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UNEXPECTED REACTION OF 2,3-EPOXY SULFONATES: NOVEL FORMATION OF TWO ENONES WITH REVERSED SUBSTITUENTS AT α- AND β-POSITIONS FROM THE SINGLE ISOMER

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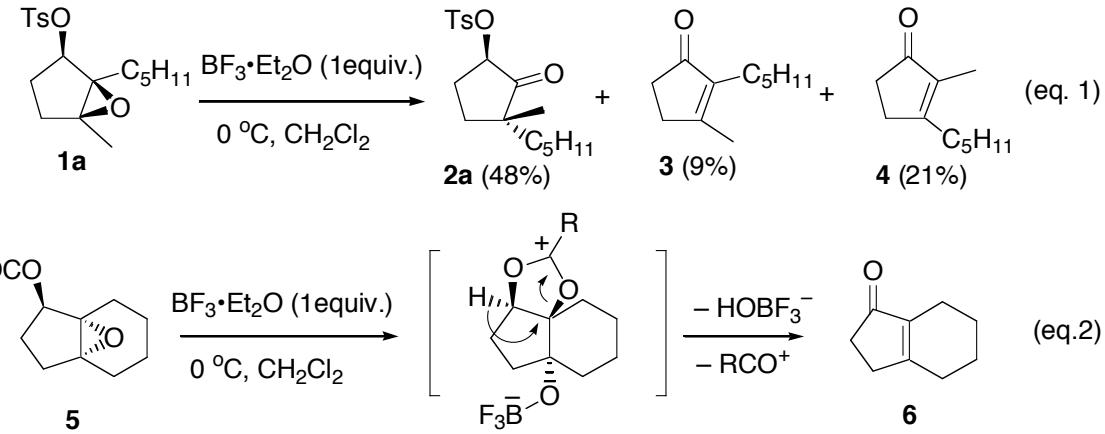
Abstract – The 2,3-epoxy sulfonates gave two types of enones with reversed substituents at the α- and β-positions under neat and weakly acidic conditions. The reaction mechanism is also discussed.

INTRODUCTION

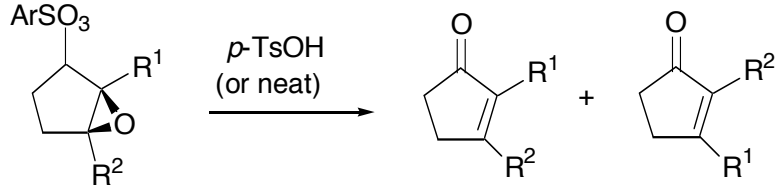
Recently, we reported that the treatment of 2,3-epoxy sulfonates including **1a** with a large excess of a Lewis acid gave the rearranged products including **2a** in high yields, and its application to the formal synthesis of (–)-aphanorphine and the total syntheses of herbertane-type sesquiterpenes, (–)-α-herbertenol and (–)-herbertenediol.[1] We then found that the treatment of *cis*-epoxy tosylate (**1a**) with 1.0 equivalent of BF_3•Et_2O produced the enones (**3**) and (**4**) along with the expected rearranged product (**2a**) under similar conditions (eq. 1). Although the formation of enone (**6**) from the bicyclic *trans*–epoxy acylates (**5**) was observed probably because of the good neighboring participating effect shown in eq. 2, the corresponding *cis*-epoxy acylate did not give **6** at all.[2] Furthermore, the sulfonyl group is well recognized not to have such a neighboring participation ability. Therefore, the formation of these enones (**3**) and (**4**) is quite strange, especially, the formation of **4** which has the reversed subsituents at the C2- and C3-positions compared to **3**.

Dedicated to Professor Leo A. Paquette on the occasion of his 70th birthday.



We have been interested in the formation of those enones and focused our attention on their selective formation. We have now found the conditions producing only enones (Scheme 1). We also studied their reaction mechanism and obtained some valuable information. We present here our study on this subject.

Scheme 1.

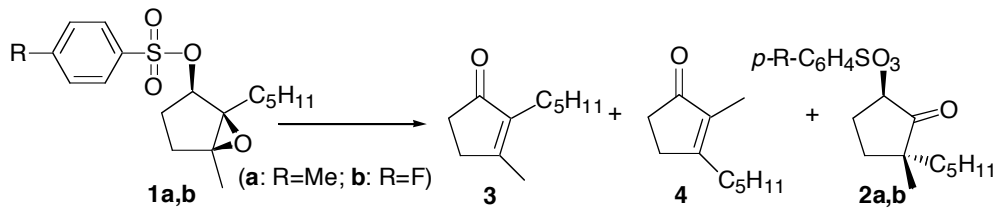


RESULTS AND DISCUSSION

In the reaction of 2,3-epoxy sulfonate (**1a**) with BF_3•Et_2O, the use of a large excess (10 equiv.) of BF_3•Et_2O selectively afforded **2a** in high yield (83%),[1] although the use of 1.0 equiv. of BF_3•Et_2O gave the enones (**3**) and (**4**) along with **2a** as shown in eq. 1. Only the difference in the amount of Lewis acid gave different results. The reaction conditions were then studied using *cis*-2,3-epoxy tosylate (**1a**) and *cis*-2,3-epoxy-*p*-fluorobenzenesulfonate (**1b**).[3] When 1.0 equiv. of BF_3•Et_2O was used, the two enones (**3**[4] and **4**[5]) were obtained along with the rearranged product (**2a**) or (**2b**), and the reaction times, chemical yields, and the ratio of the two enones from each compound (**1a**) or (**1b**) were similar to each other (entries 1 and 2 in Table 1). On the other hand, to our surprise, compounds (**1a**) and (**1b**) also afforded the enones (**3**) and (**4**) in good combined yields under neat condition without acid, and no rearranged products were obtained. Furthermore, the reactivities of the two sulfonates (**1a**) and (**1b**) were completely different from each other. The reaction of **1b** proceeded much faster than **1a** under neat conditions

(entries 3 and 4, 1 week *vs*. 1 day). The use of 1.0 equiv. of *p*-TsOH, an organic acid, significantly shortened the reaction time (entry 5). We then applied these reaction conditions to *trans*-2,3-epoxy-*p*-fluorobenzenesulfonate (**1c**), and got almost the same result as that from the *cis*-isomer (**1b**) (Scheme 2). This fact showed that the stereochemical relationship between the oxirane ring and the *p*-fluorobenzenesulfonyloxy group does not affect the reaction.

Table 1. Enone Formation under Various Conditions



entry	**1**	condition[1)]	time	yield (%) **3**	**4**	**2a** or **2b**
1	**1a**	BF_3•Et_2O (1.0 equiv.)	30 min	9	21	48
2	**1b**	"	30 min	9	28	40
3	**1a**	none[2)]	1 week	14	60	0
4	**1b**	"	1 day	28	61	0
5	**1b**	*p*-TsOH (1.0 equiv.)	30 min	28	61	0

1) 1.0 M in CH_2Cl_2 except for entries 3 and 4.
2) no solvent

Scheme 2. Enone Formation from *trans*-Epoxy Sulfonate (**1c**)

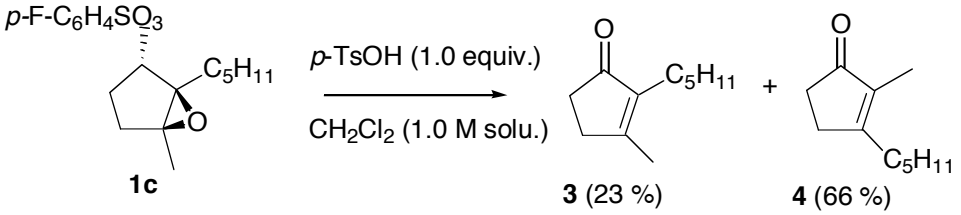
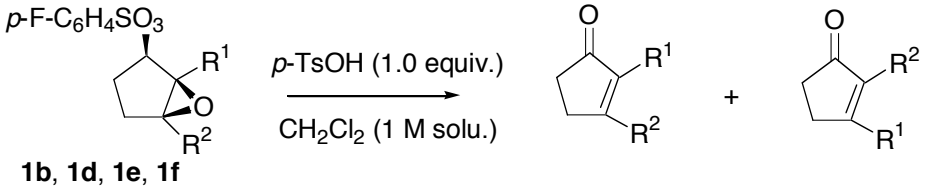
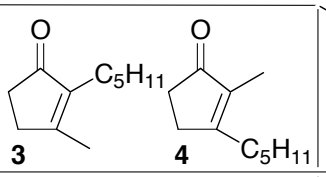
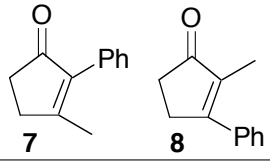
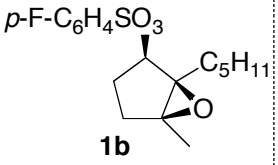
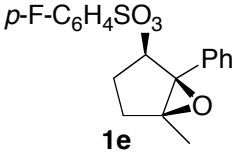
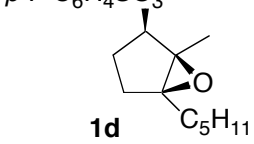
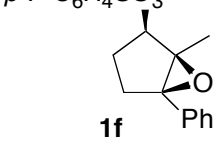


Table 2 shows the results using various *cis*-2,3-epoxy-*p*-fluorobenzenesulfonates (**1d-f**). For comparison, the result of 3-methyl-2-*n*-pentylepoxy sulfonate (**1b**) is also shown. The epoxides with the reversed substituents (**1b**) and (**1d**) gave the same proportions of the enones (**3**) and (**4**). A similar tendency was observed in the reactions of the 2-phenyl- and 3-phenyl-isomers (**1e**) and (**1f**). Thus, two epoxy sulfonates (**1e**) and (**1f**) resulted in the formation of **8**[6] as a major product with **7**[7] as a minor product in each reaction. These results suggested that the reactions proceed through the same intermediates.

Table 2. Enone Formation from the Various Epoxides

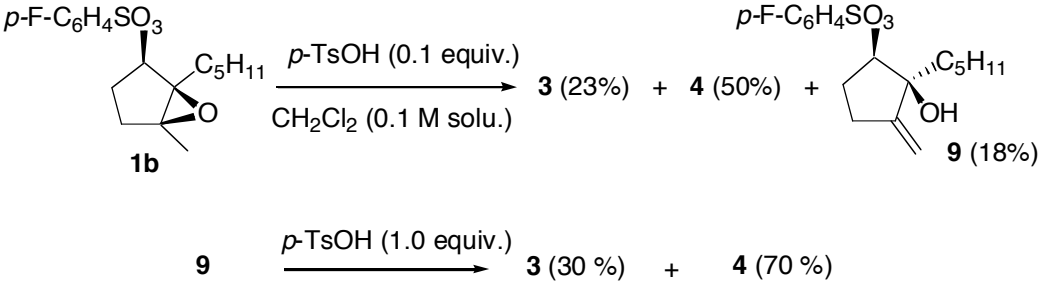


1b, **1d**, **1e**, **1f**

substrate \ product	 **3** **4**		substrate \ product	 **7** **8**	
 **1b**	28%	61%	 **1e**	12%	82%
 **1d**	28%	61%	 **1f**	20%	73%

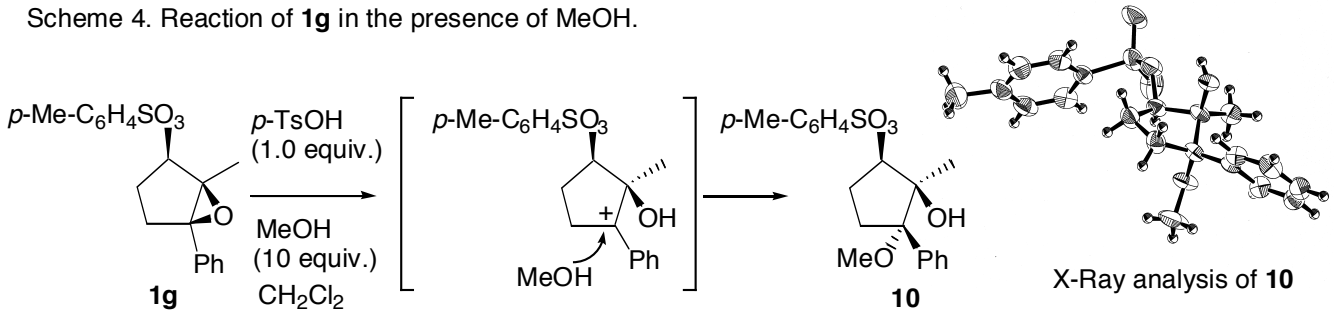
We next studied the reaction mechanism of the enone formation. Although even in diluted solution (0.1 M concentration; the reactions in Table 1, Scheme 2 and Table 2 were conducted in 1.0 M solution) no intermediates were detected on TLC in the reactions of **1e** or **1f**, the reaction of **1b** fortunately gave a small amount of the allyl alcohol sulfonate (**9**) with a large amount of two enones (**3**) and (**4**) by the use of 0.1 equiv. of *p*-TsOH. The treatment of **9** under the same acidic condition (1.0 equiv. of *p*-TsOH) gave two enones (**3**) and (**4**) in a similar ratio to that obtained by the direct acid treatment of the starting epoxy sulfonate (**1b**) (Scheme 3; cf. Table 1, entry 5). These facts would show **9** or its olefinic isomer as an intermediate, at least, in the reaction of **1b** into two enones (**3**) and (**4**).

Scheme 3. Acquisition of the Intermediate



Furthermore, the treatment of *cis*-2,3-epoxy-*p*-toluenesulfonate (**1g**)[1b] having the same substituent pattern as **1f** with *p*-TsOH in the presence of 10 equiv. of MeOH gave the product (**10**) having a C3-methoxy group. This result proved the first formation of the C3-carbocation in the reaction of **1f**.

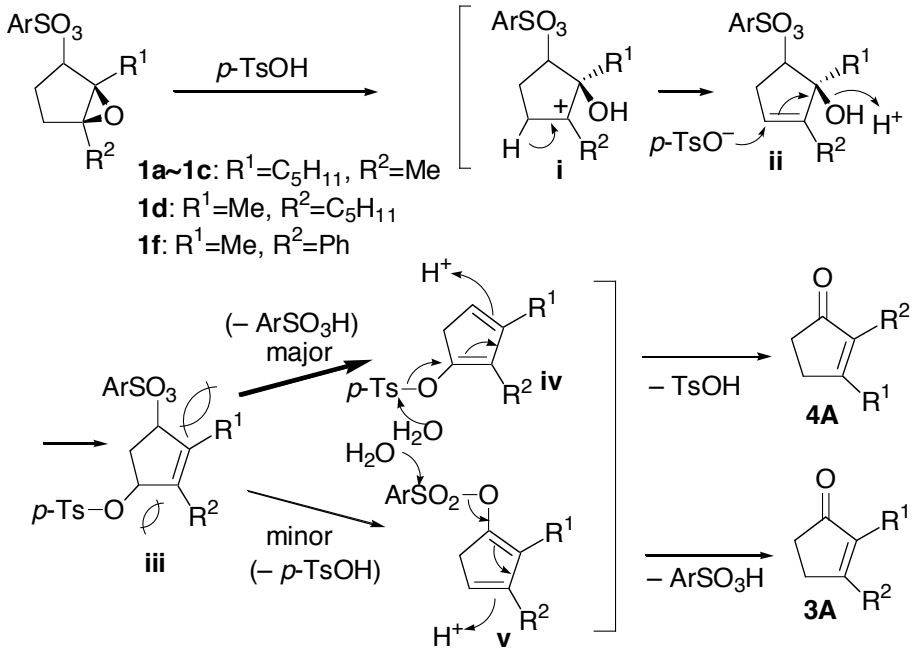
Scheme 4. Reaction of **1g** in the presence of MeOH.



These results prompted us to propose the following reaction mechanism for **1a~1d** and **1f**. Thus, first cleavage of the oxiran ring occurs at the C3-position because of a strong electron-withdrawing nature of sulfonyloxyalkyl group leading to the allyl alcohol (**ii**) *via* the cation intermediate (**i**). In the case of **1f**, C3-carbocation is more preferable than C2-carbocation.[2e] Real driving force of this reaction is still not clear, because just neat conditions also gave the enones although they need long reaction times (see Table 1, entries 3 and 4). Maybe a small amount of *p*-toluenesulfonic acid or *p*-fluorobenzenesulfonic acid formed from the epoxy sulfonates for some reason even under neat conditions would accelerate the ring opening reaction. Based on the consideration of the formation of the enones as will be discussed next, compound (**ii**) must have an *endo*-olefin, and the less reactive *exo*-olefin (**9**) would be isolated under diluted conditions. Attack of the *p*-tosyloxy anion on **ii** affords the disulfoxylated olefin (**iii**), from which desulfonyloxylation occurs in two ways. The proportion of the two reaction routes would be determined by the steric repulsion between the sulfonyloxy group and the next substituent. In other words, the bulkiness of the next substituent would determine the reaction path. Each product would then be obtained *via* intermediate (**iv**) or (**v**). This mechanistic consideration shown in Scheme 5 might not be similar for the epoxy sulfonate (**1e**) with C2-aryl substituent, because epoxides with C2-aryl group prefer the formation of the C2-carbocation.[2f–h] To verify sure the reaction mechanism from **1e** to the enones (**7**) and (**8**), we tried to trap the first carbocation species with MeOH. However this attempt was unsuccessful and gave complex mixture. No product having a methoxy group was obtained. Therefore, the mechanism from **1e** to the enones (**7**) and (**8**) is still not clarified.

In conclusion, we found a novel transformation of the 2,3-epoxy sulfonates to two types of enones under neat, acidic, or a small amount of Lewis acid conditions. The main driving force for the formation of the

Scheme 5. Plausible Mechanism of the Enone Formation from **1b~d** and **1f**



enones must be the strong leaving ability of the sulfonyloxy groups, and the epoxy alcohol derivatives with such a strong leaving group as the sulfonyloxy groups need careful acid treatment for selectively obtaining rearrangement reaction. The fact obtained here is a useful knowledge in the rearrangement reaction of epoxy alcohol derivatives.

ACKNOWLEDGEMENTS

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EXPERIMENTAL

All melting points are uncorrected. The NMR spectra were measured using 270 MHz or 300 MHz spectrometers with $CDCl_3$ as the solvent and $SiMe_4$ as the internal standard. IR spectra were recorded as a KBr pellet. All solvents were distilled and dried according to standard procedures.

General Procedure for Epoxy Sulfonates: The corresponding sulfonyl chloride (1.2 mmol) was added to the epoxy alcohol[3] (1.0 mmol) in pyridine (1 mL) under N_2 and the reaction mixture was stirred for 10

h at rt. The resulting mixture was poured into ice–water and extracted with AcOEt. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography using hexane–AcOEt (3/1 ~ 5/1) as the eluent to give the epoxy sulfonate.

The epoxy sulfonates tend to cause the formation of the enones under neat as described in the text. Then HRMS was conducted in place of elemental analysis for the epoxy sulfonates.

For epoxy sulfonates (**1a**, **1b**, and **1g**), see ref. 1b.

***trans*-5-Methyl-1-pentyl-6-oxabicyclo[3.1.0]hex-2-yl 4-Fluorobenzenesulfonate (1c)**

1c (60 mg, 67%) was obtained from *trans*-epoxy alcohol, *trans*-2-hydroxy-5-methyl-1-pentyl-6-oxabicyclo[3.1.0]hexane (48 mg, 0.26 mmol). IR (KBr) 1593, 1495, 1371, 1157 cm^{-1}; ^1H NMR ($CDCl_3$) 0.85 (t, 3H, *J* = 6.9 Hz), 1.00–1.36 (m, 10H), 1.59–1.88 (m, 5H), 4.94 (br d, 1H, *J* = 3.9 Hz), 7.24 (d, 1H, *J* = 8.7 Hz), 7.28 (d, 1H, *J* = 8.7 Hz), 7.95 (d, 1H, *J* = 8.7 Hz), 7.98 (d, 1H, *J* = 8.7 Hz); ^{13}C NMR ($CDCl_3$) 13.8, 14.9, 22.3, 24.3, 24.9, 27.1, 30.0, 31.9, 68.4, 68.9, 83.6, 116.4, 116.7, 130.4, 130.6, 132.8, 163.9; EI-HRMS Calcd for $C_{11}H_{19}O_2$ (M^+–$C_6H_4O_2FS$): 183.1385, found: 183.1402.

***cis*-1-Methyl-5-pentyl-6-oxabicyclo[3.1.0]hex-2-yl 4-Fluorobenzenesulfonate (1d)**

1d (493 mg, 86%) was obtained from *cis*-epoxy alcohol, *cis*-2-hydroxy-1-methyl-5-pentyl-6-oxabicyclo[3.1.0]hexane (310 mg, 1.68 mmol). IR (KBr) 2928, 2853, 1495, 1371, 1186, 1159 cm^{-1}; ^1H NMR ($CDCl_3$) 0.88 (t, 3H, *J* = 6.7 Hz), 1.37 (s, 3H), 1.23–1.65 (m, 10H), 1.69–1.93 (m, 1H), 1.96–2.01 (m, 1H), 4.79 (t, 1H, *J* = 8.2 Hz), 7.20–7.28 (m, 2H), 7.92–7.98 (m, 2H); ^{13}C NMR ($CDCl_3$) 12.4, 13.9, 22.5, 24.6, 25.0, 27.0, 29.7, 29.9, 31.8, 66.2, 68.2, 85.5, 116.4, 116.7, 130.5, 130.6, 163.5; EI-HRMS Calcd for $C_{11}H_{19}O_2$ (M^+–$C_6H_4O_2FS$): 183.1385, found: 183.1418.

***cis*-5-Methyl-1-phenyl-6-oxabicyclo[3.1.0]hex-2-yl 4-Fluorobenzenesulfonate (1e)**

1e (118 mg, 89%) was obtained from *cis*-epoxy alcohol, *cis*-2-hydroxy-2-methyl-1-phenyl-6-oxabicyclo[3.1.0]hexane (71 mg, 0.38 mmol). IR (KBr) 1593, 1493, 1367, 1186, 1157 cm^{-1}; ^1H NMR ($CDCl_3$) 1.10 (s, 3H), 1.66–1.84 (m, 2H), 2.07–2.22 (m, 2H), 5.30 (t, 1H, *J* = 7.8 Hz), 6.94–7.00 (m, 2H), 7.11–7.29 (m, 5H), 7.57–7.62 (m, 2H); ^{13}C NMR ($CDCl_3$) 15.3, 25.5, 30.1, 68.1, 84.5, 116.0, 116.3, 126.6, 127.8, 128.2, 130.2, 130.3, 132.4, 132.5, 163.6, 167.0; EI-HRMS Calcd for $C_{12}H_{13}O_2$ (M^+–$C_6H_4O_2FS$): 189.0915, found: 189.0947.

***cis*-1-Methyl-5-phenyl-6-oxabicyclo[3.1.0]hex-2-yl 4-Fluorobenzenesulfonate (1f)**

1f (80 mg, 91%) was obtained from *cis*-epoxy alcohol, *cis*-2-hydroxy-1-methyl-5-phenyl-6-oxabicyclo[3.1.0]hexane (41 mg, 0.25 mmol). IR (KBr) 1593, 1495, 1371, 1186, 1157 cm^{-1}; ^1H NMR ($CDCl_3$) 1.03 (s, 3H), 1.47–1.61 (m, 1H), 1.81–1.91 (m, 1H), 2.08–2.13 (m, 2H), 4.87 (t, 1H, *J* = 8.2

Hz), 7.12–7.29 (m, 7H), 7.87–7.92 (m, 2H); ^{13}C NMR ($CDCl_3$) 11.9, 24.8, 28.7, 68.6, 68.9, 85.0, 116.4, 116.7, 126.3, 126.4, 128.2, 128.3, 130.5, 130.6, 132.9, 135.2, 164.0, 167.4; EI-HRMS Calcd for $C_{12}H_{13}O_2$ (M^+–$C_6H_4O_2FS$): 189.0915, found: 189.0969.

Enones from Epoxy Sulfonates

***Reaction with BF_3•Et_2O* or *p*–TsOH.** To a solution of epoxy sulfonate (0.15 mmol) in CH_2Cl_2 (0.15 mL) was added BF_3•Et_2O or *p*–TsOH (0.15 mmol) at 0°C under N_2, and the reaction mixture was stirred at 0°C for BF_3•Et_2O or at rt for *p*–TsOH (The reaction was checked by TLC). After having been diluted with CH_2Cl_2, sat. aq. $NaHCO_3$ was added to the mixture. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography using hexane–AcOEt as the eluent to give the products.

Reaction under neat condition. Epoxy sulfonate was left at rt. The reaction was checked by TLC. After having been diluted with CH_2Cl_2, sat. aq. $NaHCO_3$ was added to the mixture. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography using benzene–AcOEt (10/1) as the eluent to give the enones.

Treatment of 1b with 0.1 equiv. of *p*-TsOH: To a solution of **1b** (280 mg, 0.83 mmol) in CH_2Cl_2 (8.3 mL) was added *p*–TsOH (13 mg) at 0°C under N_2, and the reaction mixture was stirred at rt for 1 day (The reaction was checked by TLC). After having been diluted with CH_2Cl_2, sat. aq. $NaHCO_3$ was added to the mixture. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by SiO_2 column chromatography using benzene–AcOEt (20 :1) as the eluent to give **3** (22 mg, 23%), **4** (69 mg, 50%) and **9** (51 mg, 18%). Compound (**9**) is rather unstable and its structure was determined by IR, ^{1}H NMR and ^{13}C NMR spectra. **9**: IR (KBr) 3501, 1593, 1366, 1186, 910 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.78 (t, 3H, *J* = 6.6 Hz), 1.26–1.42 (m, 8H), 1.80–1.96 (m, 2H), 2.16–2.24 (m, 1H), 2.37–2.60 (m, 1H), 4.53 (t, 1H, *J* = 3.6 Hz), 4.94 (t, 1H, *J* = 2.4 Hz), 5.03 (t, 1H, *J* = 2.4 Hz), 7.26 (d, 2H, *J* = 8.1 Hz), 7.72 (d, 2H, *J* = 8.1 Hz); ^{13}C NMR ($CDCl_3$) 14.0, 21.6, 22.5, 22.8, 26.4, 27.0, 32.0, 36.9, 80.6, 86.8, 108.9, 127.8, 129.8, 133.9, 144.8, 151.8.

Reaction of 1g in the Presence of MeOH: To a solution of **1g** (170 mg, 0.494 mmol) in CH_2Cl_2 (0.5 mL) was added MeOH (0.2 mL, 4.94 mmol) and *p*–TsOH (85 mg, 1.0 equiv.) at 0°C under N_2, and the reaction mixture was stirred at rt for 12 h (The reaction was checked by TLC). After having been diluted with CH_2Cl_2, sat. aq. $NaHCO_3$ was added to the mixture. The organic layer was separated and the

aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by SiO_2 column chromatography using benzene–AcOEt (15 :1) as the eluent to give **10** (167 mg, 90%). **10:** Colorless crystals; mp 112.5–112.6 °C (*n*-hexane–AcOEt); IR (KBr) 3522, 1798, 1739, 1599, 912 cm^{-1}; ^1H NMR ($CDCl_3$) □ 0.98 (s, 3H), 1.72–2.02 (m, 4H), 2.44 (s, 3H), 2.71–2.80 (m, 1H), 3.99 (s, 3H), 4.97 (dd, 1H, *J* = 8.7, 3.0 Hz), 7.27–7.38 (m, 7H), 7.81–7.84 (m, 2H); ^{13}C NMR ($CDCl_3$) □ 17.4, 21.9, 25.9, 26.0, 50.5, 80.9, 87.1, 89.2, 127.5, 127.7, 127.8, 128.0, 128.1,129.7, 136.5, 144.7; EI-HRMS Calcd for $C_{13}H_{16}O_2$ (M^+–$C_7H_8O_3S$): 204.1150, found: 204.1165; *Anal.* Calcd for $C_{20}H_{24}O_5S$: C, 63.81; H, 6.43; S, 8.52. Found: C, 63.87; H, 6.44; S, 8.37.

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