocycle proved to be stable under the reaction conditions to give 1*H*-imidazole *N*-oxides **8a–c** in satisfactory yields (entries 1–3). Similarly, the series of β-sulfenyl α-oximinoketones **7a–c** afforded the expected 1*H*-imidazole *N*-oxides **8d–f** in good yields (entries 4–6). Although the reaction of **12a** was also reported by the same authors,[34] in our hands the desired product **8g** was obtained in almost quantitative yield (entry 7). For most of the rest of the series **12b–f**, the desired 1*H*-imidazole *N*-oxides **8h–l** were prepared in high yields (entries 8–12). The structure of these compounds, including hexahydrotriazine **13**, was characterized by NMR and the signals were assigned by 2D experiments (HMQC and HMBC), mass spectrometry (low and high resolution), and/or elemental analysis. The structure of **8g** was also established by X-ray diffraction crystallography (Fig. 3), which shows that the chiral auxiliary adopts a conformation in which the phenyl group is orthogonal to the plane formed by the heterocycle ((b) view), while the proton is oriented toward the C-5 methyl group (vide infra).

We were able to obtain a monocrystal of hexahydrotriazine **13** to establish its structure by X-ray diffraction (Fig. 4). The

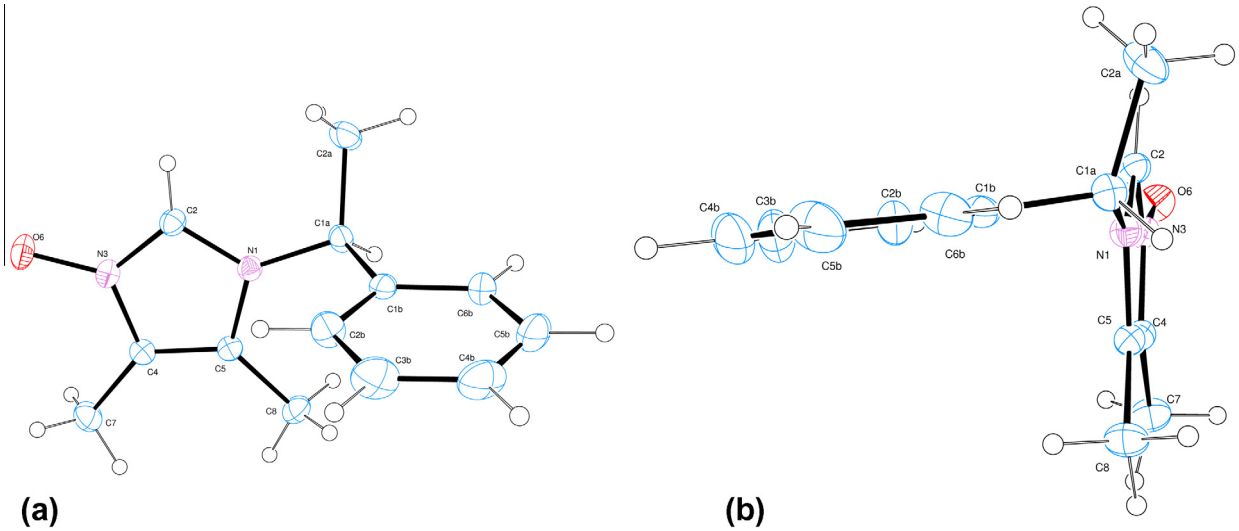


Figure 3. X-ray structure of 1*H*-imidazole *N*-oxide **8g** (ellipsoids at the 30% probability level): (a) frontal view; (b) lateral view.

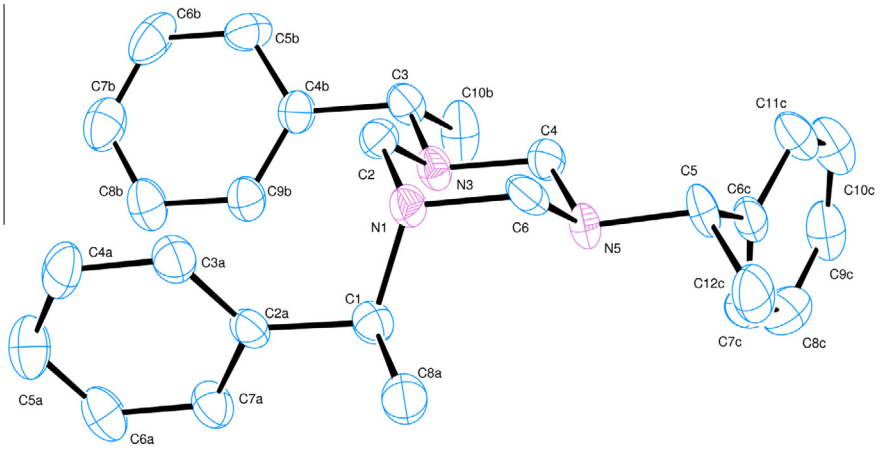
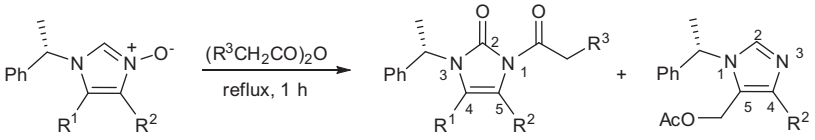


Figure 4. X-ray structure of hexahydrotriazine **13** (ellipsoids at the 30% probability level; the hydrogen atoms were removed for a better view).

Table 4
Preparation of 1-acyl 4-imidazolin-2-ones **14d–p** by treatment of 1*H*-imidazole *N*-oxides **8a–c** and **8e–l** with acetic and propionic anhydrides



8a-c, 8e-l **14a-p** **15a-c**

Entry	8	R^1	R^2	R^3	14[a] (%)	15[a] (%)
1	**8a**	Me	CH_2OMe	H	**14a** (b)	—
2	**8b**	Me	CH_2OEt	H	**14b** (b)	—
3	**8c**	Me	CH_2Oi-Pr	H	**14c** (b)	—
4	**8e**	Me	$CH_2SC_6H_4$-4-Cl	H	**14d** (94)	—
5	**8f**	Me	$CH_2SC_6H_4$-4-Br	H	**14e** (97)	—
6	**8g**	Me	Me	H	**14f** (54)	**15a** (20)
7	**8h**	Et	Et	H	**14g** (60)	—
8	**8i**	Me	Et	H	**14h** (53)	**15b** (18)
9	**8j**	Et	Me	H	**14i** (60)	—
10	**8k**	Me	*n*-Pr	H	**14j** (39)	**15c** (16)
11	**8l**	C_6H_4-4-OMe	Me	H	**14k** (46)	—
12	**8g**	Me	Me	Me	**14l** (54)	—
13	**8h**	Et	Et	Me	**14m** (72)	—
14	**8i**	Me	Et	Me	**14n** (60)	—
15	**8k**	Me	*n*-Pr	Me	**14o** (30)	—
16	**8l**	C_6H_4-4-OMe	Me	Me	**14p** (50)	—

[a] Yields after column chromatography.
[b] A complex mixture.

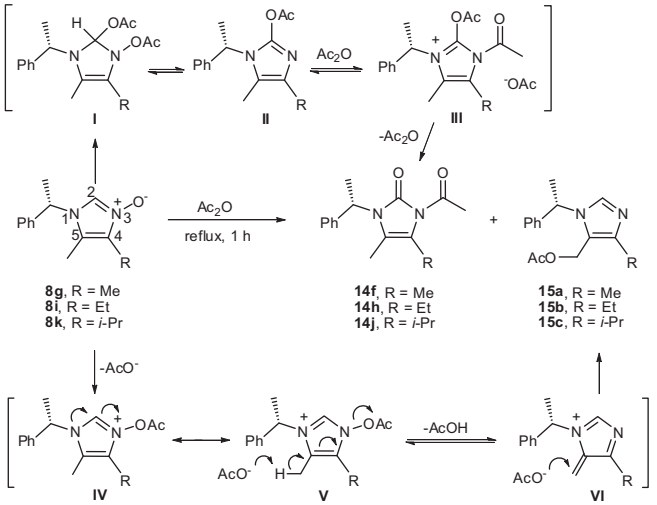
six-membered ring adopts a chair-like conformation, and only two of the chiral *N*-benzyl substituents assume the equatorial conformation, leaving the third one in an axial position.

Treated under similar conditions as those reported previously,[17a] the series of alkoxymethyl 1*H*-imidazole *N*-oxides **8a–c** when treated with acetic anhydride at reflux for 1 h did not produce the desired *N*-acetyl 4-oxazolin-2-ones **14a–c**, but instead a complex mixture of products (Table 4, entries 1–3). It is likely that the presence of acetic acid in the middle of the reaction decomposes the ether group to yield diverse side-products. Unlike these compounds, the arylsulfenylmethyl 1*H*-imidazole *N*-oxides **8e–f** reacted with acetic anhydride at reflux for 1 h to afford 1-acetyl-4-imidazolin-2-ones **14d–e**, respectively, in high yields (entries 4 and 5).

For the case of alkyl derivative 1*H*-imidazole *N*-oxide **8g**, the reaction with acetic anhydride at reflux for 1 h produced the desired 1-acetyl 4-oxazolin-2-one **14f**, but only in a fair yield (54%) (Table 4, entry 6). We found that this unexpectedly modest yield was due to the presence of a second product appearing in the reaction mixture (Table 4). The NMR, HRMS, and elemental analysis data revealed this to be 1*H*-imidazole **15a**, which has an imidazole ring substituted by an acetoxy group in the C-5 methyl group. NOE experiments supported this assignment, showing an enhancement of the signals attributed to the methine proton and methyl group of the chiral auxiliary when the methylene attached to the acetoxy group was irradiated, thus indicating the spatial proximity of these groups.

The formation of products **14** has been previously documented, with the mechanism suggested (Scheme 3).[17] The reaction of 1*H*-imidazole *N*-oxides **8** with acetic anhydride leads to intermediate **I**, which in turn undergoes the elimination of a molecule of acetic acid to afford intermediate **II**. By N-acylation with another mole of acetic anhydride, the latter can be converted into the intermediate 2-acetoxyimidazole **III**, which is stabilized by losing a molecule of acetic anhydride to furnish the observed products **14**.

The presence of **15a** is noteworthy, since there are no reports regarding the formation of this kind of product under similar



Scheme 3.

conditions.[17] However, there are analogous results from the reaction between 1,2-dimethylbenzimidazole 3-oxide and acetic anhydride, in which the C-2 methyl group is acetoxylated.[35] Evidence of the reaction mechanism was provided, showing similarity with a vinylogous Polonovski reaction,[36] in which aliphatic tertiary amine *N*-oxides are activated with acid anhydrides to form the corresponding iminium ion as the key intermediate, resulting in a tertiary amide and an aldehyde. Considering these mechanisms, a proposal for the case of compounds **8** can be made (Scheme 3). Acetylation of the imidazole *N*-oxides **8** leads to species **IV**, whose positive charge is delocalized between both nitrogen atoms to form intermediate **V**. This is stabilized by a likely concerted elimination of the *N*-acetoxy group, affording a molecule of acetic acid with one of the protons of the C-5 methyl group to form the iminium ion **VI**. The latter can undergo an attack from the acetoxy anion to give the

neutral products **15**. This mechanism can be proposed for the generation of the whole **15a–c** series from the starting materials **8g**, **8i**, and **8k**, respectively (Table 4). Even though the process was monitored by NMR, we were unable to detect or isolate an intermediate, such as salt-species **VI**,[35] and only observed the two products **14** and **15** along with the starting material.

It is worth noting that this type of side-product **15** was exclusively detected and isolated from the 1*H*-imidazole *N*-oxides substituted by a C-5 methyl group, **8g**, **8i,** and **8k** (Table 4, entries 6, 8, and 10). This suggests that the formation of methylenic species **VI** is much more stable than that originated from the C-4 methyl group or from a C-4 or C-5 ethyl or propyl group present in the heterocycle. Likewise, the addition of the acetoxy group to the exocyclic methylene of the **VI** species would be favored by the fact that the reactive center is not substituted. Therefore, a steric effect cannot be ruled out as a controlling factor for this reaction together with the electronic factor.

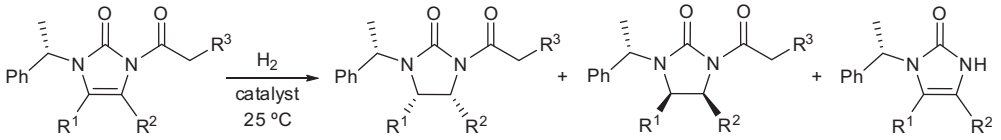
Taking into account the interesting *N*-propionyl group in the 2-oxazolidinone and 2-imidazolidinone chiral auxiliaries, which gives rise to a second chiral center in aldol or Michael additions,[37] we explored the reactions of 1*H*-imidazole 3-oxides **8g–i**, and **8k–l** with propionic anhydride under the reaction conditions similar to those used with acetic anhydride (Table 4, entries 12–16). The expected *N*-propionyl derivatives **14l–p** were obtained in moderate yields. In the case of the C-5 methyl substituted 1*H*-imidazole 3-oxides **8g**, **8i,** and **8k**, the side-products (e.g., **15a–c**) were detected by NMR from the crude mixtures as a series of minor-sized signals. None of these products were isolated by their decomposition during the purification process.

2.3. Preparation of the potential chiral auxiliaries 16–17

Due to the difference between its C-4 and C-5 substituents, derivative **14i** was selected to establish the optimum conditions of hydrogenation and therefore obtain the best diastereoselectivity and chemical yield. Table 5 summarizes the most representative assays, which included a variation in catalyst, catalyst loading, solvent, pressure, and reaction time. All of the assays were carried out at room temperature. The diastereoisomeric ratio was improved by reducing the pressure of the vessel when the reaction mixture was catalyzed with Pd/C (10%). Methanol was the best solvent, since ethyl acetate (entry 6), ethanol, isopropanol, and toluene inefficiently favored any form of transformation. Among the catalysts tested, Rh/C promoted the decomposition of the substrate. However, palladium hydroxide (20%) displayed the best profile considering the short reaction time, diastereoselectivity, and yield (entry 8). Therefore, these conditions were applied for a series of representative substrates, **14f–g**, **14j–m**, and **14p**, furnishing modest to good yields and high diastereoselectivity, in which isomer **16** was favored (entries 11–17). In the case of **14p**, the hydrogenation furnished **16h** as a single isomer. Despite the efficient and selective conversion of these substrates into the desired potential chiral auxiliaries, the sulfenyl analogues **14d** and **14e** did not endure the hydrogenation conditions, giving rise to decomposition products. The yields of products **16** were sometimes quite modest (entries 8, 13, and 14) because of the hydrolysis of the N-3 amide group of the substrates, probably due to the basic aqueous medium ($Pd(OH)_2$ being commercially available in 50% w/w H_2O), affording imidazolin-2-ones **18** as the main by-products of the reaction (entries 8 and 11–17). Eventually, the latter by-products can be recycled into the corresponding chiral compound **16**, through a two-step procedure starting with hydrogenation and followed by N-acylation.[30e]

The diastereoisomeric ratio was determined by ^{1}H NMR spectroscopy of the crude mixtures. The structure for the major isomer was assigned in agreement with previous theoretical and X-ray crystallographic studies for the condensation and hydrogenation of 4-oxazolin-2-ones bearing the same chiral auxiliary.[38] These

Table 5
Preparation of chiral auxiliaries **16–17** by hydrogenation of 1-acyl 4-oxazolin-2-ones **14**



14 **16** **17** **18**

Entry	**14**	Catalyst	% Mol equiv	Solvent	*P* (psi)	*t* (h)	**16**/**17**/**18** (ratio)[a]	dr (**16**/**17**)[a]	Yield[b] (%)
1	**14i**	Pd/C (10%)	10	MeOH	1500	24	**16c**/**17c** (50:50)	—	(c)
2	**14i**	Pd/C (10%)	10	MeOH	500	24	**16c**/**17c** (64:36)	—	(c)
3	**14i**	Pd/C (10%)	10	MeOH	300	48	**16c**/**17c** (66:34)	—	(c)
4	**14i**	Pd/C (10%)	15	MeOH	100	24	**16c**/**17c** (76:24)	—	(c)
5	**14i**	Pd/C (10%)	20	MeOH	(d)	24	**16c**/**17c** (89:11)	—	(c)
6	**14i**	Pd/C (10%)	20	EtOAc	(d)	24	(e)	—	—
7	**14i**	Rh/C (20%)	20	MeOH	(d)	96	(f)	—	—
8	**14i**	$Pd(OH)_2$ (20%)	20	MeOH	(d)	6	**16c**/**17c**/**18c** (64.4:0.6:35)	99:1	**16c**/**18c** (42:22)
9	**14i**	$Pd(OH)_2$ (20%)	20	AcOH	(d)	24	(f)	—	—
10	**14i**	$Pd(OH)_2$ (20%)	50	MeOH	(d)	24	(f)	—	—
11	**14f**	$Pd(OH)_2$ (20%)	20	MeOH	(d)	6	**16a**/**17a**/**18a** (90:3:7)	97:3	**16a**/**18a** (83:0)
12	**14g**	$Pd(OH)_2$ (20%)	20	MeOH	(d)	6	**16b**/**17b**/**18b** (74.5:0.5:25)	99:1	**16b**/**18b** (79:20)
13	**14j**	$Pd(OH)_2$ (20%)	20	MeOH	(d)	6	**16d**/**17d**/**18d** (72:7:21)	91:9	**16d**/**18d** (44:0)
14	**14k**	$Pd(OH)_2$ (20%)	20	MeOH	(d)	6	**16e**/**17e**/**18e** (76.8:6.2:17)	93:7	**16e**/**18e** (42:11)
15	**14l**	$Pd(OH)_2$ (20%)	20	MeOH	(d)	6	**16f**/**17f**/**18f** (90:5:5)	95:5	**16f**/**18d** (84:0)
16	**14m**	$Pd(OH)_2$ (20%)	20	MeOH	(d)	6	**16g**/**17g**/**18b** (69.5:0.5:30)	99:1	**16g**/**18b** (66:24)
17	**14p**	$Pd(OH)_2$ (20%)	20	MeOH	(d)	24	**16h**/**17h**/**18e** (74:0:26)	>99:1	**16h**/**18e** (61:17)

[a] Ratio determined by ^{1}H NMR of the crude mixture.
[b] Yields after column chromatography.
[c] Not determined.
[d] Atmospheric pressure (ca. 14.68 psi).
[e] Recovered starting material.
[f] Decomposition.

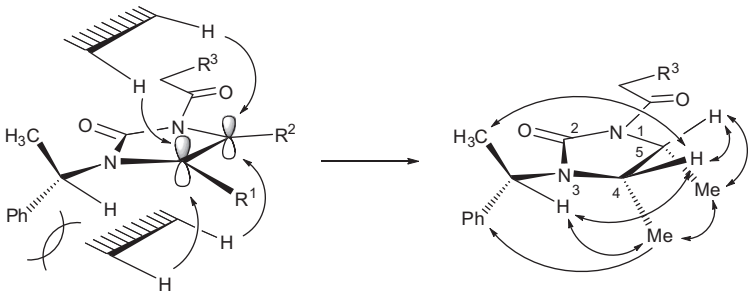


Figure 5. Interaction sites between the imidazolin-2-one double bond of **14** and the catalytic hydrogenation framework in the *alpha* (disfavored) and *beta* (favored) approaches, leading to the major diastereoisomers imidazolidin-2-ones **16**, as confirmed by the NOE experiments carried out with derivative **16a** (R^3 = H).

studies suggest a conformational preference of the chiral auxiliary, with the proton of the (*S*)-stereogenic center adopting an almost coplanar position to the heterocycle, leaving the methyl and phenyl groups above (*beta*) and below (*alpha*) this plane, respectively (Fig. 5).[30e] This conformation is in agreement with the X-ray structure of 1*H*-imidazole *N*-oxide **8g** (Fig. 3), in which the phenyl group of the chiral auxiliary clearly adopts an orthogonal conformation with respect to the double bond. It is likely that this conformation blocks an approach by the catalyst to this face. Accordingly, the catalyzed *syn*-hydrogenation preferentially takes place at the *beta* face of the heterocycle, leaving the C-4 and C-5 substituents underneath, as shown in isomers **16** (Table 5). This stereochemistry was also supported by the NOE experiments of compound **16a** (Fig. 5), showing an enhancement of the signals attributed to the methine proton and phenyl group of the chiral auxiliary as well as of the signal of the H-4 proton when the methyl group of the chiral auxiliary was irradiated. Reciprocal enhancements of the signals attributed to the methine proton and methyl group (but not to the phenyl ring) of the chiral auxiliary were observed when the H-4 proton was irradiated. Irradiation of the signal attributed to the C-4 methyl group induces an enhancement of the signals of the *syn* C-5 methyl group, the methine of the auxiliary, and the aromatic protons signal, indicating their spatial proximity as well as the conformational preference of the chiral auxiliary as indicated in Figure 5.

3. Conclusion

A four-step synthetic methodology has been developed to access to a variety of novel chiral 1-acyl-3-((*S*)-1-phenylethyl)imidazolidin-2-ones **16a**–**h** as potential auxiliaries in asymmetric aldol condensation, Michael addition and [4+2] cycloadditions, among other reactions. This versatile methodology includes the preparation of the starting materials α-oximinoketones **6**, **7,** and **12**, and a readily available approach to yield the imidazole *N*-oxides **8** and the *N*-acyl 4-imidazolin-2-ones **14**, as precursors of the chiral derivatives **16**. The latter were obtained diastereoselectively thanks to the induction accomplished by the (*S*)-methylbenzyl moiety of **14** during the hydrogenation of the heterocyclic ring. However, this approach is limited to using α-oximinoketones substituted by alkyl and aryl groups, since ethers and thioethers incorporated into these substituents were not stable enough to endure the reaction conditions. The use of these novel and potential auxiliaries in asymmetric synthesis will be studied, and the results will be reported in due course.

4. Experimental

4.1. General

Melting points were determined on an Electrothermal capillary apparatus and are uncorrected. Infrared spectra (IR) were recorded on a FT-IR 2000 Perkin–Elmer spectrophotometer. ^{1}H (300 or 500 MHz) and ^{13}C (75 or 125 MHz) NMR spectra were recorded on Varian Mercury-300 or Varian VNMR System instruments, with TMS as internal standard; chemical shifts (δ) are reported in ppm. Mass spectra (MS) and high-resolution mass spectra (HRMS) were obtained, in electron impact (EI) (70 eV) mode, on Thermo-Finnigan Polaris Q and Jeol JSM-GcMateII spectrometers, respectively. Elemental analyses were performed on a CE-440 Exeter Analytical instrument. Optical rotations were determined on a Jasco P-200 polarimeter. X-ray crystallographic structures were obtained on an Oxford XcaliburS diffractometer. Analytical thin-layer chromatography was performed on precoated silica gel plates (Merck $60F_{254}$). Flash column chromatography was performed over silica gel (230–400 mesh) (Natland International Co.) or pre-treated silica gel (230–400 mesh) with 10% of triethylamine (w/w, hexane). EtOH, MeOH, *i*-PrOH, and THF were freshly distilled over sodium, and CH_2Cl_2 over calcium hydride prior to use. All other reagents were used without further purification. The preparation of compounds **6a** and **7a** has been previously described.[31]

4.2. General procedures for the preparation of compounds 5, 6 and 7

Method A: In a two-necked round bottom flask A with a thermometer and cooled to −78 °C $BF_3{\cdot}Et_2O$ (0.16 mol equiv) was added dropwise to a solution of **1a** (1.0 mol equiv) in the corresponding alcohol **2b**–**c** (20 mL), and the mixture was stirred for 15 min. Then, at the same temperature, nitrosyl chloride [generated at room temperature in a two-necked round bottom flask B by adding concd aqueous HCl (37%) (10 mol equiv) dropwise through a funnel to $NaNO_2$ (10 mol equiv)] was bubbled into the solution of flask A through a glassware connector, which was packed with $NaNO_2$ and anhydrous Na_2SO_4. The mixture was stirred at −78 °C for 2 h and then at room temperature for 2 h. The solvent was removed under vacuum and extracted with EtOAc (3 × 10 mL), the organic layers were dried (Na_2SO_4), and the solvent removed under vacuum. The residue was purified by column chromatography over silica gel (20 g/g crude, hexane/EtOAc, 95:5) to give compounds **6b**–**c**.

Method B: In a two-necked round bottom flask at room temperature, **1a** (1.0 mol equiv) was added dropwise to a solution of the corresponding thiophenol **3a**–**c** (1.1 mol equiv) and DMAP (0.2 mol equiv) in CH_2Cl_2 (10 mL), and the mixture was stirred for 24 h. The mixture was diluted with CH_2Cl_2 (20 mL) and washed with a 5% aqueous solution of HCl (10 mL) and brine (2 × 10 mL), the organic layer was dried (Na_2SO_4) and the solvent removed under vacuum. The residue was purified by column chromatography over silica gel (15 g/g crude, hexane/EtOAc, 90:10) to give compounds **5a**–**c**.

Method C: In a two-necked round bottom flask at 0 °C, an aqueous concd solution of HCl (37%) (6.0 mol equiv) dissolved in THF (5.0 mL) was added dropwise to a mixture of **5** (1.0 mol equiv) and $NaNO_2$ (3.0 mol equiv) in THF (10 mL), and the mixture was

stirred at this temperature for 2 h, then at room temperature for 12 h. The mixture was diluted with EtOAc (20 mL) and washed with a saturated aqueous solution of K_2CO_3 until neutral and with brine (2 × 10 mL), then the organic layer was dried (Na_2SO_4) and the solvent removed under vacuum. The residue was purified by column chromatography over silica gel (15 g/g crude, hexane/EtOAc, 8:2) to give compounds **7a–c**.

Method D: In a two-necked round bottom flask at room temperature, **1a** (1.0 mol equiv) was added dropwise to a solution of the corresponding thiophenol **3a–c** (1.0 mol equiv) and DABCO (0.2 mol equiv) in THF (10 mL), and the mixture was heated to 65 °C and stirred for 4 h. At 0 °C, an aqueous concd solution of HCl (37%) (6.0 mol equiv) and $NaNO_2$ (3.0 mol equiv) in H_2O (5 mL) was successively added dropwise, and the mixture was stirred at this temperature for 2 h, then at room temperature for 12 h. The mixture was diluted with EtOAc (20 mL) and washed with a saturated aqueous solution of $NaHCO_3$ until neutral and with brine (2 × 10 mL), then the organic layer was dried (Na_2SO_4), and the solvent removed under vacuum. The residue was purified by column chromatography over silica gel (20 g/g crude, hexane/EtOAc, 8:2) to give compounds **7a–c**.

4.3. General procedures for the preparation of compounds 12a–e

Method E: In a two-necked round bottom flask at room temperature, pyridine (1.1 mol equiv) was added dropwise to a solution of the corresponding α-diketone **10a–b** (1.0 mol equiv) and hydroxylamine hydrochloride (1.0 mol equiv) in MeOH (20 mL), and the mixture was stirred for 2 h. The solvent was then removed under vacuum and the residue was extracted with EtOAc (3 × 10 mL), after which the organic layer was dried (Na_2SO_4) and the solvent removed under vacuum. The residue was purified by column chromatography over silica gel (20 g/g crude, hexane/EtOAc, 95:5) to give compounds **12a–b**.

Method F: In a two-necked round bottom flask A with a thermometer and at room temperature, the corresponding ketones **11a–c** (1.0 mol equiv) were dissolved in a mixture of Et_2O/MeOH/HCl (37%) (10:15:5 mL), and the resulting mixture was stirred for 15 min. Then at the same temperature, nitrosyl chloride [generated at room temperature in a two-necked round bottom flask B by adding concd H_2SO_4 (98%) (2.0 mol equiv) dropwise through a funnel to $NaNO_2$ (1.5 mol equiv)] was bubbled into the solution of flask A through a glassware connector, which was packed with $NaNO_2$ and anhydrous Na_2SO_4. The mixture was stirred at room temperature for 2 h, and then neutralized with $NaHCO_3$. The solvent was removed under vacuum and the residue was extracted with EtOAc (3 × 10 mL), the organic layer was dried (Na_2SO_4), and the solvent removed under vacuum. The residue was purified by column chromatography over silica gel (20 g/g crude, hexane/EtOAc, 85:15) to give compounds **12c–e**.

4.4. General procedure for the preparation of chiral 1*H*-imidazole *N*-oxides 8a–l

Method G: In a round bottom flask at room temperature, a mixture of the corresponding α-oximinoketones **6a–c**, **7a–c**, and **12a–f** (1.0 mol equiv) and the chiral hexahydrotriazine **13** (0.5 mol equiv) was dissolved in EtOH (15 mL) and stirred at reflux for 1–12 h. The solvent was removed under vacuum and the residue purified by column chromatography over silica gel (20 g/g crude, hexane/EtOAc, 1:1) to give compounds **8a–l**.

4.5. General procedure for the preparation of 1*H*-imidazolin-2-ones 14d–p, and 1*H*-imidazoles 15a–c

Method H: In a round bottom flask at room temperature, a mixture of the corresponding 1*H*-imidazole *N*-oxides **8** (1.0 mol equiv) and acetic or propionic anhydride (5 mL) was stirred at reflux for 1 h. The remaining anhydride was removed under warm air flux and the residue was purified by column chromatography over silica gel (20 g/g crude, hexane/EtOAc, 98:2) to give compounds **14d–p** and **15a–c**.

4.6. General procedures for the preparation of imidazolidin-2-ones 16a–h/17a–h, and 1*H*-imidazolin-2-ones 18a–f

Method I: In a round bottom flask under an H_2 atmosphere (ca. 759 mmHg (14.68 psi)), a mixture of the corresponding 1*H*-imidazolin-2-ones **14** (1.0 mol equiv) in MeOH and $Pd(OH)_2/C$ (20%) (0.125 mol equiv) (in w/w 50% H_2O) was stirred at room temperature for 6–24 h. The mixture was filtered over Celite, the solvent removed under vacuum, and the residue purified by column chromatography over silica gel (20 g/g crude, hexane/EtOAc, 98:2) to give compounds **16a–h**/**17a–h** and **18a–f**.

4.7. 4-Ethoxy-3-(hydroxyimino)butan-2-one 6b[31]

Synthesized according to method A, with **1a** (0.85 g, 12.1 mmol) in EtOH (**2b**) (20 mL), $BF_3{\cdot}Et_2O$ (0.28 g, 1.97 mmol), $NaNO_2$ (8.40 g, 0.12 mol) and HCl (37%) (4.49 g, 0.123 mol), **6b** (0.90 g, 51%) was afforded as a pale yellow oil. R_f 0.50 (hexane/EtOAc, 3:2). IR (film) 3273, 2979, 2879, 1692, 1444, 1365, 1263, 1089, 1024 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, J = 7.0 Hz, 3H, CH_3CH_2O), 2.40 (s, 3H, CH_3CO), 3.59 (q, J = 7.0 Hz, 2H, CH_3CH_2O), 4.44 (s, 2H, H-4), 10.38 (br s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.9 (CH_3CH_2O), 25.2 (C-1), 58.2 (C-4), 67.2 (CH_3CH_2O), 155.1 (C-3), 197.0 (C-2). MS (70 eV) m/z 145 (M^+, 7), 128 (7), 101 (61), 99 (100), 85 (47), 70 (31), 59 (64). HRMS (FAB) m/z $[M+1]^+$ Calcd for $C_6H_{12}NO_3$: 146.0817. Found: 146.0818.

4.8. 3-(Hydroxyimino)-4-isopropoxybutan-2-one 6c[31]

Synthesized according to method A, with **1a** (0.85 g, 12.1 mmol) in *i*-PrOH (**2c**) (20 mL), $BF_3{\cdot}Et_2O$ (0.28 g, 1.97 mmol), $NaNO_2$ (8.40 g, 0.12 mol) and HCl (37%) (4.49 g, 0.123 mol), **6c** (0.89 g, 46%) was afforded as a pale yellow oil. R_f 0.51 (hexane/EtOAc, 3:2). IR (film) 3213, 3046, 2976, 2880, 1693, 1421, 1368, 1265, 1175, 1122, 1057, 1019 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (d, J = 6.0 Hz, 6H, $(CH_3)_2CHO$), 2.40 (s, 3H, H-1), 3.73 (sept, J = 6.0 Hz, 1H, $(CH_3)_2CHO$), 4.44 (s, 2H, H-4), 10.47 (br s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7 ($(CH_3)_2CHO$), 25.3 (C-1), 56.4 (C-4), 73.2 ($(CH_3)_2CHO$), 155.3 (C-3), 197.1 (C-2). MS (70 eV) m/z 159 (M^+, 4), 117 (100), 99 (49), 84 (9), 70 (7). HRMS (FAB) m/z $[M+1]^+$ Calcd for $C_7H_{14}NO_3$: 160.0974. Found: 160.0964.

4.9. 4-Phenylthiobutan-2-one 5a[31,39]

Synthesized according to method B, with **1a** (0.700 g, 0.01 mol), **3a** (1.210 g, 0.011 mol) and DMAP (0.244 g, 0.002 mol), **5a** (1.62 g, 90%) was afforded as a colorless oil. R_f 0.60 (hexane/EtOAc, 9:1). IR (film) 3057, 2931, 1713, 1582, 1480, 1438, 1360, 1158, 1089, 1024, 738, 690 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 2.11 (s, 3H, CH_3CO), 2.73 (t, J = 7.0 Hz, 2H, H-3), 3.11 (t, J = 7.0 Hz, 2H, H-4), 7.15–7.19 (m, 1H, H-4′), 7.24–7.29 (m, 2H, H-3′), 7.30–7.34 (m, 2H, H-2′). ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.2 (C-4), 29.8 (C-1), 42.8 (C-3), 126.0 (C-4′), 128.8 (C-2′), 129.2 (C-3′), 135.5 (C-1′), 206.2 (CO). MS (70 eV) m/z 180 (M^+, 100), 137 (20), 123 (11), 109 (24), 108 (31), 77 (5), 65 (8).

4.10. 4-(4-Chlorophenylthio)butan-2-one 5b[31]

Synthesized according to method B, with **1a** (0.700 g, 0.01 mol), **3b** (1.600 g, 0.011 mol) and DMAP (0.244 g, 0.002 mol), **5b** (1.76 g,

83%) was afforded as colorless crystals. R_f 0.59 (hexane/EtOAc, 9:1); mp 57–58 °C. IR (KBr) 1713, 1474, 1414, 1386, 1366, 1159, 1094, 1004, 824, 806 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.16 (s, 3H, CH_3CO), 2.75 (t, J = 7.3 Hz, 2H, H-3), 3.11 (t, J = 7.3 Hz, 2H, H-4), 7.27 (s, 4H, H-2′, H-3′). ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.7 (C-4), 30.1 (C-1), 42.9 (C-3), 129.1 (C-2′), 130.9 (C-3′), 132.4 (C-4′), 134.2 (C-1′), 206.3 (CO). MS (70 eV) m/z 216 (M^++2, 47), 214 (M^+, 100), 171 (18), 157 (16), 144 (34), 143 (35), 108 (27). Anal. Calcd for $C_{10}H_{11}ClOS$: C, 55.94; H, 5.16. Found: C, 55.90; H, 5.10.

4.11. 4-(4-Bromophenylthio)butan-2-one 5c[31]

Synthesized according to method B, with **1a** (0.700 g, 0.01 mol) in CH_2Cl_2 (10 mL), **3c** (2.080 g, 0.011 mol) and DMAP (0.244 g, 0.002 mol), **5c** (2.20 g, 86%) was afforded as colorless crystals. R_f 0.63 (hexane/EtOAc, 9:1); mp 60–61 °C (hexane). IR (film) 1714, 1473, 1415, 1382, 1265, 1111, 1092, 1007, 823, 803, 737 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 2.15 (s, 3H, H-1), 2.75 (t, J = 7.0 Hz, 2H, H-3), 3.11 (t, J = 7.0 Hz, 2H, H-4), 7.17–7.21 (m, 2H, H-2′), 7.39–7.42 (m, 2H, H-3′). ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.4 (C-4), 30.0 (C-1), 42.8 (C-3), 120.1 (C-4′), 130.9 (C-2′), 132.0 (C-3′), 135.0 (C-1′), 206.2 (CO). MS (70 eV) m/z 261 (M^++2, 2), 259 (M^+, 2), 190 (100), 188 (93), 109 (90), 82 (8), 69 (13). Anal. Calcd for $C_{10}H_{11}BrOS$: C, 46.34; H, 4.28. Found: C, 46.12; H, 4.05.

4.12. 4-(4-Chlorophenylthio)-3-(hydroxyimino)butan-2-one 7b[31]

Synthesized according to method C, with **5b** (1.070 g, 0.005 mol), $NaNO_2$ (1.035 g, 0.015 mol) and HCl (37%) (2.96 g, 0.03 mol), **7b** (0.75 g, 62%) was afforded as white crystals. Synthesized according to method D, with **3b** (1.45 g, 0.01 mol), DABCO (0.224 g, 0.002 mol), **1a** (0.77 g, 0.011 mol), HCl (37%) (5.87 g, 0.06 mol) and $NaNO_2$ (2.08 g, 0.03 mol), **7b** (1.59 g, 65%) was afforded as white crystals. R_f 0.48 (hexane/EtOAc, 4:1); mp 94–95 °C. IR (KBr) 3423, 2965, 2833, 1765, 1716, 1496, 1408, 1341, 1281, 1220, 1169, 1086, 986, 837 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 3H, H-1), 3.92 (s, 2H, H-4), 7.22–7.28 (m, 2H, H-2′), 7.35–7.41 (m, 2H, H-3′), 8.07 (br s, 1H, NO*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.6 (C-4), 25.2 (C-1), 128.9 (C-2′), 132.8 (C-3′), 133.3 (C-4′), 133.4 (C-1′), 156.0 (C-3), 196.2 (C-2). MS (70 eV) m/z 243 (M^+, 80), 199 (15), 183 (35), 157 (29), 143 (100), 108 (80), 75 (12). Anal. Calcd for $C_{10}H_{10}ClNO_2S$: C, 49.28; H, 4.14; N, 5.75. Found: C, 49.11; H, 3.97; N, 5.61.

4.13. 4-(4-Bromophenylthio)-3-(hydroxyimino)butan-2-one 7c[31]

Synthesized according to method C, with **5c** (1.300 g, 0.005 mol), $NaNO_2$ (1.035 g, 0.015 mol) and HCl (37%) (2.96 g, 0.03 mol), **7c** (0.86 g, 60%) was afforded as white crystals. Synthesized according to method D, with **3c** (1.87 g, 0.01 mol), DABCO (0.224 g, 0.002 mol), **1a** (0.77 g, 0.011 mol), HCl (37%) (5.87 g, 0.06 mol) and $NaNO_2$ (2.08 g, 0.03 mol), **7c** (1.58 g, 55%) was afforded as white crystals. R_f 0.52 (hexane/EtOAc, 4:1); mp 83–84 °C. IR (film) 3257, 3166, 3032, 2883, 1675, 1473, 1419, 1368, 1168, 1090, 1001, 807, 934 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 2.34 (s, 3H, H-1), 3.94 (s, 2H, H-4), 7.30–7.33 (m, 2H, H-2′), 7.36–7.40 (m, 2H, H-3′), 10.63 (br s, 1H, NO*H*). ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.1 (C-4), 25.0 (C-1), 120.8 (C-4′), 131.7 (C-2′), 132.5 (C-3′), 134.7 (C-1′), 155.4 (C-3), 195.9 (C-2). MS (70 eV) m/z 286 (M^+, 5), 227 (40), 189 (100), 187 (65), 145 (8), 108 (92), 79 (9), 69 (19). HRMS (FAB) m/z $[M+1]^+$ Calcd for $C_{10}H_{10}BrNO_2S$: 286.9616. Found: 286.9605.

4.14. 3-(Hydroxyimino)butan-2-one 12a

Synthesized according to method E, with **10a** (0.86 g, 10.0 mmol), hydroxylamine hydrochloride (0.695 g, 10.0 mmol) and pyridine (0.869 g, 11.0 mmol), **12a** (0.96 g, 95%) was afforded as white crystals. R_f 0.40 (hexane/EtOAc, 4:1); mp 75–76 °C [Lit.[40] 76.8 °C]. IR (film) 3270, 3207, 3042, 2868, 1668, 1442, 1368, 1315, 1016, 981, 798 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 2.00 (s, 3H, H-4), 2.40 (s, 3H, H-1), 9.26 (br s, 1H, NOH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.04 (C-4), 25.1 (C-1), 157.2 (C-3), 197.5 (C-2). MS (70 eV) m/z 101 (M^+, 100), 86 (10), 84 (15), 58 (17), 54 (6), 51 (4).

4.15. 4-(Hydroxyimino)hexan-3-one 12b

Synthesized according to method E, with **10b** (1.14 g, 10.0 mmol), hydroxylamine hydrochloride (0.695 g, 10.0 mmol) and pyridine (0.869 g, 11.0 mmol), **12b** (1.19 g, 92%) was afforded as white crystals. R_f 0.56 (hexane/EtOAc, 4:1); mp 58–59 °C. IR (KBr) 3379, 1672, 1460, 1420, 1374, 1234, 1109, 1070, 999, 980, 904, 751 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.05 (t, J = 7.7 Hz, 3H, H-6), 1.12 (t, J = 7.3 Hz, 3H, H-1), 2.58 (q, J = 7.7 Hz, 2H, H-5), 2.79 (q, J = 7.3 Hz, 2H, H-2), 8.95 (br s, 1H, NOH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.0 (C-1), 10.3 (C-6), 16.1 (C-5), 30.8 (C-2), 160.9 (C-4), 199.6 (C-3). MS (70 eV) m/z 129 (M^+, 29), 112 (30), 101 (16), 84 (21), 72 (17), 57 (100). HRMS (EI) m/z [M^+] Calcd for $C_6H_{11}NO_2$: 129.0790. Found: 129.0788.

4.16. 3-(Hydroxyimino)pentan-2-one 12c

Synthesized according to method F, with **11a** (0.86 g, 10.0 mmol), $NaNO_2$ (1.03 g, 15.0 mmol) and H_2SO_4 (1.92 g, 19.6 mmol), **12c** (0.73 g, 63%) was afforded as a white solid. R_f 0.36 (hexane/EtOAc, 4:1); mp 55–56 °C. IR (film) 3202, 3045, 2978, 2947, 1668, 1432, 1377, 1248, 1074, 1051, 989, 929, 806, 741 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.05 (t, J = 8.0 Hz, 3H, H-5), 2.39 (s, 3H, H-1), 2.58 (q, J = 8.0 Hz, 2H, H-4), 9.10 (br s, 1H, NOH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.3 (C-5), 15.9 (C-4), 25.3 (C-1), 161.5 (C-3), 197.2 (C-2). MS (70 eV) m/z 115 (M^+, 51), 98 (100), 84 (22), 72 (20), 54 (19). HRMS (EI) m/z [M^+] Calcd for $C_5H_9NO_2$: 115.0633. Found: 115.0639.

4.17. 2-(Hydroxyimino)pentan-3-one 12d

Synthesized according to method F, with **11b** (0.86 g, 10.0 mmol), $NaNO_2$ (1.03 g, 15.0 mmol) and H_2SO_4 (1.92 g, 19.6 mmol), **12d** (0.75 g, 65%) was afforded as a white solid. R_f 0.36 (hexane/EtOAc, 4:1); mp 59–60 °C. IR (film) 3323, 1668, 1406, 1374, 1266, 1044, 1015, 911, 796, 731 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.11 (t, J = 7.5 Hz, 3H, H-5), 2.00 (s, 3H, H-1), 2.80 (q, J = 7.5, Hz, 2H, H-4), 8.70 (br s, 1H, NOH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.9 (C-5), 8.3 (C-1), 30.5 (C-4), 156.6 (C-2), 199.7 (C-3). MS (70 eV) m/z 115 (M^+, 50), 98 (100), 84 (21), 72 (17), 54 (18). Anal. Calcd for $C_5H_9N_1O_2$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.16; H, 7.86; N, 12.18.

4.18. 3-(Hydroxyimino)hexan-2-one 12e

Synthesized according to method F, with **11c** (1.10 g, 11.0 mmol), $NaNO_2$ (4.55 g, 66.0 mmol) and H_2SO_4 (6.857 g, 0.070 mol), **12e** (0.81 g, 57%) was afforded as a pale yellow solid. R_f 0.63 (hexane/EtOAc, 7:3); mp 43–45 °C. IR (KBr) 3333, 2965, 1680, 1418, 1367, 1227, 1135, 1063, 986, 958, 609 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, J = 7.5, 3H, H-6), 1.48 (sext, J = 7.5 Hz, 2H, H-5), 2.37 (s, 3H, H-1), 2.53 (t, J = 7.5, 2H, H-4), 8.75 (br s, 1H, NOH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2 (C-6), 19.4 (C-5), 24.3 (C-4), 25.3 (C-1), 160.5 (C-3), 197.1 (C-2). Anal. Calcd for $C_6H_{11}NO_2$: C, 55.80; H, 8.58; N, 10.84. Found: C, 55.83; H, 8.55; N, 10.81.

4.19. 1-(4-Methoxyphenyl)propan-1-one 11d

In a two-necked round bottom flask under N_2 atmosphere and at 0 °C, anisole (1.08 g, 10.0 mmol) and propionyl chloride

(1.39 g, 15.0 mmol) were mixed and the mixture stirred for 15 min. Then, at the same temperature, $BF_3{\cdot}Et_2O$ (1.42 g, 10.0 mmol) was added dropwise and the mixture stirred for 4 h. The mixture was washed with an aqueous saturated solution of $NaHCO_3$ until neutral, then the organic layer was extracted with EtOAc (3×10 mL). The organic layer was dried (Na_2SO_4) and the solvent removed under vacuum. The residue was purified by column chromatography over silica gel (20 g/g crude, hexane/EtOAc, 85:15) to give **11d** (0.73 g, 45%) as a yellow oil. R_f 0.36 (hexane/EtOAc, 8:2). IR (film) 2975, 2937, 1679, 1601, 1509, 1459, 1352, 1309, 1257, 1227, 1171, 1030, 952, 843, 799 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (t, J = 7.3 Hz, 3H, CH_3CH_2CO), 2.95 (q, J = 7.3 Hz, 2H, CH_3CH_2CO), 3.86 (s, 3H, CH_3OAr), 6.90–6.95 (m, 2H, H-3′), 7.92–7.98 (m, 2H, H-2′). ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.3 (CH_3CH_2CO), 31.4 (CH_3CH_2CO), 55.3 (CH_3OAr), 113.6 (C-3′), 129.9 (C-1′), 130.2 (C-2′), 163.2 (C-4′), 199.5 (CH_3CH_2CO). Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.20; H, 7.32.

4.20. 1-(4-Methoxyphenyl)propane-1,2-dione 10c

In a two-necked round bottom flask under N_2 atmosphere at 0 °C, to a stirred mixture of **11d** (1.64 g, 10.0 mmol) in Et_2O (10 mL) and $NaNO_2$ (4.14 g, 60.0 mmol) a concd aqueous solution of HCl (37%) (9.86 g, 0.1 mol) was added dropwise. The mixture was stirred at room temperature for 24 h, then washed with an aqueous saturated solution of $NaHCO_3$ until neutral, and the organic layer was extracted with EtOAc (3×10 mL). The combined organic layers were dried (Na_2SO_4) and the solvent removed under vacuum. The residue was purified by column chromatography over silica gel (20 g/g crude, hexane/EtOAc, 85:15) to give **10c** (0.77 g, 43%) as a yellow solid. R_f 0.36 (Hexane/EtOAc, 8:2); mp 50–51 °C [Lit.[41] 44–45 °C; Lit.[42] 38–39 °C]. IR (film) 2935, 1708, 1655, 1597, 1571, 1509, 1422, 1307, 1261, 1152, 1025, 900, 841, 755, 693 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.50 (s, 3H, CH_3CO), 3.88 (s, 3H, CH_3OAr), 6.88–7.02 (m, 2H, H-3′), 7.96–8.05 (m, 2H, H-2′). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.4 (CH_3CO), 55.5 (CH_3OAr), 114.0 (C-3′), 124.5 (C-1′), 132.6 (C-2′), 164.7 (C-4′), 189.9 (CH_3COCO), 201.1 (CH_3COCO). Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66. Found: C, 67.43; H, 5.65.

4.21. 2-(Hydroxyimino)-1-(4-methoxyphenyl)propan-1-one 12f

Prepared according to method E, with **10c** (1.78 g, 10.0 mmol), hydroxylamine hydrochloride (0.695 g, 10.0 mmol) and pyridine (0.87 g, 11.0 mmol), **12f** (1.37 g, 71%) was afforded as a yellow solid. Alternatively, prepared according to a modification of method C, with **11d** (1.64 g, 10.0 mmol), $NaNO_2$ (2.07 g, 30.0 mmol) in MeOH (30 mL), and an aqueous concd solution of HCl (37%) (3.95 g, 40.0 mmol) in MeOH (10 mL) **12f** was afforded in the following manner. After stirring at room temperature for 24 h, $NaNO_2$ (2.07 g, 30.0 mmol) in MeOH (30 mL), and an aqueous concd solution of HCl (37%) (3.95 g, 40.0 mmol) in MeOH (10 mL) were successively added and the mixture was stirred for 24 h. This operation was repeated again. The mixture was washed with an aqueous saturated solution of $NaHCO_3$ until neutral, and the organic layer was extracted with EtOAc (3×10 mL). The combined organic layers were dried (Na_2SO_4) and the solvent removed under vacuum. The residue was purified by column chromatography over silica gel (20 g/g crude, hexane/EtOAc, 97:3) to give **12f** (1.01 g, 52%) as a yellow solid. R_f 0.40 (Hex/AcOEt 7:3); mp 128–129 °C [Lit.[43] 114–118 °C]. IR (film) 3247, 2923, 1651, 1599, 1513, 1458, 1328, 1276, 1116, 1019, 899, 848, 758, 745 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.17 (s, 3H, CH_3CNOH), 3.87 (s, 3H, CH_3OAr), 6.86–6.98 (m, 2H, H-3′), 7.92–7.98 (m, 2H, H-2′), 8.31 (br s, 1H, NO*H*). ^{13}C RMN (75 MHz, $CDCl_3$) δ 10.5 (CH_3CNOH), 55.5 (CH_3OAr), 113.5 (C-3′), 128.8 (C-1′), 132.8 (C-2′), 157.0 (CH_3CNOH), 163.6 (C-4′), 190.0 ($CH_3CNOHCO$). Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.13; H, 5.75; N, 7.25.

4.22. 1,3,5-Tris((*S*)-1-phenylethyl)-1,3,5-triazine 13

In a round bottom flask at room temperature, a mixture of (*S*)-(−)-α-methylbenzylamine (4.84 g, 0.04 mol) 1.0 mol equiv) and a 38% methanolic solution of formaldehyde (3.79 g, 0.048 mol) was stirred for 1 h. The mixture was filtered, washing the solid phase with MeOH (5 mL). The solid was dried under vacuum, giving **13** (15.3 g, 96%) as a white solid. mp 45–46 °C. $[\alpha]_D^{26}$ = +120.0 (*c* 1.15, MeOH). IR (KBr) 3013, 2970, 2800, 1491, 1452, 1370, 1350, 1303, 1283, 1206, 1114, 1082, 911, 761, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (d, J = 6.5 Hz, 3H, H-2′), 3.34 (br s, 2H, H-2), 3.67 (q, J = 6.5 Hz, 1H, H-1′), 7.12–7.27 (m, 5H, H-2″, H-3″, H-4″). ^{13}C RMN (75 MHz, $CDCl_3$) δ 20.1 (C-2′), 59.4 (C-1′), 70.0 (C-2), 126.7 (C-4″), 127.3 (C-2″ or C-3″), 128.1 (C-3″ or C-2″), 144.3 (C-1″). MS (70 eV) m/z 399 (M^+, 1), 212 (4), 156 (8), 139 (14), 106 (25), 105 (100), 103 (26), 91 (10), 79 (30), 77 (19). HRMS (EI) m/z [M^+] Calcd for $C_{27}H_{33}N_3$: 399.2674. Found: 399.2691.

4.23. (*S*)-4-(Methoxymethyl)-5-methyl-1-(1-phenylethyl)-1*H*-imidazole 3-oxide 8a

Synthesized according to method G, with **6a** (0.500 g, 3.82 mmol) and **13** (0.762 g, 1.91 mmol) and heating for 4 h, **8a** (0.77 g, 82%) was afforded as a brown oil. R_f 0.28 (hexane/EtOAc/MeOH, 1:1:0.1). $[\alpha]_D^{25}$ = +94.8 (*c* 0.29, MeOH). IR (film) 3397, 2981, 2934, 1653, 1454, 1334, 1220, 1195, 1091, 768, 703 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.85 (d, J = 6.9 Hz, 3H, CH_3-2′), 2.10 (s, 3H, CH_3-5), 3.38 (s, 3H, CH_3O), 4.45 (d, J = 12.3 Hz, 1H, OCH_2-4), 4.50 (d, J = 12.3 Hz, 1H, OCH_2-4), 5.26 (q, J = 6.9 Hz, 1H, C*H*-1′), 7.09–7.15 (m, 2H, H-2″), 7.24–7.40 (m, 3H, H-3″, H-4″), 8.35 (s, 1H, H-2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.9 (CH_3-5), 22.0 (CH_3-2′), 56.1 (C*H*-1′), 58.2 (CH_3O), 60.7 (OCH_2-4), 124.2 (C-2), 125.2 (C-5), 125.6 (C-2″), 127.2 (C-4), 128.4 (C-4″), 129.2 (C-3″), 139.4 (C-1″). MS (70 eV) m/z 246 (M^+, 3), 230 (8), 200 (60), 156 (6), 105 (100), 94 (28), 77 (24). HRMS (EI) m/z [M^+] Calcd for $C_{14}H_{18}N_2O_2$: 246.1368. Found: 246.1366.

4.24. (*S*)-4-(Ethoxymethyl)-5-methyl-1-(1-phenylethyl)-1*H*-imidazole 3-oxide 8b

Synthesized according to method G, with **6b** (0.500 g, 3.45 mmol) and **13** (0.688 g, 1.72 mmol) and heating for 4 h, **8b** (0.72 g, 81%) was afforded as a brown oil. R_f 0.30 (hexane/EtOAc/MeOH, 1:1:0.1). $[\alpha]_D^{26}$ = +63.7 (*c* 0.186, MeOH). IR (film) 3390, 2976, 1619, 1494, 1452, 1402, 1330, 1219, 1199, 1089, 769, 703 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.21 (t, J = 7.0 Hz, 3H, CH_3CH_2O), 1.80 (d, J = 7.0 Hz, 3H, CH_3-2′), 2.13 (s, 3H, CH_3-5), 3.60 (q, J = 7.0 Hz, 2H, CH_3CH_2O), 4.53 (d, J = 13.0 Hz, 1H, OCH_2-4), 4.61 (d, J = 13.0 Hz, 1H, OCH_2-4), 5.26 (q, J = 7.0 Hz, 1H, C*H*-1′), 7.11 (d, J = 6.5 Hz, 2H, H-2″), 7.27–7.40 (m, 3H, H-3″, H-4″), 7.96 (s, 1H, H-2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.8 (CH_3-5), 15.0 (CH_3CH_2O), 21.8 (CH_3-2′), 55.5 (C*H*-1′), 59.1 (OCH_2-4), 65.9 (CH_3CH_2O), 122.8 (C-2), 124.6 (C-5), 125.5 (C-2″), 127.9 (C-4), 128.3 (C-4″), 129.1 (C-3″), 139.5 (C-1″). EM (70 eV) m/z 260 (M^+, 4), 189 (12), 171 (40), 145 (83), 144 (80), 130 (36), 104 (81), 103 (100), 77 (49), 59 (29). HRMS (EI) m/z [M^+] Calcd for $C_{15}H_{20}N_2O_2$: 260.1525. Found: 260.1524.

4.25. (*S*)-4-(Isopropoxymethyl)-5-methyl-1-(1-phenylethyl)-1*H*-imidazole 3-oxide 8c

Synthesized according to method G, with **6c** (0.500 g, 3.14 mmol) and **13** (0.626 g, 1.57 mmol) and heating for 4 h, **8c**

(0.65 g, 75%) was afforded as a brown oil. R_f 0.31 (hexane/EtOAc/MeOH, 1:1:0.1). $[\alpha]_D^{26}$ = +58.6 (*c* 0.11, MeOH). IR (film) 3398, 2973, 1624, 1454, 1382, 1369, 1328, 1220, 1200, 1123, 1052, 767, 704 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.19 (d, *J* = 6.0 Hz, 3H, $(CH_3)_2CH$), 1.20 (d, *J* = 6.0 Hz, 3H, $(CH_3)_2CH$), 1.82 (d, *J* = 7.0 Hz, 3H, CH_3-2′), 2.13 (s, 3H, CH_3-5), 3.76 (sept, *J* = 6.0 Hz, 1H, $(CH_3)_2CH$), 4.53 (d, *J* = 12.5 Hz, 1H, OCH_2-4), 4.61 (d, *J* = 12.5 Hz, 1H, OCH_2-4), 5.27 (q, *J* = 7.0 Hz, 1H, CH-1′), 7.13 (br d, *J* = 7.0 Hz, 2H, H-2″), 7.28–7.39 (m, 3H, H-3″, H-4″), 8.17 (s, 1H, H-2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.8 (CH_3-5), 21.87 (CH_3-2′), 21.89 ($(CH_3)_2CH$), 22.0 ($(CH_3)_2CH$), 55.6 (CH-1′), 57.1 (OCH_2-4), 71.4 ($(CH_3)_2CH$), 123.3 (C-2), 124.5 (C-5), 125.6 (C-2″), 128.1 (C-4), 128.3 (C-4″), 129.1 (C-3″), 139.6 (C-1″). EM (70 eV) *m*/*z* 200 (M^+−74, 46), 156 (6), 120 (6), 105 (100), 95 (37), 77 (24). HRMS (EI) *m*/*z* [M^+] Calcd for $C_{16}H_{22}N_2O_2$: 274.1681. Found: 274.1692.

4.26. (*S*)-5-Methyl-1-(1-phenylethyl)-4-(phenylthiomethyl)-1*H*-imidazole 3-oxide 8d

Synthesized according to method G, with **7a** (0.500 g, 2.39 mmol) and **13** (0.477 g, 1.20 mmol) and heating for 1 h, **8d** (0.66 g, 85%) was afforded as a brown oil. R_f 0.18 (hexane/EtOAc/MeOH, 1:1:0.1). $[\alpha]_D^{27}$ = −39.1 (*c* 0.0197, MeOH). IR (film) 3412, 1646, 1494, 1438, 1407, 1338, 1245, 1218, 1024, 889, 746, 696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.59 (s, 3H, CH_3-5), 1.75 (d, *J* = 6.9 Hz, 3H, CH_3-2′), 4.05 (d, *J* = 14.0 Hz, 1H, SCH_2-4), 4.13 (d, *J* = 14.0 Hz, 1H, SCH_2-4), 5.13 (q, *J* = 6.9 Hz, 1H, CH-1′), 7.01 (dd, *J* = 7.8, 2.1 Hz, 2H, H-2″), 7.10–7.22 (m, 3H, H-2‴, H-4‴), 7.30–7.40 (m, 5H, H-3″, H-4″, H-3‴), 8.00 (s, 1H, H-2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.3 (CH_3-5), 21.7 (CH_3-2′), 26.2 (SCH_2-4), 55.3 (CH-1′), 122.6 (C-2), 123.2 (C-5), 125.3 (C-2″), 126.7 (C-4), 127.1 (C-4‴), 128.1 (C-4″), 128.6 (C-2‴), 128.9 (C-3″), 132.4 (C-3‴), 134.6 (C-1‴), 139.5 (C-1″). MS (70 eV) *m*/*z* 324 (M^+, 7), 311 (5), 274 (8), 230 (9), 205 (12), 186 (17), 160 (11), 109 (100), 88 (16), 65 (25). HRMS (EI) *m*/*z* [M^+] Calcd for $C_{19}H_{20}N_2OS$: 324.1296. Found: 324.1294.

4.27. (*S*)-4-((4-Chlorophenylthio)methyl)-5-methyl-1-(1-phenylethyl)-1*H*-imidazole 3-oxide 8e

Synthesized according to method G, with **7b** (0.500 g, 2.06 mmol) and **13** (0.410 g, 1.05 mmol) and heating for 1 h, **8e** (0.583 g, 80%) was afforded as a pale yellow oil. R_f 0.19 (hexane/EtOAc/MeOH, 1:1:0.1). $[\alpha]_D^{25}$ = −61.1 (*c* 0.157, MeOH). IR (film) 3392, 1673, 1475, 1454, 1387, 1338, 1094, 1012, 817, 764, 702 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.70 (s, 3H, CH_3-5), 1.77 (d, *J* = 7.0 Hz, 3H, CH_3-2′), 4.05 (d, *J* = 14.0 Hz, 1H, SCH_2-4), 4.14 (d, *J* = 14.0 Hz, 1H, SCH_2-4), 5.15 (q, *J* = 7.0 Hz, 1H, CH-1′), 7.01 (dd, *J* = 8.0, 2.0 Hz, 2H, H-2″), 7.10–7.14 (m, 2H, H-2‴), 7.27–7.31 (m, 2H, H-3‴), 7.32–7.38 (m, 3H, H-3″, H-4″), 8.04 (s, 1H, H-2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.5 (CH_3-5), 21.6 (CH_3-2′), 26.1 (SCH_2-4), 55.7 (CH-1′), 123.0 (C-2), 123.4 (C-5), 125.3 (C-2″), 126.2 (C-4), 128.2 (C-4″), 128.7 (C-2‴), 129.0 (C-3″), 132.9 (C-4‴), 133.2 (C-1‴), 133.5 (C-3‴), 139.4 (C-1″). MS (70 eV) *m*/*z* 358 (M^+, 3), 278 (100), 245 (24), 230 (46), 214 (50), 199 (14), 139 (84), 124 (73), 96 (71). HRMS (EI) *m*/*z* [M^+] Calcd for $C_{19}H_{19}N_2OSCl$: 358.0907. Found: 358.0902.

4.28. (*S*)-4-((4-Bromophenylthio)methyl)-5-methyl-1-(1-phenylethyl)-1*H*-imidazole 3-oxide 8f

Synthesized according to method G, with **7c** (0.500 g, 1.74 mmol) and **13** (0.339 g, 0.85 mmol) and heating for 1 h, **8f** (0.55 g, 79%) was afforded as a pale yellow oil. R_f 0.19 (hexane/EtOAc/MeOH, 1:1:0.1). $[\alpha]_D^{28}$ = −57.4 (*c* 0.19, MeOH). IR (film) 3368, 3085, 2981, 1673, 1620, 1473, 1452, 1385, 1336, 1245, 1091, 1067, 1008, 813, 764, 701 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.73 (s, 3H, CH_3-5), 1.77 (d, *J* = 7.0 Hz, 3H, CH_3-2′), 4.07 (d, *J* = 14.0 Hz, 1H, SCH_2-4), 4.15 (d, *J* = 14.0 Hz, 1H, SCH_2-4), 5.15 (q, *J* = 7.0 Hz, 1H, CH-1′), 7.01 (dd, *J* = 7.5, 1.5 Hz, 2H, H-2″), 7.22–7.26 (m, 2H, H-2‴), 7.26–7.30 (m, 2H, H-3‴), 7.33–7.39 (m, 3H, H-3″, H-4″), 7.97 (s, 1H, H-2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.7 (CH_3-5), 21.8 (CH_3-2′), 25.9 (SCH_2-4), 55.7 (CH-1′), 121.2 (C-4‴), 122.8 (C-2), 123.4 (C-5), 125.4 (C-2″), 126.6 (C-4), 128.4 (C-4″), 129.2 (C-3″), 131.8 (C-2‴), 133.5 (C-3‴), 134.1 (C-1‴), 139.6 (C-1″). MS (70 eV) *m*/*z* 402 (M^+, 1), 378 (17), 376 (27), 297 (5), 189 (100), 187 (97), 108 (69), 69 (11). HRMS (EI) *m*/*z* [M^+] Calcd for $C_{19}H_{19}N_2OSBr$: 402.0401. Found: 402.0391.

4.29. (*S*)-4,5-Dimethyl-1-(1-phenylethyl)-1*H*-imidazole 3-oxide 8g

Synthesized according to method G, with **12a** (0.505 g, 5.00 mmol) and **13** (1.00 g, 2.5 mmol) and heating for 12 h, **8g** (1.05 g, 98%) was afforded as a white solid. R_f 0.41 (hexane/EtOAc/MeOH, 1:1:0.1); mp 105–106 °C [Lit.[12a] 105–106 °C; Lit.[34b] 230 °C]. $[\alpha]_D^{26}$ = +134.7 (*c* 0.835, MeOH) [Lit.[34b] +131.5 (*c* 1.02, MeOH)]. IR (film) 3394, 3058, 2983, 1631, 1453, 1407, 1379, 1332, 1196, 1147, 751, 698 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.79 (d, *J* = 7.0 Hz, 3H, CH_3-2′), 2.00 (s, 3H, CH_3-5), 2.18 (s, 3H, CH_3-4), 5.23 (q, *J* = 7.0 Hz, 1H, CH-1′), 7.08 (dd, *J* = 7.5, 1.5 Hz, 2H, H-2″), 7.28–7.33 (m, 1H, H-4″), 7.33–7.38 (m, 2H, H-3″), 7.94 (s, 1H, H-2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.1 (CH_3-4), 8.9 (CH_3-5), 21.9 (CH_3-2′), 55.4 (CH-1′), 121.1 (C-5), 122.4 (C-2), 125.5 (C-2″), 127.1 (C-4), 128.2 (C-4″), 129.1 (C-3″), 140.0 (C-1″). MS (70 eV) *m*/*z* 216 (M^+, 19), 116 (28), 111 (33), 105 (100), 103 (38), 77 (41). HRMS (EI) [M^++1] Calcd for $C_{13}H_{17}N_2O$: 217.1341. Found: 217.1340.

4.30. (*S*)-4,5-Diethyl-1-(1-phenylethyl)-1*H*-imidazole 3-oxide 8h

Synthesized according to method G, with **12b** (0.500 g, 3.88 mmol) and **13** (0.773 g, 1.94 mmol) and heating for 12 h, **8h** (0.88 g, 93%) was afforded as a white solid. R_f 0.45 (hexane/EtOAc/MeOH, 1:1:0.1). $[\alpha]_D^{24}$ = +99.8 (*c* 0.489, MeOH). IR (film) 3378, 2974, 2936, 1664, 1454, 1403, 1380, 1352, 1314, 1258, 1216, 1185, 860, 764, 702 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.00 (t, *J* = 7.5 Hz, 3H, CH_3CH_2-5), 1.23 (t, *J* = 7.5 Hz, 3H, CH_3CH_2-4), 1.80 (d, *J* = 7.0 Hz, 3H, CH_3-2′), 2.38–2.53 (m, 2H, CH_3CH_2-5), 2.58–2.74 (m, 1H, CH_3CH_2-4), 5.26 (q, *J* = 7.0 Hz, 1H, CH-1′), 7.09 (br d, *J* = 7.0 Hz, 2H, H-2″), 7.28–7.33 (m, 1H, H-4″), 7.33–7.40 (m, 2H, H-3″), 7.96 (s, 1H, H-2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.1 (CH_3CH_2-4), 14.3 (CH_3CH_2-5), 15.4 (CH_3CH_2-5), 16.5 (CH_3CH_2-4), 22.3 (CH_3-2′), 55.1 (CH-1′), 122.7 (C-2), 125.4 (C-2″), 126.6 (C-5), 128.3 (C-4″), 129.1 (C-3″), 131.7 (C-4), 140.3 (C-1″). MS (70 eV) *m*/*z* 244 (M^+, 1), 228 (100), 199 (40), 124 (29), 109 (25), 105 (85). Anal. Calcd for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.47. Found: C, 73.76; H, 8.19; N, 11.49.

4.31. (*S*)-4-Ethyl-5-methyl-1-(1-phenylethyl)-1*H*-imidazole 3-oxide 8i

Synthesized according to method G, with **12c** (0.50 g, 4.4 mmol) and **13** (0.868 g, 2.20 mmol) and heating for 12 h, **8i** (0.96 g, 96%) was afforded as a pale yellow oil. R_f 0.42 (hexane/EtOAc/MeOH, 1:1:0.1). $[\alpha]_D^{23}$ = +6.8 (*c* 1.614, MeOH). IR (film) 3410, 2981, 1647, 1494, 1455, 1352, 1316, 1265, 1218, 1145, 851, 765, 704 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.21 (t, *J* = 7.5 Hz, 3H, CH_3CH_2-4), 1.79 (d, *J* = 7.0 Hz, 3H, CH_3-2′), 2.02 (s, 3H, CH_3-5), 2.58–2.74 (m, 2H, CH_3CH_2-4), 5.22 (q, *J* = 7.0 Hz, 1H, CH-1′), 7.08 (br d, *J* = 8.0 Hz, 2H, H-2″), 7.28–7.33 (m, 1H, H-4″), 7.33–7.38 (m, 2H, H-3″), 7.91 (s, 1H, H-2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.7 (CH_3-5), 12.8 (CH_3CH_2-4), 15.3 (CH_3CH_2-4), 22.0 (CH_3-2′), 55.5 (CH-1′), 120.8 (C-5), 122.6 (C-2), 125.5 (C-2″), 128.3 (C-4″), 129.1 (C-3″), 132.3 (C-4), 140.0 (C-1″). MS (70 eV) *m*/*z* 230 (M^+, 1), 214 (16),

199 (13), 123 (9), 105 (100), 95 (15), 77 (24). HRMS (EI) [M$^+$] Calcd for $C_{14}H_{18}N_2O$: 230.1419. Found: 230.1427.

4.32. (*S*)-5-Ethyl-4-methyl-1-(1-phenylethyl)-1*H*-imidazole 3-oxide 8j

Synthesized according to method G, with **12d** (0.500 g, 4.35 mmol) and **13** (0.867 g, 2.17 mmol) and heating for 12 h, **8j** (1.00 g, 91%) was afforded as a yellow oil. R_f 0.34 (hexane/EtOAc/MeOH, 1:1:0.1). $[\alpha]_D^{26}$ = +101.7 (*c* 0.168, MeOH). IR (film) 3400, 2979, 1651, 1622, 1454, 1406, 1384, 1336, 1218, 1145, 766, 705 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, *J* = 7.5 Hz, 3H, C*H*$_3$-CH$_2$-5), 1.80 (d, *J* = 6.9 Hz, 3H, C*H*$_3$-2′), 2.21 (s, 3H, C*H*$_3$-4), 2.35–2.55 (m, 2H, CH$_3$C*H*$_2$-5), 5.27 (q, *J* = 6.9 Hz, 1H, C*H*-1′), 7.06–7.15 (m, 2H, H-2″), 7.28–7.40 (m, 3H, H-3″, H-4″), 7.93 (s, 1H, H-2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.1 (*C*H$_3$-4), 13.7 (*C*H$_3$CH$_2$-5), 16.7 (CH$_3$*C*H$_2$-5), 22.3 (*C*H$_3$-2′), 55.1 (*C*H-1′), 122.4 (C-2), 125.4 (C-2″), 126.7 (C-4), 126.9 (C-5), 128.3 (C-4″), 129.1 (C-3″), 140.3 (C-1″). MS (70 eV) *m*/*z* 230 (M$^+$, 7), 215 (12), 214 (20), 181 (7), 126 (14), 110 (60), 106 (100), 103 (21), 96 (30), 79 (22), 77 (16). HRMS (EI) [M$^+$] Calcd for $C_{14}H_{18}N_2O$: 230.1419. Found: 230.1416.

4.33. (*S*)-5-Methyl-1-(1-phenylethyl)-4-propyl-1*H*-imidazole 3-oxide 8k

Synthesized according to method G, with **12e** (0.500 g, 3.88 mmol) and **13** (0.773 g, 1.94 mmol) and heating for 12 h, **8k** (0.85 g, 90%) was afforded as a pale yellow solid. R_f 0.40 (hexane/EtOAc/MeOH, 1:1:0.1); mp 60–61 °C. $[\alpha]_D^{24}$ = +97.6 (*c* 0.101, MeOH). IR (film) 3393, 2962, 2932, 1676, 1495, 1455, 1383, 1359, 1329, 1216, 1027, 765, 703 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.5 Hz, 3H, C*H*$_3$(CH$_2$)$_2$-4), 1.67 (sext, *J* = 7.5 Hz, 2H, CH$_3$C*H*$_2$CH$_2$-4), 1.79 (d, *J* = 7.0 Hz, 3H, C*H*$_3$-2′), 2.00 (s, 3H, C*H*$_3$-5), 2.50–2.70 (m, 2H, CH$_3$CH$_2$C*H*$_2$-4), 5.23 (q, *J* = 7.0 Hz, 1H, C*H*-1′), 7.04–7.11 (m, 2H, H-2″), 7.27–7.41 (m, 3H, H-3″, H-4″), 7.99 (s, 1H, H-2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.9 (*C*H$_3$-5), 13.7 (*C*H$_3$CH$_2$CH$_2$-4), 21.3 (CH$_3$*C*H$_2$-CH$_2$-4), 22.0 (*C*H$_3$-2′), 23.7 (CH$_3$CH$_2$*C*H$_2$-4), 55.6 (*C*H-1′), 121.6 (C-5), 122.8 (C-2), 125.5 (C-2″), 128.3 (C-4″), 129.2 (C-3″), 130.8 (C-4), 140.1 (C-1″). Anal. Calcd for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.47. Found: C, 73.71; H, 8.35; N, 11.42.

4.34. (*S*)-5-(4-Methoxyphenyl)-4-methyl-1-(1-phenylethyl)-1*H*-imidazole 3-oxide 8l

Synthesized according to method G, with **12f** (1.93 g, 10.0 mmol) and **13** (2.00 g, 5.0 mmol) and heating for 12 h, **8l** (2.95 g, 96%) was afforded as a pale yellow oil. R_f 0.36 (hexane/EtOAc/MeOH, 1:1:0.1). $[\alpha]_D^{27}$ = −37.3 (*c* 0.26, MeOH). IR (film) 3289, 2977, 2932, 1713, 1603, 1513, 1453, 1418, 1326, 1252, 1175, 1021, 833, 762, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.73 (d, *J* = 7.1 Hz, 3H, C*H*$_3$-2′), 2.13 (s, 3H, C*H*$_3$-4), 3.85 (s, 3H, C*H*$_3$O), 5.19 (q, *J* = 7.1 Hz, 1H, C*H*-1′), 6.88–6.95 (m, 2H, H-3‴), 6.96–7.08 (m, 4H, H-2″, H-2‴), 7.16–7.38 (m, 3H, H-3″, H-4″), 8.23 (s, 1H, H-2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.58 (*C*H$_3$-4), 21.9 (*C*H$_3$-2′), 55.3 (*C*H$_3$O), 55.6 (*C*H-1′), 114.3 (C-3‴), 119.1 (C-1‴), 123.8 (C-2), 125.8 (C-2″), 126.5 (C-5), 127.7 (C-4), 128.3 (C-4″), 129 (C-3″), 131.8 (C-2‴), 140.1 (C-1″), 160.4 (C-4‴). HRMS (EI) [M$^+$] Calcd for $C_{19}H_{20}N_2O_2$: 308.1525. Found: 308.1520.

4.35. (*S*)-1-Acetyl-5-((4-chlorophenylthio)methyl)-4-methyl-3-(1-phenylethyl)-1*H*-imidazol-2(3*H*)-one 14d

Synthesized according to method H, with **8e** (0.300 g, 0.84 mmol) and acetic anhydride, **14d** (3.15 g, 94%) was afforded as a colorless oil. R_f 0.60 (hexane/EtOAc, 7:3). $[\alpha]_D^{27}$ = +26.8 (*c* 0.306, MeOH). IR (film) 1711, 1474, 1409, 1361, 1313, 1236, 1179, 1093, 1012, 820, 699 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 3H, C*H*$_3$-4), 1.73 (d, *J* = 7.1 Hz, 3H, C*H*$_3$-2′), 2.73 (s, 3H, C*H*$_3$-CO-1), 4.11 (s, 2H, SC*H*$_2$-5), 5.50 (q, *J* = 7.1 Hz, 1H, C*H*-1′), 7.10–7.15 (m, 2H, H-2‴), 7.19–7.26 (m, 4H, H-2″, H-3‴), 7.30–7.40 (m, 3H, H-4″, 3″). ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.8 (*C*H$_3$-4), 18.0 (*C*H$_3$-2′), 26.3 (*C*H$_3$CO-1), 32.0 (SC*H*$_2$-5), 50.6 (*C*H-1′), 113.8 (C-5), 121.9 (C-4), 126.4 (C-2″), 127.6 (C-4″), 128.7 (C-3″), 128.9 (C-2‴), 132.7 (C-4‴), 134.4 (C-1‴), 135.8 (C-3‴), 139.9 (C-1″), 152.3 (C-2), 170.9 (CH$_3$*C*O-1). MS (70 eV) *m*/*z* 400 (M$^+$, 1), 144 (100), 109 (55), 82 (25), 69 (54). HRMS (EI) *m*/*z* [M$^+$] Calcd for $C_{21}H_{21}ClN_2O_2S$: 400.1012. Found: 400.1021.

4.36. (*S*)-1-Acetyl-5-((4-bromophenylthio)methyl)-4-methyl-3-(1-phenylethyl)-1*H*-imidazol-2(3*H*)-one 14e

Synthesized according to method H, with **8f** (0.500 g, 1.24 mmol) and acetic anhydride, **14e** (0.535 g, 97%) was afforded as a colorless oil. R_f 0.80 (hexane/EtOAc, 8:2). $[\alpha]_D^{25}$ = −65.7 (*c* 0.087, MeOH). IR (film) 1709, 1655, 1472, 1409, 1361, 1312, 1235, 1179, 1009, 816, 699 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (s, 3H, C*H*$_3$-4), 1.74 (d, *J* = 7.5 Hz, 3H, C*H*$_3$-2′), 2.73 (s, 3H, C*H*$_3$-CO$_2$), 4.11 (s, 2H, SC*H*$_2$-5), 5.50 (q, *J* = 7.5 Hz, 1H, C*H*-1′), 7.14–7.17 (m, 2H, H-3‴), 7.22 (br d, *J* = 8.0 Hz, 2H, H-2″), 7.26–7.29 (m, 2H, H-2‴), 7.28–7.33 (m, 1H, H-4″), 7.34–7.39 (m, 2H, H-3″). ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.8 (*C*H$_3$-4), 18.0 (*C*H$_3$-2′), 26.2 (*C*H$_3$CO-1), 31.8 (SC*H*$_2$-5), 50.6 (*C*H-1′), 113.8 (C-5), 121.9 (C-4), 122.4 (C-4‴), 126.4 (C-2″), 127.6 (C-4″), 128.7 (C-3″), 131.9 (C-2‴), 133.5 (C-1‴), 135.9 (C-3‴), 139.9 (C-1″), 152.3 (C-2), 170.8 (CH$_3$*C*O-1); MS (70 eV) *m*/*z* 444 (M$^+$, 1), 190 (100), 188 (93), 109 (99), 84 (16), 69 (13). HRMS (EI) *m*/*z* [M$^+$] Calcd for $C_{21}H_{21}BrN_2O_2S$: 444.0507. Found: 444.0512.

4.37. (*S*)-1-Acetyl-4,5-dimethyl-3-(1-phenylethyl)-1*H*-imidazol-2(3*H*)-one 14f

4.37.1. (*S*)-5-(Acetoxymethyl)-4-methyl-1-(1-phenylethyl)-1*H*-imidazole 15a

Synthesized according to method H, with **8g** (0.500 g, 2.31 mmol) and acetic anhydride, **14f** (0.32 g, 54%) was afforded as a yellow oil and **15a** (0.12 g, 20%) as a yellow oil.

Data of **14f**: R_f 0.63 (hexane/EtOAc, 7:3). $[\alpha]_D^{25}$ = −52.25 (*c* 1.68, MeOH). IR (film) 1711, 1669, 1450, 1370, 1312, 1176, 1026, 751, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68 (d, *J* = 0.9 Hz, 3H, C*H*$_3$-4), 1.79 (d, *J* = 7.2 Hz, 3H, C*H*$_3$-2′), 2.19 (d, *J* = 1.2 Hz, 3H, C*H*$_3$-5), 2.67 (s, 3H, C*H*$_3$CO-1), 5.56 (q, *J* = 7.2 Hz, 1H, C*H*-1′), 7.22–7.37 (m, 5H, PhH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.1 (*C*H$_3$-4), 11.6 (*C*H$_3$-5), 18.1 (*C*H$_3$-2′), 26.2 (*C*H$_3$CO-1), 50.3 (*C*H-1′), 114.0 (C-5), 117.7 (C-4), 126.3 (C-2″), 127.3 (C-4″), 128.5 (C-3″), 140.4 (C-1″), 152.4 (C-2), 171.0 (CH$_3$*C*O-1). MS (70 eV) *m*/*z* 258 (M$^+$, 30), 216 (55), 112 (100), 105 (75), 77 (14). HRMS (EI) *m*/*z* [M$^+$] Calcd for $C_{15}H_{18}N_2O_2$: 258.1368. Found: 258.1379.

Data of **15a**: R_f 0.50 (hexane/EtOAc, 7:3). $[\alpha]_D^{22}$ = −44.1 (*c* 0.068, MeOH). IR (film) 2935, 1736, 1494, 1454, 1382, 1367, 1226, 1022, 962, 761, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.85 (s, 3H, C*H*$_3$-CO$_2$CH$_2$-5), 1.86 (d, *J* = 7.1 Hz, 3H, C*H*$_3$-2′), 2.26 (s, 3H, C*H*$_3$-4), 4.75 (d, *J* = 13.7 Hz, 1H, CH$_3$CO$_2$C*H*$_2$-5), 5.02 (d, *J* = 13.7 Hz, 1H, CH$_3$-CO$_2$C*H*$_2$-5), 5.36 (q, *J* = 7.1 Hz, 1H, C*H*-1′), 7.01–7.07 (m, 2H, H-2″), 7.23–7.36 (m, 3H, H-3″, H-4″), 7.67 (s, 1H, H-2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.7 (*C*H$_3$-4), 20.6 (*C*H$_3$CO$_2$CH$_2$-5), 22.6 (*C*H$_3$-2′), 54.5 (CH$_3$CO$_2$*C*H$_2$-5), 55.0 (*C*H-1′), 121.7 (C-5), 125.5 (C-2″), 127.8 (C-4″), 128.9 (C-3″), 134.9 (C-2), 139.5 (C-4), 141.8 (C-1″), 170.6 (*C*H$_3$CO$_2$CH$_2$-5). HRMS (EI) *m*/*z* [M$^+$] Calcd for $C_{15}H_{18}N_2O_2$: 258.1368. Found: 258.1357.

4.38. (*S*)-1-Acetyl-4,5-diethyl-3-(1-phenylethyl)-1*H*-imidazol-2(3*H*)-one 14g

Synthesized according to method H, with **8h** (0.500 g, 2.05 mmol) and acetic anhydride, **14g** (0.35 g, 60%) was afforded as a yellow solid. R_f 0.63 (hexane/EtOAc, 7:3); mp 76–78 °C. $[\alpha]_D^{26}$ = +46.5 (*c* 0.142, MeOH). IR (film) 2974, 2935, 1713, 1452, 1407, 1369, 1334, 1309, 1289, 1271, 1255, 1115, 754, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.5 Hz, 3H, C*H*$_3$CH$_2$-4), 1.10 (t, *J* = 7.3 Hz, 3H, C*H*$_3$CH$_2$-5), 1.86 (d, *J* = 7.5 Hz, 3H, C*H*$_3$-2′), 2.28 (q, *J* = 7.5 Hz, 2H, CH$_3$C*H*$_2$-4), 2.65 (s, 3H, C*H*$_3$CO-1), 2.68 (qd, *J* = 7.3, 0.9 Hz, 2H, CH$_3$C*H*$_2$-5), 5.34 (q, *J* = 7.5 Hz, 1H, C*H*-1′), 7.24–7.39 (m, 5H, PhH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3 (*C*H$_3$CH$_2$-4), 14.9 (*C*H$_3$CH$_2$-5), 16.2 (CH$_3$*C*H$_2$-4), 18.0 (*C*H$_3$-2′), 18.5 (CH$_3$*C*H$_2$-5), 26.5 (*C*H$_3$CO-1), 51.0 (*C*H-1′), 119.8 (C-5), 123.5 (C-4), 126.5 (C-2″), 127.4 (C-4″), 128.5 (C-3″), 140.5 (C-1″), 152.5 (C-2), 170.8 (CH$_3$-*C*O-1). Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.33; H, 7.75; N, 9.76.

4.39. (*S*)-1-Acetyl-5-ethyl-4-methyl-3-(1-phenylethyl)-1*H*-imidazol-2(3*H*)-one 14h

4.39.1. (*S*)-5-(Acetoxymethyl)-4-ethyl-1-(1-phenylethyl)-1*H*-imidazole 15b

Synthesized according to method H, with **8i** (0.500 g, 2.17 mmol) and acetic anhydride, **14h** (0.31 g, 53%) was afforded as a yellow oil and **15b** (0.106 g, 18%) as a yellow oil.

Data of **14h**: R_f 0.56 (hexane/EtOAc, 7:3). $[\alpha]_D^{22}$ = −50.0 (*c* 0.13, MeOH). IR (film) 1710, 1661, 1407, 1368, 1316, 1267, 1175, 1099, 966, 753, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (t, *J* = 7.5 Hz, 3H, C*H*$_3$CH$_2$-5), 1.72 (s, 3H, C*H*$_3$-4), 1.81 (d, *J* = 7.2 Hz, 3H, C*H*$_3$-2′), 2.63–2.69 (m, 2H, CH$_3$C*H*$_2$-5), 2.67 (s, 3H, C*H*$_3$CO-1), 5.55 (q, *J* = 7.2 Hz, 1H, C*H*-1′), 7.24–7.37 (m, 5H, PhH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.2 (*C*H$_3$-4), 14.5 (*C*H$_3$CH$_2$-5), 18.1 (*C*H$_3$-2′), 18.2 (CH$_3$CH$_2$-5), 26.4 (*C*H$_3$CO-1), 50.4 (*C*H-1′), 117.6 (C-4), 120.0 (C-5), 126.4 (C-2″), 127.3 (C-4″), 128.5 (C-3″), 140.4 (C-1″), 152.6 (C-2), 170.6 (CH$_3$*C*O-1). MS (70 eV) *m*/*z* 272 (M^+, 54), 230 (100), 126 (79), 105 (64), 77 (14). HRMS (EI) *m*/*z* [M^+] Calcd for $C_{16}H_{20}N_2O_2$: 272.1525. Found: 272.1532.

Data of **15b**: R_f 0.40 (hexane/EtOAc, 7:3). $[\alpha]_D^{26}$ = −18.1 (*c* 0.086, MeOH). IR (film) 3374, 2975, 2935, 1738, 1493, 1454, 1367, 1226, 1020, 954, 761, 700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.5 Hz, 3H, C*H*$_3$CH$_2$-5), 1.85 (s, 3H, C*H*$_3$CO$_2$CH$_2$-4), 1.86 (d, *J* = 6.9 Hz, 3H, C*H*$_3$-2′), 2.60 (q, *J* = 7.5 Hz, 2H, CH$_3$C*H*$_2$-5), 4.76 (d, *J* = 13.8 Hz, 1H, CH$_3$CO$_2$C*H*$_2$-4), 5.02 (d, *J* = 13.8 Hz, 1H, CH$_3$CO$_2$C*H*$_2$-4), 5.36 (q, *J* = 6.9 Hz, 1H, C*H*-1′), 7.01–7.06 (m, 2H, H-2″), 7.23–7.36 (m, 3H, H-3″, H-4″), 7.68 (s, 1H, H-2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5 (*C*H$_3$CH$_2$-4), 20.3 (CH$_3$*C*H$_2$-4), 20.7 (*C*H$_3$CO$_2$CH$_2$-5), 22.7 (*C*H$_3$-2′), 54.4 (CH$_3$CO$_2$*C*H$_2$-5), 55.0 (*C*H-1′), 120.9 (C-5), 125.5 (C-2″), 127.8 (C-4″), 128.9 (C-3″), 135.1 (C-2), 141.9 (C-1″), 145.3 (C-4), 170.6 (CH$_3$*C*O$_2$CH$_2$-5). MS (70 eV) *m*/*z* 272 (M^+, 10), 213 (23), 212 (89), 197 (20), 125 (30) 108 (26), 105 (100), 97 (23), 85 (26), 79 (30), 71 (31), 57 (32). HRMS (EI) *m*/*z* [M^+] Calcd for $C_{16}H_{20}N_2O_2$: 272.1525. Found: 272.1528.

4.40. (*S*)-1-Acetyl-4-ethyl-5-methyl-3-(1-phenylethyl)-1*H*-imidazol-2(3*H*)-one 14i

Synthesized according to method H, with **8j** (0.500 g, 2.17 mmol) and acetic anhydride, **14i** (0.35 g, 60%) was afforded as a yellow solid. R_f 0.56 (hexane/EtOAc, 7:3); mp 49–51 °C. $[\alpha]_D^{26}$ = −6.0 (*c* 0.133, MeOH). IR (KBr) 2978, 2934, 1708, 1497, 1454, 1370, 1318, 1234, 1205, 1174, 1108, 1030, 950, 753, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, *J* = 7.5 Hz, 3H, C*H*$_3$-CH$_2$-4), 1.85 (d, *J* = 7.5 Hz, 3H, C*H*$_3$-2′), 2.23 (s, 3H, C*H*$_3$-5), 2.26 (q, *J* = 7.5 Hz, 2H, CH$_3$C*H*$_2$-4), 2.65 (s, 3H, C*H*$_3$CO-1), 5.38 (q, *J* = 7.5 Hz, 1H, C*H*-1′), 7.22–7.40 (m, 5H, PhH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.7 (*C*H$_3$-5), 13.6 (*C*H$_3$CH$_2$-4), 16.2 (CH$_3$*C*H$_2$-4), 18.0 (*C*H$_3$-2′), 26.3 (*C*H$_3$CO-1), 50.8 (*C*H-1′), 113.8 (C-5), 123.4 (C-4), 126.4 (C-2″), 127.3 (C-4″), 128.5 (C-3″), 140.4 (C-1″), 152.7 (C-2), 171.1 (CH$_3$*C*O-1). Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.57; H, 7.38; N, 10.27.

4.41. (*S*)-1-Acetyl-4-methyl-3-(1-phenylethyl)-5-propyl-1*H*-imidazol-2(3*H*)-one 14j

4.41.1. (*S*)-5-(Acetoxymethyl)-1-(1-phenylethyl)-4-propyl-1*H*-imidazole 15c

Synthesized according to method H, with **8k** (0.500 g, 2.05 mmol) and acetic anhydride, **14j** (0.228 g, 39%) was afforded as a yellow oil and **15c** (0.099 g, 16%) as a yellow oil.

Data of **14j**: R_f 0.63 (hexane/EtOAc, 7:3). $[\alpha]_D^{28}$ = +46.5 (*c* 0.142, MeOH). IR (film) 2962, 2934, 1710, 1454, 1369, 1307, 1291, 1234, 1026, 754, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, *J* = 7.5 Hz, 3H, C*H*$_3$(CH$_2$)$_2$-5), 1.47 (sext, *J* = 7.5 Hz, 2H, CH$_3$C*H*$_2$CH$_2$-5), 1.71 (s, 3H, C*H*$_3$-4), 1.81 (d, *J* = 7.3 Hz, 3H, C*H*$_3$-2′), 2.62 (br t, *J* = 7.5 Hz, 2H, CH$_3$CH$_2$C*H*$_2$-5), 2.68 (s, 3H, C*H*$_3$CO-1), 5.57 (q, *J* = 7.3 Hz, 1H, C*H*-1′), 7.24–7.39 (m, 5H, PhH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.3 (*C*H$_3$-4), 13.5 (*C*H$_3$(CH$_2$)$_2$-5), 18.2 (*C*H$_3$-2′), 22.8 (CH$_3$-*C*H$_2$CH$_2$-5), 26.5 (*C*H$_3$CO-1), 26.6 (CH$_3$CH$_2$*C*H$_2$-5), 50.4 (*C*H-1′), 118.3 (C-4), 118.5 (C-5), 126.3 (C-2″), 127.4 (C-4″), 128.6 (C-3″), 140.4 (C-1″), 152.7 (C-2), 170.8 (CH$_3$*C*O-1). HRMS (EI) *m*/*z* [M^+] Calcd for $C_{17}H_{22}N_2O_2$: 286.1681. Found: 286.1675.

Data of **15c**: R_f 0.50 (hexane/EtOAc, 7:3). $[\alpha]_D^{29}$ = −14.4 (*c* 0.202, MeOH). IR (film) 2960, 2934, 1737, 1493, 1454, 1368, 1234, 1021, 962, 761, 700 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.5 Hz, 3H, C*H*$_3$CH$_2$CH$_2$-4), 1.67 (sext, *J* = 7.5 Hz, 2H, CH$_3$C*H*$_2$CH$_2$-4), 1.85 (s, 3H, C*H*$_3$CO$_2$CH$_2$-5), 1.86 (d, *J* = 7.0 Hz, 3H, C*H*$_3$-2′), 2.55 (t, *J* = 7.5 Hz, 2H, CH$_3$CH$_2$C*H*$_2$-4), 4.77 (d, *J* = 13.8 Hz, 1H, CH$_3$CO$_2$-C*H*$_2$-5), 5.02 (d, *J* = 13.8 Hz, 1H, CH$_3$CO$_2$C*H*$_2$-5), 5.37 (q, *J* = 7.0 Hz, 1H, C*H*-1′), 7.00–7.04 (m, 2H, H-2″), 7.24–7.28 (m, 1H, H-4″), 7.29–7.34 (m, 2H, H-3″), 7.67 (s, 1H, H-2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8 (*C*H$_3$CH$_2$CH$_2$-4), 20.6 (*C*H$_3$CO$_2$CH$_2$-5), 22.6 (*C*H$_3$-2′), 23.1 (CH$_3$CH$_2$CH$_2$-4), 29.0 (CH$_3$CH$_2$CH$_2$-4), 54.5 (CH$_3$CO$_2$CH$_2$-5), 55.0 (*C*H-1′), 120.3 (C-5), 125.4 (C-2″), 127.7 (C-4″), 128.9 (C-3″), 135.1 (C-2), 142.0 (C-1″), 143.8 (C-4), 170.6 (CH$_3$*C*O$_2$CH$_2$-5). HRMS (EI) *m*/*z* [M^+] Calcd for $C_{17}H_{22}N_2O_2$: 286.1682. Found: 286.1681.

4.42. (*S*)-1-Acetyl-4-(4-methoxyphenyl)-5-methyl-3-(-1-phenyl ethyl)-1*H*-imidazol-2(3*H*)-one 14k

Synthesized according to method H, with **8l** (0.500 g, 1.62 mmol) and acetic anhydride, **14k** (0.26 g, 46%) was afforded as a yellow oil. R_f 0.40 (hexane/EtOAc, 7:3). $[\alpha]_D^{26}$ = −10.2 (*c* 0.188, MeOH). IR (KBr) 2924, 2853, 1731, 1605, 1511, 1456, 1373, 1306, 1253, 1173, 1030, 845, 762, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.72 (d, *J* = 7.2 Hz, 3H, C*H*$_3$-2′), 2.15 (s, 3H, C*H*$_3$-5), 2.69 (s, 3H, C*H*$_3$CO-1), 3.83 (s, 3H, C*H*$_3$OAr), 5.08 (q, *J* = 7.2 Hz, 1H, C*H*-1′), 6.83–6.90 (m, 2H, H-3‴), 6.97 (br s, 2H, H-2‴), 7.15–7.36 (m, 5H, PhH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.6 (*C*H$_3$-5), 17.8 (*C*H$_3$-2′), 26.3 (*C*H$_3$CO-1), 52.1 (*C*H-1′), 55.3 (*C*H$_3$OAr), 113.9 (C-3‴), 115.8 (C-5) 120.2 (C-1‴), 123.5 (C-4), 126.7 (C-2″), 127.3 (C-4″), 128.3 (C-3″), 132.2 (C-2‴), 140.7 (C-1″), 151.9 (C-2), 159.9 (C-4‴), 171.3 (CH$_3$*C*O-1). HRMS (EI) *m*/*z* [M^+] Calcd for $C_{21}H_{22}N_2O_3$: 350.1631. Found: 350.1615.

4.43. (*S*)-4,5-Dimethyl-3-(1-phenylethyl)-1-propionyl-1*H*-imidazol-2(3*H*)-one 14l

Synthesized according to method H, with **8g** (0.500 g, 2.31 mmol) and propionic anhydride, **14l** (0.34 g, 54%) was affor-

ded as a white solid. R_f 0.80 (hexane/EtOAc, 7:3); mp 36–37 °C. $[\alpha]_D^{29} = -55.2$ (*c* 0.290, MeOH). IR (film) 2980, 2935, 1711, 1668, 1496, 1451, 1359, 1288, 1215, 1095, 1076, 1026, 955, 890, 751, 700 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.5 Hz, 3H, CH_3CH_2CO-1), 1.70 (d, *J* = 1.0 Hz, 3H, CH_3-4), 1.80 (d, *J* = 7.3 Hz, 3H, CH_3-2′), 2.21 (d, *J* = 1.0 Hz, 3H, CH_3-5), 3.14 (q, *J* = 7.5 Hz, 2H, CH_3CH_2CO-1), 5.57 (q, *J* = 7.3 Hz, 1H, CH-1′), 7.25–7.36 (m, 5H, PhH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.4 (CH_3CH_2CO-1), 9.1 (CH_3-4), 11.7 (CH_3-5), 18.2 (CH_3-2′), 31.3 (CH_3CH_2CO-1), 50.4 (CH-1′), 114.2 (C-5), 117.7 (C-4), 126.4 (C-2″), 127.3 (C-4″), 128.6 (C-3″), 140.5 (C-1″), 152.4 (C-2), 175.0 (CH_3CH_2CO-1). HRMS (EI) *m*/*z* [M^+] Calcd for $C_{16}H_{20}N_2O_2$: 272.1525. Found: 272.1525.

4.44. (*S*)-4,5-Diethyl-3-(1-phenylethyl)-1-propionyl-1*H*-imidazol-2(3*H*)-one 14m

Synthesized according to method H, with **8h** (0.500 g, 2.05 mmol) and propionic anhydride, **14m** (0.44 g, 72%) was afforded as a yellow solid. R_f 0.71 (hexane/EtOAc, 7:3); mp 33–34 °C. $[\alpha]_D^{26} = -8.25$ (*c* 0.257, MeOH). IR (film) 2976, 2937, 1711, 1453, 1367, 1290, 1249, 1114, 1065, 753, 698 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.5 Hz, 3H, CH_3CH_2-4), 1.10 (t, *J* = 7.5 Hz, 3H, CH_3CH_2-5), 1.18 (t, *J* = 7.5 Hz, 3H, CH_3CH_2CO-1), 1.86 (d, *J* = 7.5 Hz, 3H, CH_3-2′), 2.29 (q, *J* = 7.5 Hz, 2H, CH_3CH_2-4), 2.69 (qd, *J* = 7.5, 3.0 Hz, 2H, CH_3CH_2-5), 3.11 (q, *J* = 7.5 Hz, 3H, CH_3CH_2CO-1), 5.34 (q, *J* = 7.5 Hz, 1H, CH-1′), 7.24–7.36 (m, 5H, PhH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.4 (CH_3CH_2CO-1), 14.3 (CH_3CH_2-4), 14.9 (CH_3CH_2-5), 16.3 (CH_3CH_2-4), 18.0 (CH_3-2′), 18.6 (CH_3CH_2-5), 31.5 (CH_3CH_2CO-1), 51.0 (CH-1′), 119.9 (C-5), 123.4 (C-4), 126.5 (C-2″), 127.3 (C-4″), 128.5 (C-3″), 140.6 (C-1″), 152.3 (C-2), 174.7 (CH_3CH_2CO-1). HRMS (EI) *m*/*z* [M^+] Calcd for $C_{18}H_{24}N_2O_2$: 300.1838. Found: 300.1830.

4.45. (*S*)-5-Ethyl-4-methyl-3-(1-phenylethyl)-1-propionyl-1*H*-imidazol-2(3*H*)-one 14n

Synthesized according to method H, with **8i** (0.500 g, 2.17 mmol) and propionic anhydride, **14n** (0.37 g, 60%) was afforded as a yellow oil. R_f 0.63 (hexane/EtOAc, 7:3). $[\alpha]_D^{26} = -46.35$ (*c* 0.255, MeOH). IR (film) 2978, 2938, 1708, 1660, 1450, 1363, 1249, 1179, 1116, 753, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.06 (t, *J* = 7.4 Hz, 3H, CH_3CH_2-5), 1.20 (t, *J* = 7.2 Hz, 3H, CH_3CH_2CO-1), 1.72 (s, 3H, CH_3-4), 1.81 (d, *J* = 7.3 Hz, 3H, CH_3-2′), 2.67 (qd, *J* = 7.4, 1.8 Hz, 2H, CH_3CH_2-5), 3.15 (q, *J* = 7.2 Hz, 2H, CH_3CH_2CO-1), 5.56 (q, *J* = 7.3 Hz, 1H, CH-1′), 7.23–7.39 (m, 5H, PhH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.4 (CH_3CH_2CO-1), 9.0 (CH_3-4), 14.5 (CH_3CH_2-5), 18.1 (CH_3-2′), 18.3 (CH_3CH_2-5), 31.4 (CH_3CH_2CO-1), 50.4 (CH-1′), 117.6 (C-4), 120.0 (C-5), 126.4 (C-2″), 127.3 (C-4″), 128.5 (C-3″), 140.5 (C-1″), 152.4 (C-2), 174.6 (CH_3CH_2CO-1). HRMS (EI) *m*/*z* [M^+] Calcd for $C_{17}H_{22}N_2O_2$: 286.1681. Found: 286.1674.

4.46. (*S*)-4-Methyl-3-(1-phenylethyl)-1-propionyl-5-propyl-1*H*-imidazol-2(3*H*)-one 14o

Synthesized according to method H, with **8k** (0.500 g, 2.05 mmol) and propionic anhydride, **14o** (0.184 g, 30%) was afforded as a yellow oil. R_f 0.67 (hexane/EtOAc, 7:3). $[\alpha]_D^{26} = -48.6$ (*c* 0.195, MeOH). IR (film) 2962, 2936, 1709, 1660, 1455, 1404, 1364, 1281, 1229, 1022, 752, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, *J* = 7.3 Hz, 3H, $CH_3(CH_2)_2$-5), 1.20 (t, *J* = 7.2 Hz, 3H, CH_3CH_2CO-1), 1.49 (sext, *J* = 7.3 Hz, 2H, $CH_3CH_2CH_2$-5), 1.72 (s, 3H, CH_3-4), 1.81 (d, *J* = 7.2 Hz, 3H, CH_3-2′), 2.63 (t, *J* = 7.3 Hz, 2H, $CH_3CH_2CH_2$-5), 3.15 (q, *J* = 7.2 Hz, 2H, CH_3CH_2CO-1), 5.57 (q, *J* = 7.2 Hz, 1H, CH-1′), 7.22–7.38 (m, 5H, PhH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.3 (CH_3CH_2CO-1), 9.2 (CH_3-4), 13.4 ($CH_3(CH_2)_2$-5), 18.0 (CH_3-2′), 22.7 ($CH_3CH_2CH_2$-5), 26.6 ($CH_3CH_2CH_2$-5), 31.4 (CH_3CH_2CO-1), 50.2 (CH-1′), 118.1 (C-4), 118.3 (C-5), 126.2 (C-2″), 127.2 (C-4″), 128.4 (C-3″), 140.4 (C-1″), 152.4 (C-2), 174.6 (CH_3CH_2CO-1). HRMS (EI) *m*/*z* [M^+] Calcd for $C_{18}H_{24}N_2O_2$: 300.1838. Found: 300.1832.

4.47. (*S*)-4-(4-Methoxyphenyl)-5-methyl-3-(1-phenylethyl)-1-propionyl-1*H*-imidazol-2(3*H*)-one 14p

Synthesized according to method H, with **8l** (0.500 g, 1.62 mmol) and propionic anhydride, **14p** (0.30 g, 50%) was afforded as a yellow oil. R_f 0.73 (hexane/EtOAc, 7:3). $[\alpha]_D^{26} = -10.4$ (*c* 0.091, MeOH). IR (film) 2977, 2936, 1714, 1606, 1514, 1358, 1295, 1249, 1175, 1032, 940, 831, 751, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.2 Hz, 3H, CH_3CH_2CO-1), 1.72 (d, *J* = 7.2 Hz, 3H, CH_3-2′), 2.15 (s, 3H, CH_3-5), 3.16 (q, *J* = 7.2 Hz, 2H, CH_3CH_2CO-1), 3.83 (s, 3H, CH_3OAr), 5.08 (q, *J* = 7.2 Hz, 1H, CH-1′), 6.82–6.91 (m, 2H, H-3‴), 6.92–7.05 (m, 2H, H-2‴), 7.15–7.32 (m, 5H, PhH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.3 (CH_3CH_2CO-1), 12.6 (CH_3-5), 17.8 (CH_3-2′), 31.4 (CH_3CH_2CO-1), 52.1 (CH-1′), 55.3 (CH_3OAr), 113.9 (C-3‴), 115.8 (C-5), 120.3 (C-1‴), 123.4 (C-4), 126.7 (C-2″), 127.2 (C-4″), 128.3 (C-3″), 132.2 (C-2‴), 140.7 (C-1″), 151.8 (C-2), 159.9 (C-4‴), 175.2 (CH_3CH_2CO-1). HRMS (EI) *m*/*z* [M^+] Calcd for $C_{22}H_{24}N_2O_3$: 364.1787. Found: 364.1779.

4.48. (4*S*,5*R*)-1-Acetyl-4,5-dimethyl-3-((*S*)-1-phenylethyl)imidazolidin-2-one 16a

Synthesized according to method I, with **14f** (0.050 g, 0.194 mmol) and $Pd(OH)_2/C$ (20%)/H_2O (50%) (0.027 g, 0.024 mmol) and stirring for 6 h, **16a** (0.042 g, 83%) was afforded as a yellow oil. R_f 0.37 (hexane/EtOAc, 7:3). $[\alpha]_D^{26} = +1.7$ (*c* 0.241, MeOH). IR (film) 2981, 1717, 1680, 1375, 1258, 937, 778, 756, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.82 (d, *J* = 6.6 Hz, 3H, CH_3-4), 1.14 (d, *J* = 6.3 Hz, 3H, CH_3-5), 1.71 (d, *J* = 7.2 Hz, 3H, CH_3-2′), 2.54 (s, 3H, CH_3CO-1), 3.86 (dq, *J* = 7.7, 6.6 Hz, 1H, H-4), 4.33 (dq, *J* = 7.7, 6.3 Hz, 1H, H-5), 5.22 (q, *J* = 7.2 Hz, 1H, CH-1′), 7.24–7.40 (m, 5H, PhH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.1 (CH_3-5), 14.2 (CH_3-4), 15.7 (CH_3-2′), 24.2 (CH_3CO-1), 49.8 (CH-1′), 50.8 (C-4), 51.1 (C-5), 126.6 (C-2″), 127.2 (C-4″), 128.3 (C-3″), 141.8 (C-1″), 155.5 (C-2), 170.2 (CH_3CO-1). HRMS (EI) *m*/*z* [M^+] Calcd for $C_{15}H_{20}N_2O_2$: 260.1525. Found: 260.1525.

4.49. (4*S*,5*R*)-1-Acetyl-4,5-diethyl-3-((*S*)-1-phenylethyl)imidazolidin-2-one 16b

4.49.1. (*S*)-4,5-Diethyl-1-(1-phenylethyl)-1*H*-imidazol-2(3*H*)-one 18b

Synthesized according to method I, with **14g** (0.200 g, 0.70 mmol) and $Pd(OH)_2/C$ (20%)/H_2O (50%) (0.100 g, 0.089 mmol) and stirring for 6 h, **16b** (0.16 g, 79%) was afforded as a yellow oil and **18b** (0.034 g, 20%) as a pale yellow oil.

Data of **16b**: R_f 0.52 (hexane/EtOAc, 7:3). $[\alpha]_D^{25} = -11.6$ (*c* 0.093, MeOH). IR (film) 2971, 1718, 1684, 1457, 1375, 1355, 1316, 1253, 1219, 966, 756, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.79 (t, *J* = 7.2 Hz, 3H, CH_3CH_2-4), 0.95 (t, *J* = 7.5 Hz, 3H, CH_3CH_2-5), 0.93–1.08 (m, 1H, CH_3CH_2-5), 1.30–1.48 (m, 1H, CH_3CH_2-4), 1.49–1.64 (m, 1H, CH_3CH_2-5), 1.66 (d, *J* = 7.2 Hz, 3H, CH_3-2′), 1.70–1.88 (m, 1H, CH_3CH_2-4), 2.57 (s, 3H, CH_3CO-1), 3.61 (ddd, *J* = 11.7, 7.2, 3.3 Hz, 1H, H-4), 4.40–4.48 (m, 1H, H-5), 5.30 (q, *J* = 7.2 Hz, 1H, CH-1′), 7.24–7.37 (m, 5H, PhH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.6 (CH_3CH_2-5), 10.2 (CH_3CH_2-4), 15.2 (CH_3-2′), 19.9 (CH_3CH_2-4), 20.3 (CH_3CH_2-5), 24.0 (CH_3CO-1), 49.7 (CH-1′), 53.4 (C-5), 57.8 (C-4), 126.5 (C-2″), 127.0 (C-4″), 128.2

(C-3″), 141.6 (C-1″), 156.4 (C-2), 170.3 (CH_3CO-1). HRMS (EI) m/z [M^+] Calcd for $C_{17}H_{24}N_2O_2$: 288.1838. Found: 288.1837.

Data of **18b**: R_f 0.45 (hexane/EtOAc, 7:3). $[\alpha]_D^{25} = -11.4$ (c 0.109, MeOH). IR (film) 3237, 2974, 2935, 1712, 1672, 1449, 1410, 1378, 1076, 1027, 756, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.81 (t, J = 7.5 Hz, 3H, CH_3CH$_2$-5), 1.12 (t, J = 7.5 Hz, 3H, CH_3CH$_2$-4), 1.85 (d, J = 7.2 Hz, 3H, CH_3-2′), 2.22 (q, J = 7.5 Hz, 2H, CH$_3$CH_2-5), 2.32 (q, J = 7.5 Hz, 2H, CH$_3$CH_2-4), 5.39 (q, J = 7.2 Hz, 1H, CH-1′), 7.17–7.40 (m, 5H, PhH), 10.15 (br s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7 (CH_3CH$_2$-4), 14.8 (CH_3CH$_2$-5), 16.7 (CH$_3$CH_2-5), 17.4 (CH$_3$-CH_2-4), 18.7 (CH_3-2′), 50.5 (CH-1′), 118.8 (C-4), 119.1 (C-5), 126.5 (C-2″), 126.9 (C-4″), 128.3 (C-3″), 141.6 (C-1″), 154.3 (C-2). HRMS (EI) m/z [M^+] Calcd for $C_{15}H_{20}N_2O$: 244.1576. Found: 244.1561.

4.50. (4*S*,5*R*)-1-Acetyl-4-ethyl-5-methyl-3-((*S*)-1-phenylethyl)imidazolidin-2-one 16c

4.50.1. (*S*)-5-Ethyl-4-methyl-1-(1-phenylethyl)-1*H*-imidazol-2(3*H*)-one 18c

Synthesized according to method I, with **14i** (0.050 g, 0.184 mmol) and $Pd(OH)_2$/C (20%)/H_2O (50%) (0.026 g, 0.023 mmol) and stirring for 6 h, **16c** (0.021 g, 42%) was afforded as a yellow oil and **18c** (0.093 g, 22%) as a pale yellow oil.

Data of **16c**: R_f 0.43 (hexane/EtOAc, 7:3). $[\alpha]_D^{26} = -15.35$ (c 0.057, MeOH). IR (film) 2971, 2927, 1721, 1682, 1450, 1375, 1355, 1260, 1219, 1174, 758, 698 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.75 (t, J = 7.5 Hz, 3H, CH_3CH$_2$-4), 0.92–1.02 (m, 1H, CH$_3$CH_2-4), 1.15 (d, J = 6.5 Hz, 3H, CH_3-5), 1.35–1.44 (m, 1H, CH$_3$CH_2-4), 1.68 (d, J = 7.5 Hz, 3H, CH_3-2′), 2.54 (s, 3H, CH_3CO-1), 3.57 (ddd, J = 12.0, 7.7, 3.5 Hz, 1H, H-4), 4.42 (dq, J = 7.0, 6.5 Hz, 1H, H-5), 5.29 (q, J = 7.5 Hz, 1H, CH-1′), 7.24–7.37 (m, 5H, PhH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.9 (CH_3CH$_2$-4), 12.2 (CH_3-5), 15.5 (CH_3-2′), 20.4 (CH$_3$CH_2-4), 24.1 (CH_3CO-1), 49.6 (CH-1′), 49.9 (C-5), 57.3 (C-4), 126.4 (C-2″), 127.1 (C-4″), 128.4 (C-3″), 142.0 (C-1″), 155.8 (C-2), 170.1 (CH$_3$CO-1). HRMS (EI) m/z [M^+] Calcd for $C_{16}H_{22}N_2O_2$: 274.1681. Found: 274.1685.

Data of **18c**: R_f 0.51 (hexane/EtOAc, 8:2). $[\alpha]_D^{26} = +6.1$ (c 0.053, MeOH). IR (film) 3264, 2977, 2935, 1683, 1434, 1376, 1113, 1027, 758, 698 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.80 (t, J = 7.5 Hz, 3H, CH_3CH$_2$-5), 1.84 (d, J = 7.0 Hz, 3H, CH_3-2′), 1.93 (s, 1H, CH_3-4), 2.16–2.22 (m, 2H, CH$_3$CH_2-5), 5.42 (q, J = 7.0 Hz, 1H, CH-1′), 7.20–7.37 (m, 5H, PhH), 8.94 (br s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.4 (CH_3-4), 14.2 (CH_3CH$_2$-5), 16.9 (CH$_3$CH_2-5), 18.7 (CH_3-2′), 50.5 (CH-1′), 112.3 (C-4), 120.0 (C-5), 126.5 (C-2″), 127.0 (C-4″), 128.4 (C-3″), 141.7 (C-1″), 154.0 (C-2). HRMS (EI) m/z [M^+] Calcd for $C_{14}H_{18}N_2O$: 230.1419. Found: 230.1416.

4.51. (4*S*,5*R*)-1-Acetyl-4-methyl-3-((*S*)-1-phenylethyl)-5-propylimidazolidin-2-one 16d

Synthesized according to method I, with **14j** (0.200 g, 0.70 mmol) and $Pd(OH)_2$/C (20%)/H_2O (50%) (0.100 g, 0.089 mmol) and stirring for 6 h, **16d** (0.089 g, 44%) was afforded as a yellow oil. R_f 0.46 (hexane/EtOAc, 8:2). $[\alpha]_D^{21} = -21.15$ (c 0.101, MeOH). IR (film) 2961, 1717, 1682, 1450, 1373, 1353, 1253, 1224, 756, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 6.9 Hz, 3H, CH_3(CH$_2$)$_2$-5), 0.90 (d, J = 6.9 Hz, 3H, CH_3-4), 1.10–1.53 (m, 3H, CH$_3$(CH_2)$_2$-5), 1.60–1.73 (m, 1H, CH$_3$(CH_2)$_2$-5), 1.71 (d, J = 7.2 Hz, 3H, CH_3-2′), 2.56 (s, 3H, CH_3-CO-1), 3.89 (dq, J = 7.1, 6.9 Hz, 1H, H-4), 4.27–4.35 (m, 1H, H-5), 5.23 (q, J = 7.2 Hz, 1H, CH-1′), 7.24–7.46 (m, 5H, PhH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (CH_3-4), 14.2 (CH_3(CH$_2$)$_2$-5), 15.7 (CH_3-2′), 18.8 (CH$_3$-CH_2CH$_2$-5), 24.2 (CH_3CO-1), 30.6 (CH$_3$CH$_2$CH_2-5), 50.0 (CH-1′), 51.4 (C-4), 54.4 (C-5), 126.7 (C-2″), 127.2 (C-4″), 128.3 (C-3″), 141.7 (C-1″), 156.0 (C-2), 170.4 (CH$_3$CO-1). HRMS (EI) m/z [M^+] Calcd for $C_{17}H_{24}N_2O_2$: 288.1838. Found: 288.1839.

4.52. (4*S*,5*R*)-1-Acetyl-4-(4-methoxyphenyl)-5-methyl-3-((*S*)-1-phenylethyl)imidazolidin-2-one 16e

4.52.1. (*S*)-5-(4-Methoxyphenyl)-4-methyl-1-(1-phenylethyl)-1*H*-imidazol-2(3*H*)-one 18e

Synthesized according to method I, with **14k** (0.249 g, 0.71 mmol) and $Pd(OH)_2$/C (20%)/H_2O (50%) (0.100 g, 0.089 mmol) and stirring for 24 h, **16e** (0.105 g, 42%) was afforded as a yellow oil and **18e** (0.024 g, 11%) as a pale yellow oil.

Data of **16e**: R_f 0.48 (hexane/EtOAc, 8:2). $[\alpha]_D^{22} = -15.8$ (c 0.061, MeOH). IR (film) 2981, 2937, 1721, 1682, 1613, 1514, 1407, 1374, 1353, 1339, 1246, 1218, 1174, 1030, 910, 841, 729, 699 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (d, J = 6.5 Hz, 3H, CH_3-5), 1.84 (d, J = 7.5 Hz, 3H, CH_3-2′), 2.53 (s, 3H, CH_3CO-1), 3.82 (s, 3H, CH_3OAr), 4.36–4.46 (m, 2H, CH-1′, H-5), 4.67 (d, J = 9.0 Hz, 1H, H-4), 6.83–6.89 (m, 2H, H-3‴), 7.01–7.08 (m, 2H, H-2‴), 7.18–7.35 (m, 5H, PhH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.7 (CH_3-5), 18.1 (CH_3-2′), 24.5 (CH_3CO-1), 52.0 (C-5), 54.1 (CH-1′), 55.3 (CH_3OAr), 61.0 (C-4), 114.0 (C-3‴), 126.5 (C-1‴), 127.57 (C-2″), 127.60 (C-4″), 128.4 (C-3″), 129.6 (C-2‴), 140.5 (C-1″), 155.8 (C-2), 159.7 (C-4‴), 170.6 (CH$_3$CO-1). HRMS (EI) m/z [M^+] Calcd for $C_{21}H_{24}N_2O_3$: 352.1787. Found: 352.1790.

Data of **18e**: R_f 0.16 (hexane/EtOAc, 8:2). $[\alpha]_D^{26} = -12.5$ (c 0.401, MeOH). IR (film) 3219, 2934, 1676, 1607, 1514, 1374, 1287, 1249, 1175, 1037, 833, 754, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.70 (d, J = 7.5 Hz, 3H, CH_3-2′), 1.89 (s, 3H, CH_3-4), 3.81 (s, 3H, CH_3OAr), 5.20 (q, J = 7.5 Hz, 1H, CH-1′), 6.77–6.84 (m, 2H, H-3‴), 6.87–6.94 (m, 2H, H-2‴), 7.12–7.32 (m, 5H, PhH), 10.21 (br s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.8 (CH_3-4), 18.5 (CH_3-2′), 51.7 (CH-1′), 55.2 (CH_3OAr), 113.6 (C-3‴), 114.9 (C-4) 119.9 (C-5), 121.8 (C-1‴), 126.7 (C-2″), 126.8 (C-4″), 128.1 (C-3″), 132.2 (C-2‴), 142.0 (C-1″), 154.2 (C-2), 159.3 (C-4‴). HRMS (EI) m/z [M^+] Calcd for $C_{19}H_{20}N_2O_2$: 308.1525. Found: 308.1530.

4.53. (4*S*,5*R*)-4,5-Dimethyl-3-((*S*)-1-phenylethyl)-1-propionylimidazolidin-2-one 16f

Synthesized according to method I, with **14l** (0.200 g, 0.735 mmol) and $Pd(OH)_2$/C (20%)/H_2O (50%) (0.103 g, 0.092 mmol) and stirring for 6 h, **16f** (0.17 g, 84%) was afforded as a yellow oil. R_f 0.67 (hexane/EtOAc, 7:3). $[\alpha]_D^{25} = +7.6$ (c 0.651, MeOH). IR (film) 2980, 2939, 1716, 1681, 1449, 1375, 1250, 1218, 1170, 1067, 1018, 929, 779, 758, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.82 (d, J = 6.9 Hz, 3H, CH_3-4), 1.14 (d, J = 6.6 Hz, 3H, CH_3-5), 1.65 (t, J = 7.5 Hz, 3H, CH_3CH$_2$CO-1), 1.70 (d, J = 7.3 Hz, 3H, CH_3-2′), 2.84–3.12 (m, 2H, CH$_3$CH_2CO-1), 3.85 (dq, J = 7.5, 6.9 Hz, 1H, H-4), 4.33 (dq, J = 7.5, 6.6 Hz, 1H, H-5), 5.21 (q, J = 7.3 Hz, 1H, CH-1′), 7.23–7.41 (m, 5H, PhH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.6 (CH$_3$CH$_2$CO-1), 13.0 (CH$_3$-5), 14.2 (CH_3-4), 15.6 (CH_3-2′), 29.3 (CH$_3$CH_2CO-1), 49.7 (CH-1′), 50.8 (C-4), 51.1 (C-5), 126.6 (C-2″), 127.1 (C-4″), 128.3 (C-3″), 141.8 (C-1″), 155.4 (C-2), 174.0 (CH$_3$CH$_2$CO-1). HRMS (EI) m/z [M^+] Calcd for $C_{16}H_{22}N_2O_2$: 274.1681. Found: 274.1683.

4.54. (4*S*,5*R*)-4,5-Diethyl-3-((*S*)-1-phenylethyl)-1-propionylimidazolidin-2-one 16g

4.54.1. (*S*)-4,5-Diethyl-1-(1-phenylethyl)-1*H*-imidazol-2(3*H*)-one 18b

Synthesized according to method I, with **14m** (0.200 g, 0.67 mmol) and $Pd(OH)_2$/C (20%)/H_2O (50%) (0.093 g, 0.083 mmol) and stirring for 6 h, **16g** (0.133 g, 66%) was afforded as a yellow oil and **18b** (0.039 g, 24%) as a pale yellow oil.

Data of **16g**: R_f 0.87 (hexane/EtOAc, 7:3). $[\alpha]_D^{26} = -16.1$ (c 0.259, MeOH). IR (film) 2973, 2939, 1719, 1685, 1459, 1375, 1242, 1216, 1162, 756, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.79 (t, J = 7.2 Hz,

Table 6
Crystal data and structure refinement for **7a**, **8g**, and **13**

Structure	**7a**	**8g**	**13**
CCDC No.	1032284	1032149	1032287
Empirical formula	$C_{10}H_{11}NO_2S$	$C_{13}H_{16}N_2O$	$C_{27}H_{33}N_3$
Molecular weight	209.26	216.28	399.56
Temperature (K)	292(2)	292(2)	292(2)
Crystal size (mm^3)	0.51 × 0.47 × 0.45	0.60 × 0.40 × 0.39	0.74 × 0.14 × 0.12
Crystal system	Orthorhombic	Monoclinic	Monoclinic
Space group	Pca21	P21	P21
Unit cell parameters	a = 22.5929(2) Å, α = 90°	a = 6.8435(2) Å, α = 90°	a = 12.3636(16) Å, α = 90°
	b = 4.92380(10) Å, β = 90°	b = 7.2959(2) Å, β = 106.336(3)°	b = 6.0130(11) Å, β = 96.813(12)°
	c = 9.2068(2) Å, γ = 90°	c = 11.9794(4) Å, γ = 90°	c = 15.949(2) Å, γ = 90°
Volume (Å^3)	1024.19(3)	573.98(3)	1177.3(3)
Z	4	2	2
Density (mg/m^3)	1.357	1.251	1.127
Absorption coefficient (mm^{-1})	0.288	0.081	0.066
Theta range (°)	3.61–32.64	3.102–32.519	3.223–32.624
Reflections collected	40,351	6564	13,454
Independent reflections	3588	3533	7283
Observed reflections	3369	3273	1660
Final R indices	R_1 = 0.0343; $wR2$ = 0.0861	R_1 = 0.0387; $wR2$ = 0.1007	R_1 = 0.0713; $wR2$ = 0.0923
Goodness-of-fit on F^2	1.114	1.045	0.845

3H, C*H*$_3$CH$_2$-4), 0.90 (t, J = 7.5 Hz, 3H, C*H*$_3$CH$_2$-5), 0.94–1.10 (m, 1H, CH$_3$C*H*$_2$-5), 1.19 (t, J = 7.5 Hz, 1H, C*H*$_3$CH$_2$CO-1), 1.34–1.47 (m, 1H, CH$_3$C*H*$_2$-4), 1.45–1.59 (m, 1H, CH$_3$C*H*$_2$-5), 1.66 (d, J = 7.3 Hz, 3H, C*H*$_3$-2′), 1.70–1.89 (m, 1H, CH$_3$C*H*$_2$-4), 2.85–3.15 (m, 1H, CH$_3$C*H*$_2$-CO-1), 3.60 (ddd, J = 11.7, 6.9, 3.3 Hz, 1H, H-4), 4.38–4.48 (m, 1H, H-5), 5.29 (q, J = 7.3 Hz, 1H, C*H*-1′), 7.24–7.36 (m, 5H, PhH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.9 (*C*H$_3$CH$_2$CO-1), 9.7 (*C*H$_3$CH$_2$-5), 10.3 (*C*H$_3$CH$_2$-4), 15.3 (*C*H$_3$-2′), 20.1 (CH$_3$*C*H$_2$-4), 20.4 (CH$_3$*C*H$_2$-5), 29.3 (CH$_3$*C*H$_2$CO-1), 49.7 (*C*H-1′), 53.5 (C-5), 58.0 (C-4), 126.6 (C-2″), 127.0 (C-4″), 128.2 (C-3″), 141.8 (C-1″), 156.5 (C-2), 170.2 (CH$_3$CH$_2$-*C*O-1). HRMS (EI) m/z [M$^+$] Calcd for $C_{18}H_{26}N_2O_2$: 302.1994. Found: 302.1994.

4.55. (4*S*,5*R*)-4-(4-Methoxyphenyl)-5-methyl-3-((*S*)-1-phenylethyl)-1-propionylimidazolidin-2-one 16h

4.55.1. (*S*)-5-(4-Methoxyphenyl)-4-methyl-1-(1-phenylethyl)-1*H*-imidazol-2(3*H*)-one 18e

Synthesized according to method I, with **14p** (0.260 g, 0.71 mmol) and Pd(OH)$_2$/C (20%)/H$_2$O (50%) (0.100 g, 0.089 mmol) and stirring for 24 h, **16h** (0.162 g, 61%) was afforded as a yellow oil, and **18e** (0.029 g, 17%) as a pale yellow oil.

Data of **16h**: R_f 0.63 (hexane/EtOAc, 7:3). $[\alpha]_D^{26}$ = −23.3 (c 0.171, MeOH). IR (film) 2979, 2937, 1725, 1683, 1613, 1514, 1457, 1406, 1374, 1354, 1341, 1250, 1216, 1175, 1032, 843, 757, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, J = 6.3 Hz, 3H, C*H*$_3$-5), 1.12 (t, J = 7.2 Hz, 3H, C*H*$_3$CH$_2$CO-1), 1.83 (d, J = 7.5 Hz, 3H, C*H*$_3$-2′), 2.95 (qd, d, J = 7.2, 2.2 Hz, 2H, CH$_3$C*H*$_2$CO-1), 3.78 (s, 3H, C*H*$_3$OAr), 4.32–4.46 (m, 2H, C*H*-1′, H-5), 4.66 (d, J = 8.7 Hz, 1H, H-4), 6.81–6.87 (m, 2H, H-3‴), 7.01–7.08 (m, 2H, H-2‴), 7.22 (br s, 5H, PhH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.6 (*C*H$_3$CH$_2$CO-1), 15.5 (*C*H$_3$-5), 17.9 (*C*H$_3$-2′), 29.6 (CH$_3$*C*H$_2$CO-1), 51.9 (C-5), 53.8 (*C*H-1′), 55.1 (*C*H$_3$-OAr), 61.0 (C-4), 113.8 (C-3‴), 126.4 (C-1‴), 127.4 (C-2″, C-4″), 128.2 (C-3″), 129.3 (C-2‴), 140.3 (C-1″), 155.7 (C-2), 159.5 (C-4‴), 174.2 (CH$_3$CH$_2$*C*O-1). HRMS (EI) m/z [M$^+$] Calcd for $C_{22}H_{26}N_2O_3$: 366.1944. Found: 366.1942.

4.56. Single-crystal X-ray crystallography

A single-crystal of **7a** was obtained by recrystallization from hexane/EtOAc, 1:1, as a pale yellow crystal; compound **8g** was obtained from CH_2Cl_2/MeOH, 3:7, and compound **13** from MeOH, both as colorless crystals. These were mounted in glass fibers. Crystallographic measurements were performed using Mo Kα radiation (graphite crystal monochromator, λ = 71073 Å) at room temperature. Three standard reflections were monitored periodically with no change found during data collection. Intensities were corrected for Lorentz and polarization effects. Multi-scan absorption correction was applied. Anisotropic temperature factors were introduced for all non-hydrogen atoms. Hydrogen atoms were placed in idealized positions and their atomic coordinates refined. Unit weights were used in the refinement (Table 6). Structures were solved using the SHELXS-2013[44] program as implemented in the WinGX suite,[45] and refined using SHELXL-2013[46] within WinGX, on a personal computer. In all cases ORTEP and packing diagrams were made with the ORTEP package.

Acknowledgments

We thank Daniel Zárate, Pablo Montoya, and Eder I. Martínez-Mora for their help in spectrometric measurements. We thank Bruce Allan Larsen for proofreading the manuscript. J.T. gratefully acknowledges SIP-IPN (Grants 20110172, 20120830, 20130686, and 20140858) and CONACYT (Grants 83446, 178319, and PEI-181/2012) for financial support. A.R., R.U.G., R.B., J.L.V., M.S., and F.M. thank CONACYT for graduate scholarship awarded, and also thank SIP/IPN (PIFI) and Ludwig K. Hellweg Foundation for scholarship complements. L.G.Z., F.D., and J.T. are fellows of the EDI-IPN and COFAA-IPN programs.

References

1. Grimmett, M. R. Imidazoles and their Benzo Derivatives: (i) Structure In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 5, pp 345–372.
2. (a) Grimmett, M. R. Imidazoles and their Benzo Derivatives: (ii) Reactivity In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 5, pp 373–456; (b) Kamijo, S.; Yamamoto, Y. *Chem. Asian J.* **2007**, *2*, 568–578; (c) Xi, N.; Huang, Q.; Liu, L. Imidazoles In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Joule, J., Eds.; Elsevier: Oxford, 2008; Vol. 4, pp 143–364.
3. For recent synthetic applications: (a) Bellina, F.; Calandri, C.; Cauteruccio, S.; Rossi, R. *Tetrahedron* **2007**, *63*, 1970–1980; (b) Ma, H.-C.; Jiang, X.-Z. *J. Org. Chem.* **2007**, *72*, 8943–8946; (c) Boersma, A. J.; Feringa, B. L.; Roelfes, G. *Org. Lett.* **2007**, *9*, 3647–3650; (d) Xu, D.-Q.; Wang, L.-P.; Luo, S.-P.; Wang, Y.-F.; Zhang, S.; Xu, Z.-Y. *Eur. J. Org. Chem.* **2008**, 1049–1053; (e) Wu, J; Ni, B.; Headley, A. D. *Org. Lett.* **2009**, *11*, 3354–3356; (f) Behera, M.; Ragavan, R. V.; Sambaiah, M.; Erugu, B.; Reddy, J. R. K.; Mukkanti, K.; Yennam, S. *Tetrahedron Lett.* **2012**, *53*, 1060–1062; (g) Konishi, H.; Ueda, T.; Muto, T.; Manabe, K. *Org. Lett.* **2012**, *14*, 4722–4725; (h) Tong, Y.-P.; Luo, G.-T.; Zhen, J.; Shen, Y.; Liu, H.-R. *Cryst. Growth Des.* **2013**, *13*, 446–454.
4. (a) Bellina, F.; Cauteruccio, S.; Rossi, R. *Tetrahedron* **2007**, *63*, 4571–4624; (b) Pastor, I. M.; Yus, M. *Curr. Chem. Biol.* **2009**, *3*, 65–88; (c) Wang, L.; Woods, K.

W.; Li, Q.; Barr, K. J.; McCroskey, R. W.; Hannick, S. M.; Gherke, L.; Credo, R. B.; Hui, Y.-H.; Marsh, K.; Warner, R.; Lee, J. Y.; Zielinski-Mozng, N.; Frost, D.; Rosenberg, S. H.; Sham, H. L. *J. Med. Chem.* **2002**, *45*, 1697–1711; (d) Almansa, C.; Alfón, J.; de Arriba, A. F.; Cavalcanti, F. L.; Escamilla, I.; Gómez, L. A.; Miralles, A.; Soliva, R.; Bartrolí, J.; Carceller, E.; Merlos, M.; García-Rafanell, J. *J. Med. Chem.* **2003**, *46*, 3463–3475; (e) Döhlert, P.; Irran, E.; Kretschmer, R.; Enthaler, S. *Inorg. Chem. Commun.* **2015**, *51*, 4–8; (f) Jin, Z. *Nat. Prod. Rep.* **2011**, *28*, 1143–1191; (g) Zhang, L.; Peng, X.-M.; Damu, G. L. V.; Geng, R.-X.; Zhou, C.-H. *Med. Res. Rev.* **2014**, *34*, 340–437; (h) Johnston, C. I. *Lancet* **1995**, *346*, 1403–1407.

5. (a) Celanire, S.; Wijtmans, M.; Talaga, P.; Leurs, R.; de Esch, I. J. P. *Drug Discovery Today* **2005**, *10*, 1613–1627; (b) Skoumbourdis, A. P.; Moore, S.; Landsman, M.; Thomas, C. J. *Tetrahedron Lett.* **2007**, *48*, 9140–9143; (c) Funder, J. W.; Mercer, J. E. *J. Clin. Endocrinol. Metab.* **1979**, *48*, 189–191.
6. (a) Borgers, M. *Clin. Infect. Dis.* **1980**, *2*, 520–534; (b) Zhang, W.; Ramamoorthy, Y.; Kilicarslan, T.; Nolte, H.; Tyndale, R. F.; Sellers, E. M. *Drug Metab. Dispos.* **2002**, *30*, 314–318; (c) Koga, H.; Nanjoh, Y.; Makimura, K.; Tsuboi, R. *Med. Mycol.* **2009**, *47*, 640–647.
7. Demirayak, S.; Karaburun, A. C.; Kiraz, N. *Eur. J. Med. Chem.* **1999**, *34*, 275–278.
8. Karakurt, A.; Dalkara, S.; Özalp, M.; Özbey, S.; Kendi, E.; Stables, J. P. *Eur. J. Med. Chem.* **2001**, *36*, 421–433.
9. (a) Fung, H. B.; Doan, T.-L. *Clin. Ther.* **2005**, *27*, 1859–1884; (b) Saadeh, H. A.; Mosleh, I. M.; El-Abadelah, M. M. *Molecules* **2009**, *14*, 2758–2767.
10. (a) Liu, K.; Zhu, H.-L. *Anti-Cancer Agents Med. Chem.* **2011**, *11*, 687–691; (b) Baroniya, S.; Anwer, Z.; Sharma, P. K.; Dudhe, R.; Kumar, N. *Der. Pharm. Sinica* **2010**, *1*, 172–182; (c) Serrone, L.; Zeuli, M.; Sega, F. M.; Cognetti, F. *J. Exp. Clin. Cancer Res.* **2000**, *19*, 21–34; (d) Bellina, F.; Cauteruccio, S.; Monti, S.; Rossi, R. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5757–5762.
11. (a) Boiani, M.; González, M. *Mini-Rev. Med. Chem.* **2005**, *5*, 409–424; (b) Aguirre, G.; Boiani, M.; Cerecetto, H.; Gerpe, A.; González, M.; Sainz, Y. F.; Denicola, A.; Ochoa de Ocáriz, C.; Nogal, J. J.; Montero, D.; Escario, J. A. *Arch. Pharm.* **2004**, *337*, 250–270.
12. (a) Mlostoń, G.; Gendek, T.; Heimgartner, H. *Tetrahedron* **2000**, *56*, 5405–5412; (b) Laufer, S.; Wagner, G.; Kotschenreuther, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 2290–2293; (c) Mlostoń, G.; Pieczonka, A. M.; Kowalczyk, E.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **2011**, *94*, 1764–1777; (d) Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 3291–3306.
13. Mlostoń, G.; Romański, J.; Jasiński, M.; Heimgartner, H. *Tetrahedron: Asymmetry* **2009**, *20*, 1073–1080.
14. (a) Cerecetto, H.; Gerpe, A.; González, M.; Fernández Sainz, Y.; Piro, O. E.; Castellano, E. *Synthesis* **2004**, 2678–2684; (b) Alcázar, J.; Begtrup, M.; de la Hoz, A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2467–2470; (c) Alcázar, J.; Begtrup, M.; de la Hoz, A. *Heterocycles* **1996**, *43*, 1465–1470; (d) Mlostoń, G.; Rygielska, D.; Jasiński, M.; Heimgartner, H. *Tetrahedron: Asymmetry* **2011**, *22*, 669–674.
15. (a) Mlostoń, G.; Gendek, T.; Heimgartner, H. *Helv. Chim. Acta* **1998**, *81*, 1585–1595; (b) Mlostoń, G.; Wróblewska, A.; Obijalska, E.; Heimgartner, H. *Tetrahedron: Asymmetry* **2013**, *24*, 958–965.
16. (a) Ferguson, I. J.; Schofield, K. *J. Chem. Soc., Perkin Trans. 1* **1975**, 275–277; (b) Mityanov, V. S.; Kuz'mina, L. G.; Perevalov, V. P.; Tkach, I. I. *Tetrahedron* **2014**, *70*, 3545–3552; (c) Nikitina, G. V.; Pevzner, M. S. *Chem. Heterocycl. Compd.* **1993**, *29*, 127–151; (d) Gómez, F. J.; Kamber, N. E.; Deschamps, N. M.; Cole, A. P.; Wender, P. A.; Waymouth, R. M. *Organometallics* **2007**, *26*, 4541–4545; (e) Alcázar, J.; Begtrup, M.; de la Hoz, A. *J. Org. Chem.* **1996**, *61*, 6971–6973.
17. (a) Mlostoń, G.; Celeda, M.; Prakash, G. K. S.; Olah, G. A.; Heimgartner, H. *Helv. Chim. Acta* **2000**, *83*, 728–738; (b) Mlostoń, G.; Jasiński, M. *Arkivoc* **2011**, 162–175.
18. Bronson, J. J.; DenBleyker, K. L.; Falk, P. L.; Mate, R. A.; Ho, H.-T.; Pucci, M. J.; Snyder, L. B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 873–875.
19. Congiu, C.; Cocco, M. T.; Onnis, V. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 989–993.
20. Watanabe, K.; Morinaka, Y.; Hayashi, Y.; Shinoda, M.; Nishi, H.; Fukushima, N.; Watanabe, T.; Ishibashi, A.; Yuki, S.; Tanaka, M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1478–1483.
21. Francis, C. L.; Kenny, P. W.; Dolezal, O.; Saubern, S.; Kruger, M.; Savage, G. P.; Peat, T. S.; Ryan, J. H. *Aust. J. Chem.* **2013**, *66*, 1473–1482.
22. (a) Patek, M.; Weichsel, A. S.; Drake, B.; Smrcina, M. *Synlett* **2005**, 1322–1324; (b) Huguenot, F.; Delalande, C.; Vidal, M. *Tetrahedron Lett.* **2014**, *55*, 4632–4635; (c) Wendeborn, S.; Winkler, T.; Foisy, I. *Tetrahedron Lett.* **2000**, *41*, 6387–6391.
23. Duschinsky, R.; Dolan, L. A. *J. Am. Chem. Soc.* **1946**, *68*, 2350–2355.
24. Pesquet, A.; Daïch, A.; Van Hijfte, L. *J. Org. Chem.* **2006**, *71*, 5303–5311.
25. Lee, S.-H.; Clapham, B.; Koch, G.; Zimmermann, J.; Janda, K. D. *Org. Lett.* **2003**, *5*, 511–514.
26. *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 2000.
27. (a) Notz, W.; Tanaka, F.; Barbas, C. F., III *Acc. Chem. Res.* **2004**, *37*, 580–591; (b) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178–2189.
28. (a) Gnas, Y.; Glorius, F. *Synthesis* **2006**, 1899–1930; (b) Evans, D. A.; Helmchen, G.; Rüping, M. Chiral Auxiliaries in Asymmetric Synthesis. In *Asymmetric Synthesis—the Essentials*; Christmann, M., Ed.; Wiley-VCH: Weinheim, 2008; pp 3–9; (c) Morales, M. R.; Mellem, K. T.; Myers, A. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 4568–4571; (d) Chacón-García, L.; Lagunas-Rivera, S.; Pérez-Estrada, S.; Vargas-Díaz, M. E.; Joseph-Nathan, P.; Tamariz, J.; Zepeda, L. G. *Tetrahedron Lett.* **2004**, *45*, 2141–2145; (e) Lazny, R.; Nodzewska, A. *Chem. Rev.* **2010**, *110*, 1386–1434; (f) Seebach, D.; Naef, R. *Helv. Chim. Acta* **1981**, *64*, 2705–2708; (g) Oppolzer, W.; Chapuis, C.; Bernardinelli, G. *Helv. Chim. Acta* **1984**, *67*, 1397–1401; (h) Lee, A. W. M.; Chan, W. H.; Zhang, S.-J.; Zhang, H.-K. *Curr. Org. Chem.* **2007**, *11*, 213–228; (i) Bull, S. D.; Davies, S. G.; Jones, S.; Sanganee, H. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 387–398; (j) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835–875; (k) Bull, S. D.; Davies, S. G.; Garner, A. C.; Kruchinin, D.; Key, M.-S.; Roberts, P. M.; Savory, E. D.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2006**, *4*, 2945–2964.
29. (a) Davies, S. G.; Mortlock, A. A. *Tetrahedron Lett.* **1991**, *32*, 4787–4790; (b) Davies, S. G.; Mortlock, A. A. *Tetrahedron Lett.* **1991**, *32*, 4791–4794; (c) Davies, S. G.; Mortlock, A. A. *Tetrahedron Lett.* **1992**, *33*, 1117–1120; (d) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063–7064; (e) Davies, S. G.; Mortlock, A. A. *Tetrahedron: Asymmetry* **1991**, *2*, 1001–1004; (f) Drewes, S. E.; Malissar, D. G. S.; Roos, G. H. P. *Chem. Ber.* **1993**, *126*, 2663–2673; (g) Davies, S. G.; Mortlock, A. A. *Tetrahedron* **1993**, *49*, 4419–4438; (h) Davies, S. G.; Evans, G. B.; Mortlock, A. A. *Tetrahedron: Asymmetry* **1994**, *5*, 585–606; (i) Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161–3195; (j) Adams, H.; Anderson, J. C.; Peace, S.; Pennell, A. M. K. *J. Org. Chem.* **1998**, *63*, 9932–9934; (k) Alexakis, A.; Tranchier, J.-P.; Lensen, N.; Mangeney, P. *J. Am. Chem. Soc.* **1995**, *117*, 10767–10768; (l) Mangeney, P.; Gosmini, R.; Raussou, S.; Commerçon, M.; Alexakis, A. *J. Org. Chem.* **1994**, *59*, 1877–1888; (m) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580–2627; (n) Cardillo, G.; Gentilucci, L.; Tolomelli, A. *Aldrichim. Acta* **2003**, *36*, 39–50; (o) Ichikawa, Y.; Egawa, H.; Ito, T.; Isobe, M.; Nakano, K.; Kotsuki, H. *Org. Lett.* **2006**, *8*, 5737–5740.
30. (a) Roos, G. H. P.; Balasubramaniam, S. *Synth. Commun.* **1999**, *29*, 755–762; (b) MacNevin, C. J.; Moore, R. L.; Liotta, D. C. *J. Org. Chem.* **2008**, *73*, 1264–1269; (c) Caddick, S.; Parr, N. J.; Pritchard, M. C. *Tetrahedron* **2001**, *57*, 6615–6626; (d) Taguchi, T.; Shibuya, A.; Sasaki, H.; Endo, J.-I.; Morikawa, T.; Shiro, M. *Tetrahedron: Asymmetry* **1994**, *5*, 1423–1426; (e) Khatik, G. L.; Kumar, V.; Nair, V. A. *Org. Lett.* **2012**, *14*, 2442–2445; (f) Khatik, G. L.; Sharma, R.; Kumar, V.; Chouhan, M.; Nair, V. A. *Tetrahedron Lett.* **2013**, *54*, 5991–5993.
31. Bernal, P.; Tamariz, J. *Tetrahedron Lett.* **2006**, *17*, 2905–2909.
32. (a) Williams, D. H. L. *Adv. Phys. Org. Chem.* **1983**, *19*, 381–428; (b) Leis, J. R.; Peña, M. E.; Williams, D. L. H.; Mawson, S. D. *J. Chem. Soc., Perkin Trans. 2* **1988**, 157–162; (c) Iglesias, E.; Williams, D. L. H. *J. Chem. Soc., Perkin Trans. 2* **1989**, 343–346; (d) Graham, A.; Williams, D. L. H. *J. Chem. Soc., Chem. Commun.* **1991**, 407–408
33. Rüedi, G.; Oberli, M. A.; Nagel, M.; Weymuth, C.; Hansen, H.-J. *Synlett* **2004**, 2315–2318.
34. (a) Mucha, P.; Mlostoń, G.; Jasiński, M.; Linden, A.; Heimgartner, H. *Tetrahedron: Asymmetry* **2008**, *19*, 1600–1607; (b) Mlostoń, G.; Mucha, P.; Urbaniak, K.; Broda, K.; Heilmgartner, H. *Helv. Chim. Acta* **2008**, *91*, 232–238.
35. Takahashi, S.; Kano, H. *Chem. Pharm. Bull.* **1966**, *11*, 1219–1227.
36. (a) Grierson, D. *Org. React.* **1990**, *39*, 85–295; (b) Grierson, D. S.; Husson, H.-P. Polonovski- and Pummerer-type Reactions and the Nef Reaction In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 6, pp 909–947.
37. (a) Evans, D. A. *Aldrichim. Acta* **1982**, *15*, 23–32; (b) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370; (c) Amoroso, R.; Cardillo, G.; Sabatino, P.; Tomasini, C.; Trerè, A. *J. Org. Chem.* **1993**, *58*, 5615–5619; (d) Arya, P.; Qin, H. *Tetrahedron* **2000**, *56*, 917–947; (e) Cardillo, G.; Gentilucci, L.; Gianotti, M.; Tolomelli, A. *Org. Lett.* **2001**, *3*, 1165–1167.
38. González-Romero, C.; Bernal, P.; Jiménez, F.; Cruz, M. C.; Fuentes-Benites, A.; Benavides, A.; Bautista, R.; Tamariz, J. *Pure Appl. Chem.* **2007**, *79*, 181–191.
39. (a) Wabnitz, T. C.; Spencer, J. B. *Org. Lett.* **2003**, *5*, 2141–2144; (b) Chu, C.-M.; Gao, S.; Sastry, M. N. V.; Yao, C.-F. *Tetrahedron Lett.* **2005**, *46*, 4971–4974.
40. Han, X.; Balakrishnan, V. K.; vanLoon, G. W.; Buncel, E. *Langmuir* **2006**, *22*, 9009–9017.
41. Qi, C.; Jiang, H.; Huang, L.; Chen, Z.; Chen, H. *Synthesis* **2011**, 387–396.
42. Liu, Y.; Yun, X.; Zhang-Negrerie, D.; Huang, J.; Du, Y.; Zhao, K. *Synthesis* **2011**, 2984–2994.
43. Kumar, B. N. H.; Prakasam, T.; Srinivasan, P. S.; Arabindoo, B.; Ramana, D. V. *Indian J. Chem. B* **2008**, *47B*, 963–965.
44. *SHELXS-2013, Programs for Crystal Structure Analysis. Release 97-2*. Institüt für Anorganische Chemie der Universität: Tammanstrasse 4, D-3400 Göttingen, Germany.
45. WinGX; Farrugia, L. J. *J. Appl. Crystallogr.* **1999**, *32*, 837–838.
46. SHELXL-2013; Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112–122.