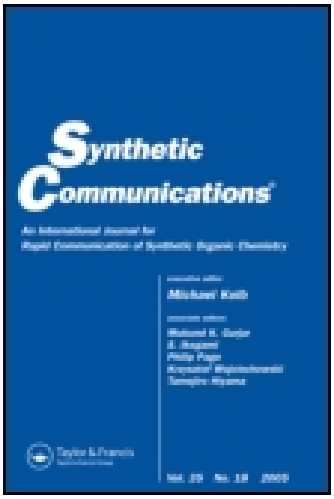

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Efficient Ce(III)-Catalyzed cis-Selective Synthetic Approach to γ-Lactones in Aqueous Media

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EFFICIENT Ce(III)-CATALYZED *cis*-SELECTIVE SYNTHETIC APPROACH TO γ-LACTONES IN AQUEOUS MEDIA

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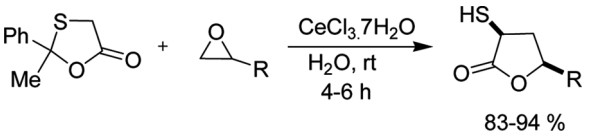
GRAPHICAL ABSTRACT



Abstract *The first $CeCl_3 \cdot 7H_2O$-catalyzed, one-pot synthesis of α-mercapto-γ-lactones via regioselective epoxide ring opening and mercaptoacetylative cyclization cascades in water is reported. The reaction between 2-methyl-2-phenyl-1,3-oxathiolan-5-one and a variety of terminal epoxides was carried out in aqueous media to afford γ-lactones in good to excellent yields (83–94%) with complete* cis *diastereoselectivity. Acetophenone obtained as a by-product was also recovered and recycled easily for further use.*

Keywords Aqueous medium; $CeCl_3 \cdot 7H_2O$; diastereoselectivity; epoxides; γ-lactones

INTRODUCTION

Since the pioneering studies by Breslow,[1] organic reactions in water have gained tremendous importance because of their environmental friendliness.[2] In addition, $CeCl_3 \cdot 7H_2O$ has attracted much attention as a Lewis acid in organic synthesis because of its special attributes, which include water tolerance, nontoxicity, and easy handling.[3] γ-Lactones constitute an important group of natural and synthetic products used as agrochemicals, as pharmaceuticals, and in the food industry and also possess a wide range of biological activities.[4a–f] In particular, some aryl substituted γ-lactones have shown cancer-preventive and anti-inflammatory activities.[4g] Moreover, γ-lactones are effective as starting materials for the synthesis of different molecules of biological and medicinal interest.[5–7] It is well known that the presence of a thiol function in many enzymes (called an –SH enzyme) is essential for their enzymatic activity. Likewise, incorporation of a thiol function in

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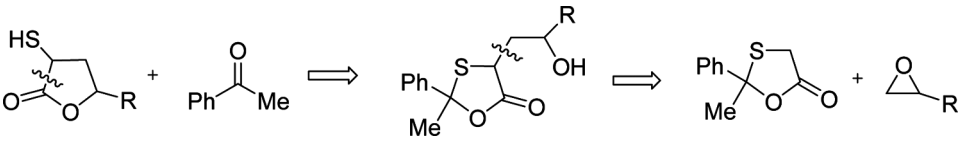
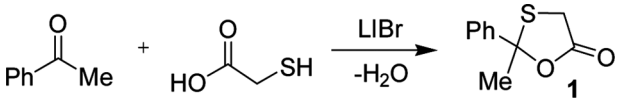


Scheme 1. Disconnection approach for target α-mercapto-γ-lactones.

heterocycles, nucleosides, or nucleotides has led to a number of analogs possessing interesting biological and therapeutic properties.[8–15]

Because of their unique chemical and biological properties, the synthesis of substituted γ-lactones has been of the great interest to synthetic chemists for several years. Several routes have been devised to access γ-lactones,[16–25] although they tend to be lengthy and cumbersome if the lactone contains any sort of substitution.[16] In most of the cases, construction of the γ-lactone ring includes ring-closing hydrogenation of diacids,[17] allylboration of aldehyde ring-closing cascades,[18] cyclization of 2-(substituted phenyl)pent-4-enoic,[19] cyclohydrocarbonylation of α-ketoalkynes,[20] electrophilic cyclization of 3-alkynoate esters/acids,[21] and epoxidation of enoates.[22] Particularly, aryl-γ-lactones have been obtained by Baeyer–Villiger reaction of aryl cyclobutanones,[23] reaction of 2-phenyloxirane with the malonate anion,[24] or photoinduced tandem Ar-C, C-O bond formation.[25] However, these methods are not environmentally friendly and suffer from one or more disadvantages such as the use of hazardous solvents, tedious workup, expensive and large amounts of catalyst, special treatment for activation, and lengthy reaction times. Recently, literature records the synthesis of γ-lactones using basic ionic liquid, but the method involves high reaction temperature, long reaction time, mixture of *cis*/*trans* diastereomers, and moderate to good yields.[26] These valid facts prompted us to developed a time-efficient, stereocontrolled, high-yielding, and environmentally benign synthetic approach to aryl-γ-lactones bearing a mercapto group on the α-position. Herein, we report an efficient $CeCl_3 \cdot 7H_2O$-catalyzed, high-yielding (83–94%), entirely *cis*-diastereoselective synthesis of α-mercapto-γ-lactones in aqueous media at ambient temperature via regioselective ring-opening of terminal epoxides (Scheme 1).

At the outset, we tried the mercaptoacetic acid for mercaptoacetylation of epoxides **2** but were not successful, probably because of the presence of free –COOH and –SH groups. Then, we turned our attention to blocking the –COOH and –SH groups of mercaptoacetic acid and thus activating its methylene group by converting it into 2-methyl-2-phenyl-1,3-oxathiolan-5-one **1** (Scheme 2).[27] The 2-methyl-2-phenyl-1,3-oxathiolan-5-one not only acted as mercaptoacetyl transfer agent for the synthesis of α-mercapto acids but also provides a completely new route to α-mercapto-γ-lactones and is the cornerstone in our approach, presenting its novel utility in furan chemistry.



Scheme 2. Formation of 2-methyl-2-phenyl-1,3-oxathiolan-5-one.

To optimize the reaction condition, several Lewis acid catalysts were used. Among these, $CeCl_3 \cdot 7H_2O$ gave the best result (Table 1, entry 1). K-10 clay afforded the product **3a** in moderate yield, while poor yields of product **3a** were obtained in the case of silica gel and neutral or acidic alumina (Table 1). Next, we estimated the reactivity of epoxide **2a** (2 mmol), 2-methyl-2-phenyl-1,3-oxathiolan-5-one **1** (2 mmol), and $CeCl_3 \cdot 7H_2O$ (0.2 mmol) by stirring at room temperature in water for 4h, and we successfully isolated the corresponding lactone **3a** in 91% yield (Table 2, entry 1). The formation of γ-lactone **3a** was entirely diastereoselective in favor of the *cis* isomer. It was noted that a higher reaction temperature, for example, in refluxing condition instead of room temperature, led to decreased diastereoselectivity without any appreciable effect on the yield. Next, to investigate the substrate scope for general validity of the present investigation, a variety of aromatic and aliphatic terminal epoxides **2** were used, employing the present optimized reaction conditions, and different γ-lactones **3** were synthesized. The yields were consistently good (Table 2), and the greatest yield was 94% (Table 2, entries 3 and 4). To compare its solvent-free version, we also carried out the reaction in a microwave (Chemical Laboratory Microwave Oven, model BP-310/50, 230 V, 50 Hz power input) for establishing its solvent-free version, but a relatively lower yield (43%) was obtained, although time required for the completion of the reaction was 12 min.

The present optimized synthesis is accomplished by stirring the mixture of epoxides **2** (1 mmol), 2-methyl-2-phenyl-1,3-oxathiolan-5-ones **1** (1 mmol), and $CeCl_3 \cdot 7H_2O$ (0.1 mmol) in water at room temperature for 4–6 h (Table 2). The isolation and purification steps are very simple and done by filtration with Buchner funnel followed by washing with water (2×10 mL) and recrystallization from EtOH. After isolation of the product, the aqueous layer was extracted with EtOAc (3×10 mL) and acetophenone was easily collected from the organic phase.

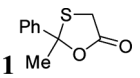
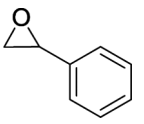
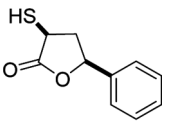
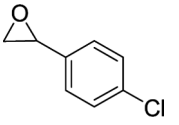
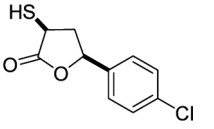
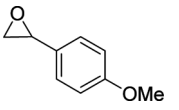
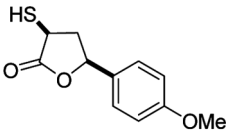
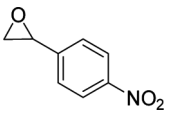
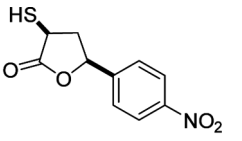
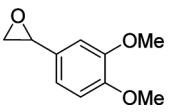
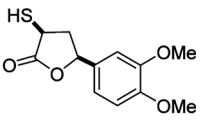
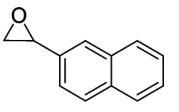
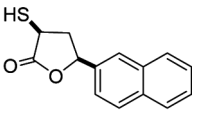
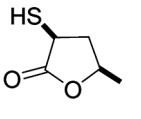
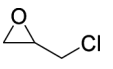
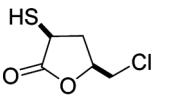
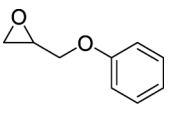
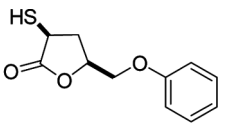
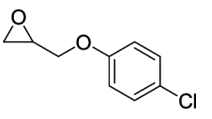
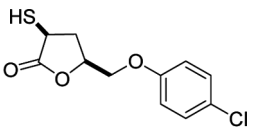
Formation of **3** can be rationalized by nucleophilic attack of the active methylene carbon (C-4) of **1′** to the less substituted carbon of epoxide **2** regiselectively, followed by protonation of epoxide oxygen, leading to the intermediate **4**. Herein, $CeCl_3 \cdot 7H_2O$ promotes the enolization step and thus it increases the nucleophilic character of methylene carbon (C-4) of **1**. Presumably, the role of water in the envisaged synthetic protocol is not only as a solvent but also to catalyze the reaction through H-bonding with epoxide oxygen and render them more susceptible to

Table 1. Optimization of catalysts for compound **3a**

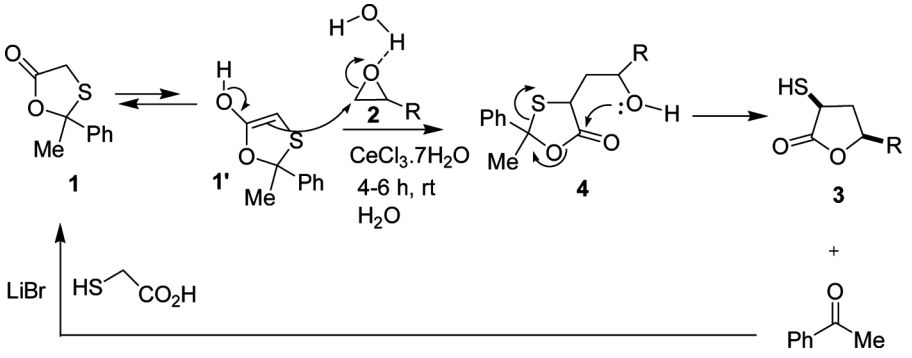
		MW		Aqueous medium	
Entry	Catalyst	Time (min)[a]	Yield (%)[b]	Time (h)[c]	Yield (%)[b]
1	$CeCl_3 \cdot 7H_2O$	12	43	4	91
2	K-10 clay	15	38	6	63
3	Silica gel	14	24	8	21
4	Neutral alumina	20	13	10	10
5	Acidic alumina	20	18	10	16

[a]Time for completion of the reaction under MW irradiation.
[b]Time for completion of the reaction at room temperature as indicated by TLC.
[c]Yield of isolated and purified product **3a**.

Table 2. $CeCl_3 \cdot 7H_2O$-catalyzed one-step synthesis of α -mercapto-γ-lactones **3**

Entry	Masked acid **1**	Epoxide **2**	Time (h)[a]	γ-Lactone **3**	Yield (%)[b,c]
1	 **1**		4	 **3a**	91
2	**1**		4	 **3b**	90
3	**1**		5	 **3c**	94
4	**1**		4	 **3d**	94
5	**1**		4	 **3e**	83
6	**1**		4	 **3f**	90
7	**1**		6	 **3g**	88
8	**1**		5	 **3h**	92
9	**1**		5	 **3i**	84
10	**1**		5	 **3j**	83

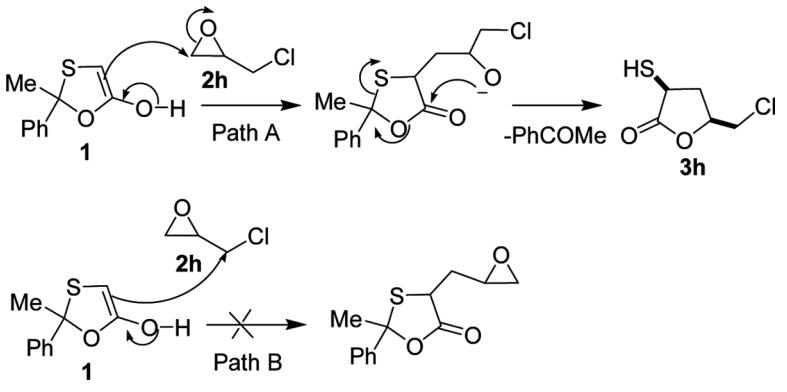
[a]Refluxing time in water at room temperature.
[b]Yield of isolated and purified products.
[c]All compounds gave C, H, and N analyses within ±0.39%, and satisfactory spectral (IR, ^{1}H NMR, ^{13}C NMR, and EIMS) data.



Scheme 3. Tentative mechanism for mercaptoacetylation of epoxides.

nucleophilic attack. The adduct **4** undergoes intramolecular nucleophilic attack of the oxygen atom of the OH group at the carbonyl carbon (C-5) of the oxathiolan-5-one moiety to yield target compounds **3** with elimination of acetophenone (Scheme 3), which was easily recovered and reused for the preparation of mercaptoacetyl transfer agent, 2-methyl-2-phenyl-1,3-oxathiolan-5-one **1**, by treatment with LiBr and mercaptoacetic acid as depicted in Scheme 2. This conclusion is based on the observation that the representative intermediate compounds **4a** (R=Ph), **4b** (R = 4-ClC$_6$H$_4$), and **4g** (R=Me) could be isolated in 49–53% yield. These could be converted into the corresponding lactones **3a**, **3b**, and **3g** in quantitative yields, and acetophenone was formed during the reaction (Scheme 3). The spectral data of compounds **3a**, **3b**, **4a**, and **4b** are in good agreement with the reported in literature.[26]

In the case of epichlorohydrin **2h**, excellent chemoselectivity was achieved, and formation of possible new mercaptoacetylative cyclization in the envisaged synthetic strategy was obtained (Scheme 3). In case of epichlorohydrin **2h**, excellent chemoselectivity was achieved and formation of possible new oxirane was not observed by extrusion of the chlorine atom (path B, Scheme 4),[28] rather we obtained the corresponding lactone **3h** (path A, Scheme 4). This can be explained: The oxygen of



Scheme 4. Chemoselectivity in the case of epichlorohydrin **2h**.

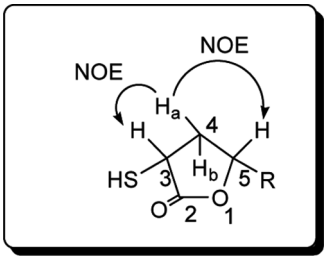


Figure 1. Determination of the *cis* stereochemistry by NOE of γ-lactones **3**.

epoxide prefers to attack at C-5 of 2-methyl-2-phenyl-1,3-oxathiolan-5-one **1** rather than the carbon containing chlorine, and the driving force for this is the easy opening of the oxathiolan ring by removal of the acetophenone (Scheme 4). The reactions were clean, and all the syntheized products were characterized by their ^{1}H NMR, ^{13}C NMR, infrared (IR), and mass spectroscopic data.

The intramolecular cyclization of adducts **4** to γ-lactones **3** was entirely diastereoselective in favor of the *cis* isomers. The relative stereochemistry of lactones **3** was established by nuclear Overhauser effect (NOE) experiments (Fig. 1). The strong NOE at 3-H/5-H upon irradiation of Ha combined with the absence of any measurable intensity enhancement at 3-H/5-H upon irradiation of Hb indicates that 4-Ha and 3-H/5-H are located on the same face of the molecule; that is, lactones **3** have 3,5-*cis* configuration (Fig. 1).

EXPERIMENTAL

Melting points were determined by the open glass capillary method and are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 993 IR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker WM-40 C (400 MHz) Fourier transform (FT) spectrometer in dimethylsulfoxide (DMSO-d_6) using tetramethyl silane (TMS) as internal reference. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz in DMSO-d_6, and TMS was used as internal reference. Mass (EI) spectra were recorded on a Jeol D-300 mass spectrometer. Elemental analyses were carried out in a Coleman automatic carbon, hydrogen, and nitrogen analyzer. A Chemical Laboratory microwave oven (model BP-310/50, 230 V, 50 Hz power input) was used. All chemicals used were reagent grade and were used as received without further purification. Silica gel G was used for thin layer chromatography (TLC).

3,5-Disubstitutedfuran-2-ones (3a–j): General Procedure

2-Methyl-2-phenyl-1,3-oxathiolan-5-one **1** (1 mmol), epoxide **2** (1 mmol), and $CeCl_3 \cdot 7H_2O$ (0.1 mmol) were taken in 10 mL water and stirred at room temperature for 4–6 h (Table 2). After the completion of reaction (monitored by TLC), the reaction mixture was filtered with a Buchner funnel and washed with water (2×10 mL). The crude product **3** thus obtained was recrystallized from EtOH to afford an

analytically pure sample of **3**. The aqueous layer was extracted with EtOAc (3×10 mL), and acetophenone was easily recovered from the organic phase. Spectral parameters of some representative compounds are given below.

Compound 3c. Colorless solid. IR (KBr): 2549, 1760 cm^{-1}. ^1H NMR (400 MHz; DMSO-d_6/TMS): $\delta = 1.61$ (d, $J = 7.7$ Hz, 1 H, SH, exchanges with D_2O), 2.69 (ddd, $J = 11.1$, 9.2, 5.5 Hz, 1 H, 4-Ha), 2.81 (ddd, $J = 11.1$, 8.0, 2.8 Hz, 1 H, 4-Hb), 3.50 (ddd, $J = 9.2$, 7.7, 5.5 Hz, 1 H, 3-H), 3.78 (s, 3 H, OMe), 5.51 (dd, $J = 2.8$, 8.0 Hz, 1 H, 5-H), 6.89–7.21 (m, 4 H_{arom}). ^{13}C NMR (100 MHz; DMSO-d_6/TMS): 38.8, 50.9, 56.8, 86.2, 121.5, 126.8, 127.5, 151.5, 177.8. MS (EI): $m/z = 224$ [M^+]. Anal. calcd. for $C_{11}H_{12}O_3S$: C, 58.91; H, 5.39. Found: C, 58.63; H, 5.61.

Compound 3d. Colorless solid. IR (KBr): 2556, 1763 cm^{-1}. ^1H NMR (400 MHz; DMSO-d_6/TMS): $\delta = 1.60$ (d, $J = 7.8$ Hz, 1 H, SH, exchanges with D_2O), 2.77 (ddd, $J = 11.2$, 9.5, 5.1 Hz, 1 H, 4-Ha), 2.86 (ddd, $J = 11.2$, 8.1, 2.9 Hz, 1 H, 4-Hb), 3.58 (ddd, $J = 9.5$, 7.8, 5.1 Hz, 1 H, 3-H), 5.46 (dd, $J = 2.9$, 8.1 Hz, 1 H, 5-H), 7.31–7.76 (m, 2 H_{arom}), 7.98–8.11 (m, 2 H_{arom}). ^{13}C NMR (100 MHz; DMSO-d_6/TMS): 38.5, 51.3, 85.8, 125.8, 128.8, 143.2, 146.8, 178.3. MS (EI): $m/z = 239$ [M^+]. Anal. calcd. for $C_{10}H_9NO_4S$: C, 50.20; H, 3.97; N, 5.85. Found: C, 50.51; H, 3.40; N, 5.57.

Compound 3e. Colorless solid. IR (KBr): 2553, 1768 cm^{-1}. ^1H NMR (400 MHz; DMSO-d_6/TMS): $\delta = 1.59$ (d, $J = 7.6$ Hz, 1 H, SH, exchanges with D_2O), 2.75 (ddd, $J = 11.2$, 9.4, 5.5 Hz, 1 H, 4-Ha), 2.88 (ddd, $J = 11.2$, 8.0, 2.9 Hz, 1 H, 4-Hb), 3.55 (ddd, $J = 9.4$, 7.6, 5.5 Hz, 1 H, 3-H), 3.69 (s, 3 H, OMe), 3.72 (s, 3 H, OMe), 5.42 (dd, $J = 2.9$, 8.0 Hz, 1 H, 5-H), 6.79–7.03 (m, 3 H_{arom}). ^{13}C NMR (100 MHz; DMSO-d_6/TMS): 38.5, 50.5, 55.9, 56.8, 86.7, 121.1, 127.2, 131.2, 135.5, 144.2, 146.8, 178.6. MS (EI): $m/z = 254$ [M^+]. Anal. calcd. for $C_{12}H_{14}O_4S$: C, 56.68; H, 5.55. Found: C, 56.91; H, 5.37.

Compound 3f. Colorless solid. IR (KBr): 2550, 1760 cm^{-1}. ^1H NMR (400 MHz; DMSO-d_6/TMS): $\delta = 1.58$ (d, $J = 7.8$ Hz, 1 H, SH, exchanges with D_2O), 2.73 (ddd, $J = 11.0$, 9.2, 5.5 Hz, 1 H, 4-Ha), 2.84 (ddd, $J = 11.0$, 8.5, 2.3 Hz, 1 H, 4-Hb), 3.51 (ddd, $J = 9.2$, 7.8, 5.5 Hz, 1 H, 3-H), 5.48 (dd, $J = 2.3$, 8.5 Hz, 1 H, 5-H), 7.30–7.85 (m, 7 H_{arom}). ^{13}C NMR (100 MHz; DMSO-d_6/TMS): 39.2, 51.6, 85.6, 125.5, 126.7, 127.4, 128.2, 130.1, 131.5, 132.0, 132.9, 133.5, 134.1, 178.1. MS (EI): $m/z = 244$ [M^+]. Anal. calcd. for $C_{14}H_{12}O_2S$: C, 68.83; H, 4.95. Found: C, 68.51; H, 5.19.

Compound 3g. Colorless solid. IR (KBr): 2551, 1770 cm^{-1}. ^1H NMR (400 MHz; DMSO-d_6/TMS): $\delta = 1.62$ (d, $J = 7.7$ Hz, 1 H, SH, exchanges with D_2O), 2.25 (s, 3 H, Me), 2.51–2.70 (m, 2 H, CH_2), 3.60 (ddd, $J = 9.5$, 7.7, 5.3 Hz, 1 H, 3-H), 4.43–4.51 (m, 1 H, 5-H). ^{13}C NMR (100 MHz; DMSO-d_6/TMS): 19.7, 38.5, 50.1, 81.2, 177.9. MS (EI): $m/z = 132$ [M^+]. Anal. calcd. for $C_5H_8O_2S$: C, 45.43; H, 6.10. Found: C, 45.81; H, 5.79.

Compound 3h. Colorless solid. IR (KBr): 2557, 1759 cm^{-1}. ^1H NMR (400 MHz; DMSO-d_6/TMS): $\delta = 1.61$ (d, $J = 7.7$ Hz, 1 H, SH, exchanges with D_2O), 2.58–2.76 (m, 2 H, CH_2), 3.52 (ddd, $J = 9.5$, 7.7, 5.1 Hz, 1 H, 3-H), 3.61 (dd, $J = 10.5$, 3.9 Hz, 1 H, 1′-Ha), 3.85 (dd, $J = 10.5$, 5.5 Hz, 1 H, 1′-Hb),

4.83–4.92 (m, 1 H, 5-H). ^{13}C NMR (100 MHz; DMSO-d_6/TMS): 38.1, 49.7, 51.5, 84.9, 178.5. MS (EI): $m/z = 166$, 168 [M^+, M + 2]. Anal. calcd. for $C_5H_7ClO_2S$: C, 36.04; H, 4.23. Found: C, 35.83; H, 4.51.

Compound 3i. Colorless solid. IR (KBr): 2553, 1765 cm^{-1}. ^{1}H NMR (400 MHz; DMSO-d_6/TMS): $\delta = 1.64$ (d, $J = 7.5$ Hz, 1 H, SH, exchanges with D_2O), 2.65–2.81 (m, 2 H, CH_2), 3.49 (ddd, $J = 9.4$, 7.5, 5.1 Hz, 1 H, 3-H), 3.93 (dd, $J = 10.9$, 3.8 Hz, 1 H, 1′-Ha), 4.17 (dd, $J = 10.9$, 5.5 Hz, 1 H, 1′-Hb), 4.91–5.03 (m, 1 H, 5-H), 7.31–7.75 (m, 5 H_{arom}). ^{13}C NMR (100 MHz; DMSO-d_6/TMS): 36.5, 50.7, 72.8, 80.8, 121.2, 126.3, 134.5, 153.7, 178.9. MS (EI): $m/z = 224$ [M^+]. Anal. calcd. for $C_{11}H_{12}O_3S$: C, 58.91; H, 5.39. Found: C, 58.62; H, 5.58.

Compound 3j. Colorless solid. IR (KBr): 2550, 1770 cm^{-1}. ^{1}H NMR (400 MHz; DMSO-d_6/TMS): $\delta = 1.59$ (d, $J = 7.9$ Hz, 1 H, SH, exchanges with D_2O), 2.83–2.89 (m, 2 H, CH_2), 3.57 (ddd, $J = 9.2$, 7.9, 5.5 Hz, 1 H, 3-H), 3.93 (dd, $J = 10.9$, 3.5 Hz, 1 H, 1′-Ha), 4.18 (dd, $J = 10.9$, 5.2 Hz, 1 H, 1′-Hb), 4.95-5.01 (m, 1 H, 5-H), 7.22–7.69 (m, 2 H_{arom}), 7.78–7.83 (m, 2 H_{arom}). ^{13}C NMR (100 MHz; DMSO-d_6/TMS): 37.2, 51.5, 72.0, 81.2, 122.2, 126.2, 128.5, 152.9, 178.8. MS (EI): $m/z = 258$, 260 [M^+, M + 2]. Anal. calcd. for $C_{11}H_{11}ClO_3S$: C, 51.07; H, 4.29. Found: C, 51.45; H, 4.03.

Isolation of 4a (R = Ph), 4b (R = 4-cl), and 4g (R = Me) and Their Cyclization into γ-Lactones 3a, 3b, and 3g

2-Methyl-2-phenyl-1,3-oxathiolan-5-one **1** (1 mmol), epoxide **2** (1 mmol), and $CeCl_3 \cdot 7H_2O$ (0.1 mmol) were taken in 10 mL water and stirred at room temperature for 2 h. Then the reaction mixture was filtered with a Buchner funnel and washed with water (2 × 10 mL). The crude products **4a**, **4b**, and **4g** thus obtained were recrystallized from EtOH to give their respective analytical samples. For converting these intermediates into final products, **4a**, **4b**, and **4g** were stirred for 2–3 h at room temperature in 10 mL of water. After completion of the reaction (monitored by TLC), the reaction mixture was filtered with a Buchner funnel and washed with water (2 × 10 mL). The crude product **3** thus obtained was recrystallized from EtOH to afford an analytically pure sample of **3**. The aqueous layer was extracted with EtOAc (3 × 10 mL), and acetophenone was easily recovered from the organic phase. Spectral parameters of representative compound **4g** are given. Colorless solid. IR (KBr): 3385, 1769 cm^{-1}. ^{1}H NMR (400 MHz; DMSO-d_6/TMS): $\delta = 2.29$ (s, 3 H, Me), 2.33 (s, 3 H, Me), 2.63–2.69 (m, 2 H, CH_2), 3.28–3.35 (m, 1 H, 2′-H), 3.57 (dd, $J = 8.0$, 5.5 Hz, 1 H, SCH), 3.65 (d, $J = 2.9$ Hz, 1 H, OH, exchanges with D_2O), 7.01–7.43 (m, 5 H_{arom}). ^{13}C NMR (100 MHz; DMSO-d_6/TMS): 20.3, 23.7, 38.8, 49.1, 77.3, 126.8, 129.5, 131.3, 133.7, 178.5. MS (EI): $m/z = 252$ [M^+]. Anal. calcd. for $C_{13}H_{16}O_3S$: C, 61.88; H, 6.39. Found: C, 62.23; H, 6.08.

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