Synthesis of the Proposed Structure of Sclerosporin with a Guaiane Skeleton[†]

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A simple synthesis of the proposed structure of sclerosporin was accomplished from a symmetrical diketone **10**. The synthetic **1** did not show sporogenic activity, although the structure of **1** was rigorously assigned by ¹H-NMR at 500 MHz.

Sclerosporin, the main sporogenic substance of a fungus *Sclerotinia fructicola*, was isolated by Katayama and Marumo¹⁾ together with the closely related sesquiterpenes, sclerosporal and sclerosporene. The structures of these three compounds were first proposed to be *trans*-guaiane sesquiterpenes, **1**, **2** and **3**, as shown Fig. 1. Because of the scarcity of the materials available from the natural source, the stereochemistry at C-7 and the absolute configuration had not been determined.²⁾

In order to confirm the structures of these metabolites as well as to develop a procedure

for providing a sufficient amount of sclerosporin, we decided to synthesize the proposed structure, ($\pm$)-**1** and two optically active isomers of **3**, **4** from (–)-carvone and **5** from (–)- α -santonin.³⁾ In this paper, the synthesis of ($\pm$)-**1** is described.

Our synthetic plan was to use a symmetrical diketone **B**. Alkylation of **B** would give the desirable product **A** via mono-alkylation at the less hindered site, which in turn, should be convertible to **1**. Readily available glutaric acid **6**⁴⁾ was therefore employed as the starting material.

The acid **6** was converted to its bis-diazoketone **8** via an acyl chloride **7**,⁵⁾ which was cyclized by adding it to a solution of cupric acetylacetonate in hot benzene under a high dilution condition^{6,7)} to give an ene-dione **9** in a 14% yield from **6**. Catalytic hydrogen-

FIG. 1.

FIG. 2.

[†] Synthetic Microbial Chemistry. Part VII, Part VI, K. Mori and K. Okada, *Tetrahedron*, in press.

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FIG. 3.

ation of **9** over palladium on carbon provided a cycloheptanedione **10** in a 95% yield. Although the overall yield through these steps was rather poor, the procedure was simple and short enough to obtain the desired skeleton. The diketone **10** was converted to its bis-acetal **11** and then, heating a 1 to 1 mixture of **10** and **11** with *p*-toluenesulfonic acid in benzene furnished a monoacetal **12** in 44% from **10**.

Alkylation of **12** with 3-bromo-2-ethyl-1-propene⁸ in the presence of lithium diisopropylamide gave a mono-alkylated ketone **13** in a 76% yield (57% efficiency) based on the unrecovered ketone **12**. Ozonolysis of **13**, followed by a reductive workup with dimethyl sulfide gave a diketone **14**, which on treatment with dilute sodium hydroxide in aqueous ethanol, afforded an enone **15**. The crude enone **15** was converted to a hexahydroazulene derivative **17** via a tosylhydrazone **16** by Kabalka's procedure⁹ in a 10% yield from **13**. At this stage, we did not have any proof that the product has

the correct structure **17**. It was presumed, however, that mono-alkylation might take place at a less-hindered position, that is, not at C-7 but at C-2 of **12**; and secondly, that the ring junction of **17** should be *trans* because Greene has reported that the analogous enone **19** gave *trans*-fused cyclopentene **20** under similar reaction conditions.¹⁰ Mild acid hydrolysis of the acetal **17** gave a ketone **18** in a nearly quantitative yield.

Introduction of a methoxycarbonyl group was effected by treating **18** with dimethyl carbonate and sodium hydride in refluxing benzene. The resulting keto ester **21** was reduced with sodium borohydride in methanol to give a hydroxy ester **22** in 42% from **18**. It was assumed again that the methoxycarbonyl group joined at the desired C-4 position because it was less sterically hindered than at the C-6 position. The hydroxy ester **22** was treated with benzoyl chloride in pyridine at 0°C for 2 days to give a benzoate **23** in a 96% yield. Elimination of the β -benzoxyloxy group was executed with potassium *t*-butoxide at 5°C for 80 min to give a diene-ester **24** in a 47% yield. Finally, alkaline hydrolysis of **24** gave a crystalline acid which on recrystallization from hexane-ether gave pure **1**; mp 156.5~158°C. In ¹³C-NMR, it showed only 15 peaks and thus, the synthetic **1** was a single isomer. In order to confirm the structure of the synthetic **1** including its stereochemistry clearly, high field ¹H-NMR analyses were examined. As shown in Fig. 4, all protons except for C-8 β and C-7 were identified using two dimensional shift correlated spectroscopy (COSY) at 500 MHz. Unfortunately, those two protons at C-8 β and C-7 had almost the same chemical shift in CDCl₃. Among the four possible structures C~F, therefore, only the desired structure, C, was suitable for the 2D-NMR result and the other three structures D~F were eliminated.

As for the stereochemistry, a triple resonance decoupling experiment was extensively studied. It showed that the coupling constant between the C-3 α proton and C-8 α proton was 9.7 Hz and thus the ring junction should be

FIG. 4.

FIG. 5.

trans-fused. This implied that only two structures, **1a** and **1b**, were possible for **1**, and it was necessary to determine the stereochemistry at C-7. In both **1a** and **1b**, the conformers, **G** and **H**, in which bulky isopropyl group is present at an equatorial-like position, should be predominant. From a molecular model study, there was not much difference between the two stable conformers, but only in **H**, the dihedral angle between the C-6 proton and C-5 olefin proton is nearly 90° and the coupling constant was expected to be almost 0 Hz; namely, the C-5 olefin proton may split into a double-doublet because of spin-spin coupling only with C-3a (long range) and C-6 α . In fact, however, the C-5 proton was observed as a doublet of a double-doublet (8 peaks) with $J_{3a-5}=2.7$ Hz, and $J_{5-6\alpha,\beta}=8.4$ and 3.0 Hz. This result could be explained only by the conformer **G**.

In conclusion, the structure of our synthetic **1** was determined as **1a** including its relative stereochemistry. In order to obtain further proof, NOE measurement was also examined. Separation of the C-7 proton from the C-8 β proton, however, was not achieved cleanly even in *d*₅-pyridine and the NOE study did not give clearcut result, although there was sharp NOE effect between the C-8a proton and C-7

plus C-8 β protons.

A biological assay of **1a** revealed that it did not have any sporogenic activity against *Sclerotinia fructicola*, and therefore, the proposed structure **1** with a *trans*-guaiane skeleton for sclerosporin was questionable.¹¹⁾ In order to solve this problem more clearly, we attempted to synthesize both possible structures, **3** and **4**, proposed for sclerosporene in optically active forms and this will be reported in the following paper.³⁾ These studies prompted a reinvestigation of the structural determination and Katayama and Marumo later revised the structure of sclerosporin and sclerosporal to *cis* cadalane sesquiterpenes.¹²⁾

EXPERIMENTAL

All bps and mps are uncorrected. IR spectra were recorded on Jasco IRA-1 and Jasco A-102 spectrophotometers. ¹H-NMR were determined on Hitachi R-24A (60 MHz), Jeol JNM-FX 100 (100 MHz) and Bruker AM-500 spectrometers; chemical shifts are given in δ with Me₄Si as the internal standard. NOE measurement was performed on a Jeol GX-1 (400 MHz) spectrometer. Low resolution mass spectra were taken on a Hitachi RMU-6L mass spectrometer. High resolution mass spectrum was obtained with a Jeol DX-300 mass spectrometer.

3-(1-Methylethyl)glutaryl chloride 7. A mixture of 3-(1-methylethyl)glutaric acid **8** (60 g, 344.45 mmol) and PCl_5 (144 g, 691.14 mmol) was stirred at ice-bath temperature for 1 hr. The excess PCl_5 was evaporated *in vacuo* and the residue distilled to give **9** (71.5 g, 96%): bp 107~108°C/10 mmHg. IR $\nu_{\text{max}}^{\text{film}} \text{cm}^{-1}$: 1800 (s), 1070 (w), 1020 (m), 960 (m). NMR (100 MHz) $\delta_{\text{ppm}}^{\text{CCl}_4}$: 0.92 (6H, d, $J=6$ Hz), 1.62~1.95 (6H, m), 2.22~2.50 (1H, m) 2.90 and 2.92 (2H $\times$ 2, each d, $J=6$ Hz).

1,7-Bisdiazo-4-(1-methylethyl)heptane-2,6-dione 8. A solution of the acyl chloride **7** (20 g, 95.24 mmol) in dry ether (150 ml) was added slowly to a stirred solution of excess diazomethane in ether with ice-cooling. After stirring for 3 hr, the solvent and excess diazomethane was removed *in vacuo*. The residue was chromatographed over SiO_2 (hexane-ether = 1:1) to give **8** (17 g, 81%). IR $\nu_{\text{max}}^{\text{film}} \text{cm}^{-1}$: 3070 (m), 2100 (s), 1630 (s), 1380 (s), 1350 (s), 1320 (s), 1140 (s), 1080 (s). NMR (60 MHz) $\delta_{\text{ppm}}^{\text{CDCl}_3}$: 0.90 (6H, d, $J=6$ Hz), 1.45~2.00 (2H, m), 2.30 (4H, broad s), 5.30 (2H, s).

6-(1-Methylethyl)-2-cycloheptene-1,4-dione 9. To a solution of $\text{Cu}(\text{acac})_2$ (550 mg, 2.09 mmol) in dry benzene (550 ml) was added dropwise a solution of **8** (20 g, 90 mmol) in dry benzene (2 liter) over 7 hr at 60°C under N_2 . The reaction mixture was stirred at 60°C for 24 hr and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (benzene). The eluent was distilled to give **9** (2.67 g, 17.9%): bp 133~134.5°C/12 mmHg, n_D^{22} 1.4969. IR $\nu_{\text{max}}^{\text{film}} \text{cm}^{-1}$: 1670 (s), 1610 (m), 1390 (m), 1290 (m), 1150 (m), 1130 (m). NMR (100 MHz) $\delta_{\text{ppm}}^{\text{CCl}_4}$: 0.96 (6H, d, $J=6$ Hz), 1.50~2.80 (6H, m), 6.28 (2H, s).

6-(1-Methylethyl)cycloheptane-1,4-dione 10. A solution of **9** (4.8 g, 28.88 mmol) in 95% EtOH (150 ml) was hydrogenated with 10% Pd-C (300 mg) under H_2 at room temperature. The reaction mixture was filtered and the filtrate concentrated. The residue was chromatographed over SiO_2 (hexane→hexane/ether = 1:1). The eluent was distilled to give **10** (4.61 g, 94.9%): bp 135~138°C/13 mmHg. IR $\nu_{\text{max}}^{\text{film}} \text{cm}^{-1}$: 1700 (s), 1270 (m), 1170 (m), 1130 (m). NMR (100 MHz) $\delta_{\text{ppm}}^{\text{CCl}_4}$: 0.96 (6H, d, $J=6$ Hz), 1.50~2.08 (2H, m), 2.48 (2H, broad s), 2.52 (6H, broad s). Anal. Found: C, 76.24; H, 3.76. Calcd. for $\text{C}_{10}\text{H}_{16}\text{O}_2$: C, 75.94; H, 3.82.

1,1,4,4-Bisethylenedioxy-6-(1-methylethyl)cycloheptane 11. A stirred solution of **10** (2.8 g, 16.64 mmol), *p*-TsOH (50 mg) and 2-ethyl-2-methyl-1,3-dioxolane (20 ml) was heated to 110°C with continuous distillation of the methyl ethyl ketone over 5 hr. After cooling, ether was added to the reaction mixture. The ether layer was washed with aq. NaHCO_3 ($\times$ 3), dried over Na_2CO_3 and concentrated. The residue was chromatographed over alumina (activity II). Elution with hexane gave **11** (3.2 g, 72.7%) and then elution with hexane-ether (1:1) gave monoacetal **12** (0.35 g, 9.9%). Distillation gave pure **11**: bp

118~120°C/5 mmHg. IR $\nu_{\text{max}}^{\text{film}} \text{cm}^{-1}$: 1300 (m), 1220 (m), 1160 (m), 1140 (m), 1100 (s), 1070 (m), 1030 (m), 995 (m). NMR (100 MHz) $\delta_{\text{ppm}}^{\text{CCl}_4}$: 0.94 (6H, d, $J=6$ Hz), 1.26~1.46 (2H, m), 1.56 (5H, broad s), 1.68 (3H, broad s), 3.68~4.00 (8H, m). Anal. Found: C, 65.32; H, 9.55. Calcd. for $\text{C}_{14}\text{H}_{24}\text{O}_4$: C, 65.59; H, 9.44.

4,4-Ethylenedioxy-6-(1-methylethyl)cycloheptanone 12. A solution of **11** (3.0 g, 11.70 mmol), **10** (1.96 g, 11.67 mmol) and *p*-TsOH (20 mg) in dry benzene (70 ml) was refluxed for 4 hr. After cooling, the reaction mixture was washed with aq. NaHCO_3 , dried over Na_2CO_3 and concentrated. The residue was distilled to give **12** (3.0 g, 60.4%): bp 130~132°C/4 mmHg. IR $\nu_{\text{max}}^{\text{film}} \text{cm}^{-1}$: 1695 (s), 1290 (w), 1260 (w), 1210 (w), 1140 (m), 1100 (s), 1020 (m). NMR (100 MHz) $\delta_{\text{ppm}}^{\text{CCl}_4}$: 0.94 (6H, d, $J=6$ Hz), 1.44~1.94 (6H, m), 2.20~2.80 (4H, m), 3.88 (4H, s). MS m/z : 212 (M^+), 169 ($\text{M}^+ - \text{CHMe}_2$), 86 (100%). Anal. Found: C, 67.92; H, 9.45. Calcd. for $\text{C}_{12}\text{H}_{20}\text{O}_3$: C, 67.89; H, 9.50%.

2-(2-Ethyl-2-propenyl)-4,4-ethylenedioxy-6-(1-methylethyl)cycloheptanone 13. To a stirred solution of LDA (51 mmol) in dry THF (20 ml) prepared in the usual manner was added dropwise a solution of **12** (3.6 g, 16.96 mmol) in dry THF (15 ml) at -70°C . The mixture was stirred at -60°C ~ -70°C for 1 hr and then raised to room temperature. To this was added dropwise a solution of 3-bromo-2-ethyl-1-propene (7.6 g, 51.01 mmol) in dry THF (20 ml). The mixture was stirred for an additional 1 hr, poured into ice-cooled water and extracted with ether ($\times$ 3). The extract was washed with brine, dried over Na_2SO_4 and concentrated. The residue was chromatographed over SiO_2 (Mallinckrodt Silicar CC-7, benzene) to give **13** (2.72 g, 57.3%) with the recovered **12** (950 mg). The yield based on the unrecovered **12** was 76.4%. **13**: IR $\nu_{\text{max}}^{\text{film}} \text{cm}^{-1}$: 3070 (w), 1695 (s), 1640 (m), 1260 (w), 1220 (m), 1100 (s), 1050 (m), 1030 (m), 980 (m), 940 (m), 890 (m). NMR (100 MHz) $\delta_{\text{ppm}}^{\text{CCl}_4}$: 0.95 (6H, d, $J=6$ Hz), 1.02 (3H, t, $J=7$ Hz), 1.40~3.10 (13H, m), 3.85 (4H, s), 4.65 (1H, broad s), 4.72 (1H, broad s). MS m/z : 280 (M^+), 86 (100%).

4,4-Ethylenedioxy-6-(1-methylethyl)-2-(2-oxobutyl)cycloheptanone 14. Ozone was bubbled into a solution of **13** (2.6 g, 9.27 mmol) in CH_2Cl_2 (10 ml) and MeOH (15 ml) at -50°C . After **13** had not been detected on TLC, introduction of ozone was continued for 10 min. The excess ozone was removed by purging with nitrogen. To the solution was added Me_2S (5 ml) and the mixture was left at room temperature for 30 min. The reaction mixture was concentrated and the residue was diluted with ether. The ether layer was washed with brine, dried over Na_2SO_4 and concentrated to give **14** (2.61 g, 98.8%). IR $\nu_{\text{max}}^{\text{film}} \text{cm}^{-1}$: 1695 (s), 1295 (w), 1140 (s), 1100 (s), 1030 (s), 990 (m), 940 (m). NMR (100 MHz) $\delta_{\text{ppm}}^{\text{CCl}_4}$: 0.90 (6H, d, $J=6$ Hz), 1.42 (3H, t, $J=8$ Hz), 1.40~1.90 (6H, m), 2.10~2.60 (6H, m), 3.14~3.30 (1H, m), 3.80~4.00 (4H, m).

MS m/z : 282 (M^+), 86 (100%).

5,5-Ethylenedioxy-1-methyl-7-(1-methylethyl)-2,3,3a,4,5,6,7,8-octahydroazulen-2-one **15**. The crude diketone **14** (2.5 g, 8.85 mmol) was added to a stirred solution of 1 N NaOH (30 ml) and EtOH (20 ml), and the mixture was refluxed for 10 min. After cooling, the reaction mixture was poured into water and extracted with ether ($\times 3$). The extract was washed with brine ($\times 2$), dried over Na_2SO_4 and concentrated to give **15** (1.6 g, 68.4%), which was not further purified. IR $\nu_{\text{max}}^{\text{film}} \text{cm}^{-1}$: 1690 (s), 1630 (s), 1260 (w), 1220 (w), 1160 (s), 1040 (m). NMR (60 MHz) $\delta_{\text{ppm}}^{\text{CDCl}_3}$: 0.90 (6H, d, $J=6$ Hz), 1.20–2.80 (11H), 1.58 (3H, s), 3.84 (4H, m). MS m/z : 264 (M^+).

5,5-Ethylenedioxy-1-methyl-7-(1-methylethyl)-3,3a,4,5,6,7,8,8a-octahydroazulene **17**. A solution of crude **15** (1.28 g, 4.84 mmol) and *p*-TsNHNH₂ (1.00 g, 5.37 mmol) in dry THF (6 ml) was stirred at room temperature for 12 hr. The solvent was evaporated and the residue evacuated by pump for 10 hr. To this was added dry CHCl_3 (12 ml) and then catechol borane (0.66 ml, 5.8 mmol) under Ar at 4°C and the mixture was stirred for 2 hr. To this was added $\text{AcONa} \cdot 3\text{H}_2\text{O}$ (1.98 g, 14.55 mmol) in one portion and the mixture was refluxed for 1 hr. After cooling, the reaction mixture was diluted with CHCl_3 , washed with 1 N NaOH and water, dried over Na_2SO_4 and concentrated. The residue was chromatographed over SiO_2 (Mallinckrodt Silicar CC-7, hexane) to give **17** (188 mg, 15.5%; 10.4% overall from **13**): IR $\nu_{\text{max}}^{\text{film}} \text{cm}^{-1}$: 1650 (w), 1240 (m), 1210 (m), 1170 (m), 1140 (m), 1090 (s), 1030 (m). NMR (60 MHz) $\delta_{\text{ppm}}^{\text{CDCl}_3}$: 0.85 (6H, d, $J=6$ Hz), 1.10–2.60 (12H), 1.60 (3H, broad s), 3.80 (4H, broad s), 5.14 (1H, broad). MS m/z : 250 (M^+).

1-Methyl-7-(1-methylethyl)-3,3a,4,5,6,7,8,8a-octahydroazulen-5-one **18**. A solution of **17** (188 mg, 0.75 mmol) in AcOH (0.9 ml), water (0.3 ml), and THF (2 ml) was refluxed for 4 hr. After cooling, the reaction mixture was diluted with ether and poured into aq. NaHCO_3 . The ether layer was washed with water, dried over MgSO_4 and concentrated. The residue was chromatographed over SiO_2 (hexane) to give **18** (150 mg, 96.8%). IR $\nu_{\text{max}}^{\text{film}} \text{cm}^{-1}$: 3040 (w), 1695 (s), 1270 (m), 1260 (m), 1240 (m), 1030 (m). NMR (100 MHz) $\delta_{\text{ppm}}^{\text{CDCl}_3}$: 0.92 (3H, d, $J=6$ Hz), 0.98 (3H, d, $J=6$ Hz), 1.30–2.00 (5H), 1.66 (3H, s), 2.00–2.60 (7H), 5.32 (1H, broad). MS m/z : 206 (M^+).

Methyl 1-methyl-7-(1-methylethyl)-5-oxo-3,3a,4,5,6,7,8,8a-octahydroazulene-4-carboxylate **21**. To a suspension of dimethyl carbonate (1 ml), NaH (55% mineral oil dispersion, 134 mg, 3.04 mmol, the mineral oil being removed by washing with *n*-hexane) in dry benzene (0.5 ml) was added dropwise **18** (158 mg, 0.77 mmol) in dry benzene (0.5 ml) at 50°C under Ar and the mixture was stirred for 1 hr. After refluxing for an additional 1 hr and cooling to room temperature, AcOH (1 ml) and water were

added. The mixture was extracted with ether. The extract was washed with aq. NaHCO_3 and water, dried over MgSO_4 and concentrated to give **21** (198 mg). IR $\nu_{\text{max}}^{\text{film}} \text{cm}^{-1}$: 3020 (w), 1735 (s), 1700 (s), 1260 (m), 1240 (m), 1200 (m), 1160 (m), 1140 (m), 1020 (m). NMR $\delta_{\text{ppm}}^{\text{CDCl}_3}$: 0.88 (3H, d, $J=6$ Hz), 0.98 (3H, d, $J=6$ Hz), 1.30–2.00 (5H), 1.64 (3H, broad s), 2.00–2.80 (6H), 3.60 (3H, s), 5.25 (1H, m). MS m/z : 264 (M^+).

Methyl 4-hydroxy-1-methyl-7-(1-methylethyl)-3,3a,4,5,6,7,8,8a-octahydroazulene-5-carboxylate **22**. To a cooled solution of **21** (198 mg, 0.75 mmol) in MeOH (0.5 ml) was added NaBH_4 (58 mg, 1.53 mmol) and the mixture was stirred for 40 min. 50% AcOH (1 ml) was added to decompose the excess NaBH_4 and the mixture was diluted with ether. The ether layer was washed with aq. NaHCO_3 and brine, dried over MgSO_4 and concentrated. The residue was chromatographed over SiO_2 (Mallinckrodt Silicar CC-7, hexane) to give **22** (83 mg, 42% from **18**). IR $\nu_{\text{max}}^{\text{film}} \text{cm}^{-1}$: 3420 (m), 3020 (w), 1715 (s), 1270 (m), 1200 (m), 1160 (m), 1120 (w), 1020 (m). NMR (100 MHz) $\delta_{\text{ppm}}^{\text{CDCl}_3}$: 0.88 (6H, d, $J=6$ Hz), 1.20–3.00 (11H), 1.63 (3H, broad s), 3.70 (3H, s), 4.10–4.40 (1H, m), 5.23 (1H, m). MS m/z : 266 (M^+), 248 ($M^+ - \text{H}_2\text{O}$), 41 (100%).

Methyl 4-benzoyloxy-1-methyl-7-(1-methylethyl)-3,3a,4,5,6,7,8,8a-octahydroazulene-5-carboxylate **23**. To a cooled solution of **22** (83 mg, 0.31 mmol) in dry pyridine (1 ml) was added benzoyl chloride (90 mg, 0.64 mmol). The mixture was stirred at 0–5°C for 1 hr and then allowed to stand in a refrigerator for 2 days. The reaction mixture was poured into cold 10% HCl and extracted with ether. The extract was washed with water, aq. NaHCO_3 and brine, dried over MgSO_4 and concentrated. The residue was chromatographed over Al_2O_3 (Wako, benzene) to give **23** (111 mg, 96%). IR $\nu_{\text{max}}^{\text{film}} \text{cm}^{-1}$: 3020 (w), 1735 (shoulder), 1715 (s), 1595 (w), 1275 (s), 1200 (m), 1170 (m), 1150 (m), 1105 (s), 1060 (m), 1020 (m), 710 (m). NMR (60 MHz) $\delta_{\text{ppm}}^{\text{CDCl}_3}$: 0.75 (3H, d, $J=6$ Hz), 0.85 (3H, d, $J=6$ Hz), 1.10–2.90 (11H), 1.65 (3H, broad s), 3.52 (3H, s), 5.30 (1H, broad s), 5.70 (1H, m), 7.25–7.80 (3H, m), 7.85–8.30 (2H, m). MS m/z : 370 (M^+), 339 ($M^+ - \text{OMe}$), 284 ($M^+ - \text{PhCO}_2\text{H}$, 100%).

Methyl 1-methyl-7-(1-methylethyl)-3,3a,4,5,6,7,8,8a-hexahydroazulene-4-carboxylate **24**. To a cooled 0.62 N solution of *t*-BuOK in *t*-BuOH (1.6 ml) was added a solution of **23** (111 mg, 0.30 mmol) in dry benzene (1 ml). The mixture was stirred for 80 min and then acidified with 50% aq. AcOH. The mixture was extracted with ether. The extract was washed with aq. NaHCO_3 and brine, dried over MgSO_4 and concentrated. The residue was purified by preparative TLC (SiO_2 , benzene) to give **24** (35 mg, 47%). IR $\nu_{\text{max}}^{\text{film}} \text{cm}^{-1}$: 3060 (w), 1720 (s), 1630 (w), 1300 (w), 1250 (s), 1200 (w), 1110 (m), 1070 (m), 1050 (m), 1010 (w). NMR (60 MHz) $\delta_{\text{ppm}}^{\text{CDCl}_3}$: 0.90 (6H, d, $J=6$ Hz), 1.65 (3H, broad s), 1.20–3.00 (9H), 3.63 (3H, s), 5.25 (1H, m),

6.60~7.00 (1H, m). MS m/z : 248 (M^+), 145 (100%).

1-Methyl-7-(1-methylethyl)-3,3a,6,7,8,8a-hexahydroazulene-4-carboxylic acid 1. A mixture of **24** (35 mg, 0.14 mmol) and 7% KOH (1.5 ml, 0.25 mmol) in MeOH (2 ml) was stirred at 60°C for 4 hr. After cooling, the reaction mixture was diluted with water and extracted with ether ($\times 3$). The aqueous layer was acidified with 0.5 N HCl and extracted with ether ($\times 3$). The extract was washed with brine, dried over Na_2SO_4 and concentrated to give crude crystals. Recrystallization from hexane-ether gave **1** (8 mg, 24.3%): mp 156.5~158°C. IR $\nu_{\text{max}}^{\text{nujol}}$ cm^{-1} : 3400~2300 (m), 1680 (s), 1625 (m), 1300 (m), 1280 (m), 1270 (s), 1210 (m), 1110 (w), 1090 (w), 1040 (w), 1000 (w), 940 (w), 905 (w). ^{13}C -NMR (25 MHz) $\delta_{\text{ppm}}^{\text{CDCl}_3}$: 14.6, 19.0, 19.5, 30.5, 32.5, 32.9, 37.3, 40.9, 44.8, 48.9, 123.4, 137.0, 142.2, 143.9, 173.4. ^1H -NMR (500 MHz) $\delta_{\text{ppm}}^{\text{CDCl}_3}$: 0.81 (3H, d, $J=6.8$ Hz, isopropyl Me), 0.82 (3H, d, $J=6.8$ Hz, isopropyl Me), 1.30 (1H, m, C-8 α H), 1.54 (6H, m, isopropyl CH), 1.60 (3H, br s, C-1 Me), 1.69 (2H, m, C-7 H), C-8 β H), 1.98 (1H, m, C-3 α H), 2.09 (1H, br d-d, $J_{6\beta-5}=8.4$ Hz, $J_{6\beta-6\alpha}=17.6$ Hz, $J_{6\beta-7}=\text{OH}$, C-6 β H), 2.17 (1H, m, $J_{6\alpha-6\beta}=17.6$ Hz, $J_{6\alpha-7}=9.8$ Hz, $J_{6\alpha-5}=3.0$ Hz, C-6 α H), 2.61 (1H, m, $J_{8\alpha-3\alpha}=9.7$ Hz, $J_{8\alpha-8\alpha}=12.0$ Hz, C-8 α H), 2.74 (1H, m, C-3 β H), 2.83 (1H, m, $J_{3\alpha-5}=2.7$ Hz, $J_{3\alpha-8\alpha}=9.7$ Hz, C-3 α H), 5.26 (1H, br s, C-2 H), 6.92 (1H, d-d-d, $J_{5-3\alpha}=2.7$ Hz, $J_{5-6\alpha}=3.0$ Hz, $J_{5-6\beta}=8.4$ Hz, C-5 H). The data size of the time domain, 2D-COSY 45 spectra used the pulse sequence [2.5 sec-90°- t_1 -45°- t_2 -FID] was a 512 (f_1) $\times$ 2K (f_2) matrix. Fourier transformation was performed with zero filling in both the f_1 and f_2 directions. In order to improve the resolution of the spectrum, a sinebell function was used in both the f_1 and f_2 directions. The chart shown in Fig 4 is the contour plot of a symmetrical treatment. MS m/z : 234 (M^+ , 94), 191 (92), 173, 147, 145 (100), 133, 119, 105 (90), 91 (88), 79, 69, 55, 41. High Mass. Found: 234.1647. Calcd. for $\text{C}_{15}\text{H}_{22}\text{O}_2$: 234.1620.

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