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Synthesis of novel isoxazoline and isoxazolidine derivatives: carboxylic acids and delta bicyclic lactones *via* the nucleophilic addition of bis(trimethylsilyl)ketene acetals to isoxazoles

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This paper is dedicated to the successful career of Professor Lanny Liebeskind

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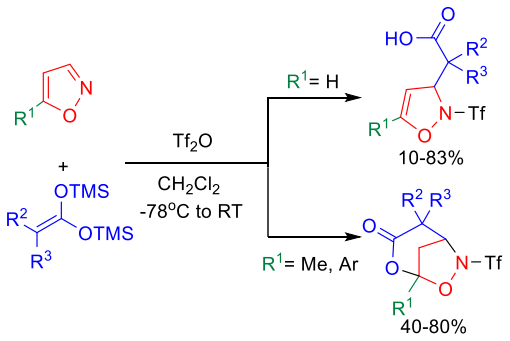
Abstract

Bis(trimethylsilyl)ketene acetals readily react with activated *N*-triflyl isoxazoles to selectively afford novel isoxazoline or isoxazolidine derivatives. The regioselectivity of the reaction strongly depends on the substrate substituents. When the isoxazole is substituted at the 5-position by a methyl or phenyl group, the lactonization product, i.e., the isoxazolidine derivative, is formed as a result of double nucleophilic addition of the ketene acetal. When the isoxazole is not substituted, the main product is the corresponding carboxylic acid, i.e., the isoxazoline derivative.



Keywords: Ketene acetals, isooxazoline, isoxazolidine, lactone, N-triflyl activation

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Introduction

Isoxazoline[1-6] and isoxazolidine[7-11] compounds represent an important class of five-membered heterocycles with contiguous nitrogen and oxygen atoms which have attracted significant attention, mainly due to their broad range of biological activities and potential application in the pharmaceutical industry. They are considered as privileged scaffolds in drug design and synthesis.[7,12-18] Furthermore, these structures are found in a number of natural products.[1,19-21]

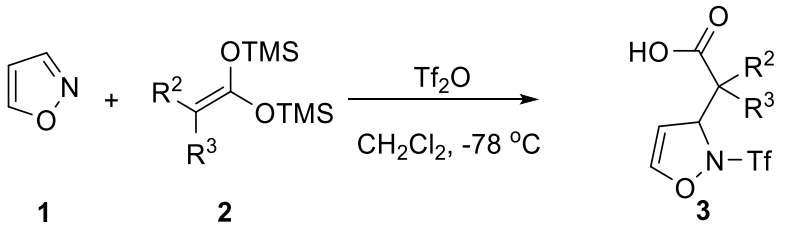
Over the last two decades, our research group and others have been interested in the nucleophilic addition of bis(trimethylsilyl)ketene acetals to different activated heterocyclic substrates[22] such as pyridine,[23-28] pyrazine,[29-31] quinoline,[32,33] imidazole,[34] 4-azabenzimidazole[35] and 4,5-dihydrooxazole[36] derivatives. In most cases, the main products of these reactions are carboxylic acids which can be transformed into the corresponding γ or δ lactones *via* the addition of electrophilic species which promote an intramolecular cyclization. Only in a few cases, depending on the nature of the heterocycle and the activating agent, did the nucleophilic addition of the bis(trimethylsilyl)ketene acetal directly afford the lactonization product.[23,28,30,31,36] The interest in these types of carboxylic acid and lactones lies in their potential biological properties, and their use as scaffolds in the synthesis of pharmaceutically interesting compounds.[37-39]

Among the examined substrates for the nucleophilic addition of bis(trimethylsilyl)ketene acetals, studies with isoxazole derivatives remain elusive. We envisaged the isoxazole structure as a good candidate to build 4-isoxazoline and isoxazolidine derivatives with potential biological properties.

Herein, we report a methodology to selectively obtain novel 4-isoxazoline carboxylic acid or isoxazolidine-δ-bicyclic lactone derivatives *via* the nucleophilic addition of bis(trimethylsilyl)ketene acetals to isoxazoles. To promote the reaction, we decided to activate the substrate by introducing the strongly electron-withdrawing triflyl group at the 2-position of isoxazole. Additionally, the CF_3SO_2 group could confer potential biological activity to the product.[40,41]

Results and Discussion

We started our study with the activation of isoxazole **1** with triflic anhydride (1.2 equiv), followed by the addition of bis(trimethylsilyl)ketene acetal **2** at -78 °C in CH_2Cl_2 as the solvent (Scheme 1).



1 **2** **3**

Scheme 1: Synthesis of 4-isoxazoline derivatives (**3**)

If substrate **1** is not activated with triflic anhydride, the carbon at the 3-position is not electrophilic enough and the reaction does not proceed (Table 1, entry 1).

As shown in Table 1, after triflic anhydride is added, the activation time has an important impact on the overall reaction effectiveness. When **1** was reacted with triflic anhydride for 1 h, and then **2** is added and stirred

for 24 h, the 4-isoxazoline carboxylic acid derivative **3** is obtained in 50% yield (Table 1, entry 2). However, if the reaction is activated for 3 h, the yield increases to 81% (Table 1, entry 3). After 4 h activation, there is not a significant change in the yield (Table 1, entries 4 and 5).

Table 1. Activation times of isoxazole **1** and yields

Entry	Activation time	Yield %
1	Without activating agent	N.R
2	1 h	50
3	3 h	81
4	4 h	83
5	6 h	83

Reagents and conditions: Tf_2O (1.2 equiv), anhydrous CH_2Cl_2 (15 mL), -78 ^oC. N.R: not reaction

In order to explore the scope of this reaction, we decided to examine the reaction of oxazole **1** with different bis(trimethylsilyl) ketene acetals **2** (Table 2). As expected, the nucleophilic addition reaction showed strong dependence on steric effects. When the bis(trimethylsilyl) ketene acetals are substituted by R^2 and R^3 substituents larger than methyl groups, i.e., cyclobutyl, cyclopentyl and cyclohexyl groups, the yields decreased dramatically as the steric-hindrance effects increased (Table 2). This result can be attributed to the presence of the voluminous -SO_2CF_3 group at the 2-position of the isoxazole, increasing the steric strain in the compound which led to product degradation.

Table 2. Yields of carboxylic acids **3** with different bis(trimethylsilyl) ketene acetals **2**

Entry	R^2	R^3	Product	Yield (%)
1	CH_3	CH_3	**3a**	83
2	-$(CH_2)_3$-		**3b**	41
3	-$(CH_2)_4$-		**3c**	38
4	-$(CH_2)_5$-		**3d**	10

Conditions: Activation time 4h, 1.2 eq of 2, overall reaction time 24h.

Compounds **3a**-**d** were fully characterized using spectroscopic techniques. As a representative example, for compound **3a**, the presence of the carboxylic acid was clearly observed in the IR spectrum by two absorption bands: a broad band between 2800 and 3200 cm^{-1} (ν(OH)), and a sharp band at 1771 cm^{-1} (ν(C=O)). The ^{1}H-NMR spectrum showed a broad singlet at 10.54 ppm corresponding to the hydrogen of the -COOH group, and a signal at 5.23 ppm (m, 1H) corresponding to the proton at the 3-position of the isoxazoline (the site of the nucleophilic addition by the bis(TMS)ketene acetal). In the ^{13}C-NMR spectrum, a signal at 181.3 ppm is observed for the carboxylic carbon, and introduction of the triflyl group is confirmed by a quartet signal at 121.74 ppm (J_{CF} 323.2 Hz). Moreover, the molecular structure of compound **3c** was unambiguously confirmed by X-ray diffraction

analysis (Fig. 1). The molecular structure shows the carboxylic acid in an *anti*-conformation with respect to the triflyl group.

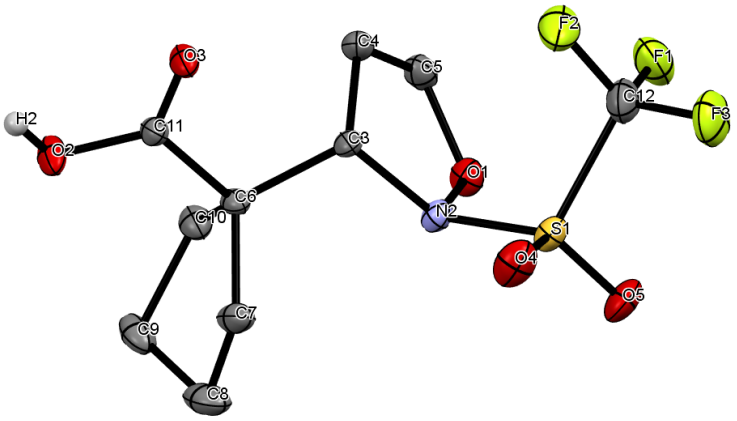
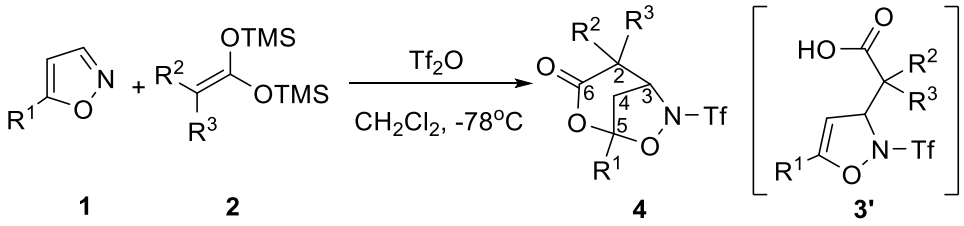


Figure 1. ORTEP view of compound **3c**. Thermal ellipsoids at the 30% probability level.

Interestingly, when the isoxazole is substituted at the 5-position by a methyl group (Scheme 2), the lactonization product **4** was isolated as the main product (Table 3, entries 1 and 2), and only some trace amounts of carboxylic acid **3'** were observed.



Scheme 2: Synthesis of δ-lactones **4**

In fact, it was possible to isolate crystals of compound **3'** (R^1 = Me, entry 2), whose structure was confirmed by X-ray diffraction analysis (Fig. 2); however, the amount was not sufficient enough to allow its characterization by NMR spectroscopy.

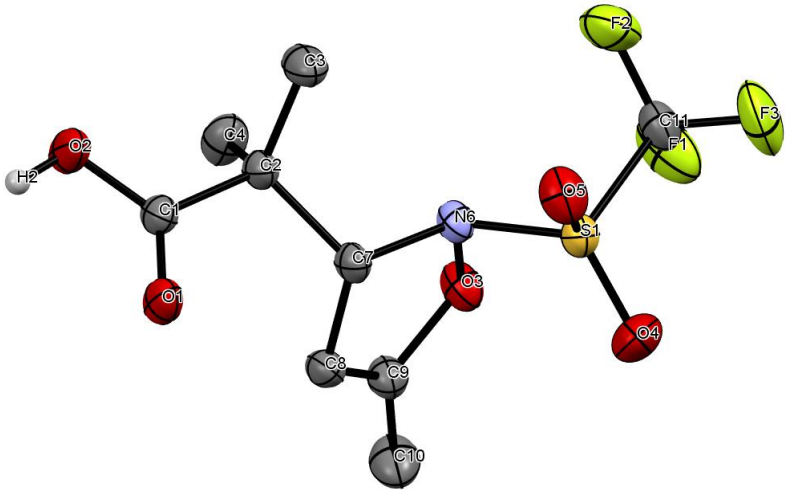


Figure 2. ORTEP view of compound **3'**. Thermal ellipsoids at the 30% probability level.

When the reaction was carried out with phenyl and para-substituted phenyl groups at the 5-position of the isoxazole, the lactonization product **4** (isoxazolidine derivative) was also obtained instead of the carboxylic acid **3**. Products **4c-g** were obtained in moderate to good yields (Table 3, entries 1-7).

Notably, derivatives **4** are easily obtained in only one step using this methodology, while the synthesis reported by Miller and co-workers[42] for a structurally similar compound required several steps.

Table 3. Yields of isoxazolidine derivates (**4**)

Entry	R^1	R^2	R^3	Product	Yield (%)	Yield 3'
1	Me	-$(CH_2)_5$-		**4a**	80	Traces
2	Me	Me	Me	**4b**	40	Traces
3	Ph	Me	Me	**4c**	65	N. O
4	4-OMePh	Me	Me	**4d**	70	N. O
5	4-ClPh	Me	Me	**4e**	50	N. O
6	4-FPh	Me	Me	**4f**	54	N. O
7	4-BrPh	Me	Me	**4g**	51	N. O

Conditions: Activation time of 12 h, overall reaction time 16 h. N.O (not observed)

The structures of compounds **4a-g** were fully characterized by spectroscopic techniques. As a representative example, for compound **4e**, in the IR spectrum, the absorption band of the carbonyl group, ν(C=O), was found at 1758 cm^{-1}, which is in the typical range of wavenumbers expected for a δ-lactone. In the ^{1}H-NMR spectrum, the clearest evidence of lactone formation were protons H3 and H4; the signal of H3 was observed as a doublet at 4.73 ppm ($^3J_{H3\text{-}H4}$ 5.16 Hz), while the signals of the methylene diastereotopic protons H4 and H4' were found at 2.82 ppm (d, $^2J_{H4\text{-}H4'}$ 13.2 Hz) and 2.68 ppm (dd, $2J_{H4\text{-}H4'}$ 13.2 Hz, $^3J_{H3\text{-}H4}$ 5.16 Hz), respectively. The ^{13}C spectrum shows the signal of C5 at 109.9 ppm, corroborating the ring closure, and the quartet signal at 120.9 ppm (J_{CF}

320.25 Hz) confirmed the presence of the triflyl group. Furthermore, the molecular structures for lactones **4c** and **4e** were unambiguously confirmed by X-ray diffraction analysis (Figs. 3 and 4, respectively).

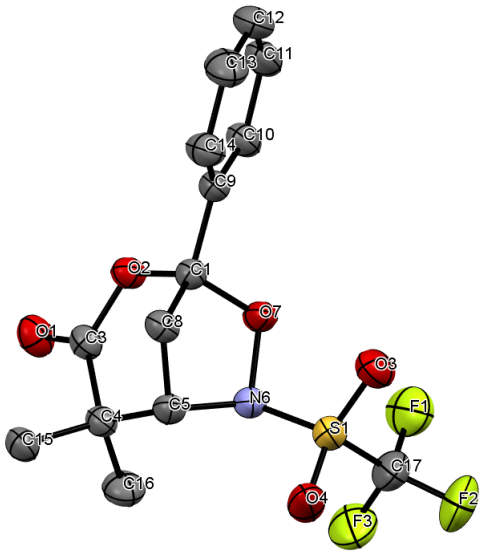


Figure 3. ORTEP view of compound **4c**. Thermal ellipsoids at the 30% probability level.

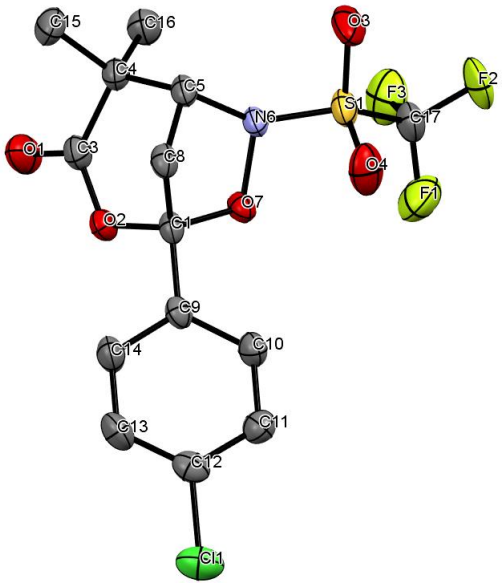
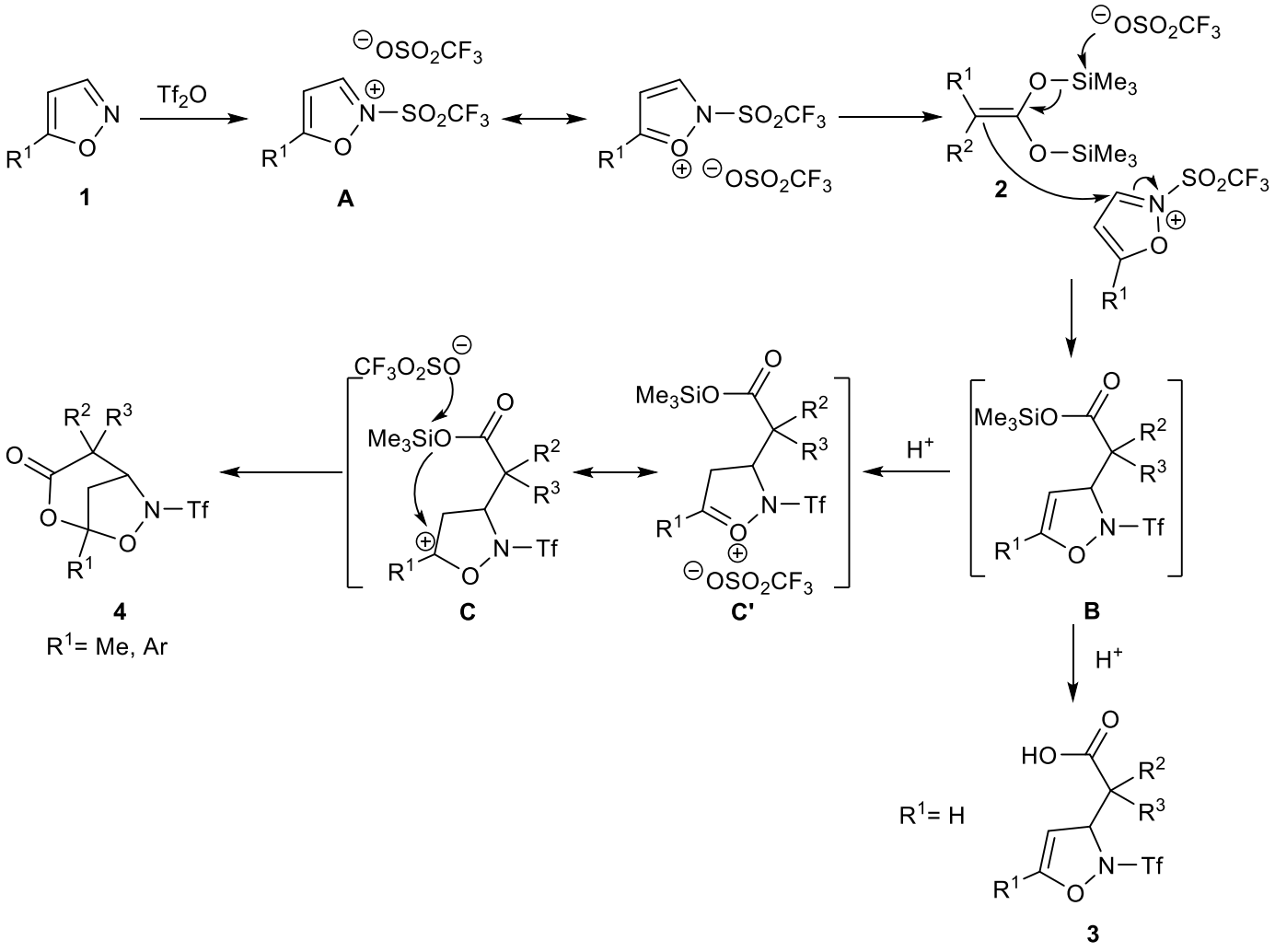


Figure 4. ORTEP view of compound **4e**. Thermal ellipsoids at the 30% probability level.

To explain the regioselectivity of the reaction, a plausible mechanism is proposed as shown in Scheme 3. In the first step, isoxazole **1** reacts with triflic anhydride to form the electrophilic iminium salt **A**, then ketene acetal **2** is activated by triflate anion generating the naked enolate which reacts with iminium salt **A** *via* the nucleophilic addition at imine carbon to yield adduct **B**. As described above, when isoxazole **1** is not substituted at the 5-position, the reaction affords the corresponding carboxylic acid **3** by hydrolysis of adduct **B**. In contrast, when the isoxazole is substituted at the 5-position by an electron-donating group like methyl or phenyl, the olefin in adduct **B** readily undergoes electrophilic addition, promoted by traces of the triflic acid generated *in situ*, to give the stabilized carbocation **C**. Finally, lactone **4** is formed through an intramolecular cyclization of intermediate **C**. In accordance with the stabilization of carbocation **C**, when the phenyl is substituted at the 4-position by an

electron-donating group, e.g., a methoxy group (Table 3, entry 2), the lactonization product **4d** was obtained in good yield (70%), while, with less electron donating groups, e.g., halogens, the yield decreases to around 50% (Table 3, entries 3-5).

A variety of methodologies have been reported for the olefinic esters cyclization mediated by Bronsted or Lewis acids, all proposed mechanisms for this kind of reaction involve the formation of carbocationic species by addition of the Bronsted or Lewis acid to the olefin, followed by the intramolecular addition of the nucleophile[43] as shown for transformation **B** to **4**. Although this reaction has been less studied with 2,3-dihidro isoxazol derivatives, a similar reactivity of intermediate C' has been proposed by Campagne et al.[44]



Scheme 3. Proposed mechanism for the formation of carboxylic acid **3** and δ-lactone **4**.

Conclusions

A straightforward methodology has been developed for the synthesis of highly functionalized 4-isoxazoline and isoxazolidine derivatives, *via* the addition of the masked dinucleophile bis(trimethylsilyl)ketene acetal to N-trifyl activated isoxazoles. The regioselectivity of the reaction is governed by the ability of the substrate to stabilize the carbocation intermediate at the 5-position of the isoxazole. In this way, when the isoxazole is substituted

by methyl or phenyl groups, the lactonization product (isoxazolidine derivative) is afforded. When the isoxazole is not substituted, the reaction stops at carboxylic acid formation (4-isoxazoline derivative).

Experimental Section

General. All substrates and solvents were purchased from specialized suppliers with analytical purity and were used as received without any further purification. Melting points were determined on a Melt Temp II apparatus. The ^{1}H and ^{13}C NMR spectra were measured with a Bruker Avance III (300 MHz) and a Bruker Avance III (400 MHz) using $CDCl_3$ or Acetone-d_6 as solvent. Chemical shifts are expressed in ppm (δ) relative to TMS. The following abbreviations are used: br=broad signal, s=singlet, d=doublet, t=triplet, dd=double doublet, q=quartet and m=multiplet. Mass spectra were obtained by DART and TOF mass spectrometer. IR spectra were obtained with a Bruker TENSOR 27 spectrophotometer. Suitable X-ray-quality crystals of **3c**, **3'**, **4c**, **4e** compounds were grown through slow evaporation of solvent. A single white crystal of compounds **3c**, **3'**, **4c**, **4e** were mounted on a glass fiber at room temperature. The crystal was then placed on a Bruker SMART APEX CCD diffractometer, equipped with MoKa radiation; decay was negligible all cases. Systematic absences and intensity statistics were used in space group determinations. The structures were determined using direct methods.[43] Anisotropic structure refinements were achieved using full-matrix, least-squares techniques on all non-hydrogen atoms. All hydrogen atoms were placed in idealized positions, based on hybridization, with isotropic thermal parameters fixed at 1.2 times the value of the attached atom. Structure solutions and refinements were performed using SHELXTL v 6.10.[44] The bis-(trimethylsilyl)ketene acetals **2** were prepared according to published methods.[45]

General procedure for the synthesis of carboxylic acids 3. Trifluoromethane sulfonic anhydride (1.2 equiv, 3.6 mmol) was slowly added by syringe to a solution of isoxazole **1** (3 mmol) in dry dichloromethane (15 mL) at -78 °C and under an inert atmosphere (N_2). After 4h at -78 °C, the corresponding bis(trimethylsilyl)ketene acetal **2** (1.2 equiv, 3.6 mmol) was added. Then the temperature was allowed to warm to room temperature and stirred for 20h. The crude was transferred to a separating funnel and washed with water (3 x 20 mL). The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The products were purified by silica gel column chromatography, eluted with mixtures of 90:10 hexane/ethyl acetate.

2-Methyl-2-(2-(((trifluoromethyl)sulfonyl)oxy)-2,3-dihydroisoxazol-3-yl)propanoic acid (3a). White powder (1000 mg, 81%), m.p. 108-110 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ (s, 1H, -COOH), 6.70 (dd, *J* 1.56, 3.06 Hz, 1H, H-2), 5.31 (br, 1H, H-1), 5.23 (t, *J* 1.47, 3.00 Hz, 1H, H-3), 1.27 (s, 3H, -CH_3) 1.12 (s, 3H, -CH_3'). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 131.38 (C-5), 144.65 (C-1), 121.74 (q, *J* 320 Hz, -CF_3), 100.25 (C-2), 70.41 (C-3), 46.86 (C-4), 22.53 (CH_3), 18.07 (CH_3'). IR (KBr, cm^{-1}) ν 3131.31 (-OH), 1771.71 (C=O). MS (DART, *m/z*): 202 [M-C$(CH_3)_2$COOH]$^+$, 290 [M+1]$^+$, 307[M+H_2O]$^+$. HRMS (DART): calculated for $C_8H_{11}F_3NO_5S$ [M+1]$^+$ 290.0200; found 290.0202.

1-(2-(((Trifluoromethyl)sulfonyl)oxy)-2,3-dihydroisoxazol-3-yl)cyclobutanecarboxylic acid (3b). White powder (537 mg, 41 %), m.p. 116-118 °C. ^{1}H NMR (400 MHz, Acetone-d_6, ppm): δ 8.93 (s, 1H, -COOH), 7.21 (br, *J* 1.48 Hz, 1H, H-1), 5.48 (m, 2H, H-2, H-3), 2.38 (m, 3H, H-6), 2.01 (m, 2H, H-7). ^{13}C NMR (100 MHz, Acetone d-6, ppm): δ 174.19 (C-5), 145.05 (C-1), 121.42 (q, *J* 300 Hz, -CF_3), 100.33 (C-2), 69.23 (C-3), 50.53 (C-4), 26.63 (C-6), 24.07 (C-6'), 14.98 (C-7). IR (KBr, cm^{-1}) ν 3130.13 (-OH), 1711.20 (C=O). MS (DART, *m/z*): 202 [M-C$(CH_3)_3$COOH]$^+$, 302 [M+1]$^+$, 319[M+H_2O]$^+$. HRMS (DART): calculated for $C_9H_{13}F_3NO_5S$ [M+1]$^+$ 302.0293; found 302.0283.

1-(2-(((Trifluoromethyl)sulfonyl)oxy)-2,3-dihydroisoxazol-3-yl)cyclopentanecarboxylic acid (3c). White powder (521 mg, 38 %), m.p. 110-112 °C. ^{1}H NMR (400 MHz, Acetone-d_6, ppm): δ 7.00 (dd, 1H, *J* 2.56, 4.68 Hz, H-1), 6.05. (d, *J* 4.64 Hz, 1H, H-2), 5.93 (br, 1H, H-3), 2.18 (m, 1H, H-6,7), 2.07 (m, 1H, H-6,7), 1.78 (m, 6H, H-6,7).

^{13}C NMR (100 MHz, Acetoone-d_6, ppm): δ 175.34 (C-5), 126.44 (C-1), 121.46 (q, *J* 327 Hz, -CF_3), 116.41 (C-2), 93.00 (C-3), 56.61 (C-4), 32.24 (C-6), 31.89 (C-6') 26.00 (C-7), 25.89 (C-7'). IR (KBr, cm^{-1}) ν 2973.70 (-OH), 1705.97 (C=O). MS (DART, *m/z*): 202 [M-C$(CH_3)_4$COOH]$^+$, 316 [M+1]$^+$, 333[M+H_2O]$^+$. HRMS (DART): calculated for $C_{10}H_{13}F_3NO_5S$ [M+1]$^+$ 316.2703; found 316.2736.

1-(2-(((Trifluoromethyl)sulfonyl)oxy)-2,3-dihydroisoxazol-3-yl)cyclohexanecarboxylic acid (3d). White powder (143 mg, 10 %), m.p. 118-122 °C. ^{1}H NMR (400 MHz, Acetone-d_6, ppm): δ 7.17 (dd, *J* 2.4, 5.0 Hz, 1H, H-1), 5.50 (br, *J* 1.12, 2.6 Hz, 1H, H-2), 5.24 (br, 1H, H-3), 2.10 (m, 3H, H-7, 8, 9), 1.71 (m, 3H, H-7, 8, 9), 1.40 (m, 6H, H-7, 8,9). ^{13}C NMR (100 MHz, Acetone-d_6, ppm): δ 173.07 (C-5), 144.98 (C-1), 121.36 (q, *J* 324 Hz, -CF_3), 99.68 (C-2), 72.06 (C-3), 51.66 (C-4), 30.01 (C-7), 28.08 (C-7'), 25.24 (C-9), 22.83 (C8), 22.72 (C-8'). IR (KBr, cm^{-1}) ν 3433.29 (-OH), 1701.84 (C=O). MS (DART, *m/z*): 202 [M-C$(CH_3)_5$COOH]$^+$, 330 [M+1]$^+$, 307[M+H_2O]$^+$. HRMS (DART): calculated for $C_{11}H_{14}F_3NO_5S$ [M+1]$^+$ 330.2921; found 330.2912.

General procedure for the synthesis of lactones 4. Trifluoromethane sulfonic anhydride (1.2 equiv, 3.6 mmol) was slowly added by syringe to a solution of aryl isoxazole **1** (3 mmol) in dry dichloromethane (15 mL) at -78 °C and under an inert atmosphere (N_2). After 12h at -78 °C, the corresponding bis(trimethylsilyl)ketene acetal **2** (1.2 equiv, 3.6 mmol) was added. Then the temperature was allowed to warm to room temperature and stirred for 4h. The crude mixture was transferred to a separating funnel and washed with water (3 x 20 mL). The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The products were purified by silica gel column chromatography, eluted with mixtures of 90:10 hexane/ethyl acetate.

1-Methyl-3-oxo-2,7-dioxa-6-azaspiro[bicyclo[3.2.1]octane-4,1'-cyclohexan]-6-yl trifluoromethanesulfonate (**4a).** White powder (1000 mg, 80%), m.p. 78-80 °C. ^{1}H NMR (400 MHz, Acetone-d_6, ppm): δ 5.23 (d, *J* 5.52 Hz, 1H, H-1), 3.04 (d, *J* 13.6, 1H, H-3) 2.55 (dd, *J* 5.52, 13.56, 1H, H-2), 1.92 (m, 4H, H-7, 8, 9), 1.79 (s, 3H, H-6), 1.47 (m. 6H, H-7, 8, 9). ^{13}C NMR (100 MHz, Acetone-d_6, ppm): δ 171.85 (C-5), 120.66 (q, *J* 321 Hz, -CF_3), 109.47 (C-1), 61.29 (C-2), 48.04 (C-3), 38.51 (C-4), 31.95 (C-7), 31.13 (C-7'), 24.77 (C-6), 20.52 (C-9), 19.70 (C-8), 19.18 (C-8'). IR (KBr, cm^{-1}) ν 1734.86 (C=O). MS (DART, *m/z*): 210 [M-Tf]$^+$, 344 [M+1]$^+$, 361 [M+H_2O]$^+$. HRMS (DART): calculated for $C_{12}H_{17}F_3NO_5S$ [M+1]$^+$ 344.07795; found 344.07738.

1,4,4-Trimethyl-3-oxo-2,7-dioxa-6-azabicyclo[3.2.1]octan-6-yl trifluoromethanesulfonate (**4b).** White powder (1000 mg, 40%), m.p. 82-84 °C. ^{1}H NMR (400 MHz, Acetone-d_6, ppm): δ 4.86 (d, *J* 5.32 Hz, 1H, H-1), 3.12 (d, *J* 13.56, 1H, H-3) 2.50 (dd, *J* 5.40, 13.60 Hz, 1H, H-2), 1.79 (s, 3H, H-6) 1.47 (s, 3H, -CH_3) 1.41 (s, 3H, -CH_3'). ^{13}C NMR (100 MHz, Acetone-d_6, ppm): δ 172.30 (C-5), 120.77 (q, *J* 321 Hz, -CF_3), 109.88 (C-1), 65.74 (C-2), 44.50 (C-4) 38.51 (C-3) 24.53 (-CH_3), 23.16 (-CH_3), 19.16 (C-6). IR (KBr, cm^{-1}) ν 1742.91 (C=O). MS (DART, *m/z*): 170 [M-Tf]$^+$, 304 [M+1]$^+$, 321[M+H_2O]$^+$. HRMS (DART): calculated for $C_9H_{13}F_3NO_5S$ [M+1]$^+$ 304.04665; found 304.04796.

4,4-Dimethyl-3-oxo-1-phenyl-2,7-dioxa-6-azabicyclo[3.2.1]octan-6-yl trifluoromethanesulfonate (**4c).** White powder (490 mg, 65 %), m.p. 88-90 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.67 (m, *J* 7.41, 3.75 Hz, 2H, H-7), 7.42 (m, *J* 5.5, 2.28 Hz, 3H, H-8), 4.71 (m, *J* 5.07 Hz, 1H, H-2), 2.87 (d, *J* 13.26 Hz, 1H, H-3), 2.67 (dd, *J* 5.04, 13.31 Hz, 1H, H-3') 1.49 (s, 3H, -CH_3), 1.42 (s, 3H, -CH_3´). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 172.44 (C-4), 131.99 (C-6), 130.37 (C-8), 128.77 (C-9), 126.12 (C-7), 116.74 (q, *J* 320 Hz, -CF_3), 110.29 (C-5), 65.52 (C-2), 44.69 (C-3), 41.29 (C-1), 25.37, 23.60 (-CH_3). IR (KBr, cm^{-1}) 1751.25 (C=O). MS (DART, *m/z*): 278 [M-C$(CH_3)_2$COO]$^+$, 366 [M+1]$^+$, 367[M+2]$^+$. HRMS (DART): calculated for $C_{14}H_{15}F_3NO_5S$ [M+1]$^+$ 366.0578; found 366.0546.

1-(4-Methoxyphenyl)-4,4-dimethyl-3-oxo-2,7-dioxa-6-azabicyclo[3.2.1]octan-6-yl trifluoromethanesulfonate (4d). White powder (472 mg, 70 %), m.p. 82-90 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.61 (d, *J* 8.4 Hz, 2H, H-7), 6.95 (d, *J* 8.4, 2H, H-8), 4.69 (d, *J* 5.1 Hz, 1H, H-2), 3.81 (s, 3H, H-10), 2.84 (d, *J* 12.9 Hz, 1H, H-3) 2.72 (dd, *J* 5.1, 13.3 Hz, 1H, H-3'), 1.51 (s, 3H, -CH_3), 1.45 (s, 3H, -CH_3´). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 172.54 (C-4), 161.10 (C-9), 127.67 (C-7), 123.69 (C-6), 120.97 (q, *J* 320 Hz, -CF_3), 114.10 (C-8), 110.45 (C-5), 65.47 (C-2), 55.30 (C-10),

44.66 (C-3), 41.27 (C-1), 25.55, 23.68 (-CH_3). IR (KBr, cm^{-1}) ν 3432.57 (O-CH_3), 1761.56 (C=O). MS (DART, *m/z*): 262 $[M\text{-}Tf]^+$, 396 $[M+1]^+$, 367$[M+H_2O]^+$. HRMS (DART): calculated for $C_{15}H_{17}F_3NO_6S$ $[M+1]^+$ 396.0729; found 396.07134.

1-(4-Chlorophenyl)-4,4-dimethyl-3-oxo-2,7-dioxa-6-azabicyclo[3.2.1]octan-6-yl trifluoromethanesulfonate (4e). White powder (332 mg, 50 %), m.p. 98-100 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.66 (d, *J* 8.61 Hz, 2H, H-7), 7.43 (d, *J* 8.64 Hz, 2H, H-8), 2.87 (d, *J* 5.1 Hz, 2H, H-2), 2.72 (d, *J* 13.20 Hz, 1H, H-3), 2.68 (dd, *J* 5.16, 13.23 Hz, 1H, H-3') 1.53 (s, 3H, -CH_3), 1.49 (s, 3H, -CH_3´). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 171.12 (C-4), 136.62 (C-9), 130.48 (C-6), 129.07 (C-7), 127.63 (C-8), 120.88 (q, *J* 320 Hz, -CF_3), 109.80 (C-5), 65.38 (C-2), 44.72 (C-1), 41.66 (C-3), 25.65, 23.67 (-CH_3). IR (KBr, cm^{-1}) ν 1758.59 (C=O). MS (DART, *m/z*): 311 $[M\text{-}C(CH_3)_2COCl]^+$, 400 (Cl, 35), 402 (Cl, 37) $[M+1]^+$. HRMS (DART): calculated for $C_{14}H_{14}ClF_3NO_5S$ $[M+1]^+$ 400.0233; found 400.0237.

1-(4-Fluorophenyl)-4,4-dimethyl-3-oxo-2,7-dioxa-6-azabicyclo[3.2.1]octan-6-yl trifluoromethanesulfonate (4f). White powder (426 mg, 54 %), m.p. 92-94 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.74 (dq, *J* 14.01, 3.81 Hz, 2H, H-8), 7.19 (t, *J* 9.15, 8.58 Hz, 2H, H-7), 4.73 (d, *J* 5.04 Hz, 1H, H-3), 2.87 (d, *J* 13.20 Hz, 1H, H-3), 2.75 (dd, *J* 13.2, 5.07 Hz, 1H, H-3), 1.56 (s, 3H, -CH_3), 1.51 (s, 3H, -CH_3´). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 172.18 (C-4), 165.53 (d, 249, C-7) 128.55 (d, 9, C-7), 127.85 (d, 3, C-6), 120.90 (q, *J* 320 Hz, -CF_3), 116.63 (d, 42, C-8), 109.91 (C-5), 65.36 (C-2), 44.71 (C-1), 41.79 (C-3), 25.75, 23.72 (-CH_3). IR (KBr, cm^{-1}) ν 1770.24 (C=O). MS (DART, *m/z*): 339 $[M\text{-}COOF]^+$, 384 $[M+1]^+$. HRMS (DART): calculated for $C_{14}H_{14}F_4NO_5S$ $[M+1]^+$ 384.0603; found 384.0603.

1-(4-Bromophenyl)-4,4-dimethyl-3-oxo-2,7-dioxa-6-azabicyclo[3.2.1]octan-6-yl trifluoromethanesulfonate (4g). White powder (303 mg, 51 %), m.p. 88-90 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.61 (s, 2H, H-8), 7.28 (s, 2H, H-7), 2.87 (d, *J* 5.1 Hz, 2H, H-2), 4.73 (d, *J* 5.04 Hz, 1H, H-2), 2.86 (d, *J* 13.17 Hz, 1H, H-3'), 2.74 (dd, *J* 5.1, 13.17 Hz, 1H, H-3'), 1.56 (s, 3H, -CH_3), 1.51 (s, 3H, -CH_3´). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 172.05 (C-4), 132.08 (C-8), 130.96 (C-9), 127.99 (C-7), 124.89 (C-6), 109.81 (C-5), 65.33 (C-2), 44.74 (C-1), 41.77 (C-3), 25.79, 23.73 (-CH_3). IR (KBr, cm^{-1}) ν 1733.21 (C=O) .MS (DART, *m/z*): 355 (Br, 79), 357 (Br, 81) $[M\text{-}CF_3S]^+$, 443 (Br, 79), 445 (Br, 81) $[M+1]^+$. HRMS (DART): calculated for $C_{14}H_{14}BrF_3NO_5S$ $[M+1]^+$ 443.9729; found 443.9743.

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Supplementary Material

Copies of ^{1}H and ^{13}C NMR spectra associated with this manuscript are presented in the Supplementary Material file in the online version.

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