Simple and Selective Oxidation of 6-Alkylazulene Derivatives

Masayuki Yokota,*[a] Rei Koyama,[a] Hiromi Hayashi,[a] Satoko Uchibori,[a] Tsuyoshi Tomiyama,[a] Hiroshi Miyazaki[b]

[a] Kotobuki Research Laboratories, Kotobuki Seiyaku Company, Ltd. 6351, Sakaki, Hanishina, Nagano J-389-06, Japan

[b] School of Medicine, Showa University, 1-5-8, Hatanodai, Shinagawa, Tokyo J-142, Japan

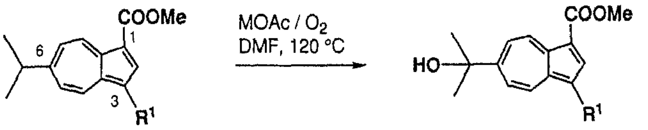
Received 2 May 1994; revised 14 July 1994

The simple and regioseletive oxidation of 6-alkylazulene derivatives with an electron-withdrawing substituent at the 1-position of the azulene ring is described. Oxidation with molecular oxygen proceeds smoothly in the presence of a base such as potassium acetate (KOAc) or tetrabutylammonium hydroxide (Bu_4NOH), and appears to proceed via enolization of the azulene derivatives. Oxidation of 6-isopropylazulene derivatives gave tertiary alcohols, which were easily converted to primary alcohols. Oxidation of 6-methylazulene derivatives provided azulene-6-carboxylate derivatives but dimethyl azulene-1,6-dicarboxylate, which had been obtained by the oxidation of methyl 6-methylazulene-1-carboxylate, was found to be reduced selectively at the 6-position by sodium borohydride ($NaBH_4$). In contrast, demethoxycarbonylation of dimethyl azulene-1,6-dicarboxylate with anhydrous phosphoric acid (100% PA) proceeded selectively at the 1-position to give methyl azulene-6-carboxylate. Those compounds obtained by the oxidation of 6-alkylazulenes are useful key intermediates for further modifications of the side chains at the 6-position of azulenes.

Azulene and its derivatives, an interesting class of compounds with a fused five-seven bicyclic aromatic ring system, have been extensively used in medicine.[1] We have recently reported that some azulene derivatives possessing an arylsulfonamide moiety, such as methyl 3-[4-(benzenesulfonylamino)butyl]-6-isopropylazulene-1-carboxylate (**1a**), exhibit potent and specific thromboxane A_2 (TXA_2) receptor antagonistic activity.[2] In this study, pharmacological evaluations of homologues of **1a** with substituted isopropyl groups at the 6-position in the azulene ring remain to be determined due to difficulties in their synthesis. Azulenes are typical examples of nonbenzenoid aromatic hydrocarbons, which are susceptible to a series of electrophilic substitution reactions at the 1- and/or 3-position.[3] However, few examples of direct oxidation of an azulene have been reported.[4] Since the azulene nucleus is sensitive to oxidizing reagents such as chromic acid, nitric acid and permanganate;[4a] selective conversion of an alkyl side chain on azulenes into other functional groups by oxidation is very difficult. It has been known for a long time that various azulenic hydrocarbons are gradually oxidized in air at room temperature. Some systematic investigations on autoxidation of naturally occurring guaiazulene have been carried out by Nozoe et al.[5] They have reported that treatment of azulenes with air in several kinds of solvents gives a number of carbonyl compounds, such as azulenoquinones, in low yields without forming any hydroxylated products.

We have investigated the oxidation of 6-isopropylazulenes **1** and 6-methylazulenes **9** with molecular oxygen for the modification of the alkyl side chain at the 6-position of the azulene ring. This paper describes simple and selective methods for the synthesis of azulene derivatives with a tertiary hydroxyl or carboxy group at the 6-position of the azulene ring, which are useful key intermediates for further modification of this side chain.

Table 1. Effect of Alkali Metal Acetates on the Oxidation of Methyl 3-[4-(Benzenesulfonylamino)butyl]-6-isopropylazulene-1-carboxylate **1a** in DMF (Method A)



1a: R^1 = $-(CH_2)_4-NHSO_2Ph$

2a

Entry	M	(mol%)	Reaction Time (h)	Yield of **2a** (%)[a]
1	Li	(20)	15	50
2	Na	(20)	15	48
3	K	(20)	12	53
4	K	(40)	12	54
5	K	(60)	12	66
6	K	(80)	12	62
7	K	(100)	12	61
8	Cs	(20)	16	50
9	None	(–)	24	no reaction

[a] Isolated yields by column chromatography.

Oxidation of methyl 3-[4-(benzenesulfonylamino)butyl]-6-isopropylazulene-1-carboxylate (**1a**) with oxygen in the presence of an alkali metal acetate in dimethylformamide (DMF) at 120°C (Method A) gave the tertiary alcohol **2a**. As shown in Table 1, various kinds of alkali metal acetates could be employed for this oxidation. Yields of the tertiary alcohol were affected by the amount of base used; 20 mol% of potassium acetate (KOAc) gave **2a** in 53% yield (Entry 3), and the yield was improved up to 66% when 60 mol % of the base was used (Entry 5). When the reaction was carried out without KOAc, the starting material **1a** was quantitatively recovered (Entry

Table 2. Oxidation of Methyl 3-[4-(Benzenesulfonylamino)butyl]-6-isopropylazulene-1-carboxylate **1a** with KOAc–O_2 in Different Solvents[a]

Entry	Solvent	Reaction Conditions	Yield of **2a** (%)[b]
10[c]	DMF	100°C, 24 h	46
11	DMF	120°C, 12 h	66
12[d]	DMF	120°C, 12 h	65
13	DMF	140°C, 12 h	45
14	HMPA	120°C, 12 h	61
15	DMSO	120°C, 12 h	65
16	toluene	reflux, 24 h	no reaction

[a] Reactions were carried out by using 60 mol % KOAc.
[b] Isolated yields by column chromatography.
[c] Recovery 28%.
[d] Reaction was carried out in the presence of one equivalent of triphenylphosphine.

Table 3. Oxidation of Isopropylazulene Derivatives with KOAc–O_2 in DMF at 120 °C[a]

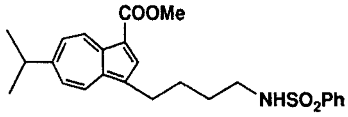
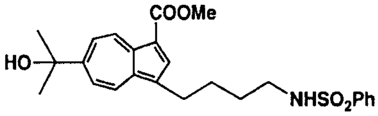
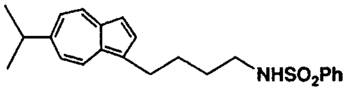
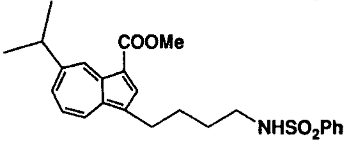
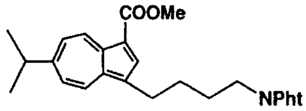
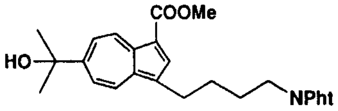
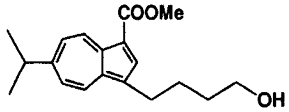
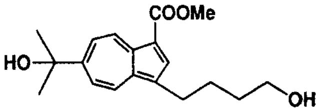
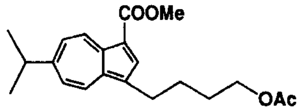
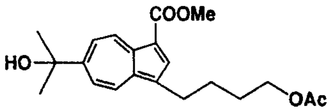
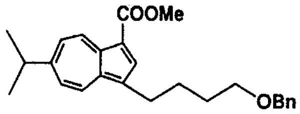
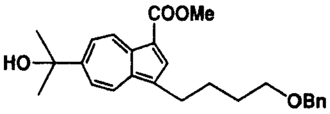
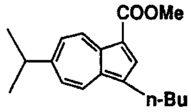
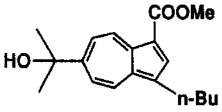
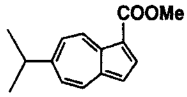
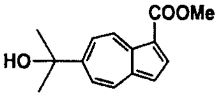
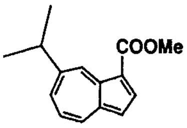
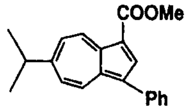
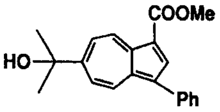
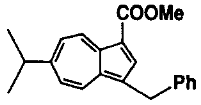
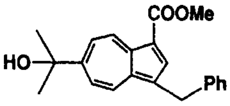
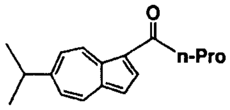
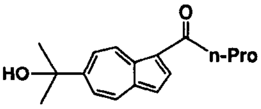
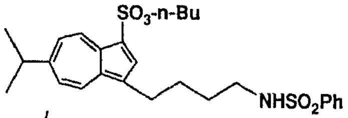
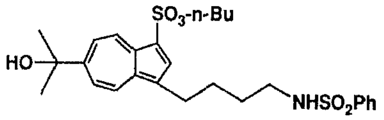
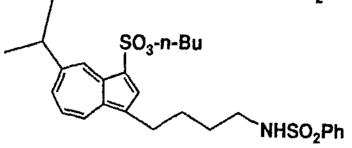
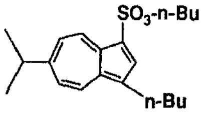
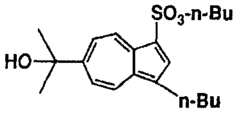
Starting Materials		Reaction Products		Yield of **2** (%)[b]
	(1a)		(2a)	66
	(1b)	——	(2b)	no reaction
	(1c)	——	(2c)	no reaction
	(1d)		(2d)	72
	(1e)		(2e)	56
	(1f)		(2f)	61
	(1g)		(2g)	60
	(1h)		(2h)	54
	(1i)		(2i)	68
	(1j)	——	(2j)	no reaction
	(1k)		(2k)	63
	(1l)		(2l)	62
	(1m)		(2m)	75

Table 3. Continued

Starting Materials		Reaction Products		Yield of **2** (%)[b]
	(**1n**)		(**2n**)	0[c]
	(**1o**)	——	(**2o**)	0[c]
	(**1p**)		(**2p**)	0[c]

[a] Reactions were carried out by using 60 mol % of KOAc at 120 °C for 12 h.
[b] Isolated yields by column chromatography.
[c] Products were potassium sulfonates of the starting materials.

9). The oxidation was also affected markedly by the solvents used. As shown in Table 2, reaction of **1a** at 120 °C for 12 h in the presence of 60 mol % of KOAc afforded **2a** in good yields when aprotic solvents such as DMF, hexamethylphosphoramide (HMPA) and dimethyl sulfoxide (DMSO) were used (Entries 11, 14 and 15); no tertiary alcohol **2a** was formed when toluene was used as solvent (Entry 16). The yield of **2a** was also found to be dependent on the reaction temperature. The reaction took place slowly at 100 °C (Entry 10) and became more efficient at 120 °C (Entry 11), but the yield decreased above 140 °C due to decomposition of the oxygenated products (Entry 13). Oxidation in the presence of both KOAc and a reducing reagent such as triphenylphosphine did not change the yield of **2a** (Entry 12).[6] It should be noted that the oxidation proceeded regioselectively; the reaction afforded exclusively **2a** without forming any other hydroxylated products, which had been observed with an α-methylene group in a side chain at the 3-position or on the azulene nucleus.

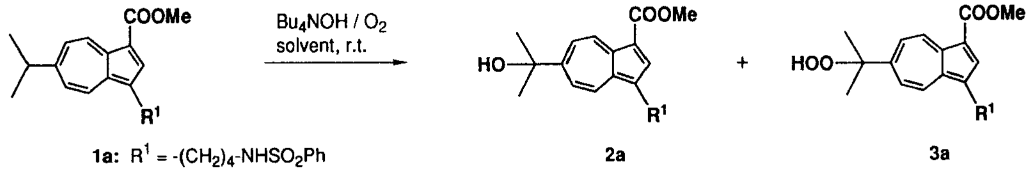
On the basis of the above experiments, the following standard conditions were adopted: a molar ratio of azulene to KOAc of to 1:0.6, DMF as the solvent, and oxidation at 120 °C for 12 h under an oxygen atmosphere. A series of isopropylazulenes[7] was studied under the standard conditions and the results are summarized in Table 3. The 6-isopropylazulene derivatives with a carboxylic acid ester or a carbonyl moiety at the 1-position of the azulene ring were successfully oxidized to give the corresponding tertiary alcohols in 54–75 % yields. A variety of functional groups in the side chain at the 3-position of the azulene ring remained intact upon the oxidation reaction. Both 6-isopropylazulene (**1b**), which has no carboxylic acid ester, and 7-isopropylazulene derivatives, **1c** and **1j**, were not found to be reactive. This method was applied to 6- and 7-isopropylazulene derivatives containing a sulfonic acid ester moiety, such as **1n**, **1o** and **1p**.[8] In these cases, there was no production of the expected tertiary alcohols due to the preferential formation of their undesired potassium sulfonates, which seems to be a general phenomenon under these conditions. In fact, it has been reported in the literature[9] that alkylation of KOAc with alkyl sulfonate takes place in DMF at high temperature.

In order to overcome the disadvantages observed under method A, tetrabutylammonium hydroxide (Bu_4NOH) was used as a base for oxidation of 6-isopropylazulene derivatives **1** with oxygen (Method B). The reaction proceeded smoothly at room temperature in either DMF or tetrahydrofuran (THF) to give the tertiary alcohols **2**, indicating that this oxidation system behaves similarly to the KOAc–oxygen system.

The effects of solvents were evaluated during the oxidation of **1a** at room temperature and the results are summarized in Table 4. The best yield was obtained using DMF as the solvent (Entry 19). No identifiable product was obtained when the oxidation was carried out with 10% Bu_4NOH in methanol solution (Entry 22), and a similar result was obtained with nonpolar solvents such as toluene (Entry 24). The use of THF required a longer reaction time than that of DMF (Entry 23). In addition, reaction in THF produced a considerable amount of the hydroperoxide **3a** as byproduct. As shown in Scheme 1, the hydroperoxide can be easily converted to the corresponding tertiary alcohol by treatment using triphenylphosphine.[6] For example, treatment of the hydroperoxide **3a** with one equivalent of triphenylphosphine in THF at room temperature for 5 min gave **2a** in quantitative yield.

It was also found that the rate of reaction was affected by the concentration of Bu_4NOH in methanol solution; the rate of oxidation was much faster with a 26% Bu_4NOH solution than with a 10% solution (Entries 19 and 21). However, the higher concentration of Bu_4NOH in methanol tended to decrease the yield of the tertiary alcohol. Oxidation with Bu_4NOH in DMF alone for 1 h at room temperature gave a complex reaction mixture but no expected tertiary alcohol. The rate of oxidation

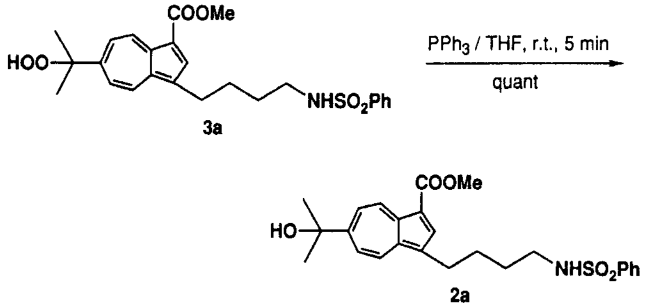
Table 4. Oxidation of Methyl 3-[4-(Benzenesulfonylamino)butyl]-6-isopropylazulene-1-carboxylate **1a** with Bu_4NOH^a–O_2 in Different Solvents at Room Temperature (Method B)



1a: R^1 = $-(CH_2)_4-NHSO_2Ph$ **2a** **3a**

Entry	Solvent	Molar Ratio of Bu_4NOH to **1a**	Reaction Time (h)	Yield of Product (%)[b]	
				tert-Alcohol **2a**	Hydroperoxide **3a**
17	DMF	None	72	no reaction	
18[c]	DMF	2	72	40	trace
19	DMF	4	40	66	trace
20[d]	DMF	4	40	62	0
21[e]	DMF	4	20	50	trace
22	MeOH	4	72	no reaction	
23[f]	THF	4	72	24	15
24	toluene	4	72	no reaction	

[a] 10% Bu_4NOH in MeOH solution was used.
[b] Isolated yields by column chromatography.
[c] Recovery 35%.
[d] Reaction was carried out in the presence of one equivalent of triphenylphosphine.
[e] 26% Bu_4NOH in MeOH solution was used.
[f] Recovery 52%.



Scheme 1

is sensitive to the concentration of Bu_4NOH and the best result was obtained with a 10% solution.

Based on these experiments, DMF or THF were selected as reaction solvents for the study of a variety of 6-isopropylazulenes, and the results are summarized in Table 5. The advantage of method B was apparent from the production of **2n** and **2p**, which could not be obtained by method A. Oxidation of the butyl sulfonates **1n** and **1p** proceeded in higher yields in THF than in DMF. The butyl sulfonates were more reactive than their methyl carboxylate derivatives, and the resulting hydroperoxides were rapidly converted into the tertiary alcohol. Thus no hydroperoxide could be isolated from the reaction mixture either with reactions in DMF or in THF solution. However, similarly to method A, the oxidation of **1b**, **1c**, **1j** and **1o** did not proceed under the same reaction conditions. Method B also appeared to be suitable for large-scale production.

A possible reaction pathway for the oxidation of 6-isopropylazulenes is described in Scheme 2. In methods A and B both oxygen and a base were essential for the oxidation of 6-isopropyl-**1** to **2** but the oxidation of **1b**, which has no carboxylic acid ester at the 1-position of the azulene ring, resulted in quantitative recovery of the starting materials. These findings suggest that the oxidation was initiated by the formation of an enolate of azulene. The high regioselectivity in this oxidation strongly supports the generation of enolate **4** from the starting material **1** by the base in the reaction mixture. Enolate **4** could then react with molecular oxygen to yield the peroxy anion **6**, which could then be transformed into the tertiary alcohol **2**.

In order to confirm the formation of enolate in the KOAc–oxygen system (Method A), a deuterium exchange reaction was performed. Oxidation of **1i** in deuterated DMF was carried out using 60 mol % of KOAc at 120 °C under an oxygen atmosphere. After 1, 3 and 6 h respectively, the reaction mixture was quenched with deuterated water, but it was found that no deuterium was incorporated in the recovered starting material. These results indicate that the oxidation of enolate is very fast in comparison with the slow enolization of starting material with base. The reaction of **1i** was monitored by ^1H NMR spectroscopy in deuterated DMF. When a solution of **1i** in deuterated DMF was heated with 60 mol % of KOAc at 120 °C in the absence of oxygen, a small singlet immediately appeared at δ 1.89 ppm which disappeared when the mixture was cooled to room temperature. This signal could be assigned to the methyl protons of the enolate form **4i** (Scheme 2). However, no change was observed by ^1H NMR spectroscopy in the reaction of 7-isopropylazulene **1j**, regioisomer of **1i**, in deuterated DMF with 60 mol % KOAc either in the absence or in the presence of oxygen, even when the mixture was heated

Table 5. Oxidation of Isopropylazulene Derivatives with Bu_4NOH^a–O_2 at Room Temperature

				Yield of Product (%)[b]	
1	Solvent	Molar Ratio of Bu_4NOH to 1	Reaction Time (h)	*tert*-Alcohol 2	Hydroperoxide 3
1a	DMF	4	40	**2a** (66)	**3a** (trace)
	THF[c]	4	72	**2a** (24)	**3a** (15)
1b	DMF	4	72	no reaction	
	THF	4	72	no reaction	
1c	DMF	4	72	no reaction	
	THF	4	72	no reaction	
1h	DMF	2	24	**2h** (66)	**3h** (trace)
	THF[d]	2	72	**2h** (31)	**3h** (18)
1i	DMF	2	18	**2i** (68)	**3i** (0)
	THF[e]	2	72	**2i** (42)	**3i** (6)
1j	DMF	2	72	no reaction	
	THF	2	72	no reaction	
1m	DMF	2	8	**2m** (59)	**3m** (0)
	THF	2	20	**2m** (60)	**3m** (0)
1n	DMF	4	10	**2n** (59)	**3n** (0)
	THF	4	24	**2n** (63)	**3n** (0)
1o	DMF	4	72	no reaction	
	THF	4	72	no reaction	
1p	DMF	2	2	**2p** (60)	**3p** (0)
	THF	2	20	**2p** (65)	**3p** (0)

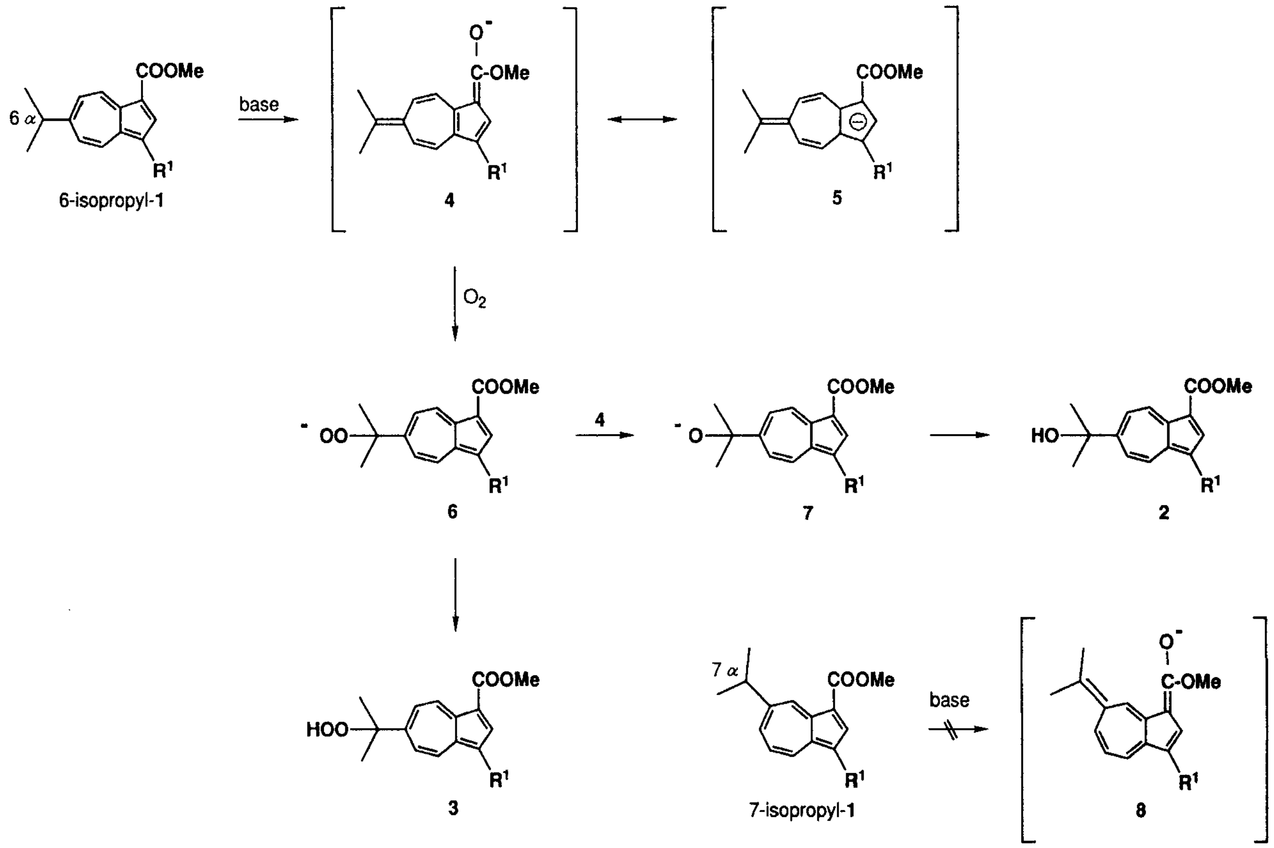
[a] 10% Bu_4NOH in MeOH solution was used.
[b] Isolated yields by column chromatography.
[c] Recovery 52%.
[d] Recovery 43%.
[e] Recovery 21%.

at 120 °C for 12 h. This indicates that enolate formation did not occur during the reaction of 7-isopropylazulenes.

Molecular orbital calculations were carried out using MM2 and MOPAC programs on two samples of the methyl 6- and 7-isopropylazulene-1-carboxylates, (**1i**) and (**1j**), and also on the corresponding enolate forms **4i** and **8j**. The energies of heat of formation of the two enolates were found to be − 53.0 kcal/mol for **4i** and − 43.2 kcal/mol for **8j**, indicating that **4i** is more stable than **8j**. The difference in energy between the two is probably accounted for by the enolates' resonance structures. Hafner and Scholz reported that 4- and 6-methylazulene reacted with sodium *N*-methylanilide to produce the sodium 4- and 6-methyleneazulenates, which were carbonylated with carbon dioxide to give 4- and 6-azulylacetic acid, respectively.[10] However, McDonald reported that reaction of 5-methylazulene with lithium *N*,*N*-dicyclohexylamide followed by treatment with carbon dioxide afforded the azulene nuclear carbonylation products, such as 5- or 7-methyl-1-azulenecarboxylic acid, without forming 5-azulylacetic acid which it is expected would be formed from lithium 5-methyleneazulenate.[11] These findings indicate that the methyl group of 5-methyleneazulene is not activated toward proton abstraction as it is in the 4- and 6-methylazulenes, because the 5-methyleneazulenate anion is unstable owing to a lack of cyclopentadienyl anion-type resonance contribution. The enolate **4** of 6-isopropylazulene seems to be stabilized by the contribution of resonance form **5**. The failure to form the tertiary alcohols from 7-isopropylazulenes is probably due to the preclusion of delocalization of charge in the enolate **8**, which would be formed by deprotonation of the 7α-methine of the isopropyl group. The regioselectivity which occurs at the 3- and 6-positions during oxidation in methyl 3-alkyl-6-isopropylazulene-1-carboxylates can also be explained by the above mechanism; the formation of enolates with a 6π-electronic system is precluded by the deprotonation from the 3α-methylene group of 3-alkyl-6-isopropylazulenes.

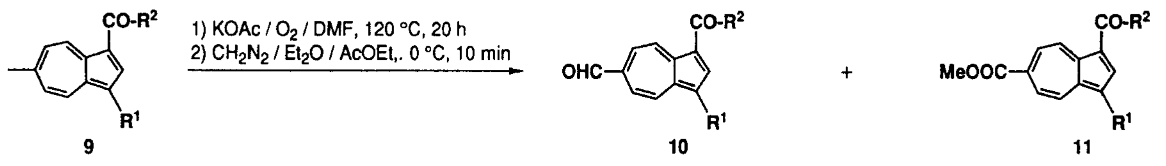
The hydroperoxide **3**, a key intermediate in the oxidation of the methyl carboxylate in method B, was isolated from the crude reaction product by silica gel column chromatography (Entry 23 in Table 4). Oxidation by method A did not give the expected hydroperoxide as a product, but its presence was confirmed by formation of triphenylphosphine oxide, since oxidation of **1a** with 60 mol % of KOAc and one equivalent of triphenylphosphine in DMF at 120 °C gave 65% of **2a** and 96% of triphenylphosphine oxide (Entry 12 in Table 2). In addition, the formation of the hydroperoxide **3a** could be detected by thin-layer chromatography (TLC) in the early stages of the oxidation.

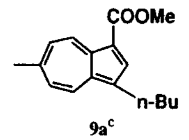
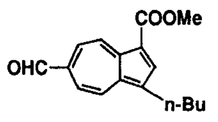
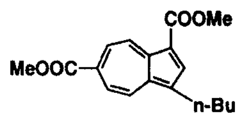
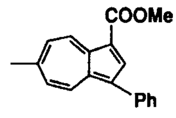
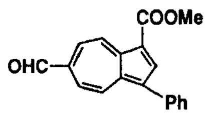
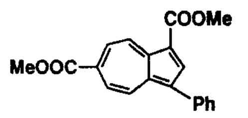
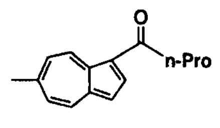
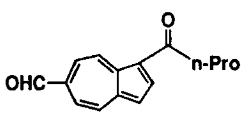
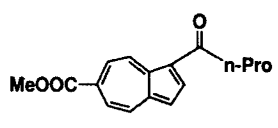
The methods for simple and regioselective oxidation of 6-isopropylazulenes were also applicable to the oxidation of 6-methylazulenes **9**.[7] Method A was found to be more suitable for the oxidation of 6-methylazulenes than method B (Table 6). Oxidation of methyl 3-butyl-6-methylazulene-1-carboxylate (**9a**) using KOAc and oxygen in DMF followed by esterification with diazomethane gave the aldehyde **10a** and the diester **11a**. As shown in Scheme 3, it is postulated that the oxidation of 6-methylazulenes



Scheme 2. Possible mechanism for oxidation of methyl 6-isopropylazulene-1-carboxylates

Table 6. Oxidation of 6-Methylazulene Derivatives with KOAc–O_2 in DMF at 120 °C (Method A)[a]



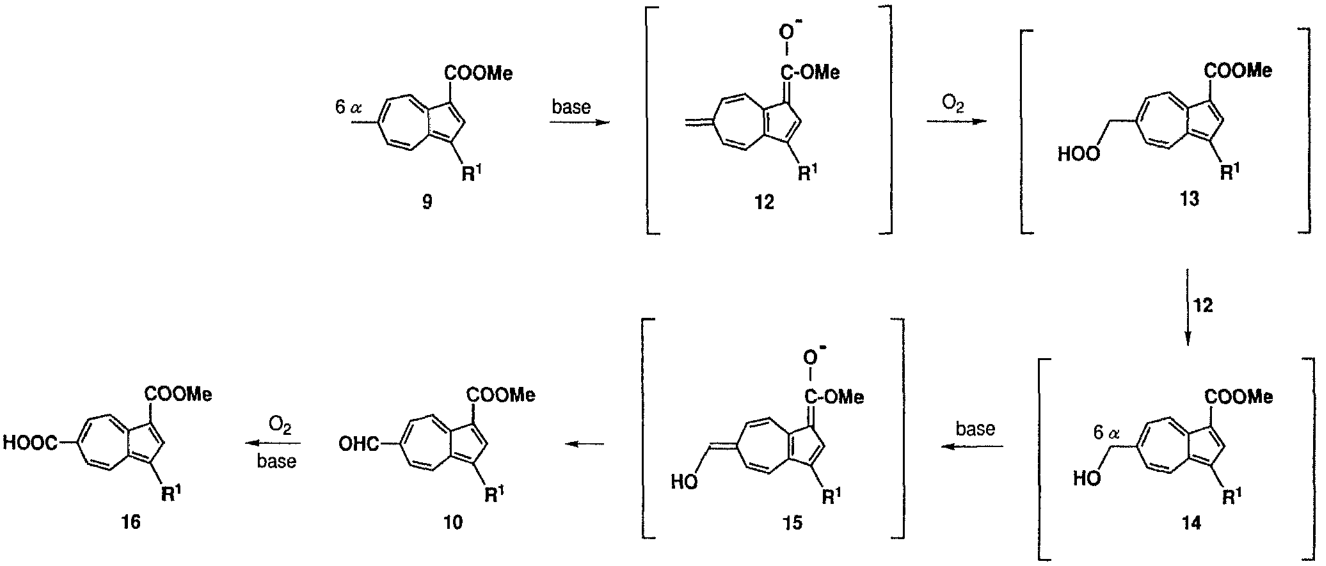
Starting Materials	Reaction Products (Yield, %)[b]	
 9a[c]	 10a (4)	 11a (39)
 9b	 10b (trace)	 11b (33)
 9c	 10c (0)	 11c (40)

---

[a] Reactions were carried out by using 60 mol % of KOAc at 120 °C for 20 h.

[b] Isolated yields by column chromatography.

[c] Oxidation of **7a** with $Bu_4NOH–O_2$ in DMF at room temperature (Method B) gave only the diester **11a** in 4% yield.



Scheme 3. Possible mechanism for oxidation of methyl 6-methylazulene-1-carboxylates

9 proceeds through the hydroperoxide **13** to produce the corresponding primary alcohol **14**, as previously described in the case of the oxidation of 6-isopropylazulenes. The resulting primary alcohol was then easily converted to the carboxylic acid **16**. The expected primary alcohol could not be isolated from the crude product of this oxidation, although the presence of the hydroperoxide precursor was confirmed by formation of triphenylphosphine oxide in the reaction.

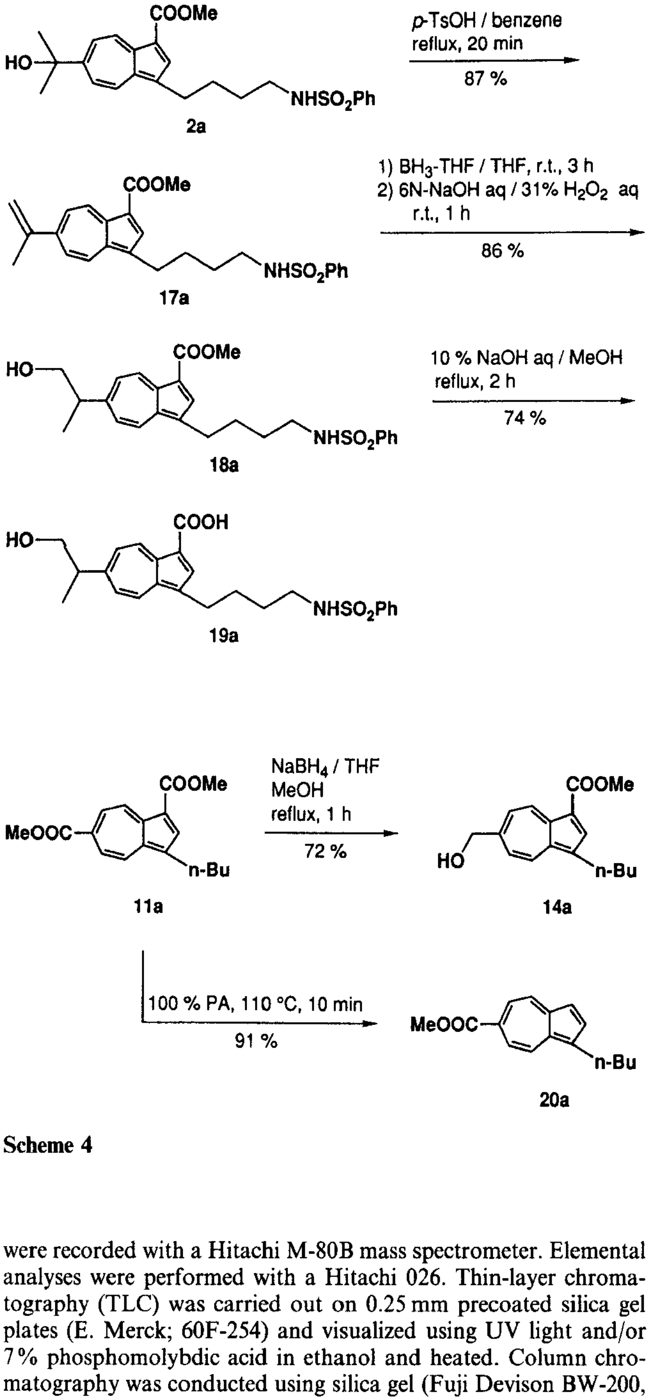
Treatment of primary alcohol **14a**, which was prepared independently by reduction of aldehyde **10a** using sodium borohydride ($NaBH_4$), with 60 mol % of KOAc in DMF at 120°C for 15 min in the absence of oxygen, showed that **14a** was completely consumed and afforded only the aldehyde **10a** in 89 % yield. This result suggests that the deprotonation at 6α-position of primary alcohol with KOAc proceeds rapidly to form the aldehyde. Aldehyde **10a** was converted to the carboxylic acid **16a** in 79 % yield by treatment with 60 mol % of KOAc in DMF at 120°C under an oxygen atmosphere, and the reaction was complete in approximately 20 h. Therefore, oxidation of 6-methylazulenes requires longer reaction time than that of 6-isopropylazulenes due to the slow rate of oxidation of the aldehydes to carboxylic acids. The oxidations of a variety of 6-methylazulenes are shown in Table 6.

In order to demonstrate the synthetic utility of the tertiary alcohol **2a**, obtained by the oxidation of 6-isopropylazulene derivative **1a**, transformation to a primary alcohol **18a** was undertaken as shown in Scheme 4. The tertiary alcohol **2a** underwent dehydration by treatment with a catalytic amount of *p*-toluenesulfonic acid in benzene to give the olefin **17a** in 84% yield which was subjected to hydroboration using borane–THF complex. Oxidative workup gave the primary alcohol **18a** in 93 % yield. The corresponding carboxylic acid **19a** was shown to exhibit potent and specific TXA_2 receptor antagonistic activity.[12]

Next, we examined the reactivity of dimethyl 3-butylazulene-1,6-dicarboxylate (**11a**), obtainable by oxidation of the 6-methylazulene derivative **9a**. Hansen reported the selective reduction of dimethyl 4,6,8-trimethylazulene-1,2-dicarboxylate with diisobutylaluminium hydride (DIBAH),[13] however attempts to reduce **11a** with DIBAH in THF or in diethyl either gave a complex reaction mixture. In both cases, only a small amount of methyl 3-butyl-6-hydroxymethylazulene-1-carboxylate (**14a**) was isolated. Use of $NaBH_4$ instead of DIBAH as a reducing reagent gave selective reduction to give **14a** in 72% yield as shown in Scheme 4.[14] Further studies on the difference of reactivity in reduction of carboxylic acid esters at the 1- and 6-positions of the azulene ring are now in progress. Protonation was found to occur selectively at the 1-position of the azulene ring; demethoxycarbonylation of **11a** proceeded smoothly with anhydrous phosphoric acid (100 % PA) to give methyl 1-butylazulene-6-carboxylate (**20a**) in 91 % yield.[7]

In conclusion, the developed oxidation methods are useful for the synthesis of tertiary alcohols of 6-isopropylazulene and 6-carboxylate derivatives which have electron-withdrawing substituents such as carboxylic acid esters, carbonyl and sulfonic acid esters at the 1-position of the azulene ring. The oxidation occurs regioselectively on an alkyl side chain at the 6-position of the azulene ring. The resulting compounds can be used as key intermediates for further modifications of side chains at the 6-position. Further studies are now in progress on transformation of the tertiary alcohols and carboxylic acid esters to a variety of functionalized azulene derivatives, which might have considerable pharmacological interest.

Melting points were recorded on a Yamato MP-21 without additional correction. ^1H NMR spectra were recorded on a Hitachi R-90 (90 MHz) FT-NMR spectrometer. Chemical shifts were expressed in parts per million relative to internal tetramethylsilane ($\delta = 0$). Coupling constants (J values) were expressed in Hz. IR spectra were obtained on a Hitachi-270-30 spectrophotometer. Mass spectra



Scheme 4

were recorded with a Hitachi M-80B mass spectrometer. Elemental analyses were performed with a Hitachi 026. Thin-layer chromatography (TLC) was carried out on 0.25 mm precoated silica gel plates (E. Merck; 60F-254) and visualized using UV light and/or 7% phosphomolybdic acid in ethanol and heated. Column chromatography was conducted using silica gel (Fuji Devison BW-200, 150–325 mesh). Reaction solvents were distilled under an argon atmosphere from various drying agents; benzene and toluene from CaH_2, MeOH from sodium methoxide, THF and ether from sodium benzophenone ketyl. DMF, DMSO and HMPA were distilled under reduced pressure from CaH_2. All new compounds gave satisfactory microanalyses: C $\pm$ 0.37, H $\pm$ 0.40 and N $\pm$ 0.36. Compounds **3a**, **h** and **i** were not analysed.

The conformation study on the representative compounds **1i** and **1j** was performed using MM2 and MOPAC AM3 programs to minimise geometries and conformation with the aid of a CAChe molecular modeling system (V6.10). The MO calculation was carried out using the PM30 (EF) method.

Methyl 3-[4-(Benzenesulfonylamino)butyl]-6-(1-hydroxyethyl-1-methyl)azulene-1-carboxylate (2a); Typical Procedure (Method A): Potassium acetate (0.017 g, 0.17 mmol) was added to a solution of **1a** (0.127 g, 0.29 mmol) in DMF (7.0 mL) and subjected to oxidation by bubbling oxygen gas through the solution from the bottom of the flask for 12 h at 120 °C. The reaction mixture was poured into ice-water, extracted with EtOAc (30 mL), washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by silica gel column chromatography (EtOAc/hexane, 1:1) to give **2a** (0.087 g, 66% yield) as violet crystals; mp 142–143 °C.

^{1}H NMR (DMSO-d_6): $\delta = 1.25$–1.85 (4 H, m, $CH_2\underline{CH}_2\underline{CH}_2CH_2NHSO_2$), 1.56 (6 H, s, $C(CH_3)_2$), 2.60–3.03 (4 H, 2 t, $\underline{CH}_2CH_2CH_2\underline{CH}_2NHSO_2$), 3.28 (1 H, bs, OH), 3.92 (3 H, s, $COOCH_3$), 5.46 (1 H, s, NH), 7.38–7.95 (7 H, m, ArH, C5-H and C7-H), 8.00 (1 H, s, C2-H), 8.48 (1 H, d, J = 11 Hz, C4-H), 9.39 (1 H, d, J = 11 Hz, C8-H).

IR (KBr): ν = 3394, 3202, 2926, 1656, 1582 cm^{-1}.

MS: m/z = 455 (M$^+$), 424, 282, 257 (100%), 199, 165, 141, 110, 77.

Methyl 6-(1-Hydroxyethyl-1-methyl)-3-(4-phthalimidebutyl)azulene-1-carboxylate (**2d**): violet crystals; mp 95–96 °C.

^{1}H NMR ($CDCl_3$): $\delta = 1.54$–1.89 (4 H, m, $CH_2\underline{CH}_2\underline{CH}_2CH_2NPht$), 1.71 (6 H, s, $C(CH_3)_2$), 2.50 (1 H, bs, OH), 3.01 (2 H, bt, $\underline{CH}_2CH_2CH_2CH_2NPht$), 3.72 (2 H, bt, $CH_2CH_2CH_2\underline{CH}_2NPht$), 3.91 (3 H, s, $COOCH_3$), 7.56–7.89 (6 H, m, ArH, C5-H and C7-H), 8.11 (1 H, s, C2-H), 8.32 (1 H, d, J = 11 Hz, C4-H), 9.45 (1 H, d, J = 11 Hz, C8-H).

IR (KBr): ν = 3466, 2926, 1704, 1581 cm^{-1}.

MS: m/z = 445 (M$^+$), 414, 298, 257 (100%), 225, 199, 160, 130, 104, 77.

Methyl 3-(4-Hydroxybutyl)-6-(1-hydroxyethyl-1-methyl)azulene-1-carboxylate (**2e**): violet oil.

^{1}H NMR ($CDCl_3$): δ = 1.40–2.15 (4 H, m, $CH_2\underline{CH}_2\underline{CH}_2CH_2OH$), 1.69 (6 H, s, $C(CH_3)_2$), 2.50 (2 H, bs, OH), 3.01 (2 H, t, J = 7 Hz, $\underline{CH}_2CH_2CH_2CH_2OH$), 3.66 (3 H, t, J = 6 Hz, $CH_2CH_2CH_2\underline{CH}_2OH$), 3.91 (3 H, s, $COOCH_3$), 7.60–7.82 (2 H, dm, C5-H and C7-H), 8.14 (1 H, s, C2-H), 8.33 (1 H, d, J = 11 Hz. C4-H), 9.47 (1 H, d, J = 11 Hz, C8-H).

IR (neat): ν = 3432, 2926, 1668, 1599 cm^{-1}.

MS: m/z = 316 (M$^+$), 285, 257 (100%), 225, 199, 178, 155, 128, 85.

Methyl 3-(4-Acetoxybutyl)-6-(1-hydroxyethyl-1-methyl)azulene-1-carboxylate (**2f**): violet crystals; mp 83–84 °C.

^{1}H NMR ($CDCl_3$): $\delta = 1.58$–1.89 (4 H, m, $CH_2\underline{CH}_2\underline{CH}_2CH_2OAc$), 1.70 (6 H, s, $C(CH_3)_2$), 2.03 (3 H, s, $OCOCH_3$), 2.41 (1 H, bs, OH), 2.99 (2 H, t, J = 7 Hz, $\underline{CH}_2CH_2CH_2CH_2OAc$), 3.91 (3 H, s, $COOCH_3$), 4.08 (2 H, t, J = 6 Hz, $CH_2CH_2CH_2\underline{CH}_2OAc$), 7.61–7.81 (2 H, dm, C-5 and C-7), 8.14 (1 H, s, C2-H), 8.33 (1 H, d, J = 11 Hz, C4-H), 9.47 (1 H, d, J = 11 Hz, C8-H).

IR (KBr): ν = 3424, 3010, 1725, 1677, 1584 cm^{-1}.

MS: m/z = 358 (M$^+$), 327, 298, 257 (100%), 207, 183, 155, 59.

Methyl 3-(4-Benzyloxybutyl)-6-(1-hydroxyethyl-1-methyl)azulene-1-carboxylate (**2g**): violet oil.

^{1}H NMR ($CDCl_3$): δ = 1.50–2.85 (4 H, m, $CH_2\underline{CH}_2\underline{CH}_2CH_2OBz$), 1.69 (6 H, s, $C(CH_3)_2$), 2.31 (1 H, bs, OH), 3.00 (2 H, t, J = 7 Hz, $\underline{CH}_2CH_2CH_2CH_2OBz$), 3.50 (2 H, t, J = 6 Hz, $CH_2CH_2CH_2\underline{CH}_2OBz$), 3.93 (3 H, s, $COOCH_3$), 4.49 (2 H, s, CH_2Ar), 7.31 (5 H, s, ArH), 7.59–7.81 (2 H, dm, C5-H and C7-H), 8.16 (1 H, s, C2-H), 8.33 (1 H, d, J = 11 Hz, C4-H), 9.48 (1 H, d, J = 11 Hz, C8-H).

IR (neat): ν = 3424, 2926, 1674, 1584 cm^{-1}.

MS: m/z = 406 (M$^+$), 375, 315, 283, 257, 225, 199, 155, 128, 91 (100%), 59.

Methyl 3-Butyl-6-(1-hydroxyethyl-1-methyl)azulene-1-carboxylate (**2h**): violet oil.

^{1}H NMR ($CDCl_3$): δ = 0.95 (3 H, t, J = 6 Hz, $CH_2CH_2CH_2\underline{CH}_3$), 1.04–2.25 (4 H, m, $CH_2\underline{CH}_2\underline{CH}_2CH_3$), 1.71 (6 H, s, $C(CH_3)_2$), 2.99 (2 H, t, J = 7 Hz, $\underline{CH}_2CH_2CH_2CH_3$), 3.93 (3 H, s, $COOCH_3$), 7.63–7.78 (2 H, dm, C5-H and C7-H), 8.16 (1 H, s, C2-H), 8.36 (1 H, d, J = 11 Hz, C4-H), 9.48 (1 H, d, J = 11 Hz, C8-H).

IR (neat): ν = 3424, 2920, 1668, 1581 cm^{-1}.

MS: m/z = 300 (M$^+$), 257 (100%), 225, 199, 155, 115, 59.

Methyl 6-(1-Hydroxyethyl-1-methyl)azulene-1-carboxylate **(2i)**: reddish violet crystals; mp 63–65 °C.

^{1}H NMR ($\mathrm{CDCl_3}$): $\delta = 1.67$ (6 H, s, $\mathrm{C(CH_3)_2}$), 2.48 (1 H, bs, OH), 3.91 (3 H, s, $\mathrm{COOCH_3}$), 7.14 (1 H, d, $J = 11$ Hz, C3-H), 7.62–7.87 (2 H, dm, C5-H and C7-H), 8.27 (1 H, d, $J = 5$ Hz, C2-H), 8.36 (1 H, d, $J = 11$ Hz, C4-H), 9.49 (1 H, d, $J = 11$ Hz, C8-H).

IR (KBr): $\nu = 3424, 2968, 1668, 1581\ \mathrm{cm^{-1}}$.

MS: $m/z = 244$ ($\mathrm{M^+}$, 100 %), 213, 187, 155, 127, 99, 59.

Methyl 6-(1-Hydroxyethyl-1-methyl)-3-phenylazulene-1-carboxylate **(2k)**: violet crystals; mp 135–137 °C.

^{1}H NMR ($\mathrm{CDCl_3}$): $\delta = 1.69$ (s, 6 H, $\mathrm{C(CH_3)_2}$), 2.35 (1 H, bs, OH), 3.94 (3 H, s, $\mathrm{COOCH_3}$), 7.31–7.89 (7 H, ArH, C5-H and C7-H), 8.36 (1 H, s, C2-H), 8.43 (1 H, d, $J = 11$ Hz, C4-H), 9.57 (1 H, d, $J = 11$ Hz, C8-H).

IR (KBr): $\nu = 3418, 2956, 1659, 1578, 1170\ \mathrm{cm^{-1}}$.

MS: $m/z = 320$ ($\mathrm{M^+}$, 100 %), 289, 231, 201, 165, 125, 100.

Methyl 3-Benzyl-6-(1-hydroxyethyl-1-methyl)azulene-1-carboxylate **(2l)**: violet crystals; mp 153–154 °C.

^{1}H NMR ($\mathrm{CDCl_3}$): $\delta = 1.69$ (s, 6 H, $\mathrm{C(CH_3)_2}$), 2.02 (1 H, bs, OH), 3.91 (3 H, s, $\mathrm{COOCH_3}$), 4.36 (2 H, s, $\mathrm{CH_2Ar}$), 7.21 (5 H, s, ArH), 7.54–7.83 (2 H, dm, C5-H and C7-H), 8.11 (1 H, s, C2-H), 8.37 (1 H, d, $J = 11$ Hz, C4-H), 9.53 (1 H, d, $J = 11$ Hz, C8-H).

IR (KBr): $\nu = 3490, 1662, 1578, 1443, 1407, 1197, 1059\ \mathrm{cm^{-1}}$.

MS: $m/z = 334$ ($\mathrm{M^+}$), 303, 275, 241, 215, 189, 165, 139, 115, 91 (100 %).

1-(4-Butyryl)-6-(1-hydroxyethyl-1-methyl)azulene-1-carboxylate **(2m)**: red oil.

^{1}H NMR ($\mathrm{CDCl_3}$): $\delta = 1.05$ (3 H, t, $J = 7$ Hz, $\mathrm{COCH_2CH_2\underline{CH}_3}$), 1.70 (6 H, s, $\mathrm{C(CH_3)_2}$), 1.54–2.05 (2 H, m, $\mathrm{COCH_2\underline{CH}_2CH_3}$), 2.70 (1 H, bs, OH), 3.04 (2 H, t, $J = 7$ Hz, $\mathrm{CO\underline{CH}_2CH_2CH_3}$), 7.17 (1 H, d, $J = 4$ Hz, C3-H), 7.70–7.93 (2 H, dm, C5-H and C7-H), 8.21 (1 H, d, $J = 4$ Hz, C2-H), 8.39 (1 H, d, $J = 11$ Hz, C4-H), 9.78 (1 H, d, $J = 11$ Hz, C8-H).

IR (KBr): $\nu = 3394, 2956, 1617, 1581\ \mathrm{cm^{-1}}$.

MS: $m/z = 256$ ($\mathrm{M^+}$), 213 (100 %), 197, 155, 127, 101, 75.

Butyl 3-[4-(Benzenesulfonyl)amino]butyl-6-(1-hydroxyethyl-1-methyl)azulene-1-sulfonate (2n); Typical Procedure (Method B):

$\mathrm{Bu_4NOH}$ (400.0 mL, 154.8 mmol, 10 % solution in MeOH) was added to a solution of **1n** (20.0 g, 38.7 mmol) in THF (800.0 mL) and subjected to oxidation by bubbling oxygen gas through the solution from the bottom of the flask at r.t. for 24 h. The reaction mixture was then quenched with sat. aq $\mathrm{NH_4Cl}$ (400 mL), extracted with EtOAc (400 mL), and the organic phase was washed with water (400 mL) and brine (400 mL), dried ($\mathrm{MgSO_4}$), and concentrated. The crude product was purified by silica gel column chromatography (EtOAc/hexane, 1 : 2) to give **2n** (13.1 g, 63 % yield) as violet crystals; mp 89–90 °C.

^{1}H NMR ($\mathrm{CDCl_3}$): $\delta = 0.79$ (3 H, t, $J = 6$ Hz, $\mathrm{SO_3CH_2CH_2CH_2\underline{CH}_3}$), 1.73 (6 H, s, $\mathrm{C(CH_3)_2}$), 1.10–2.07 (8 H, m, $\mathrm{SO_3CH_2\underline{CH}_2\underline{CH}_2CH_3}$ and $\mathrm{CH_2\underline{CH}_2\underline{CH}_2CH_2NHSO_2}$), 2.30 (1 H, bt, OH), 2.73–3.13 (4 H, t+m, $\mathrm{\underline{CH}_2CH_2CH_2\underline{CH}_2NHSO_2}$), 3.97 (2 H, t, $J = 6$ Hz, $\mathrm{SO_3CH_2CH_2CH_2\underline{CH}_3}$), 4.67 (1 H, bt, NH), 7.30–7.60 (3 H, m, ArH), 7.75–8.00 (5 H, s+m, ArH, C2-H, C5-H and C7-H), 8.41 (1 H, d, $J = 11$ Hz, C4-H), 9.03 (1 H, d, 11 Hz, C8-H).

IR (KBr): $\nu = 3490, 3286, 2956, 1584\ \mathrm{cm^{-1}}$.

MS: $m/z = 533$ ($\mathrm{M^+}$), 516, 379, 317, 261, 221, 165, 115, 77 (100 %), 56.

Butyl 3-Butyl-1-(1-hydroxyethyl-1-methyl)azulene-1-sulfonate **(2p)**: violet oil.

^{1}H NMR ($\mathrm{CDCl_3}$): $\delta = 0.77$ (3 H, t, $J = 7$ Hz, $\mathrm{SO_3CH_2CH_2CH_2\underline{CH}_3}$), 0.94 (3 H, t, $J = 7$ Hz, $\mathrm{CH_2CH_2CH_2\underline{CH}_3}$), 1.11–1.98 (8 H, m, $\mathrm{SO_3CH_2\underline{CH}_2\underline{CH}_2CH_3}$ and $\mathrm{CH_2\underline{CH}_2\underline{CH}_2CH_3}$), 1.71 (6 H, s, $\mathrm{C(CH_3)_2}$), 2.27 (1 H, bs, OH), 2.99 (2 H, t, $J = 7$ Hz, $\mathrm{\underline{CH}_2CH_2CH_2CH_3}$), 3.95 (2 H, t, $J = 6$ Hz, $\mathrm{SO_3\underline{CH}_2CH_2CH_2CH_3}$), 7.82–8.00 (2 H, dm, C5-H, and C7-H), 8.02 (1 H, s, C2-H), 8.45 (1 H, d, $J = 11$ Hz, C4-H), 9.02 (1 H, d, $J = 11$ Hz, C8-H).

IR (neat): $\nu = 3502, 2930, 1581\ \mathrm{cm^{-1}}$.

MS: $m/z = 378$ ($\mathrm{M^+}$), 335, 321, 305, 279 (100 %), 221, 180, 155, 128, 89, 59.

Methyl 3-[4-(Benzenesulfonylamino]butyl-6-(1-hydroperoxyethyl-1-methyl)azulene-1-carboxylate **(3a)**: violet oil.

^{1}H NMR ($\mathrm{CDCl_3}$): $\delta = 1.10$–1.87 (4 H, m, $\mathrm{CH_2\underline{CH}_2\underline{CH}_2CH_2NHSO_2}$), 1.71 [6 H, s, $\mathrm{C(CH_3)_2}$], 2.75–3.15 (4 H, t+m, $\mathrm{\underline{CH}_2CH_2CH_2\underline{CH}_2NHSO_2}$), 3.92 (3 H, s, $\mathrm{COOCH_3}$), 4.74 (1 H, bt, NH), 7.38–7.94 (7 H, m, ArH, C5-H and C7-H), 8.06 (1 H, s, C2-H), 8.21 (1 H, bs, OOH), 8.30 (1 H, d, $J = 11$ Hz, C4-H), 9.56 (1 H, d, $J = 11$ Hz, C8-H).

IR (neat): $\nu = 3298, 2920, 1669, 1581\ \mathrm{cm^{-1}}$.

MS: $m/z = 455$ $[\mathrm{M}-16]^+$, 424, 300, 268, 227, 185, 114, 77 (100 %).

Methyl 3-Butyl-6-(1-hydroperoxyethyl-1-methyl)azulene-1-carboxylate **(3h)**: violet oil.

^{1}H NMR ($\mathrm{CDCl_3}$): $\delta = 0.95$ (3 H, t, $J = 6$ Hz, $\mathrm{CH_2CH_2CH_2\underline{CH}_3}$), 1.09–1.88 (4 H, m, $\mathrm{CH_2\underline{CH}_2\underline{CH}_2CH_3}$), 1.71 [6 H, s, $\mathrm{C(CH_3)_2}$], 2.97 (2 H, t, $J = 7$ Hz, $\mathrm{\underline{CH}_2CH_2CH_2CH_3}$), 3.92 (3 H, s, $\mathrm{COOCH_3}$), 7.58–7.70 (2 H, dm, C5-H and C7-H), 8.15 (1 H, s, C2-H), 8.36 (1 H, d, $J = 11$ Hz, C4-H), 8.91 (1 H, bs, OOH), 9.48 (1 H, d, $J = 11$ Hz, C8-H).

IR (neat): $\nu = 3328, 2920, 1671, 1581\ \mathrm{cm^{-1}}$.

MS: $m/z = 300$ $[\mathrm{M}-16]^+$, 257 (100 %), 199, 155, 115.

Methyl 6-(1-Hydroperoxyethyl-1-methyl)azulene-1-carboxylate **(3i)**: violet oil.

^{1}H NMR ($\mathrm{CDCl_3}$): $\delta = 1.71$ (6 H, s, $\mathrm{C(CH_3)_2}$), 3.92 (3 H, s, $\mathrm{COOCH_3}$), 7.23 (1 H, d, $J = 3$ Hz, C3-H), 7.60–7.85 (2 H, dm, C5-H and C7-H), 8.28 (1 H, d, $J = 4$ Hz, C2-H), 8.40 (1 H, d, $J = 11$ Hz, C4-H), 8.87 (1 H, bs, OOH), 9.53 (1 H, d, $J = 11$ Hz, C8-H).

IR (neat): $\nu = 3352, 2978, 1665, 1584\ \mathrm{cm^{-1}}$.

MS: $m/z = 260$ ($\mathrm{M^+}$), 244, 227, 196, 170 (100 %), 141, 114, 83.

Methyl 3-Butyl-6-formylazulene-1-carboxylate (10a) and Dimethyl 3-Butylazulene-1,6-dicarboxylate (11a); Typical Procedure (Method A):

Potassium acetate (0.087 g, 0.89 mmol) was added to a solution of **9a** (0.380 g, 1.48 mmol) in DMF (14.0 mL) and subjected to oxidation by bubbling oxygen gas through the solution from the bottom of the flask for 20 h at 120 °C. Then, the reaction mixture was poured into ice-water, acidified with 10 % aq HCl and extracted with EtOAc (30 mL). The EtOAc extract was washed with water (20 mL) and brine (20 mL), dried ($\mathrm{MgSO_4}$), and then concentrated. The product was first purified with a short column of silica gel (EtOAc/hexane, 1 : 2). The less polar fraction was purified by additional silica gel column chromatography (EtOAc/hexane, 1 : 6) to give **10a** (0.015 g, 4 % yield) as green crystals; mp 63–65 °C.

^{1}H NMR ($\mathrm{CDCl_3}$): $\delta = 0.89$ (3 H, t, $J = 7$ Hz, $\mathrm{CH_2CH_2CH_2\underline{CH}_3}$), 1.10–1.95 (4 H, m, $\mathrm{CH_2CH_2\underline{CH}_2CH_3}$), 2.98 (2 H, t, $J = 7$ Hz, $\mathrm{\underline{CH}_2CH_2CH_2CH_3}$), 3.90 (3 H, s, $\mathrm{COOCH_3}$), 7.65–7.92 (2 H, dm, C5-H and C7-H), 8.34 (1 H, s, C2-H), 8.47 (1 H, d, $J = 10$ Hz, C4-H), 9.63 (1 H, d, $J = 10$ Hz, C8-H), 10.08 (1 H, s, CHO).

IR (KBr): $\nu = 2914, 1689, 1449, 1257\ \mathrm{cm^{-1}}$.

MS: $m/z = 270$ ($\mathrm{M^+}$), 227 (100 %), 199, 168, 139, 115, 57.

The more polar fraction was treated with ethereal diazomethane. After evaporation, the residue was purified by silica gel column chromatography (EtOAc/hexane, 1 : 6) to give **11a** (0.177 g, 39 % yield) as green crystals; mp 101–102 °C.

^{1}H NMR (DMSO-d)$_6$: $\delta = 0.92$ (3 H, t, $J = 7$ Hz, $\mathrm{CH_2CH_2CH_2\underline{CH}_3}$), 1.13–1.74 (4 H, m, $\mathrm{CH_2\underline{CH}_2\underline{CH}_2CH_3}$), 3.03 (2 H, t, $J = 7$ Hz, $\mathrm{\underline{CH}_2CH_2CH_2CH_3}$), 3.88 (3 H, s, $\mathrm{COOCH_3}$), 3.96 (3 H, s, $\mathrm{COOCH_3}$), 8.00–8.25 (2 H, dm, C5-H and C7-H), 8.32 (1 H, s, C2-H), 8.69 (1 H, d, $J = 11$ Hz, C4-H), 9.54 (1 H, *d*, $J = 11$ *Hz*, C8-H).

IR (KBr): $\nu = 2938, 1716, 1689, 1446, 1215, 1074\ \mathrm{cm^{-1}}$.

MS: $m/z = 300$ ($\mathrm{M^+}$), 257 (100 %), 183, 139, 115, 57.

Dimethyl 3-Phenylazulene-1,6-dicarboxylate **(11b)**: green crystals; mp 135–137°C.

^1H NMR ($CDCl_3$): $\delta = 3.84$ (3H, s, $COOCH_3$), 3.95 (3H, s, $COOCH_3$), 7.35–7.70 (5H, m, ArH), 8.15–8.44 (2H, dm, C5-H and C7-H), 8.56 (1H, s, C2-H), 8.68 (1H, d, $J = 11$ Hz, C4-H), 9.70 (1H, d, $J = 11$ Hz, C8-H).

IR (KBr): $\nu = 1725, 1698, 1440, 1266, 1215, 1077\ cm^{-1}$.

MS: $m/z = 320$ (M^+, 100%), 289, 246, 202, 176, 144, 99.

Methyl 1-(4-Butyryl)azulene-6-carboxylate **(11c)**: green crystals; mp 72–74°C.

^1H NMR (CD_3OD): $\delta = 1.08$ (3H, t, $J = 7$ Hz, $COCH_2CH_2\underline{CH}_3$), 1.50–2.08 (2H, m, $COCH_2\underline{CH}_2CH_3$), 3.10 (2H, t, $J = 7$ Hz, $CO\underline{CH}_2CH_2CH_3$), 3.88 (3H, s, $COOCH_3$), 7.41 (1H, d, $J = 4$ Hz, C3-H), 8.20–8.30 (2H, dm, C5-H and C7-H), 8.55 (1H, d, $J = 4$ Hz, C2-H), 8.63 (1H, d, $J = 11$ Hz, C4-H), 9.78 (1H, d, $J = 11$ Hz, C8-H).

IR (KBr): $\nu = 2940, 1713, 1638, 1404, 1272, 1221, 1059\ cm^{-1}$.

MS: $m/z = 256$ (M^+), 213 (100%), 153, 125, 70.

Methyl 3-[4-(Benzenesulfonylamino)butyl]-6-isopropenylazulene-1-carboxylate (17a):

p-Toluenesulfonic acid (0.13 g) was added to a solution of **2a** (1.31 g, 2.88 mmol) in benzene (40.0 mL), and the reaction mixture was heated at reflux with a Dean–Stark trap for 20 min. The mixture was allowed to cool, diluted with EtOAc (40 mL), washed using sat. aq $NaHCO_3$ (30 mL), water (30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by silica gel column chromatography (EtOAc/hexane, 1:1) to give **17a** (1.10 g, 87% yield) as a violet oil.

^1H NMR ($CDCl_3$): $\delta = 1.33–1.93$ (4H, m, $CH_2\underline{CH}_2\underline{CH}_2CH_2NHSO_2$), 2.28 (3H, s, CH_3), 2.78–3.20 (4H, t+m, $\underline{CH}_2CH_2CH_2\underline{CH}_2NHSO_2$), 3.93 (3H, s, $COOCH_3$), 4.50 (1H, bs, NH), 5.24–5.45 (2H, m, $C{=}CH_2$), 7.29–7.65 (5H, m, ArH), 7.66–7.91 (2H, dm, C5-H and C7-H), 8.06 (1H, s, C2-H), 8.13 (1H, d, $J = 11$ Hz, C4-H), 9.45 (1H, d, $J = 11$ Hz, C8-H).

IR (neat): $\nu = 3280, 2932, 1689, 1578, 1499\ cm^{-1}$.

MS: $m/z = 437$ (M^+), 406, 279, 239, 207, 165, 115, 77 (100%).

Methyl 3-[4-(Benzenesulfonylamino)butyl]-6-(2-hydroxyethyl-1-methyl)azulene-1-carboxylate (18a):

BH_3–THF complex (12.6 mL, 12.6 mmol, 1 M solution in THF) was added to a solution of **17a** (1.10 g, 2.52 mmol) in THF (12.6 mL) at 0°C, and the mixture was stirred at the same temperature for 3 h under Ar. Then, aq 6 N NaOH (4.7 mL) and 31% H_2O_2 (2.6 mL) were added, and the reaction mixture was stirred for 1 h at r.t. After separation of THF, the reaction mixture was extracted with EtOAc (100 mL). The combined organic layers were washed with aq $Na_2S_2O_3$ (50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by silica gel column chromatography (EtOAc/hexane, 2:1) to give **18a** (0.980 g, 86% yield) as a violet oil.

^1H NMR ($CDCl_3$): $\delta = 1.20–1.95$ (4H, m, $CH_2\underline{CH}_2\underline{CH}_2NHSO_2$), 1.37 (3H, d, $J = 7$ Hz, CH_3), 2.80–3.40 (5H, t+m, $\underline{CH}_2CH_2CH_2\underline{CH}_2NHSO_2$), 3.70 (1H, bs, OH), 3.85 (2H, dd, $\underline{CH}_2OH$), 3.94 (3H, s, $COOCH_3$), 4.59 (1H, bt, NH), 7.20–7.60 (5H, m, ArH), 7.70–7.94 (2H, dm, C5-H and C7-H), 8.05 (1H, s, C2-H), 8.26 (1H, d, $J = 11$ Hz, C4-H), 9.45 (1H, d, $J = 11$ Hz, C8-H).

IR (neat): $\nu = 3500, 3290, 2920, 1674, 1580, 1449\ cm^{-1}$.

MS: $m/z = 455$ (M^+), 425, 394, 282, 257, 227, 195, 165, 141, 115, 77 (100%).

3-[4-(Benzenesulfonylamino)butyl]-6-(2-hydroxyethyl-1-methyl)-azulene-1-carboxylic acid (19a):

To a solution of **18a** (0.170 g, 0.374 mmol) in MeOH (10.0 mL) was added 10% aq NaOH (5.0 mL), and the mixture was heated under reflux for 2 h. The mixture was cooled to r.t., and solvent removal was performed under reduced pressure. The aqueous layer was washed with $CHCl_3$ (30 mL), and the solution was adjusted to pH 2–3 with 10% aq HCl followed by extraction using EtOAc (30 mL). The EtOAc extract was washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by silica gel column chromatography ($CHCl_3$/MeOH, 20:1) to give **19a** (0.114 g, 74% yield) as violet crystals; mp 157–158°C.

^1H NMR (DMSO-d_6): $\delta = 1.17–1.90$ (4H, m, $CH_2\underline{CH}_2\underline{CH}_2CH_2NHSO_2$), 1.30 (3H, d, $J = 6$ Hz, CH_3), 2.60–3.79 (5H, t+m, $\underline{CH}_2CH_2CH_2\underline{CH}_2NHSO_2$), 3.63 (2H, dd, $\underline{CH}_2OH$), 4.59 (3H, bs, NH), 7.20–7.85 (7H, m, ArH), 8.00 (1H, s, C2-H), 8.39 (1H, d, $J = 11$ Hz, C4-H), 9.38 (1H, d, $J = 11$ Hz, C8-H).

IR (KBr): $\nu = 3274, 2920, 1641, 1580, 1449\ cm^{-1}$.

MS: $m/z = 397$ $[M-44]^+$, 239, 199 (100%), 167, 141, 115, 77.

Methyl 3-Butyl-6-hydroxymethylazulene-1-carboxylate (14a):

To a solution of **11a** (0.050 g, 0.166 mmol) in THF (4.0 mL) was added $NaBH_4$ (0.016 g, 0.415 mmol). The mixture was heated at 60°C and then MeOH (0.8 mL) was added. The mixture was stirred at reflux for 1 h under Ar. Acetone was added at 0°C and stirred for 10 min, the mixture was neutralized with sat. aq NH_4Cl. The solvent was removed under reduced pressure, and then the aqueous solution was extracted with EtOAc (20 mL). The organic extract was washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by silica gel column chromatography (EtOAc/hexane, 1:1) to give **14a** (0.033 g, 72% yield) as green crystals; mp 60–62°C.

^1H NMR ($CDCl_3$): $\delta = 0.95$ (3H, t, $J = 7$ Hz, $CH_2CH_2CH_2\underline{CH}_3$), 1.13–1.82 (4H, m, $CH_2\underline{CH}_2\underline{CH}_2CH_3$), 2.21 (1H, bs, OH), 2.99 (2H, t, $J = 7$ Hz, $\underline{CH}_2CH_2CH_2CH_3$), 3.94 (3H, s, $COOCH_3$), 4.88 (2H, s, $\underline{CH}_2OH$), 7.33–7.54 (2H, dm, C5-H and C7-H), 8.17 (1H, s, C2-H), 8.34 (1H, d, $J = 10$ Hz, C4-H), 9.47 (1H, d, $J = 10$ Hz, C8-H).

IR (KBr): $\nu = 3304, 2908, 1674, 1446, 1419, 1212\ cm^{-1}$.

MS: $m/z = 272$ (M^+), 229 (100%), 197, 169, 140, 115, 58.

Methyl 1-Butylazulene-6-carboxylate (20a):

A mixture of **11a** (0.100 g, 0.33 mmol) and anhydrous phosphoric acid (5.0 mL) was heated and stirred at 110°C for 10 min. The reaction mixture was then poured into ice–water, extracted using Et_2O (30 mL), washed with water (10 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by silica gel column chromatography (Et_2O/hexane, 1:4) to give **20a** (0.073 g, 91% yield) as green crystals; mp 45–46°C.

^1H NMR (DMSO-d_6): $\delta = 0.94$ (3H, t, $J = 7$ Hz, $CH_2CH_2CH_2\underline{CH}_3$), 1.15–1.84 (4H, m, $CH_2\underline{CH}_2\underline{CH}_2CH_3$), 3.06 (2H, t, $J = 7$ Hz, $\underline{CH}_2CH_2CH_2CH_3$), 3.96 (3H, s, $COOCH_3$), 7.35 (1H, d, $J = 4$ Hz, C3-H), 7.74 (1H, d, $J = 4$ Hz, C2-H), 7.84 (2H, dm, C5-H and C7-H), 8.26 (1H, d, $J = 11$ Hz, C4-H), 8.30 (1H, d, $J = 11$ Hz, C8-H).

IR (KBr): $\nu = 2914, 1710, 1431, 1266, 1206, 1065\ cm^{-1}$.

MS: $m/z = 242$ (M^+), 199 (100%), 139, 115, 57.

The authors would like to thank Professor M. Shibasaki, University of Tokyo, for his useful suggestions and encouragement throughout the present study, and to express their thanks to Professor M. Ohashi, University of Electro-communications, for his profitable discussions on the mechanism of the present reaction. We also would like to thank Dr. S. Hotta, Sony / Tektronics, Tokyo for his helpful discussions on the results of the MO calculation, and Dr. K. Fujikura, Varian Instruments Ltd, for the measurements of high resolution ^1H *NMR.*

(1) Yamasaki, H.; Irino, S.; Uda, A.; Uchida, K.; Ohno, H.; Saito, N.; Kondo, K.; Jinzenji, K.; Yamamoto, T. *Nippon Yakurigaku Zasshi* **1958**, *54*, 362.
Plattner, A.; Furst, A.; Marti, L.; Schmid, H. *Helv. Chim. Acta* **1949**, *32*, 2137, 2452.
Okabe, S.; Takeuchi, K.; Honda, K.; Takagi, K. *Oyoyakuri* **1975**, *9*, 31.

(2) Tomiyama, T.; Wakabayashi, S.; Kosakai, K.; Yokota, M. *J. Med. Chem.* **1990**, *33*, 2323.
Tomiyama, T.; Yokota, M.; Wakabayashi, S.; Kosakai, K.; Yanagisawa, T. *J. Med. Chem.* **1993**, *36*, 791.

(3) Anderson, A.G.; Scotoni, R.; Cowies, E.J.; Firtz, C.G. *J. Org. Chem.* **1957**, *29*, 1193.
Hafner, K. *Angew. Chem.* **1958**, *70*, 419.
Anderson, A.G.; McDonald, R.N. *J. Am. Chem. Soc.* **1959**, *81*, 4941.
Anderson, A.G.; Steckler, B.M. *J. Am. Chem. Soc.* **1959**, *81*, 5669.
Nozoe, T.; Ito, S. *Fortschr. Chem. Org. Naturst.* **1961**, *19*, 33.
Anderson, A.G.; Anderson, R.G. *J. Org. Chem.* **1962**, *27*, 3578.
Anderson Jr, A.G.; Gale, D.J.; McDonald, R.N.; Anderson, A.G.; Rhodes, R.C. *J. Org. Chem.* **1964**, *29*, 1373.
Hafner, K. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 167.
Replogle, L.L.; Arluck, R.M.; Maynard, J.R. *J. Org. Chem.* **1965**, *30*, 2715.
McDonald, R.N.; Richmond, J.M.; Curtis, J.R.; Petty, H.E.; Hoskins, T.L. *J. Org. Chem.* **1976**, *41*, 1811.
Takase, K.; Yasunami, M. *J. Syn. Org. Chem. Jpn.* **1981**, *39*, 1172.
Fujimori, K.; Kitahashi, H.; Koyama, S.; Yamane, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 33.

(4) (a) Treibs, W. *Chem. Ber.* **1957**, *90*, 761.
(b) Kohara, K. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 3229.
(c) Amemiya, T.; Yasunami, M.; Takase, K. *Chem. Lett.* **1977**, 587.

(5) Pailer, M.; Lovenwein, H. *Monatsh. Chem.* **1971**, *102*, 1558.
Nozoe, T.; Takekuma, S.; Doi, M.; Matsubara, Y.; Yamamoto, H. *Chem. Lett.* **1984**, 627.
Matsubara, Y.; Takekuma, S.; Yokoi, K.; Yamamoto, H.; Nozoe, T. *Chem. Lett.* **1984**, 631.
Matsubara, Y.; Takekuma, S.; Yamamoto, H.; Nozoe, T. *Chem. Lett.* **1987**, 455.
Matsubara, Y.; Takekuma, S.; Yokoi, K.; Yamamoto, H.; Nozoe, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 14.
Takekuma, S.; Matsubara, Y.; Yamamoto, H.; Nozoe, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 475.
Matsubara, Y.; Matsui, S.; Takekuma, S.; Quo, Y.P.; Yamamoto, H.; Nozoe, T. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2040.

(6) Burgstahler, A.W.; Nordin, I.C. *J. Am. Chem. Soc.* **1961**, *83*, 198.
Dang, H.-S.; Davies, A.G.; Davison, I.E.; Schiesser, C.H. *J. Org. Chem.* **1990**, *55*, 1432.

(7) Methyl carboxylates (**1a–l, 9a** and **b**) and ketones (**1m** and **9c**) were synthesized from methyl 5- or 6-isopropyl-2-oxo-2*H*-cyclohepta[*b*]furan-3-carboxylate according to the methods reported by Takase et al.
Yang, P.M.; Yasunami, M.; Takase, K. *Tetrahedron Lett.* **1971**, 4275.
Yasunami, M.; Chen, A.; Yang, P.M.; Takase, K. *Chem. Lett.* **1980**, 579.
Yanagisawa, T.; Kosakai, K.; Tomiyama, T.; Yasunami, M.; Takase, K. *Chem. Pharm. Bull.* **1990**, *38*, 3355.
Yasunami, M.; Miyoshi, S.; Kanagae, N.; Takase, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 892.

(8) Butyl sulfonates (**1n–p**) were synthesized according to the method reported by Suzuka et al: A solution of the corresponding sodium sulfonate and butyl iodide (3 eq) in HMPA was stirred at r.t. in the dark for 48 h under Ar.
Suzuka, H.; Takeshita, M.; Sato, M.; Tomiyama, T.; Miyazaki, H. *Xenobiotic Metabolism and Disposition* **1990**, *5*, 217.

(9) Meyer zu Reckendorf, W.; Wassiliadou-Micheli, N. *Chem. Ber.* **1970**, *103*, 37.

(10) Hafner, K.; Peiser, H.; Patzett, H. *Liebigs Ann. Chem.* **1961**, *650*, 80.
Scholz, M.; Vien, L.; Fischer, G.; Tschapka, B.; Muhistadt, M. *Chem. Ber.* **1967**, *100*, 375.

(11) McDonald, R.N.; Petty, H.E.; Wolfe, N.L.; Paukstelis, J.V. *J. Org. Chem.* **1974**, *39*, 1877.

(12) Yokota, M.; Kosakai, K.; Nishimura, M.; Uchibori, S.; Tomiyama, T. 203rd ACS Meeting (San Francisco), *Abstract* **1992**, Medi 124.

(13) Fallahpour, R.A.; Hansen, H.-J. *Helv. Chim. Acta* **1992**, *75*, 2210.

(14) Soai, K.; Oyamada, H.; Ookawa, A. *Synth. Commun.* **1982**, *12*, 463.
Soai, K.; Oyamada, H.; Takase, M.; Ookawa, A. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1948.