# SYNTHESIS OF SODIUM 3-ETHYL-7-ISOPROPYL-[2-$^{14}$C]-AZULENE-1-SULFONATE

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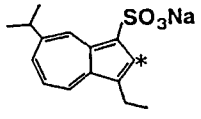
## SUMMARY

Sodium 3-ethyl-7-isopropylazulene-1-sulfonate 1, which has been found to be a potent and chemically stable agent having anti-inflammatory and anti-ulcerous activity, was synthesized in $^{14}$C-labelled form by using potassium [$^{14}$C]-cyanide. $^{14}$C-Labelled 1 with a specific activity of 9.02 mCi/mmol was prepared in eight steps in 21.9% overall chemical yield from 3-(t-butyldiphenylsilyloxy)propyl tosylate 10.

Key Words: alkylazulene, anti-ulcer, sodium 3-ethyl-7-isopropyl-[2-$^{14}$C]-azulene-1-sulfonate

## INTRODUCTION

It is well known that among alkylazulenes there appear useful derivatives exhibiting anti-inflammatory and anti-ulcerous activity.[1] Recently, sodium guaiazulenesulfonate has been widely used in clinical treatment for these purposes.[2] However, a number of their derivatives have been designed and synthesized for developing a new stable analogue owing to the chemical instability of the compound. Sodium 3-ethyl-7-isopropylazulene-1-sulfonate 1 is an excellent candidate, because it exhibits more potent activity and is a more chemically stable analogue. Labelling of 1 with carbon-14 was required for the study of metabolism in the preclinical stage. Thus, in this paper, the synthesis of the C-14 labelled compound 1 is described.

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## RESULTS AND DISCUSSION

Considering the stability of azulene skeleton in the metabolism[3], it would be best to label with carbon-14 at the 2-position in the azulene ring. Therefore, in the first cold experiment, the synthesis of n-butyraldehyde was

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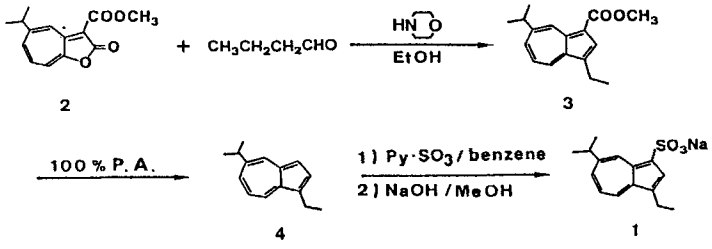
carried out by C1-elongation of n-propyl group in order to use the original synthetic route depicted in Scheme 1.[4,5] The cyanation of n-propyl halide (Br, Cl and I) or n-propyl tosylate with potassium cyanide followed by reduction with diisobutylaluminum hydride (DIBAH) was examined. However, the desired compounds were not detected due to a high volatility of n-butyronitrile and n-butyraldehyde. In order to decrease its volatility, an aldehyde with a functional group which can be easily converted to the original alkyl chain will be required.

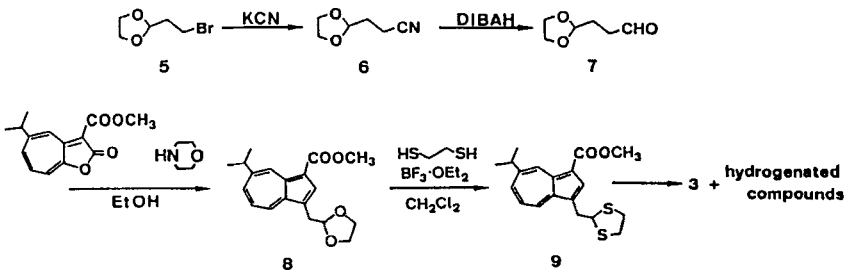



SCHEME 1

In response to the above requirement, the following two groups could be chosen. 1) A 1,3-dioxolanyl group can be converted to the corresponding dithiolane derivative followed by desulfurization of 9 to give the alkyl chain (Scheme 2). 2) A t-butyldiphenylsilyloxy group can be desilylated with tetrabutylammonium fluoride (TBAF) followed by radical deoxygenation via the thionocarbonate 15 or the bromide 16 to give the alkyl chain. Moreover, the introduction of the later protective group with phenyl chromophore makes it easy to monitor the reaction by TLC.

As shown in Scheme 2, the cyanation of 2-(2-bromoethyl)-1,3-dioxolane 5 with potassium cyanide in dimethyl sulfoxide (DMSO)[6] provided the nitrile 6 followed by reduction with DIBAH and hydrolysis to afford the aldehyde 7. The condensation of the aldehyde 7 with methyl 5-isopropyl-2-oxo-2H-cyclohepta[b]-furan-3-carboxylate 2 in the presence of amine gave the desired azulene 8 in 32% yield from 5. The dithiolane 9 was prepared by using 1,2-ethanedithiol and boron trifluoride-etherate in methylene chloride in 70% yield, and then reduced with Raney Ni (W2). Although some amounts of the 3-ethylazulene 3 was prepared, hydrogenated azulenes were obtained as the undesirable by-products in various

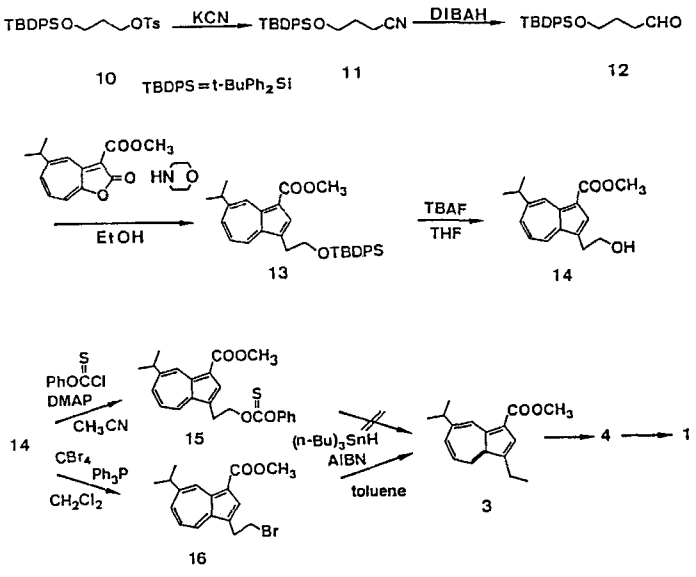
ratios by depending on the amount of the catalyst used. This result indicates that the first route is unsuitable for labelling which requires high reproducibility.




SCHEME 2

In the next approach (Scheme 3), the nitrile 11 was prepared by using potassium cyanide in the presence of crown ether[7] from 3-(t-butyldiphenylsilyl-oxy)propyl tosylate 10, and then treated with DIBAH followed by hydrolysis to give the aldehyde 12. Under similar conditions described above, 12 was converted to the azulene 13 in 67.3% yield from 10. The silyl ether 13 was deprotected with TBAF in THF to afford the hydroxyethylazulene 14 in 88.5% yield, and then the radical deoxygenation of the alcohol 14 by treatment of 15 or 16 with tri-n-butyltin hydride in the presence of α, α-azobisisobutyronitrile (AIBN) was attempted. Initial trial on the reductive removal of the O-phenoxy-thiocarbonyloxy group[8] in 15 which was prepared in 76.2% yield failed in the formation of the desired product 3 , resulting in the interesting fact that the azulene ring could endure this reduction. Thus, in the second trial, the reduction of the bromoethylazulene 16 prepared from 14 by using carbon tetra-bromide and triphenylphosphine in methylene chloride[9] was carried out under similar conditions to the previous procedure to afford 3 in 71.7% yield from 14.

Finally, the conversion of 3 to the final compound 1 was achieved according to the reported method[5] involving decarboxylation by heating with 100% phosphoric acid followed by sulfonation with pyridine-sulfur trioxide complex. The averages of yields based on repeated cold runs were as follows: 60.4% (10→13), 60.6% (13→3), 68.0% (3→4), 89.3% (4→1) and 22.2% (overall process; 10→1).




SCHEME 3

Starting with potassium [$^{14}$C]-cyanide (20 mCi, 60.3 mCi/mmol) according to the procedure (Scheme 3) established, 3.87 mCi of $^{14}$C-labelled 1 was finally obtained in 21.9% overall chemical yield and in 19.4% radiochemical yield with the specific activity of 9.02 mCi/mmol.

## EXPERIMENTAL

Potassium [ $^{14}$C]-cyanide (5 mCix4, 60.3 mCi/mmol) was purchased from Amersham International plc. All solvents were dried and distilled. Unless otherwise indicated, organic layers were dried over anhydrous sodium sulfate. The reactions in the labelling synthesis were monitored by thin layer chromatography (TLC). Analytical TLC was carried out on a Merck silica gel 60 F254 plate (0.25 mm). Fuji Devison BM-820MH silica gel was used for column chromatography. Melting points were determined on a micro melting point apparatus. $^{1}$H NMR spectra were obtained with a Varian EM-360 or XL-100A spectrometer. Chemical shifts were reported in $\delta$ (ppm) downfield from tetramethylsilane (TMS) as an internal standard. Infrared spectra were obtained with a Hitachi 215 spectrophotometer. Mass spectra were obtained with a JMS-D300 mass spectrometer. These spectra data were obtained in trial experiments using unlabelled material. Radioactivity was determined with a

Beckmann LS-9000 liquid scintillation counter using 2,5-diphenyloxazole in toluene or a mixture of toluene and Triton X-100 as a liquid scintillator. Radiochemical purity was determined with a Packard TLC radiochromatogram scanner model 7230.

2-(2-Cyanoethyl)-1,3-dioxolane 6

Potassium cyanide (130 mg, 2 mmol) was added to a solution of 2-(2-bromoethyl)-1,3-dioxolane 5 (362 mg, 2 mmol) in DMSO (3 mL) at 20 °C, and the resulting pale yellow solution was stirred at this temperature for 4 h. Water (10 mL) was added and the whole mixture was extracted with ethyl acetate (4x8 mL). The organic layer was washed with satd. brine, dried and then evaporated in vacuo to afford the nitrile 6 (282 mg) as a slightly yellow oil: IR (neat) 2240 $cm^{-1}$ (CN); $^1H$ NMR ($CDCl_3$) δ 1.78-2.69 (4H,m,$C\underline{H}_2C\underline{H}_2CN$), 3.92 (4H, s,$OC\underline{H}_2C\underline{H}_2O$), 4.94 (1H,t,J=4Hz,$C\underline{H}CH_2CH_2CN$).

3-(1,3-Dioxolan-2-yl)propionaldehyde 7

A solution of 1.76 M DIBAH in n-hexane (1.25 mL, 2.2 mmol) was added dropwise to a solution of nitrile 6 (282 mg) in ether (3 mL) at -78 °C under argon atmosphere. After stirring at this temperature for 1.5 h, 5% sulfuric acid (3 mL) was added at 0 °C and the stirring was continued for another 30 min. The whole mixture was extracted with ethyl acetate (4x10 mL), and the organic layer was washed with satd. brine and then dried. Filtration and evaporation in vacuo furnished the aldehyde 7 (164 mg) as a colorless oil: IR (neat) 1725 $cm^{-1}$ (C=O); $^1H$ NMR ($CDCl_3$) δ 1.78-2.77 (4H,m,$CHC\underline{H}_2C\underline{H}_2CHO$), 3.91 (4H,s, $OC\underline{H}_2C\underline{H}_2O$), 4.96 (1H,t,$C\underline{H}CH_2CH_2CHO$), 9.76 (1H,s,-$C\underline{H}O$).

Methyl 3-(1,3-dioxolan-2-yl)methyl-7-isopropylazulene-1-carboxylate 8

A mixture of the aldehyde 7 (164 mg), morpholine (132 mg, 1.57 mmol) and methyl 5-isopropyl-2-oxo-2H-cyclohepta[b]furan-3-carboxylate 2 (465 mg, 1.89 mmol) in ethyl alcohol (5 mL) was stirred under reflux for 7 h. After cooling, benzene (5 mL) was added and the whole was washed with 5% hydrochloric acid and satd. brine. The benzene layer was dried and evaporated in vacuo to leave a dark green oil, which was chromatographed on a silica gel column using a 10:1 mixture of n-hexane and ethyl acetate as an eluent to give 8 (204 mg, 22.4%

based on 5) as a violet oil: $^1$H NMR ($CDCl_3$) δ 1.41 (6H,d,J=7Hz,$(CH_3)_2$CH-), 3.06-3.43 (1H,m,$(CH_3)_2$CH-), 3.36 (2H,d,J=4.4Hz,Az-$CH_2$CH-), 3.72-4.00 (4H,m, $OCH_2CH_2O$), 3.92 (3H,s,-$COOCH_3$), 5.17 (1H,t,J=4.4Hz,Az-$CH_2$CH-), 7.42 (1H,d, J=10Hz,H-5), 7.71 (1H,d,J=10Hz,H-6), 8.27 (1H,s,H-2), 8.35 (1H,dd,J=10,1.4Hz, H-4), 9.73 (1H,d,J=2Hz,H-8).

Methyl 3-(1,3-dithiolan-2-yl)methyl-7-isopropylazulene-1-carboxylate 9

1,2-Ethanedithiol (13.3 μL, 0.16 mmol) and boron trifluoride-etherate (16.3 μL, 0.13 mmol) were added to a solution of 8 (41.6 mg, 0.13 mmol) in methylene chloride (1.5 mL) at 20 °C. After stirring at this temperature for 1 h, the reaction mixture was poured into ice-satd. $NaHCO_3$ and the whole was extracted with ethyl acetate (20 mL). The organic layer was washed with satd. $NaHCO_3$ and satd. brine, dried and evaporated in vacuo. The residual oil was chromatographed on a silica gel column using a 5:1 mixture of n-hexane and ethyl acetate as an eluent to give 9 (31.5 mg, 69.9% based on 8) as a violet oil: $^1$H NMR ($CDCl_3$) δ 1.41 (6H,d,J=7Hz,$(CH_3)_2$CH-), 2.95-3.39 (5H,m,$(CH_3)_2$CH- and $SCH_2CH_2S$), 3.52 (2H,d,J=7Hz,Az-$CH_2$CH-), 3.94 (3H,s,-$COOCH_3$), 4.88 (1H,t, J=7Hz,Az-$CH_2$CH-), 7.43 (1H,d,J=10Hz,H-5), 7.73 (1H,d,J=10Hz,H-6), 8.28 (1H,s, H-2), 8.32 (1H,dd,J=10, 1.5Hz,H-4), 9.74 (1H,d,J=2Hz,H-8).

Methyl 3-[2-(phenoxythiocarbonyloxy)ethyl]-7-isopropylazulene-1-carboxylate 15

Phenyl chlorothionocarbonate (27 μL, 0.20 mmol) and 4-dimethylaminopyridine (DMAP, 44.1 mg, 0.36 mmol) were added to a solution of 1-hydroxyethylazulene 14 (49.2 mg, 0.18 mmol) in acetonitrile (4.5 mL), and the mixture was stirred at 20 °C under argon atmosphere. After stirring for 5 h, the mixture was concentrated and the residue was dissolved in ethyl acetate (8 mL). The solution was washed successively with 5% hydrochloric acid, satd. $NaHCO_3$ and satd. brine, dried and evaporated in vacuo. The residue was chromatographed on a silica gel column using a 10:1 mixture of n-hexane and ethyl acetate as an eluent to afford O-phenoxythiocarbonyl derivertive 15 (56.0 mg, 76.2% based on 14) as a violet oil: $^1$H NMR ($CDCl_3$) δ 1.35 (6H,d,J=6.6Hz,$(CH_3)_2$CH-), 2.89-3.69 (1H,m,$(CH_3)_2$CH-), 3.46 (2H,t,J=7.2Hz,Az-$CH_2CH_2$-), 3.89 (3H,s,-$COOCH_3$), 4.75 (2H,t,J=7.2Hz,Az-$CH_2CH_2$-), 6.86-7.87 (7H,m,-OPh and H-5,6), 8.13-8.49 (2H,m, H-2,4), 9.69 (1H,s,H-8).

4-(t-Butyldiphenylsilyloxy)-n-butyronitrile 11

A solution of 3-(t-butyldiphenylsilyloxy)propyl tosylate 10 (469 mg, 1 mmol) and 18-crown-6 (123 mg, 0.5 mmol) in acetonitrile (4 mL) was stirred at 90-100 °C. Potassium cyanide (78 mg, 1.2 mmol) was added to the solution in three portions (0.2, 0.2 and 0.8 equivalents) at intervals of 1.5 h, and the stirring was continued at this temperature for 9 h. After cooling, water (6 mL) was added to the mixture and the whole was extracted with ethyl acetate (2x10 mL). The organic layer was washed with satd. brine, dried over magnesium sulfate and evaporated in vacuo, leaving the nitrile 11 (331 mg) as a slightly yellow oil: IR (neat) 2240 $cm^{-1}$ (CN); $^1H$ NMR ($CDCl_3$) δ 1.01 (9H,s,t-Bu), 1.67-1.95 (2H,m,-$CH_2CH_2CH_2CN$), 2.45 (2H,t,J=6.8Hz,-$CH_2CH_2CH_2CN$), 3.70 (2H,t, J=5.6Hz, -$CH_2CH_2CH_2CN$), 7.27-7.80 (10H,m,$Ph_2Si$-).

4-(t-butyldiphenylsilyloxy)-n-butyraldehyde 12

A solution of 1.76 M DIBAH in n-hexane (0.62 mL, 1.1 mmol) was added to a solution of the nitrile 11 (331 mg) in ether (1.5 mL) at -25 °C under nitrogen atmosphere. After stirring at this temperature for 2 h, 5% sulfuric acid (2 mL) was added at 0 °C and the stirring was continued for another 30 min. The whole mixture was extracted with ethyl acetate (2x10 mL) and the organic layer was washed with satd. brine, dried and evaporated in vacuo. The aldehyde 12 was obtained as an yellow oil (326 mg): IR (neat) 1725 $cm^{-1}$ (C=O); $^1H$ NMR ($CDCl_3$) δ 1.05 (9H,s,t-Bu), 1.63-2.17 (2H,m,-$CH_2CH_2CH_2CHO$), 2.56 (2H,t,J=7.0Hz, -$CH_2CH_2CH_2CHO$), 3.70 (2H,t,J=5.5Hz,-$CH_2CH_2CH_2CHO$), 7.30-7.83 (10H,m,$Ph_2Si$-), 9.82 (1H,s,-CHO).

Methyl 3-[2-(t-butyldiphenylsilyloxy)ethyl]-7-isopropylazulene-1-carboxylate 13

A mixture of the aldehyde 12 (326 mg), morpholine (104 mg, 1.2 mmol) and methyl 5-isopropyl-2-oxo-2H-cyclohepta[b]furan-3-calboxylate 2 (271 mg, 1.1 mmol) in ethyl alcohol (4 mL) was stirred under reflux for 8 h. After cooling, the mixture was diluted with benzene (15 mL) and the whole mixture was washed successively with 5% hydrochloric acid, satd. $NaHCO_3$ and satd. brine, dried and evaporated in vacuo. The residue was chromatographed on a silica gel column using a 10:1 mixture of n-hexane and ethyl acetate as an eluent to give

13 (343 mg, 67.3% based on 10) as a violet oil: $^1$H NMR ($CDCl_3$) δ 1.03 (9H,s, t-Bu), 1.40 (6H,d,J=7.0Hz,$(CH_3)_2CH$-), 3.05-3.36 (1H,m,$(CH_3)_2CH$-), 3.25 (2H,t, J=7.2Hz,Az$CH_2CH_2$-), 3.94 (2H,t,J=7.2Hz,Az$CH_2CH_2$-), 3.94 (3H,s,-COO$CH_3$), 7.19-7.75 (12H,m,$Ph_2$Si- and H-5,6), 8.03 (1H,d,J=9.8Hz,H-4), 8.14 (1H,s,H-2), 9.67 (1H,d,J=2Hz,H-8).

Methyl 3-(2-hydroxyethyl)-7-isopropylazulene-1-carboxylate 14

A solution of 1 M TBAF in THF (2.0 mL, 2.0 mmol) was added to a solution of 13 (260 mg, 0.51 mmol) in THF (5 mL) at 20 °C under nitrogen atmosphere. After stirring at this temperature for 1 h, the solution was poured into satd. ammonium chloride (20 mL), and the mixture was extracted with ethyl acetate (10 mL). The organic layer was washed with satd. ammonium chloride and satd. brine, dried and evaporated in vacuo to afford 1-hydroxyethylazulene 14 (283 mg) as a violet oil: IR (neat) 3400 $cm^{-1}$ (OH), 1680 $cm^{-1}$ (C=O); $^1$H NMR ($CDCl_3$) δ 1.41 (6H,d,J=7.0Hz,$(CH_3)_2CH$-), 1.64 (1H,s,-OH), 3.08-3.40 (1H,m, $(CH_3)_2CH$-), 3.27 (2H,t,J=6.6Hz,Az$CH_2CH_2$OH), 3.94 (3H,s,-COO$CH_3$), 3.97 (2H,t, J=6.6Hz,Az$CH_2CH_2$OH), 7.42 (1H,d,J=10Hz,H-5), 7.73 (1H,ddd,J=10,2,1.2Hz,H-6), 8.22 (1H,s,H-2), 8.32 (1H,dd,J=10,1.2Hz,H-4), 9.73 (1H,d,J=2Hz,H-8).

Methyl 3-(2-bromoethyl)-7-isopropylazulene-1-carboxylate 16

Carbon tetrabromide (338 mg, 1.0 mmol) and triphenylphosphine (268 mg, 1.0 mmol) were added to a solution of 14 (283 mg) in methylene chloride (2 mL), and the mixture was stirred at 0 °C for 1.5 h under nitrogen atmosphere. The ice-water bath was removed, and then the stirring was continued at 20 °C for another 30 min. The mixture was diluted with n-hexane (20 mL) and filtered off the insoluble material. The filtrate was washed with satd. $NaHCO_3$ and satd. brine, dried and evaporated in vacuo. The residue was triturated in n-hexane followed by filtration and evaporation to give 1-bromoethylazulene 16 (415 mg) as a violet oil: IR (neat) 1680 $cm^{-1}$ (C=O); $^1$H NMR ($CDCl_3$) δ 1.41 (6H,d,J=7.2Hz,$(CH_3)_2CH$-), 2.84-3.52 (1H,m,$(CH_3)_2CH$-), 3.62 (4H,s,Az$CH_2CH_2$Br), 3.97 (3H,s,-COO$CH_3$ ), 7.33-8.08 (2H,m,H-5,6), 8.29 (1H,s,H-2), 8.35 (1H,d, J=9.6Hz,H-4), 9.82 (1H,d,J=2Hz, H-8).

Methyl 3-ethyl-7-isopropylazulene-1-carboxylate 3

A mixture of 16 (415 mg), AIBN (17 mg, 0.1 mmol) and tri-n-butyltin hydride (0.3 mL, 1.0 mmol) in toluene (5 mL) was heated at 100 °C for 2.5 h under nitrogen atmosphere. The solvent was removed, and the residue was chromatographed on a silica gel column using a 40:1 mixture of n-hexane and ethyl acetate as an eluent to give 3 (97 mg, 74.2% based on 13) as violet prisms: mp 62 °C; IR (KBr) 1680 $cm^{-1}$ (C=O); $^1$H NMR ($CDCl_3$) δ 1.39 (3H,t, J=7.6Hz,-$CH_2\underline{CH_3}$), 1.41 (6H,d,J=7.4Hz,($\underline{CH_3}$)$_2$CH-), 3.02 (2H,q,J=7.6Hz,-$\underline{CH_2}CH_3$ ), 3.14 (1H,sep,J=7.4Hz,($CH_3$)$_2\underline{CH}$-), 3.95 (3H,s,-COO$\underline{CH_3}$), 7.39 (1H,d,J=10Hz,H-5), 7.71 (1H,d,J=10Hz,H-6), 8.20 (1H,s,H-2), 8.25 (1H,d,J=10Hz,H-4), 9.70 (1H,d, J=2Hz,H-8).

1-Ethyl-5-isopropylazulene 4

A mixture of 3 (203 mg, 0.79 mmol) and 100% phosphoric acid (2.5 mL) was heated at 100 °C for 50 min, cooled and poured into water (10 mL). The whole was extracted with n-hexane (3x10 mL), and the organic layer was washed with satd. $NaHCO_3$ and satd. brine, dried and evaporated in vacuo. The residue was chromatographed on a silica gel column using n-hexane as an eluent to give 4 (108 mg, 68.9% based on 3) as a blue violet oil: $^1$H NMR ($CDCl_3$) δ 1.34 (6H,d, J=7.0Hz,($\underline{CH_3}$)$_2$CH-), 1.36 (3H,t,J=7.6Hz,-$CH_2\underline{CH_3}$), 3.06 (2H,q,J=7.6Hz,-$\underline{CH_2}CH_3$ ), 2.66-3.40 (1H,m,($CH_3$)$_2\underline{CH}$-), 6.87-8.37 (6H,m,H-2,3,4,6,7,8).

Sodium 3-ethyl-7-isopropylazulene-1-sulfonate 1

A mixture of 4 (108 mg, 0.54 mmol) and pyridine-sulfur trioxide (173 mg, 1.1 mmol) in benzene (2 mL) was stirred under reflux for 8 h. After cooling, the mixture was filtered, and the solid was extracted with chloroform. The chloroform was removed in vacuo, and the resulting solid was dissolved in methyl alcohol (4 mL) and a solution of sodium hydroxide (35 mg, 0.87 mmol) in methyl alcohol (2 mL) was added at 0 °C. After stirring at 20 °C for 1 h, the solution was concentrated and the residue was dissolved in ethyl acetate (8 mL). The solution was washed with satd. brine and dried. The aqueous layer was extracted with n-butyl alcohol (5 mL), and the n-butyl alcohol layer was washed with satd. brine, dried. The combined ethyl acetate and n-butyl alcohol extracts were evaporated, and the residue was chromatographed on a silica gel column

using a 3:1 mixture of chloroform and methyl alcohol as an eluent followed by recrystallization from ethyl alcohol to afford 1 (141 mg, 86.4% based on 4) as violet needles: mp 178-179 °C; IR (KBr) 3430 $cm^{-1}$ (OH), 1175, 1050 $cm^{-1}$ (S=O); $^1H$ NMR ($CD_3OD$) δ 1.36 (3H,t,J=7.5Hz,-$CH_2\underline{CH_3}$) 1.40 (6H,d,J=7.0Hz,($\underline{CH_3}$)$_2$CH-), 3.04 (2H,q,J=7.5Hz,-$\underline{CH_2}CH_3$), 3.18 (1H,sep,J=7.0Hz,($CH_3$)$_2\underline{CH}$-), 7.25 (1H,d,J=9.6Hz, H-5), 7.70 (1H,bd,J=10Hz,H-6), 8.04 (1H,s,H-2), 8.29 (1H,dd,J=9.6,1.2Hz,H-4), 9.21 (1H,d,J=2Hz,H-8); MS 198 $[M-SO_3Na]^+$, 183 (b.p.), 167, 155.

Sodium 3-ethyl-7-isopropyl-[2-$^{14}$C]-azulene-1-sulfonate 1

$^{14}$C-labelled 1 was prepared according to the procedures described for the unlabelled material. Potassium [$^{14}$C]-cyanide was added to the initial reaction mixture in place of the second addition (0.2 eq.) of unlabelled one. All intermediate products were used without further purification except for 13, 3 and 4. The yields of each step were 56.8% (10→3), 67.5% (13→3), 64.1% (3→4) and 93.7% (4→1). Starting from potassium [$^{14}$C]-cyanide (5 mCix4, 60.3 mCi/mmol), 1 was obtained as violet needles (133 mg, 3.87 mCi, 9.02 mCi/mmol) in 21.9% overall chemical yield and 19.4% radiochemical yield.

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