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Diastereoselective synthesis of γ-hydroxy α,β-epoxyesters and their conversion into β-hydroxy α-sulfenyl γ-butyrolactones

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Abstract—The diastereoselectivity of the nucleophilic epoxidation of γ-hydroxy-α,β-unsaturated esters has been studied. The γ-hydroxy-α,β-unsaturated esters were obtained through treatment of ethyl (*E*)-4-oxo-2-butenoate with the corresponding Grignard reagent and were used as a racemic mixture. The resulting γ-hydroxy α,β-epoxyesters were treated with thiophenol for transformation into α-phenylsulfanyl trisubstituted γ-butyrolactones. The *syn*,*syn*-lactones isomerize easily in basic media into the *syn*,*anti* structures. In order to explain this interconversion, a retroaldol–aldol sequence has been proposed and a sulfur–oxygen interaction has been invoked to explain the *syn* stereochemical preference of the α-sulfured aldols resulting from the intramolecular aldol reaction.

1. Introduction

α,β-Epoxyesters are versatile functionalities in organic synthesis since they can be converted into interesting synthetic compounds through the opening of the oxirane ring.[1] The most convenient method for their preparation is through epoxidation of unsaturated esters using a hydroperoxide in the presence of a base.[2] A deeper understanding of the stereoselectivity of the epoxidation of unsaturated esters would increase the synthetic applications of these intermediates. We previously reported the influence of solvent and temperature on the epoxidation of γ-hydroxy-α,β-unsaturated esters[3] and now wish to report a general study of this reaction including a correction of the previous stereochemical assignment of some of the resulting epoxides.

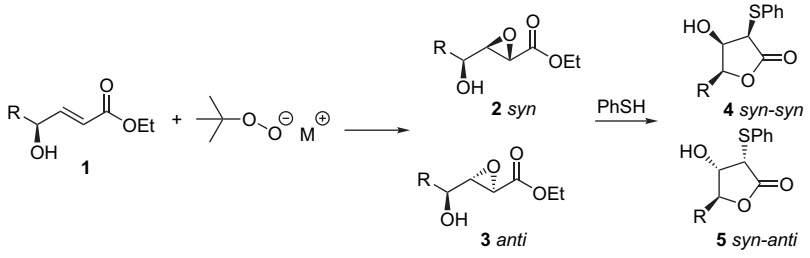
In this paper we also show that the thiophenol-mediated transformation of the γ-hydroxy α,β-epoxyesters into α-phenylsulfanyl γ-butyrolactones **4/5** was useful for the stereochemical determination of the preceding epoxyesters (Scheme 1). Trisubstituted γ-butyrolactones are an interesting family of compounds,[4] which could be then obtained starting from chiral γ-hydroxy α,β-epoxyesters.

The stereoselectivity of the epoxidation reactions was measured as the ratio between *syn*/*anti* diastereomers **2** and **3** (Scheme 1) and must be interpreted as a conjugate addition to an unsaturated ester modulated by a stereocenter in the γ-position.[5]

2. Results

2.1. Preparation of substrates

We wanted to study the selectivity of epoxidation of γ-hydroxy-α,β-unsaturated esters with a range of R alkyl



Scheme 1. General scheme of reactions.

Keywords: Diastereoselective epoxidation; Epoxyesters; Lactonization; γ-Butyrolactones.
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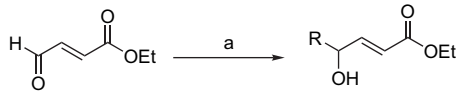
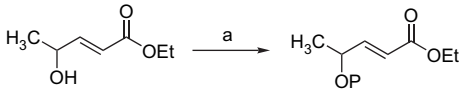
groups. Commonly γ-hydroxy-α,β-unsaturated esters are obtained in enantiopure form through Wittig–Horner reaction of chiral aldehydes or enzymatic resolutions of the corresponding racemic mixtures,[6] we synthesized the γ-hydroxy-α,β-unsaturated esters through treatment of ethyl (*E*)-4-oxo-2-butenoate[3] with the corresponding Grignard reagent and they were used as a racemic mixture in the epoxidation process (Scheme 2).



1a, R=Ph
1b, R=Me
1c, R=*i*-Propyl
1d, R=*i*-Pentyl
1e, R=*n*-Butyl
1f, R=Chx
1g, R=*p*-MeOPh
1h, R=*t*-Butyl

Scheme 2. Preparation of γ-hydroxy-α,β-unsaturated esters: (a) RMgBr, THF, −78 °C–0 °C.

We also prepared *O*-protected α,β-unsaturated esters in order to study the influence of the hydroxyl protecting group on the epoxidation. These compounds were synthesized through protection of compound **1b** via standard conditions (Scheme 3).



1b

6a, P=TPS
6b, P=TIPS
6c, P=MOM

Scheme 3. Protection of γ-hydroxy-α,β-unsaturated esters: (a) P–Cl, base.

2.2. Epoxidation of γ-hydroxy-α,β-unsaturated ethyl esters

Esters **1** were epoxidized using lithium *tert*-butylperoxide as the oxidizing reagent in THF as solvent at −20 °C. Table 1 shows that the diastereomeric ratios are similar for all conditions examined, furnishing the **2** *syn* isomer as the major product. The *syn*/*anti* assignment for **2b/3b** represents a correction to our previous work,[3] an explanation for which is provided subsequently.

These results showed that stereoselectivity does not depend on the nature of the pendant R alkyl group for all γ-hydroxy-α,β-unsaturated esters examined.

In order to study the influence of the temperature over the stereoselectivity, we carried out the epoxidation reaction of compound **1b** at different temperatures (Table 2).

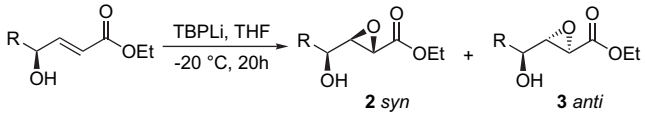
Table 2 shows that there is no temperature dependence since the diastereomeric ratios at different temperatures in a range between −80 and 50 °C are same within experimental error.

Similar $J_{3,4}$ coupling constants were observed for diastereomers *syn* α,β-epoxyesters **2a–h** and also for *anti* α,β-epoxyesters **3a–h** (Table 3). For *syn* isomers, $J_{3,4}$ values were between 3.5 and 4.5 Hz whilst for the *anti* form, $J_{3,4}$ ranged from 2.5 to 3.5 Hz.

Thus, the measurement of $J_{3,4}$ represented a convenient method for the stereochemical assignment of these compounds whenever both isomers were available.

We also epoxidized compound **1b** by using oxidants other than lithium *tert*-butylperoxide (Table 4).

Table 1. Epoxidation of γ-hydroxy-α,β-unsaturated esters using lithium *tert*-butylperoxide

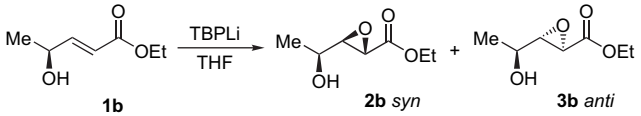


2 *syn* **3** *anti*

Entry	Substrate	R	*T* (°C)/*t* (h)	**2**:**3**[a]	Yield (%)
1	**1a**	Ph	−20/20	80:20	78
2	**1b**	Me	−20/20	70:30	60
3	**1c**	*i*-Pr	−20/20	80:20	55
4	**1d**	*i*-Pent	−20/20	78:22	44
5	**1e**	*n*-Bu	−20/20	81:19	48
6	**1f**	Chx	−20/15	76:24	47
7	**1g**	*p*-MeOPh	−20/15	77:23	69
8	**1h**	*t*-Bu	−20/72	70:30	41

[a] Ratio measured by ^{13}C NMR of the crude reaction mixtures.

Table 2. Epoxidation of **1b** at different temperatures

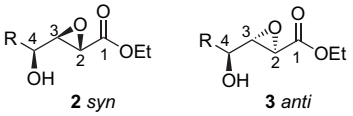


1b **2b** *syn* **3b** *anti*

Entry	*T* (°C)/*t* (h)	**2b**:**3b**[a]	Yield (%)
1	−80/72	73:27	30
2	−60/46	78:22	55
3	−40/24	77:23	54
4	−20/20	70:30	60
5	0/14	74:26	55
6	25/3	78:22	52
7	50/5	76:24	45

[a] Ratio measured by ^{13}C NMR of the crude reaction mixtures.

Table 3. Coupling constants of epoxyalcohols



2 *syn* **3** *anti*

R	$J_{3,4}$ **2** *syn* (Hz)	$J_{3,4}$ **3** *anti* (Hz)
Ph	4.5	2.5
Me	4.2	3.1
i-Pr	4	3
i-Pent	4	3.5
n-Bu	4	[a]
Chx	4	3
p-MeOPh	4.5	2.5
t-Bu	3.5	2.5

[a] Coupling constant could not be measured because of overlapping signals.

Table 4. Epoxidation of ester **1b** using other conditions

Entry	Reagent	Solvent	*T* (°C)/*t*	**2b**:**3b**[b]	Yield (%)
1	TBHP, EtLi	THF	−20/20 h	70:30	60
2	TBHP, EtLi, 12-cr-4[a]	THF	−20/60 h	81:19	39
3	TBHP, EtLi, TMEDA[a]	THF	−20/20 h	88:12	50[c]
4	TBHP, EtLi	THF/HMPA	−20/20 h	88:12	42
5	TBHP, EtLi	THF/DMF	−20/20 h	85:15	51
6	TBHP, Et_2Zn[a]	CH_2Cl_2	0 °C/120 h	20:80	15[c]
7	TBHP, Bu_2Mg	THF	−20/20 h	—	N.R.
8	TBHP, NaH	THF	Rt/1.5 h	56:44	22
9	TBHP, NaH	THF	−20/20 h	79:21	18
10	TBHP, NaH	THF	−80/72 h	68:32	25
11	TBHP, KH	THF	−20/20 h	62:38	30
12	TBHP, Ti(O-*i*-Pr)$_4$	CH_2Cl_2	0/4 days	40:60	74[c]
13	TBHP, EtLi, Ti(O-*i*-Pr)$_4$	THF	Rt/6 days	—	N.R.
14	CMHP, EtLi	THF	−20/20 h	77:23	65
15	*m*-CPBA	CH_2Cl_2	−20/4 days	67:33	70[c]
16	*m*-CPBA, K_2CO_3	CH_2Cl_2	Rt/20 h	—	N.R.
17	TBHP, EtLi	Hexanes	−20/20 h	46:54	25
18	TBHP, EtLi	Toluene	−20/20 h	68:32	53

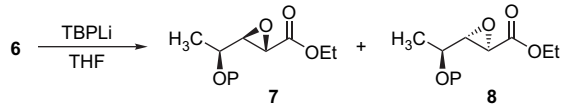
[a] 12-Cr-4 (2.5 equiv) was used in entry 2; 2 equiv of TMEDA were used in entry 3; 1.1 equiv of Et_2Zn were used in entry 6.
[b] Ratio measured by ^{13}C NMR of the crude reaction mixtures.
[c] Starting material was recovered: 31% for entry 3; 29% for entry 6; 50% for entry 12; 25% for entry 15.

If the reaction was carried out using lithium *tert*-butylperoxide in the presence of a cation scavenger (entries 2 and 3) or in a more polar solvent (entries 4 and 5), then a better selectivity was observed. On the other hand, in the alkaline peroxides series, potassium gave poorer stereoselectivity than either lithium or sodium (entries 1 and 8–11). The *anti* isomer predominated when zinc[7] peroxide was used, as opposed to the selectivity achieved using alkaline cations. Magnesium[8] (entry 7) was not reactive. When titanium isopropoxide (entry 12) was used, starting material was recovered and stereoselectivity was poor, furnishing the *anti* isomer as the major product. The reaction using lithium *tert*-butylperoxide and titanium isopropoxide (entry 13) did not give reaction product.

Lithium cumylperoxide gave the same result as lithium *tert*-butylperoxide (entry 14). The rate of the epoxidation using *m*-CPBA[9] (entry 15) was slower than with the other oxidants, affording the *syn* isomer as the major one. When *m*-CPBA was used in the presence of potassium carbonate[10] (entry 16), only starting material was recovered.

If the reaction was carried out using lithium *tert*-butylperoxide in non-polar solvents (entries 17 and 18) then a poor selectivity was observed.

Table 5. Epoxidation of *O*-protected-γ-hydroxy-α,β-unsaturated esters



Entry	*T* (°C)/*t*	**6**	**7**:**8**[a]	Yield (%)
1	Rt/5 days	**6a**	55:45	50
2	2/10 days	**6b**	81:19	56
3	−20/100 h	**6b**	84:16	75[b]
4	−20/5 days	**6c**	63:37	47[b]

[a] Ratio measured by ^{13}C NMR of the crude reaction mixtures.
[b] Starting material was recovered: 50% for entry 3; 44% for entry 4.

O-Protected unsaturated esters **6** were subjected to epoxidation using lithium *tert*-butylperoxide (Table 5).

All the *O*-protected esters (**6a**–**c**) were less reactive than free compound **1b** since the epoxidation reactions took longer time (a few days for all cases). The triisopropylsilyl protecting group gave the best selectivity, furnishing the *syn* isomer **7** as the major one.

Studies to rationalize the stereoselectivity of these epoxidation reactions are currently underway in our laboratory.

2.3. Synthesis of γ-butyrolactones

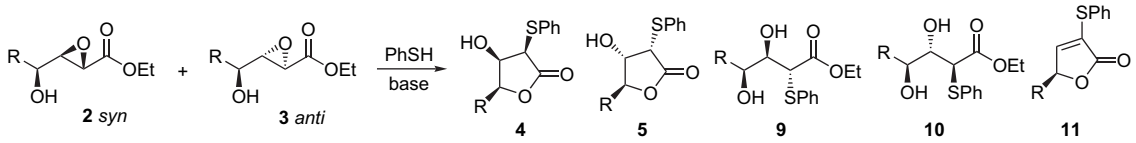
The γ-hydroxy α,β-epoxyesters **2/3** were treated with thiophenol in the presence of a base resulting in the opening of the oxirane ring. The products derived from these reactions were the corresponding γ-butyrolactones **4/5** or the diols **9/10** depending on the conditions and the substrate (Table 6).

When epoxides **2a/3a** (from entry 1, Table 1) were treated with thiophenol in the presence of triethylamine at room temperature for 1 h, only diols **9a/10a** were obtained (entry 1, Table 6) but with longer time, partial cyclization of diols furnished lactones **4a/5a** (entry 2, Table 6) in 1:1 ratio. This mixture of diols and lactones was directly subjected to acid treatment, furnishing a mixture of diastereomeric lactones with lactone **4a** being the major one (Table 7).

When epoxides **2b/3b** (from entry 2, Table 1) were treated with thiophenol and triethylamine in acetonitrile, diol **9b**, lactones **4b/5b** in 1:1 ratio, and butenolide **11b** derived from dehydration of the lactones were obtained (entry 3, Table 6). When the reaction was performed in methanol instead of acetonitrile for longer time (entry 4), only lactones were obtained and, surprisingly, **5b** was the major lactone, thus showing opposite stereoselection to **2a/3a**.

A similar result was obtained using Sharpless conditions with sodium thiophenolate buffered with thiophenol[11] (entry 5).

Table 6. Treatment of epoxyesters **2/3** with thiophenol



Entry	Substrate	*T* (°C)/*t*	Reagents	4	5	9	10	11	Yield (%)
1	**2a/3a** (R=Ph)	Rt/1 h	PhSH/Et_3N/CH_3CN			**9a** (75)	**10a** (25)		65
2	**2a/3a** (R=Ph)	Rt/16 h	PhSH/Et_3N/CH_3CN	**4a** (25)	**5a** (25)	**9a** (50)			—[a]
3	**2b/3b** (R=Me)	0/45′	PhSH/Et_3N/CH_3CN	**4b** (19)	**5b** (23)	**9b** (28)		**11b** (30)	43
4	**2b/3b** (R=Me)	Rt/6 h	PhSH/Et_3N/MeOH	**4b** (32)	**5b** (68)				55
5	**2b/3b** (R=Me)	Rt/2 h	PhSH/PhSNa/THF	**4b** (37)	**5b** (63)				50
6	**2b/3b** (R=Me)	rt/1 h	PhSH/PhSNa/THF	**4b** (21)	**5b** (33)	**9b** (46)			—[a]
7	**2b/3b** (R=Me)	−40/80′	PhSH/PhSNa/THF			**9b** (72)	**10b** (28)		67
8	**2c/3c** (R=*i*-Pr)	Rt/22 h	PhSH/Et_3N/CH_3CN	**4c** (19)	**5c** (17)	**9c** (57)		**11c** (7)	45
9	**2c/3c** (R=*i*-Pr)	Rt/1 h	PhSH/PhSNa/THF	**4c** (33)	**5c** (67)				89
10	**2c** (R=*i*-Pr)	Rt/2 h	PhSH/PhSNa/THF	**4c** (40)	**5c** (60)				70
11	**2e/3e** (R=*n*-Bu)	Rt/2 h	PhSH/PhSNa/THF	**4e** (34)	**5e** (66)				66
12	**2f/3f** (R=Chx)	Rt/2 h	PhSH/PhSNa/THF	**4f** (34)	**5f** (66)				77

[a] Crude oil was directly subjected to acid cyclization (see Table 6).

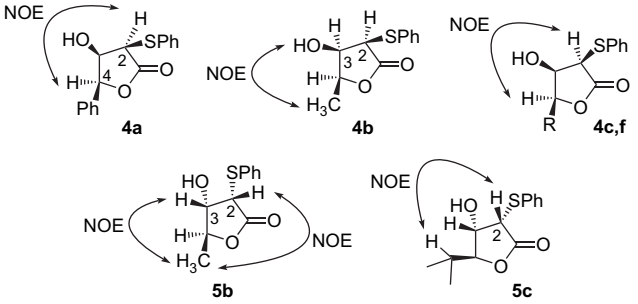
When this reaction was conducted for shorter time (entry 6), diol **9b** and a mixture of lactones were obtained and at low temperature (entry 7) diols **9b/10b** were obtained, furnishing **9b** as the major one. The mixture of diols and lactones obtained from entry 6 was directly subjected to acid treatment (Table 6), furnishing **4b/5b** but **4b** being the major product, a result opposite to that for entries 4 and 5.

The results obtained with epoxides **2c/3c** were similar to **2b/3b**. When epoxides **2c/3c** (entry 3, Table 1) were treated with thiophenol and triethylamine in acetonitrile, then diol **9c** and lactones **4c/5c** were obtained along with butenolide **11c** (entry 8). Using sodium thiophenolate, the result was also similar to **2b/3b**, yielding lactones **4c/5c** (entry 9). Curiously, a mixture of **4c/5c** was obtained when the substrate was pure major epoxyester (entry 10).

The reaction of epoxides **2e/3e** and **2f/3f** (entries 5 and 6, Table 1) with sodium thiophenolate gave a similar result to the other epoxides, furnishing a mixture of lactones **4/5** in 34:66 ratio for both cases (entries 11 and 12).

2.4. Stereochemical determination of lactones 4/5 and diols 9/10

The stereochemical assignment of the lactones was performed by NOE experiments. Lactone **4a** gave NOE between H-2 and H-4 whilst **5a** did not. Lactone **5b** gave NOE between the methyl and H-2 and between the methyl and H-3, whilst the lactone **4b** gave NOE between the methyl and OH but not between the methyl and H-2. **4c** and **4f** gave NOE between the H-2 and H-4 whilst **5c** H-2 gave NOE with the isopropylic hydrogen.



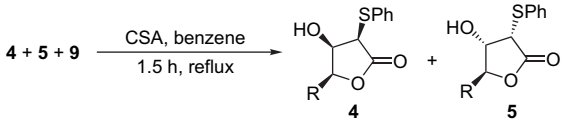
The X-ray crystal structures of **4a–c** confirmed definitively the stereochemistry of *syn*,*syn*-lactones.[12] The conformation of all three γ-butyrolactones in the X-ray structures is very similar, having the R alkyl groups and the thiophenyl substituents in equatorial position and the hydroxyl groups in axial position (Fig. 1).

In comparing the shifts of the ring protons and ring ^{13}C nuclei for all lactones (Table 8) some similarities were observed: *syn*,*anti*-lactones **5** show H2 upfield shift with respect to the *syn*,*syn* **4**, while H3 and H4 appear downfield in **5** with respect to **4**, and C2 appears shifted upfield for **5** while C4 appears downfield in **5** in relation to **4**.[13]

The resulting diols from these reactions were transformed into cyclic carbonates: the mixture of diols **9a/10a** (from entry 1, Table 6) and **9b/10b** (from entry 7, Table 6) was submitted to reaction with triphosgene giving carbonates **12a/13a** and **12b/13b**, respectively (Table 9).

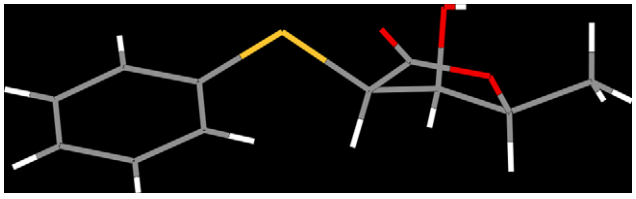
The stereochemistry of the carbonates was assigned by NMR: coupling constants ($J_{4,5}$ for **13**, higher than for **12**) and by NOE experiments.

Table 7. Cyclization of diol **9** in acidic media

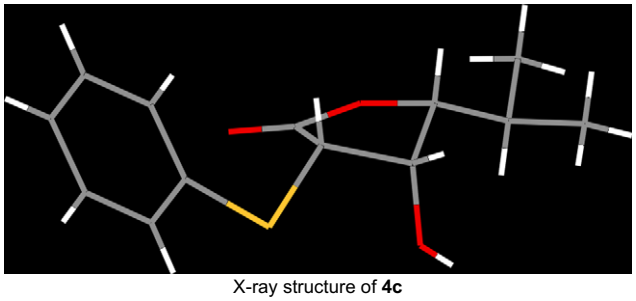


Entry	Substrate	**4**:**5**	Yield (%)
1	Entry 2, Table 6	76:24	57
2	Entry 6, Table 6	65:35	45

X-ray structure of **4a**



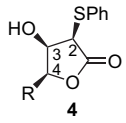
X-ray structure of **4b**



X-ray structure of **4c**

Figure 1. X-ray structures of lactones **4a**, **4b**, and **4c**.

Table 8. ^{1}H and ^{13}C NMR shifts of lactones **4** and **5**



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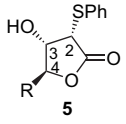
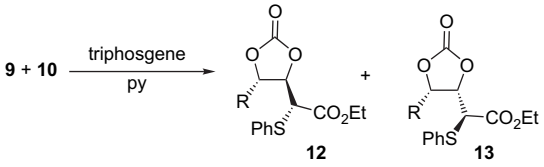


5

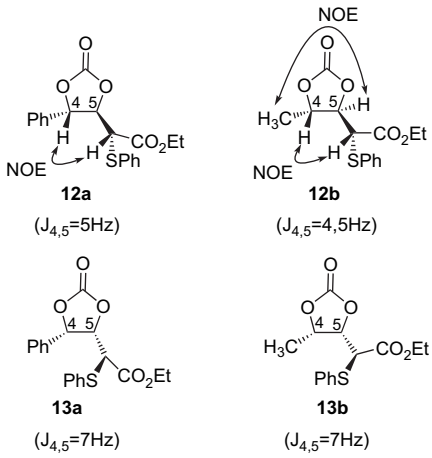
Lactone	δ H2	δ H3	δ H4	δ C2	δ C3	δ C4
4a (R=Ph)	4.25	4.46	5.37	56.5	83.0	71.4
5a (R=Ph)	3.89	4.39	5.50	52.2	83.3	75.5
4b (R=Me)	4.24	4.24	4.51	57.3	79.0	69.9
5b (R=Me)	3.81	4.31	4.65	53.0	78.7	74.7
4c (R=*i*-Pr)	4.25	4.31	3.86	57.6	88.3	68.6
5c (R=*i*-Pr)	3.80	4.35	4.06	53.5	88.4	74.0
4e (R=*n*-Bu)	4.18	4.20	4.26	56.9	83.2	69.4
5e (R=*n*-Bu)	3.73	4.23	4.35	52.9	83.2	74.3
4f (R=Chx)	4.16	4.23	3.88	57.5	87.1	68.3
5f (R=Chx)	3.72	4.29	4.06	53.3	87.0	73.8

Table 9. Cyclization of diols **9/10**



12 **13**

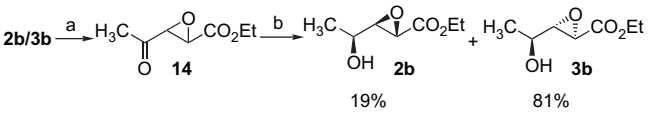
Entry	Diols (**9**/**10**)	**12**	**13**	Yield (%)
1	Entry 1, Table 6	**12a** (75)	**13a** (25)	65
2	Entry 7, Table 6	**12b** (72)	**13b** (28)	42



12a ($J_{4,5}$=5Hz) **12b** ($J_{4,5}$=4,5Hz)

13a ($J_{4,5}$=7Hz) **13b** ($J_{4,5}$=7Hz)

We have also assured the stereochemical assignment of **2b/3b** by reduction of epoxyketone **14** using zinc borohydride. As expected, the reduction of an epoxyketone using zinc borohydride gave the *anti* isomer as the major one[14] (Scheme 4).

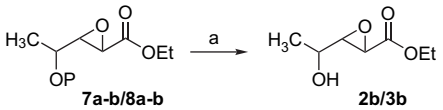


Scheme 4. Reduction of compound **14**: (a) Dess–Martin, 70%; (b) $Zn(BH_4)_2$, 75%.

The NMR spectra of the major isomer were identical to the minor in the **2b/3b** mixture derived from the epoxidation (entry 2, Table 1). The major diastereomer in **2b/3b** mixture was the *syn* one, correcting the stereochemical assignment we previously published.[3]

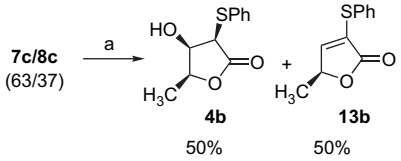
2.5. Stereochemical determination of *O*-protected epoxides

The stereochemistry of the *O*-silyl protected epoxides (**7a–c/8a–c**) was established through deprotection affording the known epoxides **2b/3b** (Scheme 5).



Scheme 5. Deprotection of *O*-silyl protected epoxides: (a) TBAF, THF.

In case of the *O*-methoxymethyl protected epoxides, the stereochemistry was established through treatment with thiol and Lewis acid,[15] which furnished lactone **4b** and butenolide **13b** (Scheme 6).

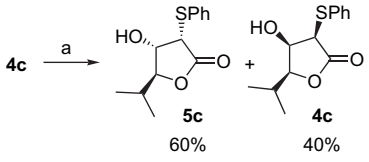


Scheme 6. Deprotection of epoxides **7c/8c**: (a) PhSH, $BF_3 \cdot Et_2O$, 70%.

3. Discussion

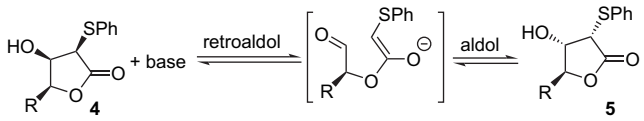
We were unable to make a definitive assignment for the stereochemistry of epoxides **2b/3b** since carbonates and lactones obtained in acidic media would yield as the major epoxide **2b** (same stereoselectivity as epoxides **2a/3a**) but for lactones obtained in basic media, the major isomer would be **3b**, as can also be said for **2c/3c**.

We believe that an isomerization of lactone **4** into lactone **5** occurs during the opening of the epoxides under basic conditions (entries 4 and 5, 9–12 of Table 6). To confirm this speculation, pure lactone **4c** was treated with triethylamine at room temperature and a 4:6 mixture of **4c** and **5c** was obtained (Scheme 7).



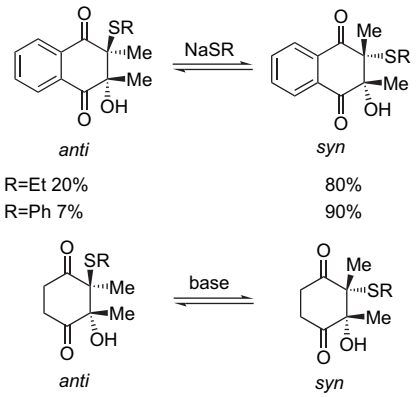
Scheme 7. Basic isomerization of lactone **4c**: (a) Et_3N, THF, 25 °C, 13 h.

The most plausible mechanism for the isomerization is a retroaldol–aldol sequence (Scheme 8). The retroaldol reaction of **4** is forced by the steric hindrance of the substituents into *syn*,*syn* relationship into the cyclic structure, then the resulting enolate–aldehyde intermediate gives an aldol cyclization to furnish a thermodynamic mixture of lactones. The major product is the more thermodynamically stable one, **5**, having substituents in *syn*,*anti* relationship.



Scheme 8. Retroaldol–aldol sequence.

A retroaldol–aldol sequence has been invoked by some authors to explain the isomerization of β-hydroxy α-sulfenyl carbonylic compounds.[16] The two examples shown in Scheme 9 are taken from the literature[16a,b] and both represent isomerizations of *anti* β-hydroxy α-sulfenyl cyclic ketones into the *syn* ones.



Scheme 9. Isomerization of β-hydroxy α-sulfenyl carbonylic compounds.

Both lactones **4** and **5** show a 2,3-*syn* relationship as the *syn*-ketones in Scheme 9.

This tendency of α-hydroxy thiols derived from an intramolecular aldol reaction to be *syn* could be explained by a sulfur–oxygen interaction;[17] this interaction over the enolate–aldehyde would orientate the aldehyde and the sulfured enolate in the *syn* position. A similar sulfur–oxygen interaction has been invoked between the carbonylic oxygen and the thiolic sulfur of 2-mercaptoacetophenones.[17b] The stereochemical outcome in the intramolecular aldol reaction would then be controlled by two factors: a steric factor about 3,4-*anti* relationship in **5** and an S–O interaction about 2,3-*syn* relationship in both **4** and **5**.

4. Conclusions

The stereoselectivity in the nucleophilic epoxidation of γ-hydroxy-α,β-unsaturated esters has been studied. The resulting *syn*/*anti* α,β-epoxyesters have been converted into trisubstituted α-phenylsulfanyl γ-butyrolactones using thiophenol. The *syn*,*syn*-lactones isomerize easily in basic media into the *syn*,*anti* structures. In order to explain this interconversion, a retroaldol–aldol sequence has been proposed and a sulfur–oxygen interaction has been invoked to explain the *syn* stereochemical preference of the α-sulfured aldols resulting from the intramolecular aldol reaction.

5. Experimental section

5.1. General experimental methods

All solvents used in reactions were freshly distilled from appropriate drying agents before use. ^{1}H NMR spectra and ^{13}C NMR spectra were measured in $CDCl_3$ (^{1}H, 7.24 ppm; ^{13}C 77.0 ppm) solution at 30 °C on a 300 MHz Mercury Varian or a 500 MHz Innova Varian NMR spectrometer at the Serveis Centrals d'Instrumentació Científica de la Universitat Jaume I. Mass spectra were measured in a QTOF I (quadrupole–hexapole-TOF) mass spectrometer with an orthogonal Z-spray-electrospray interface (Micromass, Manchester, UK). IR spectra were recorded as oily films on NaCl plates on a Perkin–Elmer 2000 FTIR spectrometer. EM Science Silica Gel 60 was used for column chromatography while TLC was performed with E. Merck precoated plates (Kieselgel 60, F_{254}, 0.25 mm). Unless otherwise specified, all reactions were carried out under argon atmosphere with magnetic stirring.

5.1.1. General experimental procedure for the syntheses of esters 1. To a liquid N_2/acetone cold solution of ethyl (*E*)-4-oxo-2-butenoate (65.1 mmol) in THF (150 mL) was added alkyl magnesium chloride solution (26 mL, 78.1 mmol) drop wise under N_2 atmosphere for a period of 5 min. The resulting mixture was left to warm up to room temperature for 1 h and then quenched with satd aq NH_4Cl solution and extracted with Et_2O (3×40 mL), the organic layers were washed (brine), dried (Na_2SO_4), and concentrated. The crude oil was purified through chromatography (silica-gel, hexanes/EtOAc (8:2) and (7:3)) to afford an oil.

Spectroscopic data for **1a** (yield=29%): ^{1}H NMR ($CDCl_3$) δ 7.32–7.24 (6H, m), 6.98 (1H, dd, J=15.5, 5.5 Hz), 6.09 (1H, dd, J=15.5, 1.5 Hz), 5.30 (1H, m), 4.13 (2H, q, J=7.5 Hz), 2.00 (1H, br s), 1.21 (3H, t, J=7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 166.52, 148.37, 141.02, 128.93, 128.46, 126.63, 120.49, 73.68, 60.55, 14.26 ppm. IR (NaCl) ν 3467, 3064, 3032, 2983, 2937, 2905, 1779, 1717, 1656, 1494, 1455, 1369, 1304, 1175, 1097, 1032, 700 cm^{-1}. HRMS *m/z* calcd for $C_{12}H_{14}O_3Na$ [M+Na$^+$]: 229.0841, found: 229.0814.

Spectroscopic data for **1b** (yield=72%): ^{1}H NMR ($CDCl_3$) δ 6.88 (1H, dd, J=15.8, 4.8 Hz), 5.94 (1H, dd, J=15.6, 1.7 Hz), 4.39 (1H, m), 4.12 (2H, q, J=7.1 Hz), 3.03 (1H, s), 1.26 (3H, d, J=6.6 Hz), 1.22 (1H, t, J=7.1 Hz). ^{13}C NMR ($CDCl_3$) δ 166.76, 151.32, 119.34, 66.84, 60.40, 22.48, 14.07 ppm. IR (NaCl) ν 3429, 2983, 1722, 1448, 1369, 1307, 1185, 1039, 980, 868 cm^{-1}. HRMS *m/z* calcd for $C_7H_{12}O_3$ [M+H$^+$]: 145.0865, found: 145.0828; calcd for $C_7H_{11}O_3Na$ [M+Na$^+$]: 167.0684, found: 167.0488.

Spectroscopic data for **1c** (yield=45%): ^{1}H NMR ($CDCl_3$) δ 6.92 (1H, dd, J=15.8, 5.1 Hz), 6.00 (1H, dd, J=15.6, 1.7 Hz), 4.17 (2H, q, J=7.1 Hz), 4.06 (1H, td, J=5.3, 0.9 Hz), 1.96 (1H, br s), 1.80 (1H, ddd, J=6.8, 6.6, 5.9 Hz), 1.26 (3H, t, J=7.1 Hz), 0.92 (3H, d, J=6.9 Hz), 0.91 (3H, d, J=6.9 Hz). ^{13}C NMR ($CDCl_3$) δ 166.54, 148.91, 121.13, 75.91, 60.43, 33.65, 18.24, 17.43, 14.21 ppm. IR (NaCl) ν 3483, 2964, 2934, 2876, 1722, 1656, 1467, 1370, 1274, 1179, 1036, 873 cm^{-1}. HRMS *m/z* calcd for $C_9H_{16}O_3Na$ [M+Na$^+$]: 195.0997, found: 195.0976.

Spectroscopic data for **1d** (yield=22%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.89 (1H, dd, J=15.6, 4.8 Hz), 5.97 (1H, dd, J=15.6, 1.5 Hz), 4.21 (1H, dq, J=5.4, 1.8 Hz), 4.14 (2H, q, J=6.9 Hz), 2.61 (1H, br s), 1.52 (3H, m), 1.26 (2H, m), 1.24 (3H, t, J=7.2 Hz), 0.84 (3H, d, J=6.6 Hz), 0.83 (1H, d, J=6.6 Hz). ^{13}C NMR ($CDCl_3$) δ 166.71, 150.49, 119.99, 71.24, 60.40, 34.47, 34.19, 27.92, 22.45, 22.36, 14.13 ppm. IR (NaCl) ν 3449, 2957, 1720, 1655, 1467, 1369, 1275, 1177 cm^{-1}. HRMS *m/z* calcd for $C_{11}H_{20}O_3Na$ [M+Na$^+$]: 223.1310, found: 223.1288.

Spectroscopic data for **1e** (yield=44%): ^{1}H NMR ($CDCl_3$) δ 6.93 (1H, dd, J=15.5, 5 Hz), 6.02 (1H, dd, J=15.6, 1.5 Hz), 4.29 (1H, m), 4.20 (2H, q, J=7.1 Hz), 1.82 (1H, d, J=4.2 Hz), 1.59 (2H, m), 1.33 (2H, m), 1.29 (3H, t, J=7.2 Hz), 0.9 (3H, t, J=7.0 Hz). ^{13}C NMR ($CDCl_3$) δ 166.59, 150.21, 120.20, 71.19, 60.45, 36.41, 27.34, 22.56, 14.25, 13.94 ppm. IR (NaCl) ν 3449, 2959, 2872, 1721, 1656, 1466, 1369, 1305, 1275, 1179, 1040, 985 cm^{-1}. HRMS *m/z* calcd for $C_{10}H_{18}O_3Na$ [M+Na$^+$]: 209.1154, found: 209.1141.

Spectroscopic data for **1f** (yield=25%): ^{1}H NMR ($CDCl_3$) δ 6.94 (1H, dd, J=16, 5.5 Hz), 6.01 (1H, dd, J=15.5, 1.5 Hz), 4.19 (1H, q, J=7 Hz), 4.07 (1H, td, J=5.5, 1.5 Hz), 1.97 (1H, br s), 1.62–1.81 (6H, m), 1.4 (1H, m), 1.28 (3H, t, J=7.5 Hz), 0.99–1.33 (4H, m). ^{13}C NMR ($CDCl_3$) δ 166.54, 149.25, 120.95, 75.44, 60.40, 43.58, 36.41, 28.83, 27.98, 26.31, 26.06, 26.01, 14.20 ppm. IR (NaCl) ν 3460, 2925, 2855, 1715, 1658, 1450, 1369, 1276, 1176, 1113, 1039, 985, 893, 869, 733 cm^{-1}. HRMS *m/z* calcd for $C_{12}H_{20}O_3Na$ [M+Na$^+$]: 235.1310, found: 235.1302.

Spectroscopic data for **1g** (yield=31%): ^{1}H NMR ($CDCl_3$) δ 7.19 (2H, d, J=8.5 Hz), 6.97 (1H, dd, J=15.5, 5.0 Hz), 6.82 (2H, d, J=15.5 Hz), 6.06 (1H, d, J=15.5 Hz), 5.19 (1H, d, J=4.5 Hz), 4.12 (2H, q, J=7.5 Hz), 3.37 (1H, br s), 1.23 (3H, t, J=7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 166.57, 159.60, 148.83, 133.19, 127.98, 120.02, 114.19, 73.04, 60.48, 55.31, 14.18 ppm. IR (NaCl) ν 3468, 2982, 2838, 1719, 1655, 1610, 1586, 1513, 1465, 1369, 1304, 1251, 1173, 1095, 1034, 982, 834, 775 cm^{-1}. HRMS *m/z* calcd for $C_{13}H_{16}O_4Na$ [M+Na$^+$]: 259.0946, found: 259.0954.

Spectroscopic data for **1h** (yield=19%): ^{1}H NMR ($CDCl_3$) δ 6.98 (1H, dd, J=16, 5.5 Hz), 6.00 (1H, dd, J=15.5, 1.5 Hz), 4.15 (2H, q, J=7.5 Hz), 3.90 (1H, dd, J=5.5, 1.5 Hz), 1.25 (3H, t, J=7.5 Hz), 0.9 (9H, s). ^{13}C NMR ($CDCl_3$) δ 166.51, 147.84, 121.78, 78.90, 60.35, 35.46, 25.65, 14.15 ppm. IR (NaCl) ν 3497, 2964, 2907, 2873, 1770, 1722, 1655, 1479, 1369, 1280, 1164, 1112, 1038, 871, 774 cm^{-1}. HRMS *m/z* calcd for $C_{10}H_{19}O_3$ [M+H$^+$]: 187.1334, found: 187.1307.

5.1.2. General experimental procedure for the epoxidation of esters 1. To a −78 °C cold THF (3.5 mL) was added TBHP (3.3 M in toluene[18]) (2.2 mmol) and then ethyllithium (0.5 M in benzene/cyclohexane (9:1)[19]) (1.61 mmol). The resulting mixture was stirred at −78 °C for 15 min and then a solution of compound **1** (1.46 mmol) in THF (2 mL) was added drop wise and then the mixture was left at −20 °C (fridge) for 20 h. Then solid Na_2SO_3 (120 mg) was added in one portion and stirred for 15 min, then diluted with satd aq NH_4Cl solution and extracted with Et_2O (3×30 mL), the organic layers were washed (brine), dried (Na_2SO_4), and concentrated. The crude oil was purified through chromatography (silica-gel, hexanes/EtOAc (7:3) and (6:4)).

Spectroscopic data for **2a/3a**: ^{1}H NMR ($CDCl_3$) δ 7.22–7.34 (5H, m, majoritary and minoritary), 4.78 (1H, d, J=2.5 Hz, minoritary), 4.58 (1H, d, J=4.5 Hz, majoritary), 4.14 (2H, m, majoritary and minoritary), 3.63 (1H, d, J=2 Hz, minoritary), 3.50 (1H, d, J=2 Hz, majoritary), 3.41 (1H, dd, J=4.5, 2 Hz, majoritary), 3.35 (1H, t, J=2.5 Hz, minoritary), 1.23 (3H, t, J=6.5 Hz, majoritary and minoritary). ^{13}C NMR ($CDCl_3$) δ 168.71 (minoritary), 168.49 (majoritary), 139.42 (majoritary), 139.67 (minoritary), 128.74, 128.70, 128.49, 128.43, 126.47, 126.39, 72.18 (majoritary), 70.40 (minoritary), 61.75 (majoritary), 61.70 (minoritary), 60.88 (majoritary), 60.64 (minoritary), 51.10 (majoritary), 49.81 (minoritary), 13.99 (majoritary and minoritary) ppm. IR (NaCl) ν 3467, 3058, 3024, 2976, 2926, 2853, 1732, 1452, 1372, 1205, 1093, 1066, 1025, 904, 760, 701 cm^{-1}. HRMS *m/z* calcd for $C_{12}H_{14}O_4Na$ [M+Na$^+$]: 245.079, found: 245.0790.

Spectroscopic data for **2b/3b**: ^{1}H NMR ($CDCl_3$) δ 4.21 (2H, m, majoritary and minoritary), 3.97 (1H, dq, J=6.4, 3.1 Hz), 3.97 (1H, dq, J=6.4, 3.1 Hz, minoritary), 3.78 (1H, dq, J=6.4, 4.2 Hz, majoritary), 3.48 (1H, d, J=2.0 Hz, minoritary), 3.43 (1H, d, J=2.0 Hz, majoritary), 3.20 (1H, m, minoritary), 3.18 (1H, dd, J=4.2, 2.0 Hz, majoritary), 1.28

(3H, d, J=6.6 Hz, majoritary and minoritary), 1.26 (1H, d, J=6.4 Hz, majoritary), 1.25 (1H, d, J=6.2 Hz, minoritary). ^{13}C NMR ($CDCl_3$) δ 168.97 (minoritary), 168.75 (majoritary), 65.96 (majoritary), 64.31 (minoritary), 61.65 (majoritary and minoritary), 61.49 (majoritary), 61.09 (minoritary), 50.88 (majoritary), 49.73 (minoritary), 19.80 (majoritary), 18.75 (minoritary), 14.00 (majoritary and minoritary) ppm. IR (NaCl) ν 3477, 2983, 2921, 1738, 1656, 1452, 1372, 1285, 1202, 1028, 978, 901, 806, 720 cm^{-1}. HRMS m/z calcd for $C_7H_{12}O_4Na$ [M+Na$^+$]: 183.0633, found: 183.0625.

Spectroscopic data for **2c/3c**: ^{1}H NMR ($CDCl_3$) δ 4.21 (2H, m, majoritary and minoritary), 3.63 (1H, dd, J=5.0, 3.0 Hz, minoritary), 3.53 (1H, d, J=1.5 Hz, minoritary), 3.45 (1H, d, J=2.0 Hz, majoritary), 3.35 (1H, d, J=4.0, 6.5 Hz, majoritary), 3.26 (1H, dd, J=4.0, 2.0 Hz, majoritary), 3.24 (1H, dd, J=3.0, 2.0 Hz, minoritary), 1.87 (2H, m, majoritary and minoritary), 1.29 (3H, t, J=7.0 Hz, majoritary and minoritary), 1.00 (3H, d, J=6.5 Hz, majoritary and minoritary), 0.98 (3H, d, J=6.5 Hz, majoritary and minoritary). ^{13}C NMR ($CDCl_3$) δ 169.09 (minoritary), 168.89 (majoritary), 74.29 (majoritary), 72.31 (minoritary), 61.75 (majoritary), 61.69 (minoritary), 59.34 (minoritary), 59.22 (minoritary), 50.81 (majoritary), 49.73 (minoritary), 32.69 (majoritary), 31.61 (minoritary), 18.46 (majoritary), 18.75 (minoritary), 17.92 (majoritary), 17.34 (minoritary), 14.12 (majoritary and minoritary) ppm. IR (NaCl) ν 3497, 2964, 2877, 1732, 1468, 1371, 1285, 1244, 1199, 1028, 905 cm^{-1}. HRMS m/z calcd for $C_9H_{16}O_4Na$ [M+Na$^+$]: 211.0946, found: 211.0926.

Spectroscopic data for **2d/3d**: ^{1}H NMR ($CDCl_3$) δ 4.17 (2H, m, majoritary and minoritary), 3.74 (1H, dq, J=4.0, 3.5 Hz, minoritary), 3.53 (1H, dq, J=4.0, 4.0 Hz, majoritary), 3.46 (1H, d, J=2.0 Hz, minoritary), 3.42 (1H, d, J=2.5 Hz, majoritary), 3.16 (1H, dd, J=4.0, 2.0 Hz, majoritary), 3.15 (minoritary, signal overlapped with majoritary), 2.11 (1H, br s), 1.46–1.58 (4H, m, majoritary and minoritary), 1.32 (1H, m, majoritary and minoritary), 1.24 (3H, t, J=7.0 Hz, majoritary and minoritary), 0.84 (3H, d, J=7.0 Hz, majoritary and minoritary), 0.83 (3H, d, J=7.0 Hz, majoritary and minoritary). ^{13}C NMR ($CDCl_3$) δ 169.09 (minoritary), 168.81 (majoritary), 69.93 (majoritary), 68.33 (minoritary), 61.66 (majoritary), 61.64 (minoritary), 60.73 (majoritary), 60.45 (minoritary), 50.89 (majoritary), 49.69 (minoritary), 34.23 (majoritary), 34.10 (minoritary), 32.30 (majoritary), 31.26 (minoritary), 28.01 (minoritary), 27.93 (majoritary), 22.46 (majoritary), 22.34 (minoritary), 14.03 (majoritary and minoritary) ppm.

Spectroscopic data for **2e/3e**: ^{1}H NMR ($CDCl_3$) δ 4.21 (2H, m, majoritary and minoritary), 3.71 (1H, m, minoritary), 3.58 (1H, m, majoritary), 3.49 (1H, d, J=1.8 Hz, minoritary), 3.44 (1H, d, J=2.0 Hz, majoritary), 3.17 (1H, dd, J=4.0, 2.0 Hz, majoritary), 3.17 (minoritary, signal overlapped with majoritary), 1.58 (2H, m), 1.33 (4H, m), 1.27 (3H, t, J=7.1 Hz, majoritary and minoritary), 0.88 (1H, t, J=7.1 Hz, majoritary and minoritary). ^{13}C NMR ($CDCl_3$) δ 169.04 (minoritary), 168.80 (majoritary), 69.66 (majoritary), 67.99 (minoritary), 61.68 (majoritary), 61.65 (minoritary), 60.74 (majoritary), 60.45 (minoritary), 50.89 (majoritary), 49.63 (minoritary), 34.14 (majoritary), 33.05 (minoritary), 27.32 (majoritary), 27.20 (minoritary), 22.59 (minoritary), 22.53 (majoritary), 14.05 (majoritary and minoritary), 13.87 (majoritary and minoritary) ppm. IR (NaCl) ν 3480, 2934, 2860, 1738, 1633, 1468, 1372, 1200, 1031, 959, 906, 809, 748 cm^{-1}. HRMS m/z calcd for $C_{10}H_{18}O_4Na$ [M+Na$^+$]: 225.1103, found: 225.1109; calcd for $C_{10}H_{18}O_4K$ [M+K$^+$]: 241.842, found: 241.0849.

Spectroscopic data for **2f/3f**: ^{1}H NMR ($CDCl_3$) δ 4.18 (2H, m, majoritary and minoritary), 3.56 (1H, dd, J=5.5, 3.0 Hz, minoritary), 3.46 (1H, d, J=2.0 Hz, minoritary), 3.39 (1H, d, J=2.0 Hz, majoritary), 3.28 (1H, dd, J=6.5, 4.0 Hz, majoritary), 3.21 (1H, dd, J=4.0, 2.0 Hz, majoritary), 3.19 (1H, dd, J=3.0, 2.0 Hz, minoritary), 1.97 (1H, br s), 1.58–1.87 (5H, m, majoritary and minoritary), 1.50 (1H, m, majoritary and minoritary), 1.24 (3H, t, J=7.5 Hz, majoritary and minoritary), 0.95–1.22 (5H, m, majoritary and minoritary). ^{13}C NMR ($CDCl_3$) δ 169.10 (minoritary), 168.84 (majoritary), 73.77 (majoritary), 71.90 (minoritary), 61.67 (majoritary), 61.63 (minoritary), 59.43 (majoritary), 59.22 (minoritary), 50.90 (majoritary), 49.78 (minoritary), 42.30 (majoritary), 41.43 (minoritary), 28.77 (minoritary), 28.71 (majoritary), 28.43 (majoritary), 27.78 (minoritary), 26.28 (minoritary), 26.24 (majoritary), 26.08 (minoritary), 25.96 (minoritary), 25.94 (majoritary), 25.84 (majoritary), 14.07 (majoritary and minoritary), 13.87 (majoritary and minoritary) ppm. IR (NaCl) ν 3484, 2928, 2855, 1737, 1450, 1371, 1282, 1199, 1096, 1030, 906, 735 cm^{-1}. HRMS m/z calcd for $C_{12}H_{20}O_4Na$ [M+Na$^+$]: 251.1259, found: 251.1255; calcd for $C_{12}H_{20}O_4K$ [M+K$^+$]: 267.0999, found: 267.1006.

Spectroscopic data for **2g/3g**: ^{1}H NMR ($CDCl_3$) δ 7.33 (2H, d, J=9.0 Hz, majoritary), 7.30 (2H, d, J=8.5 Hz, minoritary), 6.90 (2H, d, J=8.5 Hz, majoritary and minoritary), 4.86 (1H, d, J=2.5 Hz, minoritary), 4.61 (1H, d, J=4.0 Hz, majoritary), 4.20 (2H, m, majoritary and minoritary), 3.68 (1H, d, J=2 Hz, minoritary), 3.54 (1H, d, J=1.5 Hz, majoritary), 3.45 (1H, dd, J=4.5, 2 Hz, majoritary), 3.39 (1H, dd, J=2.5, 2.0 Hz, minoritary), 2.55 (1H, br s, majoritary), 1.84 (1H, br s, minoritary), 1.27 (3H, t, J=7.0 Hz, majoritary), 1.26 (3H, t, J=7.0 Hz, minoritary). ^{13}C NMR ($CDCl_3$) δ 168.75 (minoritary), 168.56 (majoritary), 159.83 (minoritary), 159.74 (majoritary), 131.67 (majoritary), 130.68 (minoritary), 127.90 (minoritary), 127.81 (majoritary), 114.18 (majoritary and minoritary), 71.79 (majoritary), 70.03 (minoritary), 61.76 (majoritary), 61.72 (minoritary), 60.93 (majoritary), 60.63 (minoritary), 55.30 (majoritary and minoritary), 51.10 (majoritary), 49.82 (minoritary), 14.04 (majoritary and minoritary) ppm. IR (NaCl) ν 3483, 3058, 2985, 2939, 2909, 2839, 1740, 1613, 1586, 1515, 1466, 1444, 1421, 1372, 1304, 1225, 1202, 1178, 1113, 1096, 1069, 1032, 964, 907, 836, 737, 703 cm^{-1}. HRMS m/z calcd for $C_{13}H_{16}O_5Na$ [M+Na$^+$]: 275.0895, found: 275.0855; calcd for $C_{13}H_{16}O_5K$ [M+K$^+$]: 291.0635, found: 291.0657.

Spectroscopic data for **2h/3h**: ^{1}H NMR ($CDCl_3$) δ 6.98 (1H, dd, J=16, 5.5 Hz), 6.00 (1H, dd, J=15.5, 1.5 Hz), 4.15 (2H, q, J=7.5 Hz), 3.90 (1H, dd, J=5.5, 1.5 Hz), 1.25 (3H, t, J=7.5 Hz), 0.9 (9H, s). ^{13}C NMR ($CDCl_3$) δ 166.51, 147.84, 121.78, 78.90, 60.35, 35.46, 25.65, 14.15 ppm. IR (NaCl) ν 3497, 2964, 2907, 2873, 1770, 1722, 1655, 1479, 1369, 1280, 1164, 1112, 1038, 871, 774 cm^{-1}. HRMS m/z calcd for $C_{10}H_{18}O_4Na$ [M+Na$^+$]: 225.1103, found:

225.1103; calcd for $C_{10}H_{18}O_4Na$ [M+K$^+$]: 241.0842, found: 241.0882.

5.1.2.1. 4-(*tert*-Butyl-diphenyl-silanyloxy)-pent-2-enoic acid ethyl ester 6a. To an ice-bath cold solution of compound **1b** (266 mg, 1.85 mmol) in DMF (5 mL) was added imidazole (138 mg, 2.03 mmol) and then *tert*-butyldiphenylsilylchloride (528 μL, 2.03 mmol). The resulting mixture was stirred at room temperature (21 °C) for 70 h and then was quenched with brine and extracted with Et_2O (3×30 mL), the organic layers were washed (brine), dried (Na_2SO_4), and concentrated. The crude oil was purified through chromatography (silica-gel, hexanes/EtOAc (9:1) to afford 542 mg (77%) of an oil. ^{1}H NMR ($CDCl_3$) δ 7.76 (2H, dd, J=7.7, 1.3 Hz), 7.71 (2H, dd, J=8.1, 1.5 Hz), 7.41 (6H, m), 6.99 (1H, dd, J=15.6, 4.6 Hz), 6.10 (1H, dd, J=15.6, 1.5 Hz), 4.54 (1H, m), 4.24 (2H, m), 1.32 (3H, t, J=7.2 Hz), 1.20 (1H, d, J=6.4 Hz), 1.17 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 166.42, 151.16, 135.66, 135.62, 133.85, 133.29, 129.66, 127.53, 127.50, 119.16, 68.59, 60.02, 26.88, 23.18, 19.10, 14.13 ppm. IR (NaCl) ν 3072, 3050, 2960, 2859, 1722, 1428, 1369, 1295, 1157, 1112, 978, 822, 741, 703 cm^{-1}. HRMS m/z calcd for $C_{23}H_{30}O_3SiNa$ [M+Na$^+$]: 405.1862, found: 405.1822.

5.1.2.2. 4-Triisopropylsilanyloxy-pent-2-enoic acid ethyl ester 6b. To an ice-bath cold solution of compound **1b** (582 mg, 4.04 mmol) in DMF (12 mL) was added imidazole (358 mg, 5.25 mmol) and then triisopropylsilylchloride (980 μL, 4.44 mmol). The resulting mixture was stirred at room temperature (21 °C) for 42 h and then was quenched with brine and extracted with Et_2O (3×30 mL), the organic layers were washed (brine), dried (Na_2SO_4), and concentrated. The crude oil was purified through chromatography (silica-gel, hexanes/EtOAc (9:1)) to afford 1 g (83%) of an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 (1H, dd, J=15.3, 4.2 Hz), 5.95 (1H, dd, J=15.3, 1.8 Hz), 4.51 (1H, dq, J=6.3, 1.8 Hz), 4.12 (2H, q, J=6.9 Hz), 1.23 (3H, d, J=6.3 Hz), 1.22 (3H, t, J=6.3 Hz), 1.01 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 166.59, 151.99, 118.92, 67.81, 60.07, 23.84, 17.92, 17.90, 14.13, 12.24 ppm. IR (NaCl) ν 2930, 2868, 1723, 1465, 1369, 1294, 1159, 1094, 883 cm^{-1}. HRMS m/z calcd for $C_{16}H_{32}O_3SiNa$ [M+Na$^+$]: 323.2018, found: 323.1956; calcd for $C_{16}H_{33}O_3Si$ [M+H$^+$]: 301.2199, found: 301.2172.

5.1.2.3. 4-Methoxymethoxy-pent-2-enoic acid ethyl ester 6c. To an ice-bath cold solution of compound **1b** (730 mg, 5.1 mmol) in CH_2Cl_2 (16 mL) were added diisopropylethylamine (3.55 ml, 20.4 mmol), chloromethyl methyl ether (1.55 ml, 20.4 mmol), and then 4-dimethylaminopyridine (464 mg, 3.8 mmol). The resulting mixture was stirred at room temperature (23 °C) for 20 h and then was quenched with brine and extracted with CH_2Cl_2 (3×30 mL), the organic layers were washed (brine), dried (Na_2SO_4), and concentrated. The crude oil was purified through chromatography (silica-gel, hexanes/EtOAc (8:2) and (7:3)) to afford 460 mg (48%) of an oil. ^{1}H NMR ($CDCl_3$) δ 6.58 (1H, dd, J=15.5, 6.0 Hz), 5.72 (1H, dd, J=15.5, 1.5 Hz), 4.35 (2H, s), 4.08 (2H, dq, J=7.0, 7.0 Hz), 3.92 (2H, q, J=7.5 Hz), 3.08 (s, 3H), 1.03 (3H, d, J=6.5 Hz), 1.01 (3H, t, J=7.0 Hz). ^{13}C NMR ($CDCl_3$) δ 165.45, 148.31, 120.36, 93.91, 70.49, 59.63, 54.56, 19.92, 13.61 ppm. IR (NaCl) ν 2981, 2976, 2824, 1718, 1659, 1449, 1370, 1299, 1272, 1158, 1099, 1033, 982, 919, 869, 734 cm^{-1}. HRMS m/z calcd for $C_9H_{16}O_4Na$ [M+Na$^+$]: 211.0946, found: 211.0919.

5.1.3. General experimental procedure for the epoxidation of esters 6. To a −78 °C cold THF (3.5 mL) was added TBHP (3.3 M in toluene[18]) (600 μL, 1.97 mmol) and then ethyllithium (0.5 M in benzene/cyclohexane (9:1)) (2.9 mL, 1.45 mmol), gas evolution was observed. The resulting mixture was stirred at −78 °C for 15 min and then a solution of compound **6** (1.31 mmol) in THF (2 mL) was added drop wise and then the mixture was stirred at the desired temperature for the desired time (see Table 4). Then solid Na_2SO_3 (110 mg) was added in one portion and stirred for 15 min, then diluted with satd aq NH_4Cl solution and extracted with Et_2O (3×30 mL), the organic layers were washed (brine), dried (Na_2SO_4), and concentrated. The crude oil was purified through chromatography (silica-gel, hexanes/EtOAc (7:3)) to afford an oil.

Spectroscopic data for **7a/8a**: ^{1}H NMR ($CDCl_3$) δ 7.61 (4H, m), 7.27 (6H, m), 4.11 (2H, m), 3.67 (1H, m), 3.23 (1H, d, J=2 Hz), 3.17 (1H, d, J=5.2 Hz), 3.13 (1H, d, J=1.5 Hz), 3.06 (1H, dd, J=4.5, 1.5 Hz), 1.18 (3H, t, J=7 Hz), 1.08 (3H, d, J=6.5 Hz), 1.01(1H, d, J=6.5 Hz), 0.98 (9H, m). ^{13}C NMR ($CDCl_3$) δ 169.02, 168.92, 135.90, 135.83, 135.81, 135.32, 134.80, 133.97, 133.77, 133.32, 133.14, 129.82, 129.77, 129.73, 129.56, 127.66, 127.65, 127.60, 68.89, 67.38, 61.94, 61.53, 61.48, 61.30, 50.99, 50.77, 26.91, 26.85, 26.57, 20.55, 19.76, 19.23, 19.18, 18.99, 14.09, 14.07 ppm. IR (NaCl) ν 3072, 2960, 2932, 2892, 2858, 1737, 1472, 1428, 1391, 1374, 1305, 1197, 1113, 1029, 998, 822, 740, 702 cm^{-1}. HRMS m/z calcd for $C_7H_{12}O_4Na$ [M+Na$^+$]: 421.1811, found: 421.1844.

Spectroscopic data for **7b/8b**: ^{1}H NMR ($CDCl_3$) δ 4.20 (2H, m, majoritary and minoritary), 3.97 (1H, dq, J=6.5, 4.0 Hz, minoritary), 3.80 (1H, dq, J=5.5, 6.5 Hz, majoritary), 3.42 (1H, d, J=2.0 Hz, minoritary), 3.31 (1H, d, J=2.0 Hz, majoritary), 3.19 (1H, dd, J=5.5, 2.0 Hz, majoritary), 3.10 (1H, dd, J=4.0, 2.0 Hz), 1.27 (3H, t, J=7.5 Hz, minoritary), 1.26 (3H, t, J=7.0 Hz, majoritary), 1.23 (3H, d, J=6.5 Hz, majoritary), 1.23 (3H, d, J=6.5 Hz, minoritary), 1.04 (21H, m, majoritary and minoritary). ^{13}C NMR ($CDCl_3$) δ 169.28 (minoritary), 168.97 (majoritary), 68.41 (majoritary), 66.07 (minoritary), 62.29 (majoritary), 61.63 (minoritary), 61.53 (majoritary), 61.48 (minoritary), 50.79 (majoritary), 50.52 (minoritary), 20.48 (minoritary), 20.33 (majoritary), 17.95, 17.91 (majoritary and minoritary), 14.06 (majoritary and minoritary), 12.29 (majoritary and minoritary) ppm. IR (NaCl) ν 2944, 2887, 2860, 1755, 1465, 1373, 1284, 1244, 1196, 1170, 1122, 1099, 1059, 1031, 999, 907, 883, 827, 761, 681 cm^{-1}. HRMS m/z calcd for $C_{16}H_{32}SiO_4Na$ [M+Na$^+$]: 339.1968, found: 339.1966.

Spectroscopic data for **7c/8c**: ^{1}H NMR ($CDCl_3$) δ 4.64 (1H, d, J=7.0 Hz, minoritary), 4.55 (1H, d, J=7.0 Hz, minoritary), 4.54 (1H, d, J=7.0 Hz, majoritary), 4.51 (1H, d, J=7.0 Hz, majoritary), 4.12 (2H, m, majoritary and minoritary), 3.55 (1H, dq, J=6.5, 5.0 Hz, majoritary), 3.54 (1H, dq, J=6.5, 6.0 Hz, majoritary), 3.33 (1H, d, J=2.0 Hz, majoritary), 3.26 (3H, s, minoritary), 3.23 (3H, s), 3.22 (1H, d,

J=2.0 Hz, minoritary), 3.13 (1H, dd, J=6.0, 2.0 Hz, minoritary), 3.05 (1H, dd, J=5.0, 2.0 Hz, majoritary), 1.19 (3H, t, J=6.5 Hz, majoritary and minoritary), 1.16 (3H, d, J=6.5 Hz, majoritary and minoritary). ^{13}C NMR ($CDCl_3$) δ 168.77 (majoritary), 168.66 (minoritary), 95.61 (majoritary), 95.07 (minoritary), 71.67 (minoritary), 71.14 (majoritary), 61.65 (minoritary), 61.53 (majoritary), 60.57 (minoritary), 59.96 (majoritary), 55.43 (majoritary), 55.30 (minoritary), 51.44 (majoritary), 50.14 (minoritary), 17.75 (majoritary), 17.04 (minoritary), 14.04 (majoritary), 14.02 (minoritary) ppm. HRMS m/z calcd for $C_9H_{16}O_5Na$ [M+Na$^+$]: 227.0895, found: 227.0874.

5.1.4. General experimental procedure for the treatment of 2 with sodium thiophenolate to furnish 4/5. An ice-bath cold suspension of sodium hydride (60% in mineral oil) (1.12 mmol) in THF (1 mL) was treated with thiophenol (2.25 mmol). The mixture was stirred at room temperature for 15 min and then a solution of the epoxyester **2** (0.75 mmol) in THF (1 mL) was added drop wise and the mixture was stirred at room temperature for the required time (see Table 5). Then brine was added and extracted with Et_2O (3×20 mL), the organic layers were washed (brine), dried (Na_2SO_4), and concentrated. The crude oil was purified through chromatography (silica-gel, hexanes/EtOAc (7:3) and (6:4)).

Spectroscopic data for **4a**: ^{1}H NMR ($CDCl_3$) δ 7.50–7.53 (m, 2H), 7.35–7.45 (8H, m), 5.47 (1H, d, J=3.0 Hz), 4.56 (1H, ddd, J=4.0, 3.0, 2.0 Hz), 4.35 (1H, d, J=4.0 Hz), 2.37 (1H, d, J=2.0 Hz). ^{13}C NMR ($CDCl_3$) δ 172.63, 133.04, 132.59, 129.57, 129.05, 128.71, 128.59, 126.52, 82.98, 71.38, 56.64 ppm. IR (NaCl) ν 3460, 3060, 2916, 1951, 1886, 1752, 1581, 1498, 1456, 1438, 1326, 1290, 1214, 1179, 1110, 1024, 994, 954, 942, 815, 790, 701, 634 cm^{-1}. HRMS m/z calcd for $C_{16}H_{14}O_3SNa$ [M+Na$^+$]: 309.0562, found: 309.0580 (recrystallized from hexanes/EtOAc, mp 151.5–154.5 °C).

Spectroscopic data for **5a**: ^{1}H NMR ($CDCl_3$) δ 7.48–7.50 (m, 2H), 7.24–7.35 (8H, m), 5.49 (1H, d, J=4.0 Hz), 4.38 (1H, dd, J=4.0, 1.0 Hz), 3.89 (1H, d, J=1.0 Hz), 2.20 (1H, s). ^{13}C NMR ($CDCl_3$) δ 173.05, 132.93, 132.54, 131.21, 129.53, 129.12, 128.98, 128.89, 126.31, 83.27, 75.49, 52.17 ppm. IR (NaCl) ν 3389, 3053, 2987, 1776, 1440, 1265, 1156, 1070, 1023, 909, 650 cm^{-1}. HRMS m/z calcd for $C_{16}H_{14}O_3SNa$ [M+Na$^+$]: 309.0562, found: 309.0562 (recrystallized from hexanes/EtOAc, mp 142.5–144.3 °C).

Spectroscopic data for **4b**: ^{1}H NMR ($CDCl_3$) δ 7.33–7.57 (m, 5H), 4.51 (1H, dq, J=6.5, 3 Hz), 4.24 (2H, m), 2.75 (1H, s), 1.50 (3H, d, J=6.0 Hz). ^{1}H NMR (C_6D_6) δ 7.19 (2H, dd, J=6, 3.5 Hz), 6.90 (3H, t, J=6 Hz), 3.50 (1H, dq, J=6.5, 3 Hz), 3.41 (1H, d, J=5 Hz), 3.24 (1H, m), 2.11 (1H, d, J=2.5 Hz), 1.09 (3H, d, J=6.5 Hz). ^{13}C NMR ($CDCl_3$) δ 172.94, 132.41, 129.68, 128.71, 78.99, 69.86, 57.31, 14.13 ppm. IR (NaCl) ν 3381, 2921, 2860, 1752, 1630, 1436, 1174, 1113 cm^{-1}. HRMS m/z calcd for $C_{11}H_{12}O_3SNa$ [M+Na$^+$]: 247.0405, found: 247.0376.

Spectroscopic data for **5b**: ^{1}H NMR ($CDCl_3$) δ 7.33–7.57 (m, 5H), 4.65 (1H, dq, J=6.6, 4.4 Hz), 4.31 (1H, dd, J=4.4, 2.8 Hz), 3.81 (1H, d, J=2.8 Hz), 1.40 (3H, d, J=6.6 Hz). ^{13}C NMR ($CDCl_3$) δ 172.94, 133.21, 132.26, 129.53, 129.50, 128.87, 78.66, 74.74, 53.02, 13.68 ppm. IR (NaCl) ν 3399, 2922, 2853, 1759, 1721, 1623, 1439, 1313, 1259, 1113, 1052 cm^{-1}. HRMS m/z calcd for $C_{11}H_{12}O_3SNa$ [M+Na$^+$]: 247.0405, found: 247.0412.

Spectroscopic data for **4c**: ^{1}H NMR ($CDCl_3$) δ 7.52–7.54 (2H, m), 7.33–7.36 (3H, m), 4.31 (1H, m), 4.24 (1H, d, J=4.0 Hz), 3.86 (1H, dd, J=10.0, 2.5 Hz), 2.75 (1H, s), 2.27 (1H, m), 1.11 (3H, d, J=7.0 Hz), 0.99 (3H, d, J=6.5 Hz). ^{13}C NMR ($CDCl_3$) δ 172.21, 132.37, 132.00, 129.68, 128.67, 88.34, 68.55, 57.64, 27.64, 19.83, 17.51 ppm. IR (NaCl) ν 3423, 2965, 1760, 1471, 1440, 1392, 1339, 1171, 1072, 1026, 873, 778, 745, 690 cm^{-1}. HRMS m/z calcd for $C_{13}H_{16}O_3SNa$ [M+Na$^+$]: 275.0718, found: 275.0761 (recrystallized from hexanes/EtOAc, mp 147.8–148.5 °C).

Spectroscopic data for **5c**: ^{1}H NMR ($CDCl_3$) δ 7.52–7.54 (2H, m), 7.33–7.36 (3H, m), 4.35 (1H, m), 4.06 (1H, dd, J=10.0, 3.0 Hz), 3.80 (1H, s), 2.42 (1H, d, J=5.0 Hz), 2.15 (1H, m), 1.10 (3H, d, J=6.5 Hz), 0.95 (3H, d, J=7.0 Hz). ^{13}C NMR ($CDCl_3$) δ 173.51, 132.83, 131.58, 129.49, 128.76, 88.43, 73.96, 53.50, 27.01, 19.86, 17.62 ppm. IR (NaCl) ν 3449, 3060, 2965, 2876, 1759, 1583, 1471, 1440, 1391, 1370, 1340, 1199, 1173, 1121, 1070, 1024, 955, 916, 821, 778, 747, 690 cm^{-1}. HRMS m/z calcd for $C_{13}H_{16}O_3SNa$ [M+Na$^+$]: 275.0718, found: 275.0721.

Spectroscopic data for **4e**: ^{1}H NMR ($CDCl_3$) δ 7.45–7.49 (m, 2H), 7.27–7.30 (3H, m), 4.26 (1H, m), 4.20 (1H, m), 4.18 (1H, d, J=4.0 Hz), 2.70 (1H, s), 1.73–1.90 (2H, m), 1.29–1.39 (4H, m), 0.86 (3H, t, J=7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 172.17, 132.38, 132.06, 129.67, 128.67, 82.70, 69.20, 57.24, 28.27, 27.39, 22.54, 13.91 ppm. IR (NaCl) ν 3449, 3060, 2958, 2872, 1759, 1583, 1467, 1440, 1307, 1177, 1089, 1024, 938, 832, 745, 691 cm^{-1}. HRMS m/z calcd for $C_{14}H_{18}O_3SNa$ [M+Na$^+$]: 289.0874, found: 289.0856.

Spectroscopic data for **5e**: ^{1}H NMR ($CDCl_3$) δ 7.44–7.45 (2H, m), 7.24–7.35 (3H, m), 4.35 (1H, m), 4.23 (1H, m), 3.89 (1H, d, J=1.0 Hz), 2.90 (1H, s), 1.59–1.85 (2H, m), 1.22–1.40 (4H, m), 0.83 (3H, t, J=7.0 Hz). ^{13}C NMR ($CDCl_3$) δ 173.72, 132.83, 131.58, 129.49, 128.76, 83.22, 74.20, 52.87, 27.70, 27.52, 22.42, 13.84 ppm. IR (NaCl) ν 3441, 3059, 2959, 2921, 2859, 1748, 1583, 1479, 1439, 1343, 1274, 1187, 1123, 996, 945, 739, 690 cm^{-1}. HRMS m/z calcd for $C_{14}H_{18}O_3SNa$ [M+Na$^+$]: 289.0874, found: 289.0848.

Spectroscopic data for **4f**: ^{1}H NMR ($CDCl_3$) δ 7.45–7.47 (2H, m), 7.27–7.30 (3H, m), 4.23 (1H, m), 4.16 (1H, d, J=4.5 Hz), 3.88 (1H, dd, J=10.5, 2.5 Hz), 2.70 (1H, s), 0.83–2.03 (11H, m). ^{13}C NMR ($CDCl_3$) δ 172.16, 132.43, 131.97, 129.68, 128.69, 87.10, 68.33, 57.47, 36.58, 30.16, 27.62, 26.32, 25.35, 25.27 ppm. IR (NaCl) ν 3470, 3055, 2910, 2854, 1751, 1439, 1265, 1173, 1097, 1001, 944, 895, 704 cm^{-1}. HRMS m/z calcd for $C_{16}H_{20}O_3SNa$ [M+Na$^+$]: 315.1031, found: 315.1040.

Spectroscopic data for **5f** (partially contaminated with **4f**): ^{1}H NMR ($CDCl_3$) δ 7.46–7.50 (2H, m), 7.28–7.30 (3H, m), 4.30 (1H, m), 4.06 (1H, dd, J=10.5, 3.5 Hz), 3.72 (1H,

s), 0.85–2.00 (12H, m). ^{13}C NMR ($CDCl_3$) δ 172.16, 132.92, 131.59, 129.52, 128.81, 86.85, 73.86, 53.29, 36.08, 30.08, 27.82, 26.23, 25.37, 25.28 ppm. IR (NaCl) ν 3443, 3060, 2923, 2854, 1750, 1650, 1439, 1261, 1224, 1189, 1097, 1017, 735, 687 cm^{-1}. HRMS *m/z* calcd for $C_{16}H_{20}O_3SNa$ [M+Na$^+$]: 315.1031, found: 315.1026.

5.1.5. General experimental procedure for the cyclization of 9/10 into carbonates 12/13. An ice-bath cold solution of diols **9/10** (0.44 mmol) in THF (11 mL) was treated with pyridine (0.22 mmol) and triphosgene (0.48 mmol). The mixture was refluxed for 7.5 h. Then brine was added and extracted with Et_2O (3×20 mL), the organic layers were washed (brine), dried (Na_2SO_4), and concentrated. The crude oil was purified through chromatography (silica-gel, hexanes/EtOAc (8:2) and (7:3)).

Spectroscopic data for **12a**: ^{1}H NMR ($CDCl_3$) δ 7.13–7.50 (10H, m), 5.60 (1H, d, *J*=4.5 Hz), 4.87 (1H, dd, *J*=8.0, 4.5 Hz), 4.11 (2H, m), 3.81 (1H, d, *J*=7.5 Hz), 1.16 (1H, t, *J*=7.5 Hz). IR (NaCl) ν 3064, 2983, 1815, 1735, 1593, 1458, 1440, 1368, 1312, 1267, 1158, 1069, 1020, 952, 863, 765, 737 cm^{-1}. HRMS *m/z* calcd for $C_{19}H_{18}O_5SNa$ [M+Na$^+$]: 381.0773, found: 381.0758.

Spectroscopic data for **13a**: ^{1}H NMR ($CDCl_3$) δ 7.06–7.38 (10H, m), 5.86 (1H, d, *J*=7.0 Hz), 5.22 (1H, dd, *J*=10.5, 7.0 Hz), 4.11 (2H, m), 3.31 (1H, d, *J*=10.5 Hz), 1.16 (1H, t, *J*=7.5 Hz). IR (NaCl) ν 3063, 2982, 1810, 1728, 1594, 1475, 1441, 1369, 1264, 1157, 1020, 952, 862, 752, 698 cm^{-1}. HRMS *m/z* calcd for $C_{19}H_{18}O_5SNa$ [M+Na$^+$]: 381.0773, found: 381.0765.

Spectroscopic data for **12b/13b**: ^{1}H NMR ($CDCl_3$) δ 7.19–7.49 (5H, m, **12b** and **13b**), 4.83 (1H, dq, *J*=7.0, 6.5 Hz, **13b**), 4.73 (1H, dq, *J*=6.5, 4.5 Hz, **12b**), 4.53 (1H, d, *J*=8.0, 4.5 Hz, **12b**), 4.45 (1H, d, *J*=10.5, 7.0 Hz, **13b**), 4.14 (2H, m, **12b** and **13b**), 3.70 (1H, d, *J*=8.0 Hz, **12b**), 3.63 (1H, d, *J*=10.5 Hz, **13b**), 1.52 (3H, d, *J*=6.5 Hz, **12b**), 1.31 (3H, d, *J*=6.5 Hz, **13b**), 1.19 (1H, t, *J*=7.0 Hz, **12b**), 1.18 (1H, t, *J*=7.0 Hz, **13b**). IR (NaCl) ν 3060, 2955, 2854, 1805, 1732, 1466, 1377, 1259, 1157, 1069, 746, 685 cm^{-1}. HRMS *m/z* calcd for $C_{14}H_{16}O_5SNa$ [M+Na$^+$]: 319.0616, found: 319.0582.

5.1.5.1. 3-Acetyl-oxirane-2-carboxylic acid ethyl ester 14. An ice-bath cold solution of compound **1b** (163 mg, 1.02 mmol) in CH_2Cl_2 (4 mL) was treated with pyridine (463 μL, 5.72 mmol) and Dess–Martin periodinane (574 mg, 1.53 mmol). The mixture was stirred at room temperature (21 °C) for 1.5 h. Then satd aq $NaHCO_3/Na_2S_2O_3$ solution was added, diluted with Et_2O, then extracted with Et_2O (3×20 mL), the organic layers were washed (brine), dried (Na_2SO_4), and concentrated. The crude oil was purified through chromatography (silica-gel, hexanes/EtOAc (8:2) and (7:3)) to afford 113 mg (70%) of an oil. ^{1}H NMR ($CDCl_3$) δ 4.27 (2H, m), 3.63 (1H, d, *J*=2.0 Hz), 3.59 (1H, d, *J*=2.0 Hz), 2.12 (3H, s), 1.32 (3H, t, *J*=7.0 Hz). ^{13}C NMR ($CDCl_3$) δ 202.56, 166.71, 62.38, 57.86, 51.83, 24.49, 14.07 ppm. IR (NaCl) ν 2983, 2915, 1745, 1718, 1459, 1365, 1310, 1202, 1095, 1030, 874, 806 cm^{-1}. HRMS *m/z* calcd for $C_7H_{10}O_4Na$ [M+Na$^+$]: 181.0477, found: 181.0462.

5.1.6. Experimental procedure for the reduction of 14. An ice-bath cold solution of compound **14** (48 mg, 0.30 mmol) in Et_2O (4 mL) was treated with zinc borohydride solution[20] (0.17 M in Et_2O) (18 ml, 3 mmol). The mixture was stirred cold with an ice-bath for 30 min. Then satd aq NH_4Cl solution was added and extracted with Et_2O (3×20 mL), the organic layers were washed (brine), dried (Na_2SO_4), and concentrated. The crude oil was purified through chromatography (silica-gel, hexanes/EtOAc (7:3) and (6:4)) to afford 36 mg (75%) of an oil.

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