Organic & Biomolecular Chemistry

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Cite this: *Org. Biomol. Chem.*, 2013, **11**, 6650

A synthesis of γ-trifluoromethyl α,β-unsaturated γ-butyrolactones using CF_3SiMe_3 as a trifluoromethylating agent†

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Received 17th June 2013,
Accepted 31st July 2013

DOI: 10.1039/c3ob41247d

www.rsc.org/obc

A general synthesis of γ-trifluoromethyl α,β-unsaturated γ-butyrolactones is described. The fluoride-catalyzed nucleophilic addition of a trifluoromethyl (CF_3) group generated from (trifluoromethyl)trimethylsilane (CF_3SiMe_3, Ruppert–Prakash reagent) to a masked maleic anhydride **1** (cyclopentadiene–maleic anhydride adduct) provides the corresponding adducts **2** with high stereoselectivity. The γ-trifluoromethyl α,β-unsaturated γ-butyrolactones **4** were obtained after treatment of the adducts **2** with Grignard reagents, followed by flash-vacuum pyrolysis.

Fluorine containing compounds possess unique physical and chemical properties because of the special size of the fluorine atom, the high carbon–fluorine bond energy and the special inductive and resonance effects caused by fluorine atom.[1] Therefore, they receive intensive attention in various fields including agrochemical, pharmaceutical and materials chemistry.[2] For example, in medicinal chemistry, incorporation of trifluoromethyl (CF_3) groups into the molecular framework of pharmaceuticals is commonly found to improve their biological activity as a result of the resilience of the trifluoromethyl group to metabolism.[3] Hence, the development of synthetic strategies that achieve incorporation of the trifluoromethyl functionality in a series of substrates has been the subject of intense research efforts.[4] Methods for the direct trifluoromethylation of aryl halides, aryl and vinylboronic acids, terminal alkenes, and primary and secondary alkylboronic acids have been reported.[5–18] Among these, fluoride-catalyzed nucleophilic addition of the trifluoromethyl (CF_3) group generated from (trifluoromethyl)trimethylsilane (CF_3SiMe_3, Ruppert–Prakash reagent) to various electrophiles, *e.g.*, carbonyl compounds, esters, imines, enones and cyclic amides has been extensively exploited as a useful method for the preparation of trifluoromethyl-containing compounds.[19]

A few reports were found in the literature related to the nucleophilic trifluoromethylation of anhydrides. For example, Wakselman and co-workers reported nucleophilic addition of CF_3ZnBr to anhydrides in pyridine.[8] Later, Viner reported the fluoride-catalyzed trifluoromethylation of succinic anhydride using CF_3SiMe_3 as a reagent for the synthesis of acetylcholinesterase (AChE) inhibitors.[20] A recent study on fluoride-catalyzed nucleophilic addition of $PhSCF_2SiMe_3$ to anhydrides yielding the corresponding γ-lactones, which could be further transformed to γ-difluoromethylated γ-lactams was reported by us.[21]

Our research group has longheld an interest in the development of synthetic strategies for the preparation of fluorine-containing compounds. Herein, we report our efforts in exploring a general approach to the synthesis of γ-trifluoromethyl α,β-unsaturated γ-butyrolactones using CF_3SiMe_3 as a trifluoromethylating agent. It was anticipated that fluoride-catalyzed trifluoromethylation of a masked maleic anhydride **1** (cyclopentadiene–maleic anhydride adduct)[22] with CF_3SiMe_3 would afford the corresponding adduct **2**. Treatment of **2** with Grignard reagents gives γ-trifluoromethyl γ-butyrolactones **3**, which upon flash-vacuum pyrolysis (FVP) lead to the desired γ-trifluoromethyl α,β-unsaturated γ-butyrolactones **4** as depicted in Scheme 1. It is worth mentioning that a different approach to the synthesis of trifluoromethylated lactones was previously reported by Yoshida.[23] α,β-Unsaturated γ-butyrolactones are important structural motifs, which are widely found in bioactive natural products.[24] This type of compound has also been employed as a versatile starting material for

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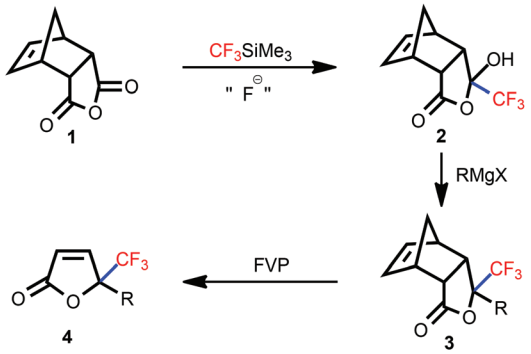
†Electronic supplementary information (ESI) available: Spectroscopic data for all compounds (copies of ^1H, ^{13}C and ^{19}F NMR), and NOESY and NOE of **3a**. CCDC 933155 and 933154. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ob41247d



Scheme 1 Proposed synthetic strategy for γ-trifluoromethyl α,β-unsaturated γ-butyrolactone **4**.

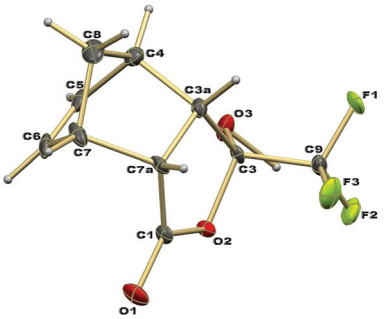
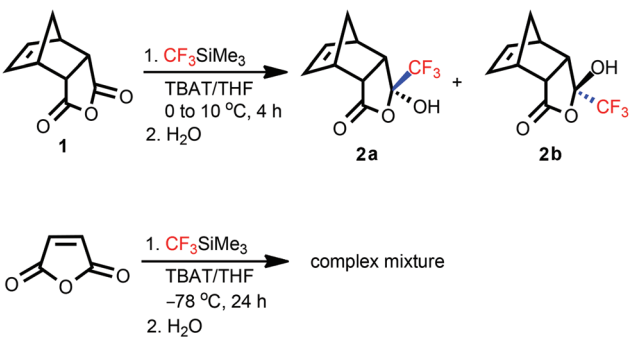


Fig. 1 X-ray crystallographic structure of **2a**.

further synthetic applications. Hence, there is continuing interest in synthetic approaches for the α,β-unsaturated γ-butyrolactone synthesis.[25]

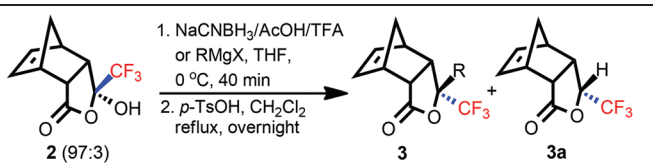
Our initial studies focused on the optimization of the fluoride-catalyzed trifluoromethylation of the masked maleic anhydride **1**. After screening for the optimum reaction conditions, it was found that treatment of **1** with CF_3SiMe_3 (2 equiv.) catalyzed by 10 mol% TBAT (tetrabutylammoniumtriphenyl difluorosilicate) in THF at 0 °C, in a reaction mixture which was then kept below 10 °C for 4 h, followed by quenching with H_2O provided the desired trifluoromethylated adduct **2** in 90% yield (Scheme 2). It should be mentioned that a longer reaction time was needed and lower yields of the product **2** were observed when a lesser amount of CF_3SiMe_3 (1 and 1.5 equiv.) was used. The reaction proceeded with high stereoselectivity to give a 97 : 3 mixture of the isomers as determined by ^{19}F and ^{1}H NMR. The relative stereochemistry of the major isomer **2a** was determined by X-ray crystallography (Fig. 1).[26] It was reasoned that formation of **2a** as the major diastereomer occurred because nucleophilic trifluoromethylation selectively took place at the less sterically hindered convex side of **1**. It is worth mentioning that the reaction of **1** with CF_3SiMe_3 catalyzed by TBAF (THF, 0 to 10 °C, 4 h) or CsF (THF, 0 °C to rt, 24 h) gave the adduct **2** with similar stereoselectivity but in lower yields, 78 and 43%, respectively. Notably, the direct addition of CF_3SiMe_3 to naked maleic anhydride under the standard reaction conditions or at a lower temperature (−78 °C) failed to provide the desired adduct, with only a complex mixture being obtained.



Scheme 2 The fluoride-catalyzed addition of CF_3SiMe_3 to the masked maleic anhydride **1** and maleic anhydride.

Having established efficient access to compound **2**, we further demonstrated that our method could be used as a general route for the synthesis of γ-trifluoromethyl α,β-unsaturated γ-butyrolactones. Thus, **2** was subjected to a nucleophilic addition reaction using hydride or organometallic reagents. Treatment of **2** with $NaCNBH_3$ in acetic acid with a catalytic amount of trifluoroacetic acid at 50 °C for 16 h gave an 88% yield of γ-butyrolactone **3a** as a single isomer (Table 1, entry 1). The reaction of **2** with Grignard reagents as listed in Table 1 in THF followed by acid-catalyzed lactonization afforded the corresponding γ-butyrolactones **3b–3i** as single isomers in moderate to high yields (Table 1, entries 2–9). Using isopropylmagnesium chloride to react with **2** gave the expected product **3d** along with the reduction product **3a** in 40 and 35% yields, respectively (Table 1, entry 4). Improved results were obtained when the addition of isopropylmagnesium chloride was carried out at −78 °C. Thus, **3d** was obtained in 50% yield

Table 1 Nucleophilic addition reactions of **2** with $NaCNBH_3$ and Grignard reagents



Entry	Reagent	R	Yield[a] (%) 3	3a
1	$NaCNBH_3$	H–	—	88
2	CH_3MgCl	CH_3–	**3b**, 86	—
3	CH_3CH_2MgCl	CH_3CH_2–	**3c**, 86	—
4	$(CH_3)_2CHMgCl$	$(CH_3)_2CH$–	**3d**, 40 (50)[b]	35 (19)[b]
5	$CH_3(CH_2)_3MgCl$	$CH_3(CH_2)_3$–	**3e**, 86	—
6	$CH_2{=}CHMgCl$	$CH_2{=}CH$–	**3f**, 87	—
7	$CH_2{=}CH(CH_2)_2MgBr$	$CH_2{=}CH(CH_2)_2$–	**3g**, 80	—
8	PhMgCl	Ph–	**3h**, 91	—
9	4-MeO(Ph)MgBr	4-MeO(Ph)–	**3i**, 69	—

[a] Yields of isolated products. [b] The reaction was carried out at −78 °C for 1 h.

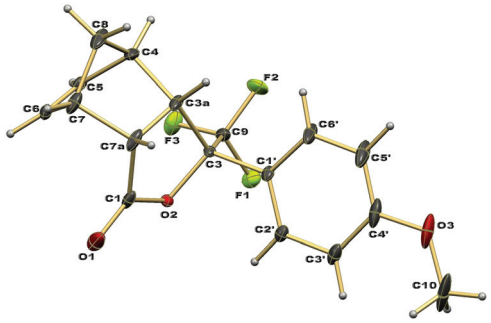


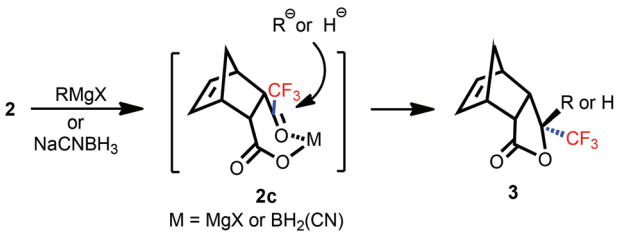
Fig. 2 X-ray crystallographic structure of **3i**.

together with **3a** in 19% yield (Table 1, entry 4). The stereochemistry of compound **3a** was confirmed by NOESY and NOE experiments and in the case of **3i** the stereochemistry was confirmed by X-ray crystallography (Fig. 2 and see ESI†).

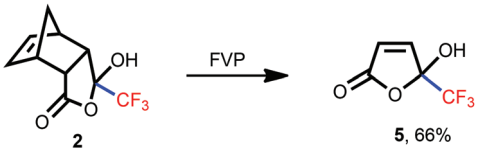
Based on the NOESY and NOE experimental data of **3a** and the X-ray crystallography of **3i**, a transition state for selective nucleophilic addition to **2** was proposed as shown in Scheme 3. Initially, proton abstraction of **2** with $NaCNBH_3$ or RMgX followed by ring-opening led to the formation of the keto-carboxylate **2c**, which then underwent stereoselective nucleophilic addition on the convex side leading to **3** as a single isomer after lactonization (Scheme 3).

In order to test the possibility of obtaining the required γ-trifluoromethyl α,β-unsaturated γ-butyrolactones, the adduct **2** (as a 97 : 3 diastereomeric mixture) was directly subjected to flash-vacuum pyrolysis (375 °C, 0.05 mmHg). It was found that the reaction of **2** provided γ-hydroxy-γ-trifluoromethyl α,β-unsaturated γ-butyrolactone (**5**) in 66% yield (Scheme 4).

Finally, based on the conditions used to synthesize **5**, the preparation of γ-trifluoromethyl α,β-unsaturated γ-butyrolactone **4** was accomplished by performing flash-vacuum pyrolysis of adduct **3**. Thus, **3a–3i** were subjected to flash-vacuum pyrolysis conditions (375 °C, 0.05 mmHg) to give high yields of

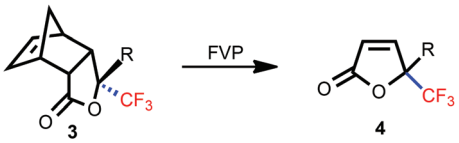


Scheme 3 Proposed stereoselective addition of $NaCNBH_3$ or RMgX to **2**.



Scheme 4 Flash-vacuum pyrolysis of **2**.

Table 2 Preparation of **4** by flash-vacuum pyrolysis of adduct **3**



Entry	**3**, R	**4**, yield[a] (%)
1	**3a**, H–	**4a**, 82
2	**3b**, CH_3–	**4b**, 54
3	**3c**, CH_3CH_2–	**4c**, 87
4	**3d**, $(CH_3)_2CH$–	**4d**, 91
5	**3e**, $CH_3(CH_2)_3$–	**4e**, 98
6	**3f**, CH_2=CH–	**4f**, 87
7	**3g**, CH_2=CH$(CH_2)_2$–	**4g**, 99
8	**3h**, Ph–	**4h**, 96[b]
9	**3i**, 4-MeO(Ph)–	**4i**, 97[b]

[a] Yields of the analytical pure products after FVP. [b] Isolated yields after preparative thin-layer chromatography (SiO_2).

the corresponding γ-trifluoromethyl α,β-unsaturated γ-butyrolactones **4a–4i** as summarized in Table 2.

Conclusions

We have reported a general fluoride-catalyzed nucleophilic addition of a CF_3 group to an anhydride. The method has been utilized for the preparation of γ-trifluoromethyl α,β-unsaturated γ-butyrolactones by performing a fluoride-catalyzed nucleophilic addition of a CF_3 group to a masked maleic anhydride (cyclopentadiene–maleic anhydride adduct) followed by reaction with a Grignard reagent and flash-vacuum pyrolysis. This type of compound may be useful as the starting material for the synthesis of trifluoromethylated organic compounds including some natural compounds. Investigations in this area are now in progress.

Experimental

General information

The ^1H NMR spectra were recorded using a Bruker 400 (400 MHz) or a Bruker 500 (500 MHz) spectrometer using $CDCl_3$ as a solvent and tetramethylsilane as an internal standard. The ^{13}C NMR spectra were recorded using a Bruker 400 (100 MHz) or a Bruker 500 (125 MHz) spectrometer using $CDCl_3$ as a solvent and the residual non-deuterated solvent peaks as an internal standard. The ^{19}F NMR spectra were recorded using a Bruker 400 (376 MHz) or 500 (470 MHz) spectrometer and the chemical shifts (δ) were measured with fluorotrichloromethane ($\delta = 0$) as an internal standard. The IR spectra were recorded using either a Jasco A-302 or a Perkin Elmer 683 infrared spectrometer with the solvent $CHCl_3$ or neat. The mass spectra were recorded using a Thermo Finnigan Polaris Q mass spectrometer. The high resolution mass spectra were recorded using either a HR-TOF-MS Micromass

model VQ-TOF2 or a Finnigan MAT 95 mass spectrometer. Melting points were measured (uncorrected) using a Büchi 501 melting point apparatus. The X-ray crystallographic analysis was performed by Kappa CCD. Tetrahydrofuran (THF) was distilled over sodium benzophenone ketyl. Dichloromethane (CH_2Cl_2) and toluene were distilled over calcium hydride and were stored over activated molecular sieves (4 Å). All glassware and syringes were oven-dried and kept in a desiccator before use. Preparative thin-layer chromatography plates were performed using Merck silica gel 60 PF_{254} (Art 7747). Column chromatography was performed using Merck silica gel 60 PF_{254} (Art 7734). Flash column chromatography was performed using Merck silica gel 60 PF_{254} (Art 7736). Other common solvents (CH_2Cl_2, hexanes, ethyl acetate (EtOAc), methanol, and acetone) were distilled before use.

General procedure for the synthesis of γ-hydroxy γ-trifluoromethyl γ-butyrolactones 2

A solution of (trifluoromethyl)trimethylsilane (CF_3SiMe_3, 0.6 mL, 4.0 mmol) and **1** (328 mg, 2.0 mmol) in dry THF (10 mL) was treated with a solution of 10 mol% TBAT (108 mg, 0.2 mmol) in dry THF (10 mL) at 0 °C under an argon atmosphere. The reaction mixture was stirred and kept below 10 °C for 4 h, then quenched with water and extracted with EtOAc (4 × 20 mL). The combined organic phase was washed successively with water (20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. After removal of the solvents, the crude product was purified by column chromatography (SiO_2, 5% EtOAc in hexanes) to give a 97 : 3 diastereomeric mixture of **2a** and **2b** (423 mg, 90%) as a white solid (mp 105–107 °C (CH_2Cl_2–hexanes)). IR ($CHCl_3$): ν_{max} 3189 br, 3030 m, 2998 m, 2875 w, 1785 s, 1312 m, 1241 m, 1183 s, 1049 m, 1004 s cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, minor isomer marked *): δ 6.38–6.36 (m, 1H, C*H*), 6.27–6.21 (m, 1H, C*H**), 6.20–6.18 (m, 1H, C*H*), 6.14–6.07 (m, 1H, C*H**), 4.65 (s, 1H, O*H**), 4.49 (s, 1H, O*H*), 3.61–3.54 (m, 1H, C*H**), 3.51–3.48 (m, 1H, C*H*), 3.36–3.29 (br, 1H, C*H*), 3.28–3.25 (m, 2H, 2 × C*H*), 3.13–3.05 (m, 2H, 2 × C*H**), 1.73 (d, J = 8.8 Hz, 1H, C*H*H*), 1.67 (d, J = 8.8 Hz, 1H, C*H*H), 1.50 (d, J = 8.8 Hz, 1H, C*H*H). Due to their low intensity, some peaks for **2b** could not be detected by ^1H NMR. ^{13}C NMR (100 MHz, $CDCl_3$, minor isomer marked *): δ 174.0 (C), 136.5 (C), 135.9 (C*), 134.1 (C), 122.0 (q, J = 284.0 Hz, CF_3), 100.5 (q, J = 34.0 Hz, C), 53.7 (CH_2*), 52.0 (CH_2), 49.8 (CH), 48.8 (CH*), 47.1 (CH*), 45.8 (CH), 45.0 (CH), 44.8 (CH), 44.3 (CH*), 44.2 (CH*). Due to their low intensity, some peaks for **2b** could not be detected by ^{13}C NMR. ^{19}F NMR (376 MHz, $CDCl_3$, minor isomer marked *): δ −86.8 (s, 3F), −79.4 (s, 3F*); MS: m/z (% relative intensity) 235 (M^+ + H, 31), 217 (17), 190 (19), 119 (13), 91 (48), 66 (100); HRMS (ESI–TOF) calcd for $C_{10}H_9F_3O_3Na$ $[M + Na]^+$: 257.0401, found 257.0402.

General procedure for the synthesis of γ-trifluoromethyl γ-butyrolactones 3

General procedure A. A solution of **2a** and **2b** (0.5 mmol) in dry THF (30 mL) was treated with alkyl or arylmagnesium chloride solution (2.5 mmol) at −78 °C or 0 °C under an argon atmosphere. After stirring the reaction mixture for 1 h at −78 °C, or at 0 °C for 40 min, 10% HCl (2 mL) was added at −78 °C or at 0 °C. The aqueous phase was extracted with EtOAc (4 × 20 mL). The combined organic phase was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. After the removal of the solvents, the crude product was treated with a catalytic amount of *p*-TsOH in dry CH_2Cl_2 (12 mL) under reflux overnight (16 h). The reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (4 × 10 mL). The combined organic phase was washed with brine (10 mL), and dried over anhydrous Na_2SO_4. After removal of the solvent, the crude product was purified by column chromatography (SiO_2) or preparative thin-layer chromatography (SiO_2).

General procedure B. A solution of alkyl or arylbromide (10.0 mmol) in dry THF (8 mL) was added dropwise to a suspension of Mg (turnings) (0.4 g, 20.0 mmol) in dry THF (7 mL) under an argon atmosphere at room temperature. After 2 h, the solution of freshly prepared Grignard reagent was transferred dropwise to a mixed solution of **2a** and **2b** (0.5 mmol) in THF (20 mL) *via* a canular at −78 °C or 0 °C under an argon atmosphere and then stirred for 1 h. The reaction mixture was quenched with 10% HCl (5 mL) at −78 °C or 0 °C and extracted with EtOAc (4 × 20 mL). The combined organic phase was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. After removal of the solvent, the crude product was treated with a catalytic amount of *p*-TsOH in dry CH_2Cl_2 (12 mL) under reflux overnight (16 h). The reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (4 × 10 mL). The combined organic phase was washed with brine (10 mL), and dried over anhydrous Na_2SO_4. After removal of the solvent, the crude product was purified by column chromatography (SiO_2) or preparative thin-layer chromatography (SiO_2).

(3*R,3a*S**,4*R**,7*S**,7a*R**)-3-(Trifluoromethyl)-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1(3*H*)-one (3a).** A mixture of **2a** and **2b** (118 mg, 0.5 mmol) in acetic acid (3 mL) and a catalytic amount of TFA was treated with $NaCNBH_3$ (0.3 g, 1.5 mmol) at 0 °C. After stirring for 5 min, the reaction mixture was heated at 50 °C overnight (16 h). It was quenched with 10% NaOH (5 mL), then diluted with water (5 mL) and extracted with EtOAc (4 × 10 mL). The combined organic phase was washed successively with water (10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. After removal of the solvent, the crude product was purified by column chromatography (SiO_2, 5% EtOAc–hexanes) to give **3a** (96 mg, 88%) as a colorless oil. IR (neat): ν_{max} 2987 m, 2952 w, 2878 w, 1788 s, 1407 m, 1305 m, 1214 m, 1167 s, 1111 m, 1052 m, 1029 s cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.25–6.18 (m, 2H, 2 × C*H*), 4.71 (dq, J = 7.6, 7.6 Hz, 1H, C*H*), 3.46 (dd, J = 8.7, 5.1 Hz, 1H, C*H*), 3.32–3.26 (br.s, 1H, C*H*), 3.23–3.12 (m, 2H, 2 × C*H*), 1.71 (d, J = 8.7 Hz, 1H, C*H*H), 1.48 (d, J = 8.7 Hz, 1H, C*H*H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.8 (C), 136.1 (CH), 134.6 (t, J = 4.0, Hz, CH), 122.8 (q, J = 278.0 Hz, CF_3), 75.6 (q, J = 36.0 Hz, CH), 53.6 (d, J = 16.0 Hz, CH_2), 47.4 (CH), 44.6 (2 × CH), 41.4 (CH); ^{19}F NMR (367 MHz, $CDCl_3$): δ −71.5 (s, 3F); MS: m/z (% relative intensity) 218 (M^+, 11), 200 (76), 179 (84), 150 (43), 149 (19), 134 (38), 122 (60), 96 (62), 81 (100), 67 (50); HRMS

(ESI–TOF) calcd for $C_{10}H_9F_3O_2Na$ $[M + Na]^+$: 241.0452, found 241.0443.

(3*R,3a*S**,4*R**,7*S**,7a*R**)-3-Methyl-3-(trifluoromethyl)-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1(3*H*)-one (3b).** According to the general procedure A, the reaction of **2a** and **2b** (118 mg, 0.5 mmol) and methylmagnesium chloride (3.0 M in THF, 0.83 mL, 2.5 mmol) at 0 °C followed by lactonization gave **3b** (100 mg, 86%) as a white semi-solid after column chromatography (SiO_2, 10% EtOAc in hexanes). IR ($CHCl_3$): ν_{max} 2992 m, 1781 s, 1460 m, 1341 m, 1168 m, 1098 m, 963 m cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.25–6.22 (m, 1H, C*H*), 6.19–6.08 (m, 1H, C*H*), 3.50 (dd, J = 8.5, 5.2 Hz, 1H, C*H*), 3.25 (br.s, 1H, C*H*), 3.18 (br.s, 1H, C*H*), 2.87 (dd, J = 8.5, 3.2 Hz, 1H, C*H*), 1.71 (d, J = 8.6 Hz, 1H, C*H*H), 1.53 (s, 3H, CH_3), 1.46 (d, J = 8.6 Hz, 1H, C*H*H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.7 (C), 135.9 (CH), 134.7 (q, J = 5.0 Hz, CH), 123.8 (q, J = 280.0 Hz, CF_3), 81.9 (q, J = 32.5 Hz, C), 53.8 (CH_2), 49.2 (CH), 47.6 (CH), 45.2 (CH), 44.1 (CH), 25.2 (CH_3); ^{19}F NMR (470 MHz, $CDCl_3$): δ −75.1 (s, 3F); MS: m/z (% relative intensity) 233 (M^+ + H, 40), 211 (9), 178 (25), 169 (13), 128 (15), 115 (16), 91 (28), 66 (100); HRMS (ESI–TOF) calcd for $C_{11}H_{11}F_3O_2Na$ $[M + Na]^+$: 255.0609, found 255.0603.

(3*R,3a*S**,4*R**,7*S**,7a*R**)-3-Ethyl-3-(trifluoromethyl)-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1(3*H*)-one (3c).** According to the general procedure A, the reaction of **2a** and **2b** (118 mg, 0.5 mmol) and ethylmagnesium chloride (2.0 M in THF, 1.25 mL, 2.5 mmol) at 0 °C followed by lactonization gave **3c** (106 mg, 86%) as a colorless oil after column chromatography (SiO_2, 10% EtOAc in hexanes). IR ($CHCl_3$): ν_{max} 3028 m, 2992 m, 2950 m, 2877 w, 1781 s, 1465 m, 1328 m, 1263 m, 1168 m, 1100 m, 992 m cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.18–6.17 (m, 1H, C*H*), 6.13–6.12 (m, 1H, C*H*), 3.38 (dd, J = 8.8, 5.2 Hz, 1H, C*H*), 3.20–3.16 (m, 1H, C*H*), 3.15–3.11 (br.s, 1H, C*H*), 2.86 (dd, J = 8.8, 3.4 Hz, 1H, C*H*), 1.89–1.76 (m, 2H, CH_2), 1.66 (d, J = 8.6 Hz, 1H, C*H*H), 1.42 (d, J = 8.6 Hz, 1H, C*H*H), 0.97 (dt, J = 7.5, 0.9 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.0 (C), 135.6 (CH), 135.1 (q, J = 4.6 Hz, CH), 142.1 (q, J = 281.9 Hz, CF_3), 84.4 (q, J = 30.6 Hz, C), 54.1 (CH_2), 48.3 (CH), 47.2 (CH), 45.5 (CH), 44.1 (CH), 31.2 (CH_2), 7.3 (CH_3); ^{19}F NMR (470 MHz, $CDCl_3$): δ −71.9 (s, 3F); MS: m/z (% relative intensity) 247 (M^+ + H, 9), 217 (3), 189 (2), 181 (4), 151 (5), 133 (7), 109 (5), 91 (27), 66 (100); HRMS (ESI–TOF) calcd for $C_{12}H_{13}F_3O_2Na$ $[M + Na]^+$: 269.0765, found 269.0762.

(3*R,3a*S**,4*R**,7*S**,7a*R**)-3-Isopropyl-3-(trifluoromethyl)-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1(3*H*)-one (3d).** According to the general procedure A, the reaction of **2a** and **2b** (118 mg, 0.5 mmol) and isopropylmagnesium chloride (2.0 M in THF, 1.25 mL, 2.5 mmol) at −78 °C followed by lactonization gave **3d** (65 mg, 50%) as a white solid (mp 79–80 °C (CH_2Cl_2–hexanes)) together with a reduction product **3a** (20 mg, 19%) as a colorless oil after column chromatography (SiO_2, 10% EtOAc in hexanes). IR ($CHCl_3$): ν_{max} 2977 m, 2949 w, 1780 s, 1475 w, 1298 m, 1171 m, 1028 s cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.20–6.09 (m, 2H, 2 × C*H*), 3.30 (dd, J = 9.1, 5.1 Hz, 1H, C*H*), 3.20–3.12 (m, 2H, 2 × C*H*), 2.86 (dd, J = 9.1, 3.4 Hz, 1H, C*H*), 2.18 (sept, J = 7.0 Hz, 1H, C*H*), 1.66 (d, J = 8.5 Hz, 1H, C*H*H), 1.44 (d, J = 8.5 Hz, 1H, C*H*H), 1.02 (dd, J = 7.0, 1.3 Hz, 3H, CH_3), 0.95 (d, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.1 (C), 135.4 (q, J = 4.1 Hz, CH), 135.2 (CH), 124.4 (q, J = 284.0 Hz, CF_3), 87.1 (q, J = 28.8 Hz, C), 54.4 (CH_2), 49.2 (CH), 46.0 (CH), 44.7 (CH), 44.3 (CH), 35.5 (CH), 16.9 (CH_3), 16.3 (CH_3); ^{19}F NMR (470 MHz, $CDCl_3$): δ −76.1 (s, 3F); MS: m/z (% relative intensity) 261 (M^+ + H, 22), 217 (10), 195 (9), 151 (10), 91 (19), 66 (100); HRMS (ESI-TOF) calcd for $C_{13}H_{15}F_3O_2Na$ $[M + Na]^+$: 283.0922, found 283.0925.

(3*R,3a*S**,4*R**,7*S**,7a*R**)-3-Butyl-3-(trifluoromethyl)-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1(3*H*)-one (3e).** According to the general procedure A, the reaction of **2a** and **2b** (118 mg, 0.5 mmol) and butylmagnesium chloride (2.0 M in THF, 1.25 mL, 2.5 mmol) at 0 °C followed by lactonization gave **3e** (118 mg, 86%) as a colorless oil after column chromatography (SiO_2, 10% EtOAc in hexanes). IR (neat): ν_{max} 2962 s, 2876 m, 1788 s, 1470 m, 1328 m, 1262 m, 1187 m, 1164 m, 1018 m cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.18–6.16 (m, 1H, C*H*), 6.13–6.11 (m, 1H, C*H*), 3.39 (dd, J = 8.8, 5.2 Hz, 1H, C*H*), 3.21–3.15 (m, 1H, C*H*), 3.14 (br.s, 1H, C*H*), 2.87 (dd, J = 8.8, 3.4 Hz, 1H, C*H*), 1.84–1.68 (m, 2H, CH_2), 1.65 (dt, J = 8.6, 1.6 Hz, 1H, C*H*H), 1.42 (d, J = 8.6 Hz, 1H, C*H*H), 1.40–1.33 (m, 1H, C*H*H), 1.32–1.21 (m, 3H, C*H*H and CH_2), 0.86 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.9 (C), 135.5 (CH), 135.1 (q, J = 4.8 Hz, CH), 124.1 (q, J = 282.0 Hz, CF_3), 84.2 (q, J = 30.9 Hz, C), 54.1 (CH_2), 48.3 (CH), 47.6 (CH), 45.6 (CH), 44.1 (CH), 38.0 (CH_2), 24.7 (CH_2), 22.8 (CH_2), 13.7 (CH_3); ^{19}F NMR (470 MHz, $CDCl_3$): δ −72.1 (s, 3F); MS: m/z (% relative intensity) 274 (M^+, 17), 207 (10), 182 (24), 158 (28), 147 (79), 116 (34), 96 (100), 65 (58); HRMS (ESI–TOF) calcd for $C_{14}H_{17}F_3O_2Na$ $[M + Na]^+$: 297.1078, found 297.1078.

(3*R,3a*S**,4*R**,7*S**,7a*R**)-3-(Trifluoromethyl)-3-vinyl-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1(3*H*)-one (3f).** According to the general procedure A, the reaction of **2a** and **2b** (118 mg, 0.5 mmol) and vinylmagnesium chloride (1.6 M solution THF, 1.56 mL, 2.5 mmol) at 0 °C followed by lactonization gave **3f** (107 mg, 87%) as a white semi-solid after column chromatography (SiO_2, 10% EtOAc in hexanes). IR ($CHCl_3$): ν_{max} 3020 m, 2994 m, 2949 w, 2877 w, 1788 s, 1413 w, 1329 s, 1314 m, 1170 m, 1135 m, 1009 s cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.31–6.25 (m, 1H, C*H*), 6.24–6.16 (m, 1H, C*H*), 5.96 (dd, J = 17.0, 10.8 Hz, 1H, C*H*), 5.48 (d, J = 17.0 Hz, 1H, C*H*H), 5.41 (d, J = 10.8 Hz, 1H, C*H*H), 3.35 (dd, J = 8.4, 5.3 Hz, 1H, C*H*), 3.29–3.19 (m, 2H, 2 × C*H*), 2.97 (dd, J = 8.4, 3.3 Hz, 1H, C*H*), 1.75 (d, J = 8.7 Hz, 1H, C*H*H), 1.48 (d, J = 8.7 Hz, 1H, C*H*H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.9 (C), 136.1 (CH), 134.7 (q, J = 4.5 Hz, CH), 134.4 (CH), 122.9 (q, J = 282.8 Hz, CF_3), 118.1 (CH_2), 83.1 (q, J = 32.5 Hz, C), 53.8 (CH_2), 48.2 (CH), 46.4 (CH), 45.2 (CH), 43.9 (CH); ^{19}F NMR (470 MHz, $CDCl_3$): δ −73.3 (s, 3F); MS: m/z (% relative intensity) 245 (M^+ + H, 6), 206 (24), 191 (63), 185 (10), 178 (4), 175 (7), 148 (12), 147 (33), 111 (20), 91 (100), 66 (75); HRMS (ESI–TOF) calcd for $C_{12}H_{11}F_3O_2Na$ $[M + Na]^+$: 267.0609, found 267.0635.

(3*R,3a*S**,4*R**,7*S**,7a*R**)-3-(But-3-en-1-yl)-3-(trifluoro methyl)-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1(3*H*)-one (3g).** According to the general procedure B, the reaction of **2a** and

2b (118 mg, 0.5 mmol) and but-3-en-1-ylmagnesium bromide at −78 °C followed by lactonization gave **3g** (108 mg, 80%) as a colorless oil after column chromatography (SiO_2, 5% EtOAc in hexanes). IR (neat): ν_{max} 3083 w, 2986 m, 2877 w, 1789 s, 1645 m, 1456 m, 1330 w, 1186 m, 1164 m, 1044 w, 920 m, 813 m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.20–6.11 (m, 2H, 2 × C*H*), 5.74–5.64 (m, 1H, C*H*), 5.01 (d, J = 17.2 Hz, 1H, C*H*H), 4.96 (d, J = 10.2 Hz, 1H, C*H*H), 3.40 (dd, J = 8.8, 5.2 Hz, 1H, C*H*), 3.18 (br.s, 1H, C*H*), 3.15 (br.s, 1H, C*H*), 2.89 (dd, J = 8.8, 3.3 Hz, 1H, CH), 2.20–2.00 (m, 2H, CH_2), 1.86 (t, J = 8.8 Hz, 2H, CH_2), 1.67 (d, J = 8.7 Hz, 1H, C*H*H), 1.42 (d, J = 8.7 Hz, 1H, C*H*H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.9 (C), 136.2 (CH), 135.7 (CH), 135.2 (q, J = 5.0 Hz, CH), 124.0 (q, J = 282.0 Hz, CF_3), 116.0 (CH_2), 83.8 (q, J = 30.0 Hz, C), 54.3 (CH_2), 48.3 (CH), 47.8 (CH), 45.6 (CH), 44.0 (CH), 37.5 (CH_2), 26.9 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$): δ −72.0 (s, 3F); MS: m/z (% relative intensity) 273 (M^+ + H, 17), 228 (4), 218 (4), 208 (15), 205 (3), 200 (10), 185 (7), 152 (7), 148 (4), 142 (8), 116 (7), 91 (23), 66 (100); HRMS (ESI–TOF) calcd for $C_{14}H_{15}F_3O_2Na$ $[M + Na]^+$: 295.0922, found 295.0922.

(3*S,3a*S**,4*R**,7*S**,7a*R**)-3-Phenyl-3-(trifluoromethyl)-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1(3*H*)-one (3h).** According to the general procedure A, the reaction of **2a** and **2b** (118 mg, 0.5 mmol) and phenylmagnesium chloride (2.0 M in THF, 1.25 mL, 2.5 mmol) at 0 °C followed by lactonization gave **3h** (134 mg, 91%) as a white solid (mp 128–129 °C (CH_2Cl_2–hexanes)) after column chromatography (SiO_2, 10% EtOAc in hexanes). IR ($CHCl_3$): ν_{max} 3020 w, 2994 w, 2876 w, 1788 s, 1450 m, 1328 m, 1305 m, 1216 m, 1183 s, 1117 m, 1042 s cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.53–7.51 (m, 2H, 2 × Ar*H*), 7.44–7.38 (m, 3H, 3 × Ar*H*), 6.33–6.28 (m, 2H, 2 × C*H*), 3.42 (br.s, 1H, C*H*), 3.39 (dd, J = 8.3, 3.3 Hz, 1H, C*H*), 3.26–3.21 (m, 1H, C*H*), 3.18 (dd, J = 8.3, 5.2 Hz, 1H, C*H*), 1.77 (dt, J = 8.8, 1.6 Hz, 1H, C*H*H), 1.47 (d, J = 8.8 Hz, 1H, C*H*H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.9 (C), 138.3 (C), 136.1 (CH), 134.9 (q, J = 4.3 Hz, CH), 129.2 (CH), 128.8 (2 × CH), 125.6 (2 × CH), 123.4 (q, J = 281.4 Hz, CF_3), 84.6 (q, J = 32.1 Hz, C), 53.9 (CH_2), 51.5 (CH), 46.7 (CH), 45.9 (CH), 44.0 (CH); ^{19}F NMR (470 MHz, $CDCl_3$): δ −71.2 (s, 3F); MS: m/z (% relative intensity) 295 (M^+ + H, 69), 275 (15), 249 (45), 217 (7), 209 (22), 181 (82), 77 (11), 66 (100); HRMS (ESI–TOF) calcd for $C_{16}H_{13}F_3O_2Na$ $[M + Na]^+$: 317.0765, found 317.0765.

(3*S,3a*S**,4*R**,7*S**,7a*R**)-3-(4-Methoxyphenyl)-3-(trifluoromethyl)-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1(3*H*)-one (3i).** According to the general procedure B, the reaction of **2a** and **2b** (118 mg, 0.5 mmol) and 4-methoxyphenyl magnesium bromide at 0 °C followed by lactonization gave **3i** (225 mg, 69%) as a white solid (mp 104–106 °C (CH_2Cl_2–hexanes)) after column chromatography (SiO_2, 5% EtOAc in hexanes). IR ($CHCl_3$): ν_{max} 3020 m, 2996 w, 2841 w, 1785 s, 1611 s, 1514 s, 1464 m, 1306 m, 1258 m, 1179 s, 1041 s cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, J = 8.6 Hz, 2H, 2 × Ar*H*), 6.84 (d, J = 8.6 Hz, 2H, 2 × Ar*H*), 6.24–6.20 (m, 2H, 2 × C*H*), 3.73 (s, 3H, OCH_3), 3.33–3.27 (m, 2H, 2 × C*H*), 3.15–3.09 (m, 2H, 2 × C*H*), 1.68 (d, J = 8.8 Hz, 1H, C*H*H), 1.39 (d, J = 8.8 Hz, 1H, C*H*H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.1 (C), 160.2 (C), 136.1 (CH), 135.1 (q, J = 4.0 Hz, CH), 130.0 (C), 127.1 (2 × CH), 123.4 (q, J = 281.0 Hz, CF_3), 114.1 (2 × CH), 84.5 (q, J = 32.0 Hz, C), 55.3 (OCH_3), 53.9 (CH_2), 51.3 (CH), 46.9 (CH), 45.9 (CH), 44.0 (CH); ^{19}F NMR (376 MHz, $CDCl_3$): δ −71.8 (s, 3F); MS: m/z (% relative intensity) 325 (M^+ + H, 20), 324 (78), 296 (39), 258 (9), 211 (5), 189 (100), 161 (47), 66 (9); HRMS (ESI–TOF) calcd for $C_{17}H_{15}F_3O_3Na$ $[M + Na]^+$: 347.0871, found 347.0872.

Synthesis of γ-trifluoromethyl α,β-unsaturated γ-butyrolactones 4

Flash-vacuum pyrolysis of **3** (conditions: oven temperature 240 °C, column temperature 375 °C, pressure 0.05 mmHg) gave the expected products **4**.

5-(Trifluoromethyl)furan-2(5*H*)-one (4a). Flash-vacuum pyrolysis of **3a** (78 mg, 0.36 mmol) gave **4a** (45 mg, 82%) as a colorless liquid. IR (neat): ν_{max} 3110 w, 2957 w, 2926 w, 2853 w, 1801 s, 1764 s, 1608 w, 1366 m, 1278 m, 1184 m, 1154 m, 1106 m, 1061 m, 870 s cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.48 (dd, J = 5.8, 1.5 Hz, 1H, C*H*), 6.44 (d, J = 5.8 Hz, 1H, C*H*), 5.36–5.32 (m, 1H, C*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2 (C), 146.8 (CH), 125.7 (CH), 121.5 (q, J = 281.0 Hz, CF_3), 78.5 (q, J = 36.0 Hz, CH); ^{19}F NMR (367 MHz, $CDCl_3$): δ −76.0 (s, 3F); MS: m/z (% relative intensity) 153 (M^+ + H, 13), 152 (M^+, 14), 151 (M^+ − H, 15), 127 (26), 113 (13), 97 (36), 91 (50), 83 (33), 81 (100); HRMS (APCI–TOF) calcd for $C_{12}H_{10}F_3O_3$ $[M + H]^+$: 153.0163, found 153.0185.

5-Methyl-5-(trifluoromethyl)furan-2(5*H*)-one (4b). Flash-vacuum pyrolysis of **3b** (49 mg, 0.23 mmol) gave **4b** (20 mg, 54%) as a colorless liquid. IR ($CHCl_3$): ν_{max} 3030 w, 2928 w, 2856 w, 1856 w, 1788 s, 1610 w, 1455 w, 1315 m, 1182 m, 1106 m, 1060 w, 974 m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, J = 5.7 Hz, 1H, C*H*), 6.25 (d, J = 5.7 Hz, 1H, C*H*), 1.61 (d, J = 0.5 Hz, 1H, C*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1 (C), 151.9 (CH), 124.6 (CH), 122.8 (q, J = 281.0 Hz, CF_3), 85.1 (q, J = 34.0 Hz, C), 18.0 (CH_3); ^{19}F NMR (367 MHz, $CDCl_3$): δ −79.2 (s, 3F); MS: m/z (% relative intensity) 167 (M^+ + H, 58), 151 (10), 149 (100), 141 (14), 129 (12), 125 (13), 109 (22), 97 (27); HRMS (APCI–TOF) calcd for $C_6H_6F_3O_2$ $[M + H]^+$: 167.0320, found 167.0336.

5-Ethyl-5-(trifluoromethyl)furan-2(5*H*)-one (4c). Flash-vacuum pyrolysis of **3c** (64 mg, 0.26 mmol) gave **4c** (41 mg, 87%) as a colorless liquid. IR ($CHCl_3$): ν_{max} 3098 w, 2987 w, 2949 w, 2892 w, 1809 s, 1782 s, 1610 w, 1464 w, 1298 m, 1179 m, 1127 m, 1015 m, 979 m, 904 m, 824 m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, J = 5.8 Hz, 1H, C*H*), 6.35 (d, J = 5.8 Hz, 1H, C*H*), 2.20 (dq, J = 14.8, 7.4 Hz, 1H, C*H*H), 2.01 (dq, J = 14.8, 7.4 Hz, 1H, C*H*H), 0.87 (dt, J = 7.2, 0.4 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4 (C), 150.6 (CH), 125.6 (CH), 122.9 (q, J = 282.0 Hz, CF_3), 88.1 (q, J = 31.0 Hz, C), 23.5 (CH_2), 6.3 (CH_3); ^{19}F NMR (367 MHz, $CDCl_3$): δ −77.8 (s, 3F); MS: m/z (% relative intensity) 181 (M^+ + H, 20), 151 (26), 126 (17), 123 (30), 111 (79), 82 (17), 71 (100); HRMS (ESI–TOF) calcd for $C_7H_7F_3O_2Na$ $[M + Na]^+$: 203.0296, found 203.0295.

5-Isopropyl-5-(trifluoromethyl)furan-2(5*H*)-one (4d). Flash-vacuum pyrolysis of **3d** (92 mg, 0.35 mmol) gave **4d** (63 mg, 91%) as a colorless liquid. IR (neat): ν_{max} 3097 w, 2982 m,

2949 w, 1810 s, 1794 s, 1778 s, 1608 w, 1472 w, 1291 s, 1175 s, 1122 m, 1043 m, 1026 m, 991 m, 908 m, 820 s cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, J = 5.8 Hz, 1H, C*H*), 6.37 (d, J = 5.8 Hz, 1H, C*H*), 2.49 (sept, J = 6.9 Hz, 1H, C*H*), 1.08 (dd, J = 6.9, 0.9 Hz, 3H, CH_3), 0.99 (d, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4 (C), 150.0 (CH), 125.6 (CH), 123.2 (q, J = 283.0 Hz, CF_3), 90.2 (q, J = 32.1 Hz, C), 30.5 (CH), 17.3 (d, J = 1.0 Hz, CH_3), 16.6 (CH_3); ^{19}F NMR (367 MHz, $CDCl_3$): δ −73.6 (s, 3F); MS: m/z (% relative intensity) 195 (M^+ + H, 3), 175 (15), 152 (18), 138 (16), 125 (22), 111 (42), 82 (25), 71 (46), 69 (60), 57 (100); HRMS (ESI–TOF) calcd for $C_8H_9F_3O_2Na$ $[M + Na]^+$: 217.0452, found 217.0453.

5-Butyl-5-(trifluoromethyl)furan-2(5*H*)-one (4e). Flash-vacuum pyrolysis of **3e** (118 mg, 0.43 mmol) gave **4e** (87 mg, 98%) as a colorless liquid. IR (neat): ν_{max} 3098 w, 2965 m, 2938 m, 2877 w, 1608 w, 1471 w, 1303 m, 1261 w, 1176 m, 1151 m, 1131 m, 1008 w cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, J = 5.7 Hz, 1H, C*H*), 6.27 (d, J = 5.7 Hz, 1H, C*H*), 2.14–2.00 (m, 1H, C*H*H), 1.98–1.82 (m, 1H, C*H*H), 1.36–0.98 (m, 4H, 2 × CH_2), 0.83 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4 (C), 150.9 (CH), 125.3 (CH), 122.9 (q, J = 282.0 Hz, CF_3), 87.8 (q, J = 33.5 Hz, C), 29.7 (d, J = 8.0 Hz, CH_2), 24.0 (CH_2), 22.4 (CH_2), 13.7 (CH_3); ^{19}F NMR (367 MHz, $CDCl_3$): δ −77.9 (s, 3F); MS: m/z (% relative intensity) 209 (M^+ + H, 6), 151 (7), 139 (11), 97 (55), 85 (50), 71 (79), 57 (100); HRMS (ESI–TOF) calcd for $C_9H_{11}F_3O_2Na$ $[M + Na]^+$: 231.0609, found 231.0606.

5-(Trifluoromethyl)-5-vinylfuran-2(5*H*)-one (4f). Flash-vacuum pyrolysis of **3f** (90 mg, 0.37 mmol) gave **4f** (57 mg, 87%) as a colorless liquid. IR (neat): ν_{max} 3031 w, 2928 w, 1813 m, 1786 s, 1291 m, 1183 s, 1161 s, 1004 m, 817 m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, J = 5.7 Hz, 1H, C*H*), 6.32 (d, J = 5.7 Hz, 1H, C*H*), 6.06 (dd, J = 17.2, 10.8 Hz, 1H, C*H*), 5.69 (d, J = 17.2 Hz, 1H, C*H*H), 5.57 (d, J = 10.8 Hz, 1H, C*H*H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9 (C), 150.0 (CH), 126.8 (CH), 123.9 (CH), 122.1 (q, J = 283.0 Hz, CF_3), 122.0 (CH_2), 86.8 (q, J = 33.7 Hz, C); ^{19}F NMR (367 MHz, $CDCl_3$): δ −77.6 (s, 3F); MS: m/z (% relative intensity) 178 (M^+, 31), 149 (60), 121 (28), 109 (16), 81 (43), 77 (62), 67 (35); HRMS (APCI-TOF) calcd for $C_7H_6F_3O_2$ $[M + H]^+$: 179.0320, found 179.0338.

5-(But-3-en-1-yl)-5-(trifluoromethyl)furan-2(5*H*)-one (4g). Flash-vacuum pyrolysis of **3g** (56 mg, 0.21 mmol) gave **4g** (42 mg, 99%) as a colorless liquid. IR (neat): ν_{max} 3091 w, 2939 w, 2862 w, 1804 s, 1781 s, 1644 w, 1453 w, 1311 w, 1264 w, 1176 m, 1150 m, 1071 m, 985 m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, J = 5.7 Hz, 1H, C*H*), 6.35 (d, J = 5.7 Hz, 1H, C*H*), 5.79–5.69 (m, 1H, C*H*), 5.06 (d, J = 5.3 Hz, 1H, C*H*H), 5.02 (s, 1H, C*H*H), 2.32–2.20 (m, 1H, C*H*H), 2.13–1.89 (m, 3H, C*H*H and CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2 (C), 150.6 (CH), 135.8 (CH), 127.0 (CH), 122.8 (q, J = 282.0 Hz, CF_3), 116.4 (CH_2), 87.5 (q, J = 31.0 Hz, C), 29.3 (CH_2), 26.2 (CH_2); ^{19}F NMR (367 MHz, $CDCl_3$): δ −77.9 (s, 3F); MS: m/z (% relative intensity) 207 (M^+ + H, 17), 151 (22), 149 (100), 137 (21), 125 (41), 111 (52), 95 (65), 82 (48), 71 (76), 67 (84); HRMS (ESI–TOF) calcd for $C_9H_9F_3O_2Na$ $[M + Na]^+$: 229.0452, found 229.0442.

5-Phenyl-5-(trifluoromethyl)furan-2(5*H*)-one (4h). Flash-vacuum pyrolysis of **3h** (114 mg, 0.39 mmol) gave **4h** (84 mg, 96%) as a colorless liquid. IR (neat): ν_{max} 3031 m, 1813 s, 1785 s, 1452 m, 1281 s, 1114 s, 1025 s, 958 s, 907 s, 815 s cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, J = 5.2 Hz, 1H, C*H*), 7.47 (br. s, 2H, 2 × Ar*H*), 7.37 (br.s, 3H, 3 × Ar*H*), 6.29 (d, J = 5.2 Hz, 1H, C*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8 (C), 150.9 (CH), 130.9 (C), 130.1 (CH), 129.0 (2 × CH), 126.6 (2 × CH), 124.2 (CH), 122.4 (q, J = 282.0 Hz, CF_3), 87.5 (q, J = 24.6 Hz, C); ^{19}F NMR (367 MHz, $CDCl_3$): δ −76.9 (s, 3F); MS: m/z (% relative intensity) 229 (M^+ + H, 21), 228 (M^+, 2), 184 (10), 160 (100), 152 (2), 104 (27); HRMS (ESI–TOF) calcd for $C_{11}H_7F_3O_2Na$ $[M + Na]^+$: 251.0296, found 251.0290.

5-(4-Methoxyphenyl)-5-(trifluoromethyl)furan-2(5*H*)-one (4i). Flash-vacuum pyrolysis of **3i** (114 mg, 0.35 mmol) gave **4i** (88 mg, 97%) as a colorless liquid. IR (neat): ν_{max} 3028 m, 2963 w, 2842 w, 1814 s, 1785 s, 1612 s, 1515 s, 1464 m, 1307 m, 1259 m, 1098 s, 1025 s, 958 m, 909 m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 4.8 Hz, 1H, C*H*), 7.38 (d, J = 7.8 Hz, 2H, 2 × Ar*H*), 6.87 (d, J = 7.8 Hz, 2H, 2 × Ar*H*), 6.28 (d, J = 4.8 Hz, 1H, C*H*), 3.73 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9 (C), 160.8 (C), 150.9 (CH), 128.0 (2 × CH), 124.0 (CH), 122.7 (C), 122.4 (q, J = 282.0 Hz, CF_3), 114.3 (2 × CH), 87.3 (q, J = 31.5 Hz, C), 55.3 (OCH_3); ^{19}F NMR (367 MHz, $CDCl_3$): δ −77.2 (s, 3F); MS: m/z (% relative intensity) 259 (M^+ + H, 21), 190 (100), 161 (33), 133 (18), 118 (5), 77 (5), 63 (4); HRMS (ESI–TOF) calcd for $C_{12}H_9F_3O_3Na$ $[M + Na]^+$: 281.0401, found 281.0403.

Synthesis of γ-hydroxy γ-trifluoromethyl α,β-unsaturated γ-butyrolactone 5

Flash-vacuum pyrolysis of **2** (118 mg, 0.5 mmol) (conditions: oven temperature 240 °C, column temperature 375 °C, pressure 0.05 mmHg) gave **5** (55 mg, 66%) as a white semi-solid after column chromatography (SiO_2, 30% EtOAc in hexanes). IR (neat): ν_{max} 3400 br (OH), 2876 w, 1815 s, 1786 s, 1632 m, 1444 w, 1333 m, 1291 m, 1185 s, 1085 m, 1051 m, 996 m, 916 m, 835 m cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.27 (d, J = 5.6 Hz, 1H, C*H*), 6.34 (d, J = 5.5 Hz, 1H, C*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.4 (C), 148.1 (CH), 126.8 (CH), 120.8 (q, J = 283.1 Hz, CF_3), 101.6 (q, J = 36.0 Hz, CH); ^{19}F NMR (470 MHz, $CDCl_3$): δ −82.2 (s, 3F); MS: m/z (% relative intensity) 169 (M^+ + H, 12), 167 (M^+ − H, 7), 151 (100), 123 (37), 99 (68), 81 (54), 67 (36), 55 (47); HRMS (ESI–TOF) calcd for $C_5H_3F_3O_3Na$ $[M + Na]^+$: 190.9932, Found 190.9942.

Acknowledgements

We acknowledge financial support from the Thailand Research Fund (BRG5380019), the office of the Higher Education Commission and Mahidol University under the National Research Universities Initiative, and the Center of Excellence for Innovation in Chemistry (PERCH-CIC).

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