SYNTHESIS AND CHARACTERIZATION OF [8](3,6)AZEPINOPHANE AND [8](3,6)OXEPINOPHANES

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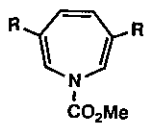
Abstract - [8](3,6)Azepinophane (methyl 3,6-octano-1H-azepine-1-carboxylate) and [8](3,6)oxepinophane (3,6-octanooxepin) were synthesized from bicyclo[8.2.2]undecadiene, and structural features of them were also studied on the basis of their spectral data. The effect of the substituents at 3 and 6 positions on the structure of 1H-azepine ring was elucidated by comparison of several 3,6-dialkyl-1H-azepine derivatives with the title azepinophane.

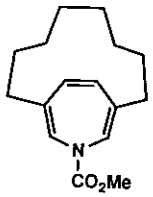
Results and Discussion

In a series of 3,6-disubstituted 1H-azepines 1c,[1] 1d,[2] 1e[3] and 1f,[4] the characteristic reaction of nitrene leading directly to corresponding bicyclic heterocycles, pyrrolo[3,2-b]pyrrole derivatives has recently been reported. A correlation between the reactivity of nitrene and substituents on 1H-azepine ring is particularly interesting. The (3,6)azepinophane system is the first to be successfully synthesized.



1a-f

a: R=H d: R=^{t}Bu
b: R=Me e: R=$SiMe_3$
c: R=^{i}Pr f: R=CO_2Me



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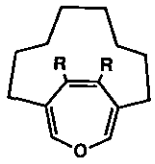


3a-b

a: R=H
b: R=CO_2Me

Synthesis of [8]p-cyclophane (5) from (i,o)-bicyclo[8.2.2]tetradecadiene (4) by means of dehydrogenation using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone was reported by Gassman *et al.*[5] However, though the mechanism is unknown so far, the present authors achieved a direct conversion from the diene 4 to [8]p-cyclophane by treating with equimolar methyl N,N-dichlorourethane (DCU) in benzene at 5℃ in 83% yield. Owing to the thermal instability of p-cyclophane 5, the ordinary thermal decomposition reaction of methyl azidoformate as a nitrene source could not be applied to the formation of 1H-azepine ring. The reaction of nitrene, generated by a base-promoted α-elimination of methyl N-(p-nitrobenzenesulfonoxy)-carbamate using triethylamine at 5℃ in dichloromethane, with [8]p-cyclophane (5) resulted in the formation of [8](3,6)azepinophane (methyl 3,6-octano-1H-azepine-1-carboxylate)(2) and methyl N-(2,5-octanophenyl)carbamate (6) in 5.9% and 3.9% yield, respectively. The former may be formed by the expected valence tautomerization *via* intermediate 7, and the latter from a C-N bond cleavage of intermediate 8.

A temperature-dependence behavior on the basis of restricted rotation of $-CO_2Me$ group on the 1H-azepine ring was observed in the ^{1}H-nmr (500 MHz) spectrum of the azepinophane. The activation enthalpy (ΔH=12.2 kcal/mol) of this restricted rotation was determined by means of DNMR method. Similar dynamic behaviors were also observed for all of the other azepines (1a-f). The chemical shifts of ring protons of 1a-d and 2, which were measured above each coalescence temperature, were shown in Figure 1. There existed a marked relation between the chemical shift of γ-proton of the azepine ring and bulkiness of the alkyl substituents in the series of 3,6-disubstituted azepines, that is to say, the more the bulkiness of the substituents increases, the more the shielding of γ-proton decreases. In addition, the electronic spectra of 1a and 1d, shown in Figure 2 together with spectrum of 2, displayed a similar tendency, that is, an obvious hypsochromic shift was observed in the case of 1d compared to that of 1a.

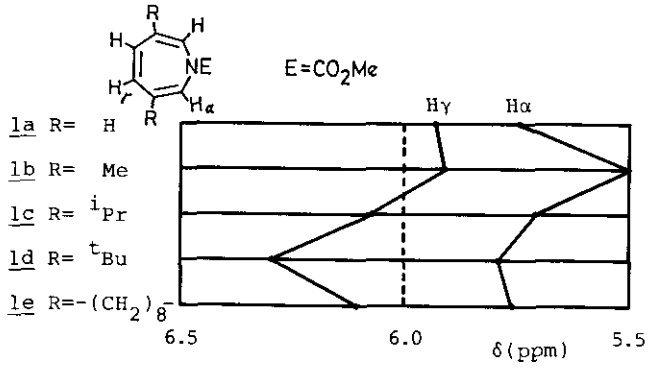
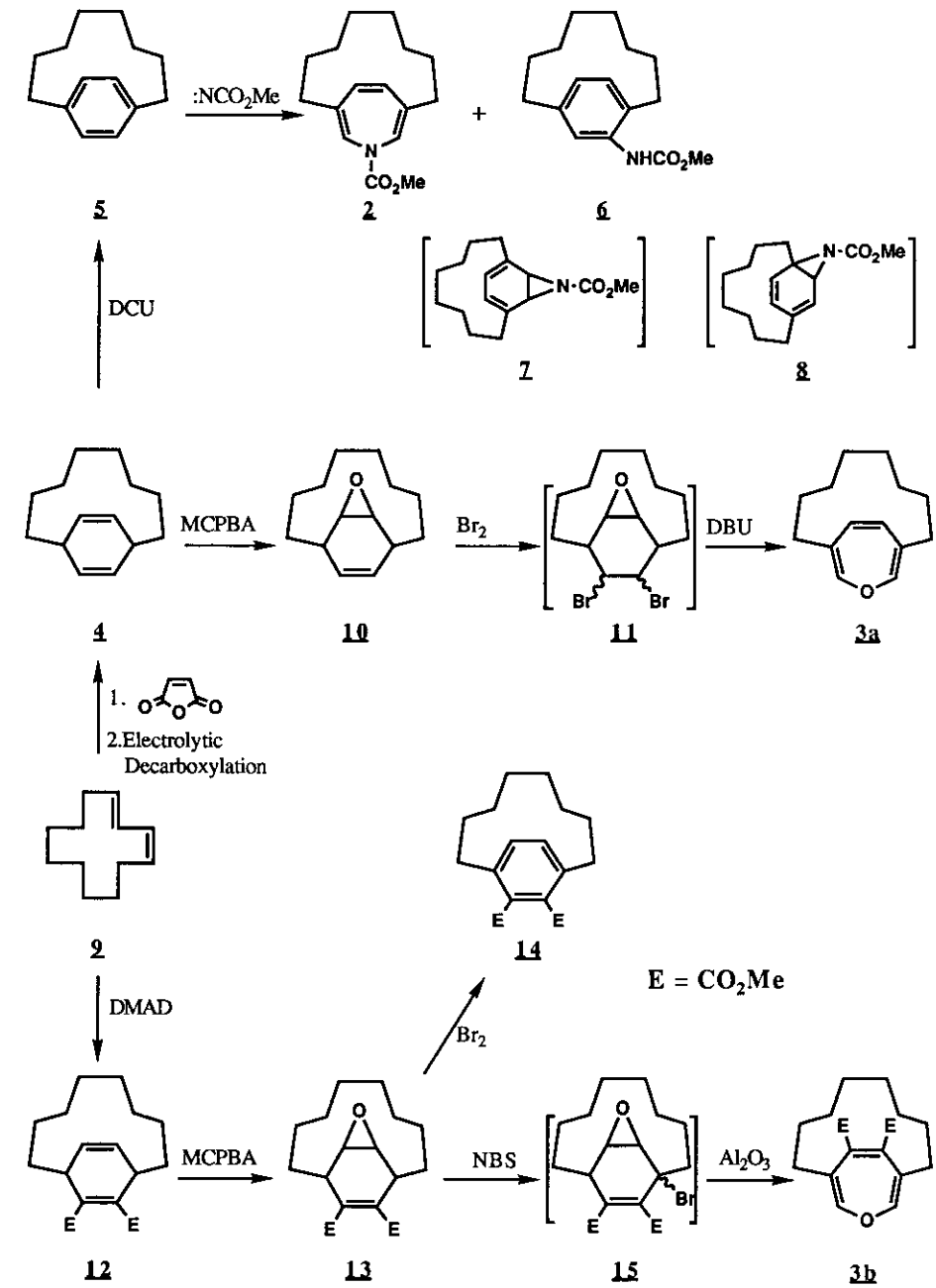


Figure 1 Chemical shift of α- and γ-protons of 1H-azepine derivatives

Scheme 1


:NCO2Me
+
NHCO2Me
N
CO2Me
5
2
6
DCU
N·CO2Me
N·CO2Me
7
8
MCPBA
Br2
DBU
O
Br
Br
4
10
11
3a
1.
2.Electrolytic
Decarboxylation
9
14
E = CO2Me
DMAD
Br2
MCPBA
NBS
Al2O3
E
E
Br
12
13
15
3b

These data suggest that the bulky alkyl substituents at 3,6-positions of the azepine ring deform the seven-membered structure effectively. In the case of 2, the effect of the octano-bridge on the seven-membered ring structure is apparently similar to that of bulky alkyl substituents. The fully optimized MNDO[6] calculation (Table 1) shows that the angles of θ_1 and θ_2, which are defined by Figure 3, increased as the bulkiness of the substituents increased. In particular, θ_1

Table 1 Selected angles (degrees) of 1H-azepine derivatives based on MNDO optimized structures

Compound	θ_1	θ_2	∠C3 or ∠C6
1a	41.2	20.4	127.8
1b	46.8	26.2	123.4
1d	50.2	35.3	118.5
2	47.8	33.6	121.4

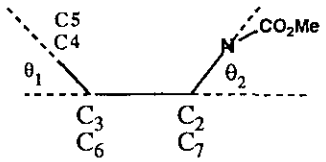


Figure 3 Side view of azepine ring. θ_1, θ_2 are dihedral angles of planes C3-C6-C4 and C2-C7-N and plane C2-C7-C3, respectively

shows a remarkable variation. The increasing in the angle θ_1 is due to decreasing in the internal angles of C_3 and C_6 compared to those of 1a. Meanwhile, in the case of azepinophane 2, we expect that the angles θ_1 and θ_2 become wider by a mechanical tension between C_3 and C_6 which is inferred from phane-structure.

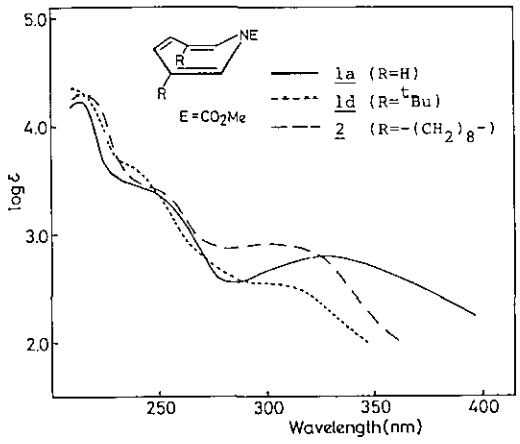


Figure 2 Electronic spectra of 1a,1d and 2 in cyclohexane

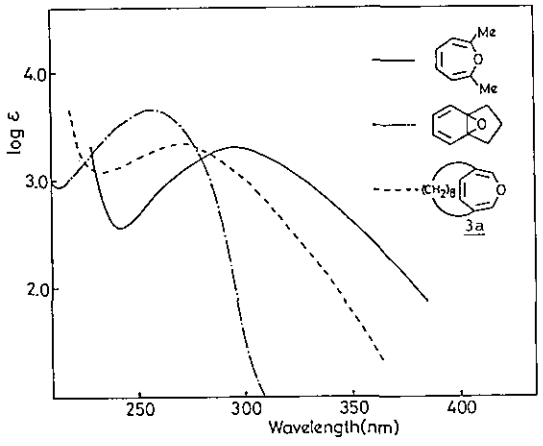


Figure 4 Electronic spectra of 3a, 2,7-dimethyloxepin and 3a,7a-indanoxide in cyclohexane

[n](3,6)Oxepinophanes (n=5,6 and 10) have been synthesized as the precursors of corresponding p-cyclophanes. However, they have one or more substituents on the ring inevitably.[7] We report here the first synthesis of [8](3,6)oxepinophane which has no substituents on the ring. Epoxidation reaction of bicyclodiene 4 using m-chloroperbenzoic acid (MCPBA) gave 12-oxatricyclo[8.3.2.$0^{11,13}$]pentadec-

14-ene (10) as a colorless oil in 98% yield.[5] This epoxide was brominated with an equivalent of bromine at 0℃ in dichloromethane and the product 11 was utilized without purification for the next step. A dehydrobromination and consequent spontaneous ring expansion of the dibromide was accomplished by refluxing in pyridine with four equivalents of 1,8-diazabicyclo[3.2.0]undec-7-ene (DBU) for 100 min. [8](3,6)oxepinophane (3a) was thus obtained as colorless needles in 50% yield from the epoxide 10.

Dimethyl bicyclo[8.2.2]tetradeca-11,13-diene-11,12-dicarboxylate (12), which was obtained by the Diels-Alder reaction of *cis,trans*-1,3-cyclododecadiene (9) with dimethyl acetylenedicarboxylate (DMAD) in 23% yield, was epoxidized to 13 in 88% yield using MCPBA. When this epoxide 13 was treated with an equivalent of bromine in dichloromethane at -78℃, an epoxy-ring opening and consequent aromatization occurred to give unexpected dimethyl 2,5-octanophthalate (14) in 7.8% yield instead of an ordinary bromine adduct. Next, the usual allylic bromination and subsequent dehydrobromination were attempted to the epoxide 13, yielding finally dicarboxylate of [8](3,6)oxepinophane (3b) as a colorless oil in 5.5% yield through valence isomerization.

An interesting question is that what kind of tautomeric character shows in the [8](3,6)oxepinophane system. In the ^{1}H-nmr spectrum, the upfield shift of the α-protons of oxepin compared to those of 4,5-dihydrooxepin has been explained on account of the rapid valence isomerization between oxepin and benzene oxide at room temperature.[8] The chemical shift of α-protons of 3a, 3b and related compounds are listed in the Table 2. The chemical shifts of α-protons of oxepino-

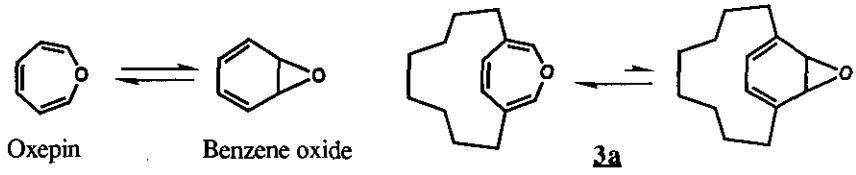


Table 2 Chemical shifts of α-protons on oxepin ring and related compounds

Compounds		Oxepin	3a	3b	
H_α (ppm)	3.3	5.2	6.0	6.2	6.1

phanes 3a and 3b were close to that in 4,5-dihydrooxepin rather than in oxepin, tautomeric character of which was confirmed from Table 2. This clearly indicated that the oxepinophane 3a and 3b favorably maintained a triene structure in contrast to oxepin's features. The electronic spectra of 3a, 3a,7a-indanoxide and 2,7-dimethyloxepin which inhibited the benzene oxide structure by the steric effect of two methyl groups (Figure 4) showed a similarity both in figure and intensity for 3a and 2,7-dimethyloxepin. It has been known that the electronic spectrum of oxepin was influenced by the polarity of solvents used owing to the valence isomerization. In the case of oxepinophane 3a, no such significant change in the spectrum was observed. Even in methanol-water (1:1 v/v), the triene structure of 3a was confirmed obviously from the spectrum. Further, a hypsochromic shift by 25 nm compared to the absorption maximum of 2,7-dimethyloxepin was observed in it. We consider that this shift is attributable to deformation of the triene system by octamethylene bridge.

ACKNOWLEDGEMENT

We are grateful to the SC-NMR laboratory of Okayama university for the measurement of ^{1}H- and ^{13}C-nmr spectra.

EXPERIMENTAL SECTION

General Information. Melting points were determined on a Yanagimoto micro melting point apparatus and were uncorrected. Infrared spectra were recorded on a Jasco IRA-1 spectrophotometer. Electronic spectra were measured on a HITACHI Model 200-10 or on a HITACHI 228 spectrophotometer. Nmr spectra were recorded in $CDCl_3$ (unless otherwise indicated) on a JEOL PMX-60 (for ^{1}H) or on a Varian VXR-500 (for ^{1}H or ^{13}C). Elemental analysis was carried out on a Yanagimoto MT2 CHN Corder. MNDO calculation was performed on a NEC ACOS1000 computer. Bicyclo[8.2.2]tetradeca-11,13-diene and 12-oxatricyclo[8.3.2.$0^{11,13}$]pentadec-14-ene were prepared according to Gassman's report.[5]

[8]Paracyclophane. To a solution of 4 (2.08 g, 10.9 mmol) in dry benzene (50 ml) was added a solution of DCU (1.57 g, 10.9 mmol) in dry benzene (20 ml) gradually under nitrogen at a rate to maintain the reaction temperature at 5-10℃. The reaction mixture was stirred at the same temperature for 10 h and then at room temperature for 5 h. A 20 % aq. $NaHSO_3$ (200 ml) was added at 5-10℃, and the mixture was stirred for 1 h. The organic layer was separated and the aqueous phase was extracted with ether. Chromatography on a silica gel column (hexane : ethyl acetate = 9:1 v/v) of the ether solution gave 1.70 g (83 % yield) of 5,

which was identical in all respects with the literature compound.[9]

Reaction of [8]paracyclophane with nitrene. To a stirred suspension of N-(p-nitrosulfonoxy)urethane (604 mg, 2.19 mmol) and 5 (2.06 g, 7.89 mmol) in dichlromethane (1.4 ml) was added slowly a solution of triethylamine (240 mg) in dichloromethane (0.5 ml) at 0°C. After 0.5 h at 0°C and 2 h at room temperature, hexane (50 ml) was added to the reaction mixture. The resulting precipitate was filtered and the filtrate was concentrated in *vacuo* and chromatographed on a silica gel column. Elution with a mixed solvent (hexane : ethyl acetate = 9 : 1 v/v) gave methyl 3,6-octano-1H-azepine-1-carboxylate (2) in 5.9 % yield, methyl 2,5-octanophenylcarbamate (6) in 3.9 % yield and unreacted 5 (1.94 g).

2 : pale yellow oil; Ir(neat) 1715 cm^{-1} (C=O); ^{1}H-nmr(CCl_4) δ 0.70-2.40(m, 16H), 3.70 (s, 3H), 5.76 (s, 2H), 6.10 (s, 2H); ^{13}C-nmr δ 21.74 (t), 26.05 (t), 26.57 (t), 31.99 (t), 52.94 (q), 127.48 (d), 133.49 (s,d) 154.64 (s); λ_{max} (cyclohexane) 216 ($\log\varepsilon$ = 4.30), 246 (3.43) 300 (3.90) 330 nm (2.73): Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.39. Found: C, 73.12; H, 8.95; N, 5.21; ms Calcd for $C_{16}H_{23}NO_2$, 261.1723: Found 261.1716.

6 : pale yellow oil; Ir(neat) 3330 (N-H), 1713 cm^{-1} (C=O); ^{1}H-nmr(CCl_4) δ 0.60-1.80 (m, 12H), 2.47 (m, 4H), 3.66 (s, 3H), 6.26 (br, 1H), 6.86(dd, J=8.0, 2.0 Hz, 1H), 7.25(d, J=8.0 Hz, 1H), 7.59 (d, J=2.0 Hz, 1H): Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.39. Found: C, 73.68; H, 8.72; N, 5.26.

12-Oxatricyclo[8.3.2.0^{11,13}]pentadec-14-ene (10). To a solution of 4 (0.537 g, 2.83 mmol) in dry dichloromethane (5 ml) was added gradually a solution of MCPBA (0.54 g, 3.13 mmol) in dry dichloromethane (5 ml) under nitrogen at 0°C. After stirring for an additional hour at the same temperature, the mixture was stirred at room temperature for 1 h. The resulting solution was washed successively with aq. Na_2SO_3 and satd. $NaHCO_3$, and dried over anhydrous $MgSO_4$. The epoxide 10 was obtained as a colorless oil (0.579 g) in 98 % yield.

10: Ir(neat) 1660, 870, 765 cm^{-1}; ^{1}H-nmr δ 1.0-1.9 (16H), 2.67 (m, 2H), 3.09 (m, 1H), 3.25 (m, 1H), 5.48(m, 2H); ^{13}C-nmr δ 23.19 (t), 24.66 (t), 25.29 (t), 25.71 (t), 25.97 (t), 28.37 (t), 28.76 (t), 31.22 (t), 31.97 (d), 37.34 (d), 55.17 (d), 58.14 (d), 127.56 (d), 130.43 (d): Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.23; H, 10.81.

[8](3,6)Oxepinophane (3,6-Octanooxepin) (3a) To a solution of epoxide 10 (0.490 g, 2.37 mmol) in dry dichloromethane (7 ml) was added slowly a solution of distilled bromine (0.380 g, 2.37 mmol) in dry dichloromethane (3 ml) under nitrogen in

a dry ice-acetone bath. The reaction mixture was stirred for 6 h at room temperature and evaporated under reduced pressure, leaving a light brown oil. Chromatography on an alumina column and elution with a mixed solvent (hexane : ethyl acetate = 4 : 1 (v/v)) gave 0.558 g (64 % yield) of dibromide as a pale yellow oil. Without further purification, the dibromide was dissolved in a mixture of dry pyridine (10 ml) and DBU (0.93 g, 6.1 mmol) and heated to a reflux for 100 min under nitrogen. After cooling, the reaction mixture was poured into 2.4N hydrochloric acid (500 ml) and extracted with dichloromethane. The organic layer was washed with satd. $NaHCO_3$ and dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (hexane) to obtain 3a as colorless needles in 78 % yield.

3a: mp 47℃; Ir(neat) 1610, 1570, 705 cm^{-1}; ^{1}H-nmr δ 0.85-1.70 (12H), 1.85 (m, 2H), 2.20 (m, 2H), 5.96 (s, 2H), 6.26 (s,2H); ^{13}C-nmr δ 21.63 (t), 26.05 (t), 26.75 (t), 29.43 (t), 129.22 (s), 132.43 (d), 138.72 (d); λ_{max}(cyclohexane) 214 ($\log \varepsilon$ =3.80), 271 (3.33) nm: Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.17; H, 9.92

Dimethyl bicyclo[8.2.2]tetradeca-11,13-diene-11,12-dicarboxylate (12) A mixture of diene 9 (7.26 g, 44.2 mmol) and dimethyl acetylenedicarboxylate (6.40 g, 45.1 mmol) was heated in a sealed Pyrex tube at 200℃ for 3 h. Chromatography on a silica gel column (ethyl acetate : hexane = 1:9 v/v) gave 3.12 g (23 % yield) of 12 as colorless needles.

12: mp 56-58℃; Ir(neat) 1710, 1640, 1605 cm^{-1}; ^{1}H-nmr(CCl_4) δ 0.90-2.20 (16H), 3.09 (m, 1H), 3.49 (m, 1H), 3.65 (s, 3H), 3.68 (s, 3H), 5.59-5.95 (m, 2H); λ_{max} (cyclohexane) 224 nm ($\log \varepsilon$, 3.64): Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.38; H, 8.51.

Dimethyl 12-oxatricyclo[8.3.2.$0^{11,13}$]pentadec-14-ene-14,15-dicarboxylate (13) A solution of 12 (1.15 g, 3.75 mmol) and MCPBA (795 mg, 4.60 mmol) in dry dichloromethane (20 ml) was stirred at room temperature for 14 h. The solution was washed successively with 10 % aq. Na_2SO_3, satd. $NaHCO_3$ and water, and dried over anhydrous $MgSO_4$. The solution was evaporated under reduced pressure and the residue was chromatographed on a silica gel column (ethyl acetate : hexane = 2:8 v/v), giving epoxide 13 as colorless needles in 88 % yield.

13: mp 72-73℃; Ir(nujol) 1750, 1622 cm^{-1}; ^{1}H-nmr δ 1.10-1.63 (15H), 2.01 (m, 1H), 3.19 (t, J=3.3 Hz, 1H), 3.22 (br t, J=5.7 Hz, 1H), 3.31 (dd, J=4.2, 1.0 Hz, 1H), 3.53 (br, 1H), 3.69 (s, 3H), 3.80 (s, 3H); ^{13}C-nmr δ 22.64 (t), 23.99 (t), 24.80

(t), 24.89 (t), 26.00 (t), 27.85 (t, two carbons), 28.44 (t), 33.61 (d), 37.26 (d), 51.97 (q), 52.19 (q), 53.98 (d), 57.30 (d), 127.14 (s), 144.96 (s), 165.39 (s), 168.26 (s); λ_{max}(cyclohexane) 226 nm ($\log \varepsilon$ =3.66): Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 67.13; H, 8.04.

Reaction of epoxide 13 with bromine. To a stirred solution of epoxide 13 (157 mg, 0.487 mmol) in dry dichloromethane (3 ml) was added gradually a solution of bromine (80 mg, 0.50 mmol)in dry dichloromethane (5 ml) under nitrogen in a dry ice-acetone bath. The reaction mixture was stirred for 4 h at room temperature and evaporated under reduced pressure. A brown residue was chromatographed on an alumina column (ethyl acetate : hexane = 3:7 v/v) and then on a reverse-phase silica gel column (FUJI GEL ODS-Q water : methyl alcohol = 3:17 v/v). The formation of usual bromine adducts could not be observed and dimethyl 2,5-octanophthalate (14) was obtained instead as a colorless oil in 7.8 % yield.

14: Ir(neat) 1720 cm^{-1}; ^{1}H-nmr δ -0.05 (br, 2H), 0.47 (m, 2H), 0.81 (m, 2H), 1.04 (m, 2H), 1.40 (m, 2H), 1.61 (m, 2H), 2.49 (ddd, J=13.2, 9.1, 5.2 Hz, 2H), 3.12(dt, J=13.2, 5.5 Hz, 2H), 3.83 (s, 6H), 7.26 (s, 2H); ^{13}C-nmr δ 25.46 (t), 29.24 (t), 30.34 (t), 33.90 (t), 52.33 (q), 132.08 (s), 132.88 (d), 140.66 (s), 168.43 (s): Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 70.78; H, 7.88.

Dimethyl 3,6-octanooxepin-4,5-dicarboxylate (3b). A stirred solution of epoxide 13 (3.86 g, 12.0 mmol), finely granulated N-bromosuccinimide (2.42 g, 13.6 mmol) and a catalytic amount of benzoyl peroxide in dry benzene (60 ml), was refluxed for 17 h under nitrogen stream. After cooling and evaporation of solvent, the residue was chromatographed on an alumina column (ethyl acetate : hexane = 1:9 v/v) for the purpose of dehydrobromination. The eluent was concentrated and chromatographed on a reverse-phase silica gel column (FUJI GEL ODS-Q, water : methanol = 1:9 v/v), giving 3b as a colorless oil in 5.5 % yield.

3b: Ir(neat) 1715, 1620, 1600 cm^{-1}; ^{1}H-nmr δ 0.97-1.35 (10H), 1.48 (m, 2H), 1.81 (ddd, J=14.2, 11.4, 2.6Hz, 2H), 2.43 (m, 2H), 3.73 (s, 6H), 6.17 (d, J=1.6Hz, 2H); ^{13}C-nmr δ 22.21 (t), 25.28 (t), 25.87 (t), 28.42 (t), 52.27 (q), 126.79 (s), 138.41 (s), 145.07 (d), 166.62 (s); λ_{max}(cyclohexane) 282 nm ($\log \varepsilon$ =3.36): Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.23; H, 7.43.

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