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An Approach to the Stereoselective Synthesis of Nidifocene. II.[1] Total Synthesis of (±)-Dehalogenonidifocene

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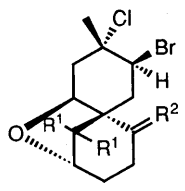
The total synthesis of (±)-dehalogenonidifocene (3), a potential key intermediate for the total synthesis of (±)-nidifocene (1), is described, in which the key steps are the construction of the basic tricyclic skeleton and the regioselective introduction of the double bond. Construction of the tricyclic skeleton could be achieved by the intramolecular Michael-type addition of the hydroxyl group of the *exo*-methylene compound 6, and the reduction of the conjugated diene moiety of 9 with ytterbium in liquid ammonia afforded the target molecule in a regioselective manner.

Keywords dehalogenonidifocene; nidifocene; stereoselective synthesis; photoisomerization; tricyclic skeleton; metal–ammonia reduction

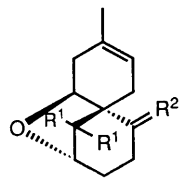
A number of halogenated sesquiterpenes of chamigrane type have been isolated from marine organisms, such as the red algae of genus *Laurencia* and the molluscs of genus *Aplysia*.[2] They are attractive targets for synthetic organic chemists[3,4] because of their specific spiro[5.5]undecane skeleton and the fact that some of these compounds have been reported to have some interesting biological activities, such as antibacterial,[5] antitumor,[6] and antiviral activities.[7] Nidifocene (**1**), isolated from *Laurencia nidifica* by Erickson and coworkers,[8] is one such compound, having a unique tricyclic structure containing a spiro[5.5]undecane skeleton.

In the previous paper,[1] we have described the stereoselective synthesis of **2**, a model compound of nidifocene (**1**), by means of stereoselective introduction of bromine and chlorine into the olefinic precursor **4** as a key step. In this paper, we describe the stereoselective synthesis of the corresponding olefinic precursor, dehalogenonidifocene (**3**), which has been prepared by reductive treatment of natural nidifocene with chromium(II) sulfate[8a] and is a potential key intermediate for the total synthesis of nidifocene (**1**). Our synthetic plan is shown in Chart 1. On starting from the spirodienone **5**,[4a] the key problems seem to be the cyclization of the C_{10}-hydroxyl group to the tetrahydrofuran ring and the regioselective introduction of the two double bonds. As regards the first problem, the cyclization reaction can be accomplished by means of the intramolecular Michael-type addition of the hydroxyl group to the cyclohexadienone moiety of compound **6** or **7**,[9] though the hydroxyl groups of these compounds are expected to occupy mainly the equatorial position, because the energy differences of the conformations between A-type (**6A**, **7A**) and B-type (**6B**, **7B**) are expected to be small due to the fact that the C_7-carbon of both compounds is an sp^2 carbon. Furthermore, inspection of molecular models suggests that the *exo*-methylene compound **6** is more suitable for the cyclization reaction than **7** because the distance between the hydroxyl group and the dienone moiety of **6B** is shorter than that of **7B**. Thus, the step of cyclization should be placed after that of formation of the C_7-*exo*-methylene group. Regioselective introduction of the double bond is a last step in the synthesis of dehalogenonidifocene (**3**) and will be achieved by the 1,4-reduction of the conjugated diene **9**, which is expected to be obtained from the enone **8**. So we began 1,3-transposition of the hydroxyl group starting from the spirodienone **5**.

The dienone moiety of **5** must be protected because otherwise the available reactions are limited due to its high reactivity. But attempts to protect the dienone moiety of **5** or the hydroxyspirodienone **10** by acetalization or thioacetalization resulted in failure because of their acid-labile character, so the dienone moiety was protected by reduction to the saturated ketone and subsequent acetalization. The spirodienone **5** was hydrogenated over 10% palladium–carbon (Pd–C) to afford the diketone **11** in 99% yield, and this was regioselectively acetalized by treatment with 1 eq of the bulky diol, 2,2-dimethyl-1,3-propanediol, and a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) under the usual conditions to afford the less-hindered monoacetal **12** in 74% yield. The structure of



nidifocene (**1**): R^1=Me, R^2=CH_2
2: R^1=H, R^2=H_2



dehalogenonidifocene (**3**): R^1=Me, R^2=CH_2
4: R^1=H, R^2=H_2

Fig. 1

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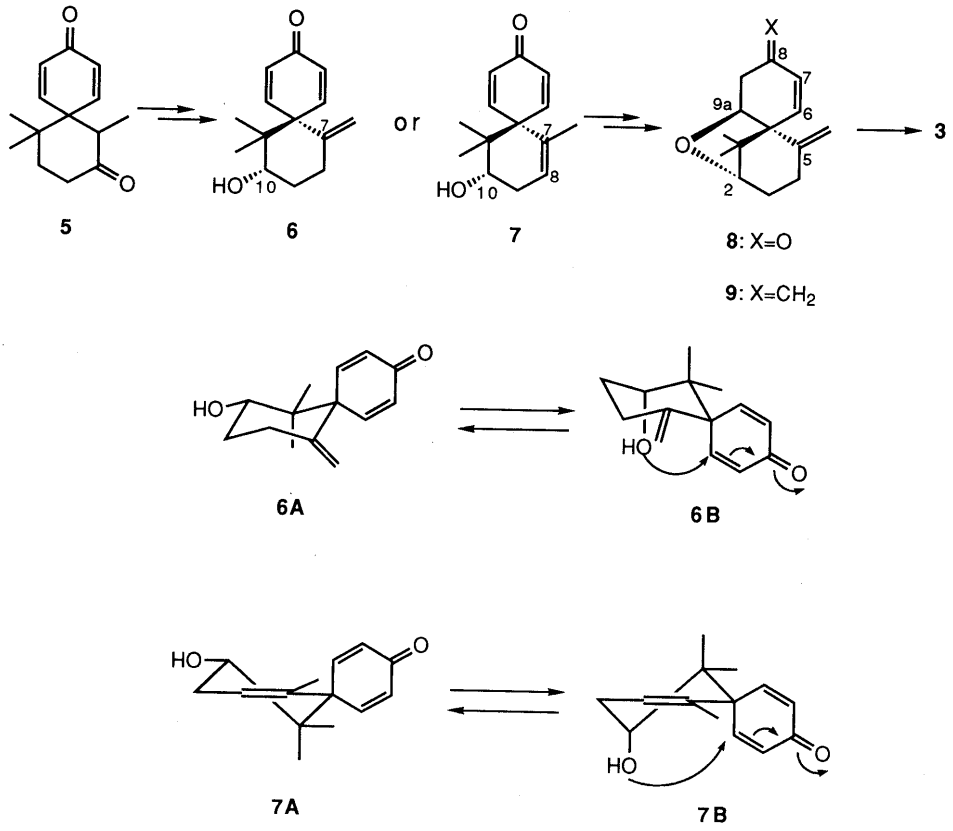

Chart 1

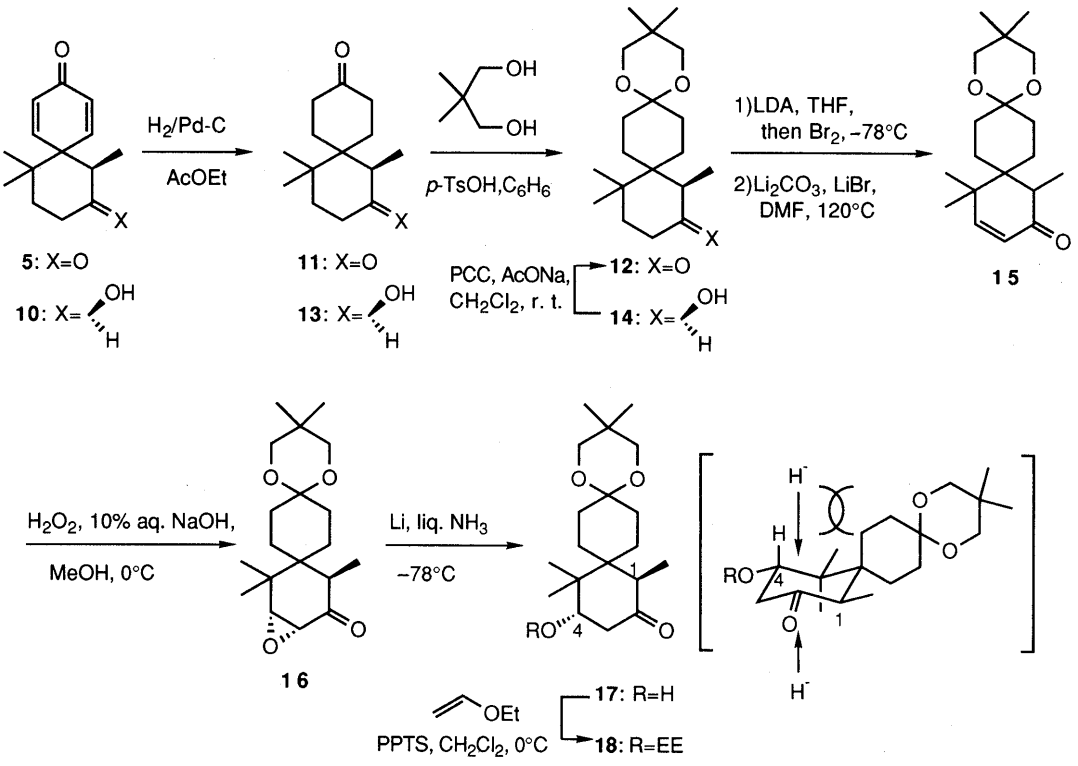

Chart 2

12 is supported by its infrared (IR) spectrum, which shows the presence of the 6-membered ring ketone at 1703 cm^{-1}, and its mass spectrum (MS), which shows the molecular ion peak at m/z 308. The regiochemistry of acetalization was confirmed by the synthesis of **12** *via* an alternative route as follows. The hydroxyspiroketone **13** reported previously[4a] was acetalized with 2,2-dimethyl-1,3-propanediol and oxidized with pyridinium chlorochromate (PCC) to

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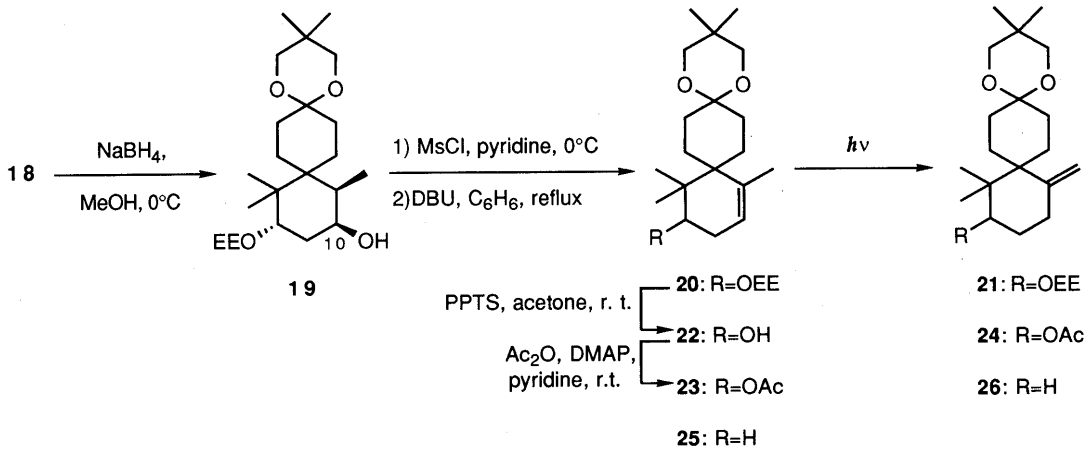

Chart 3

afford the monoacetal **12**, the physical properties [thin layer chromatographic (TLC) behavior, proton nuclear magnetic resonance (^{1}H-NMR) spectrum, and IR spectrum] of which were identical with those of **12** prepared from **11** by means of direct acetalization. Enolization of **12** with lithium diisopropylamide (LDA) under kinetically controlled conditions and subsequent treatment with bromine afforded the unstable α-bromoketone, which was dehydrobrominated without purification by treatment with lithium bromide and lithium carbonate in dimethylformamide (DMF) to give **15** in 70% overall yield. Epoxidation of **15** with alkaline hydrogen peroxide afforded the starting enone **15** in 42% recovery and the epoxide **16** as a single isomer in 50% yield (80%, based on the consumed starting material). The structure of **16** is confirmed by the fact that, in the IR spectrum, an absorption due to the 6-membered ring ketone is observed at 1717 cm^{-1} and, in the ^{1}H-NMR spectrum, the two protons attached to the epoxide ring are observed at 3.05—3.31 ppm (AB type). The stereochemistry of **16** was determined to be as shown from the correlation with the stereochemistry of the β-hydroxyketone **17** as follows. Metal–ammonia reduction of **16** afforded the β-hydroxyketone **17** in good yield (98%). In the ^{1}H-NMR spectrum of **17**, the C_4-proton signal is observed at 3.83 ppm as a doublet of doublets ($J=5$, 8 Hz), which indicates that the hydroxyl group occupies the equatorial position, that is *trans* to the C_1-methyl group. Partial dehydration of **17** occurred during purification by silica gel chromatography, so **17** was immediately converted to the ethoxyethyl derivative **18** in 94% yield by treatment with ethyl vinyl ether and pyridinium *p*-toluenesulfonate (PPTS) as a catalyst.

Formation of the *exo*-methylene group was achieved by formation of the *endo*-olefin and subsequent photoisomerization.[10] The ethoxyethyl derivative **18** was stereospecifically reduced with sodium borohydride in methanol (MeOH) to afford the desired axial alcohol **19**, which is suitable for dehydration, in 93% yield. Although the orientation of the hydroxyl group of **19** is not apparent from its ^{1}H-NMR spectrum because the signal of the C_{10}-proton is overlapped with those of the ethoxyethyl group, it is obvious from a consideration of the molecular model of **18** (Chart 2) and from the result of the reduction of compounds having a similar conformation.[4] Dehydration of **19** was achieved by mesylation with mesyl chloride in pyridine and subsequent treatment with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in refluxing benzene to afford the olefin **20** in 87% overall yield. The direction of the double bond of **20** is confirmed by the ^{1}H-NMR spectrum, which shows vinyl methyl protons at 1.86 ppm (3H, br s) and the olefin proton at 5.20 ppm (1H, m). Attempts to isomerize the *endo*-olefin **20** to *exo*-olefin **21** by photoreaction under numerous conditions[10] resulted in failure, giving a complex mixture on TLC. From the result of the model experiment that the *endo*-olefin **25** was easily isomerized to the *exo*-olefin **26** by irradiation in benzene solution using a low-pressure mercury lamp,[11] it was suspected that the highly nucleophilic character of the oxygen atom of the ethoxyethoxy group at the C-10 position of **20** would interfere with a cationic or radical intermediate of the isomerization procedure.[10] Thus, in the next step, we examined the photoisomerization of the acetyloxy derivative **23**, in which the nucleophilicity of the C_{10}-oxygen atom is less than that in the ethoxyethyl derivative **20**. Selective removal of the ethoxyethyl group was achieved to give **22** in 95% yield by treatment with a catalytic amount of PPTS in dry acetone and acetylation with acetic anhydride (Ac_2O) and 4-dimethylaminopyridine (DMAP) in pyridine afforded the desired acetyloxy derivative **23** in quantitative yield. As expected from the above, isomerization of **23** smoothly proceeded to give a mixture of the starting material **23** and the desired *exo*-olefin **24** in the ratio of 1 : 20 and in good yield (87%, 91% based on the consumed starting material) by irradiation of the benzene solution with a low-pressure mercury lamp. Both *endo*- and *exo*-isomers, **23** and **24**, were separable by medium-pressure column chromatography. The structure of the *exo*-isomer **24** is confirmed by the IR spectrum showing the absorption of an *exo*-methylene group at 1640 cm^{-1} and the ^{1}H-NMR spectrum showing two olefin proton signals at 5.13 and 4.80 ppm.

Construction of the tetrahydrofuran ring was achieved as follows. Deprotection of the acetal group was accomplished to give **27** in 98% yield by treatment with *p*-TsOH in 70% aqueous acetone without isomerization of the *exo*-methylene moiety. Dehydrogenation of **27** by the method reported by Barton's group[12] successfully afforded the spirodienone **28** in 95% yield. The structure of **28** was evident from its IR absorptions due to the dienone moiety at 1625 and 1665 cm^{-1}, and the ^{1}H-NMR spectrum showing

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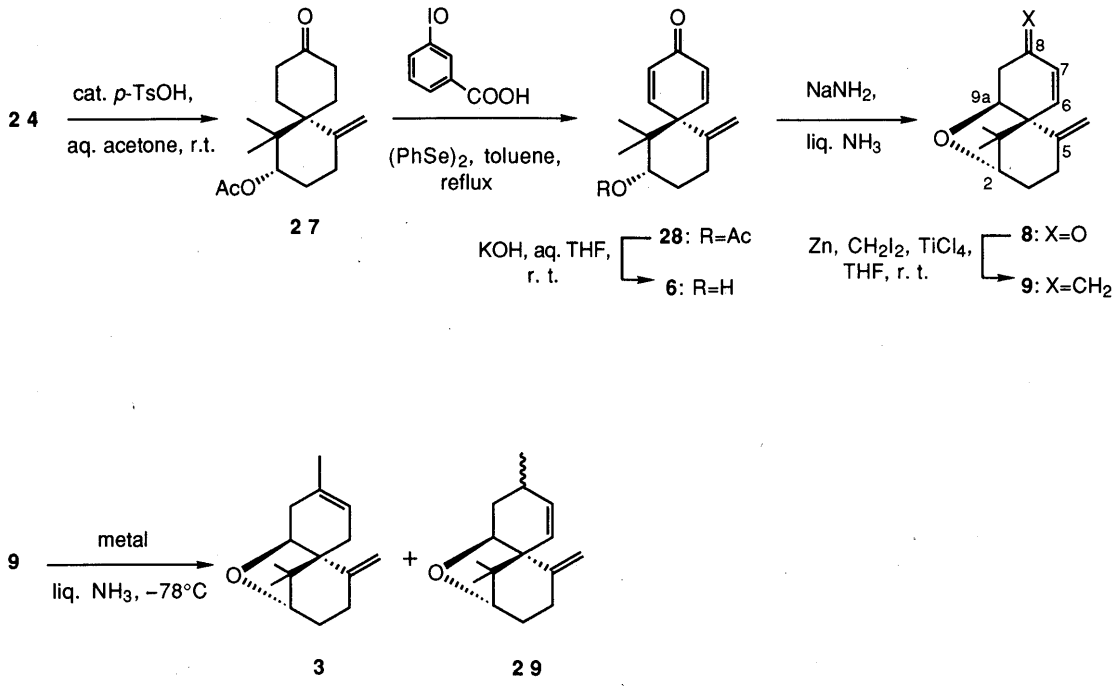

Chart 4

TABLE I. Metal–Ammonia Reduction of **9**

Run	Metal	Ratio[a]	
		3	: **29**
1	Li	50	50
2[b]	Li	8	92
3	Ca	67	33
4	Yb	90	10

a) The ratio was determined from the ^{1}H-NMR spectra. *b*) The mixture was stirred for 5 min at −78 °C, and the reaction was quenched with NH_4Cl.

the presence of the four olefin protons of the dienone moiety at 6.24—7.40 ppm. The acetyl group of **28** was removed in 95% yield under alkaline conditions to afford the desired hydroxyspirodienone **6**, which is a key compound for the construction of the tetrahydrofuran ring. In the ^{1}H-NMR spectrum, the C_{10}-proton is observed at 3.86 ppm as a doublet of doublets (J=8, 4 Hz), which indicates that the hydroxyl group is equatorially oriented, as expected. Intramolecular Michael-type addition of the hydroxyl group to the dienone moiety occurred in good yield (77%, 96% based on the consumed starting material) to give the tricyclic enone **8** as a sole product, when **6** was treated with sodium amide in liquid ammonia.[9] In the IR and ^{1}H-NMR spectra, the enone moiety is observed at 1680 cm^{-1} and at 6.13—6.94 ppm (2H, AB type). Two methine protons, C_2-H and C_{9a}-H, are observed at 4.05 ppm (1H, t-like, J=3 Hz) and 4.54 ppm (1H, dd, J=9, 8 Hz), respectively. The stereochemistry of **8** was assigned as shown from the result of a similar reaction reported before.[9] Methylenation of **8** by means of the Wittig reaction resulted in failure because the β-elimination of the C_{9a}-oxygen function caused by the basicity of the Wittig reagent predominated. But, when **8** was treated with the organotitanium reagent prepared from diiodomethane, zinc, and titanium tetrachloride,[13] the triene **9** could be obtained in 90% yield. The triene **9** has diene absorptions at 1640 and 1610 cm^{-1} in its IR spectrum and proton signals at 4.91 and 4.95 ppm in its ^{1}H-NMR spectrum due to the C_8-*exo*-methylene protons.

Unexpectedly, the last step, regioselective introduction of the double bond was not easy, but finally could be achieved by metal–ammonia reduction using a lanthanoid metal. Catalytic hydrogenation could not be used for 1,4-reduction of the conjugated diene moiety of **9** because reduction of the C_5-*exo*-methylene moiety was easier than that of the conjugated diene moiety. So, we examined metal–ammonia reduction for the purpose of selective 1,4-reduction of the conjugated diene moiety. Unexpectedly, treatment of **9** with lithium in liquid ammonia at −78 °C and immediate quenching of the reaction with ammonium chloride afforded a 1 : 1 mixture of dehalogenonidifocene (**3**) and its isomer **29**[14] as shown in Table I (run 1). On the other hand, when the reaction mixture was stirred at −78 °C for 5 min and then the reaction was quenched with ammonium chloride, the regioisomer **29** was selectively obtained (run 2). Strongly basic lithium amide may catalyze the isomerization of dehalogenonidifocene (**3**), formed in the initial stage of the reduction, to **29**. So, it was expected that metals which afforded less basic metal amides would reduce **9** to dehalogenonidifocene (**3**) without isomerization. As expected, reduction with calcium afforded the desired isomer **3** as a major product (run 3), and it was found that the best result was obtained when ytterbium was used as a reducing metal (run 4). White and Larson have reported the reduction of aromatic rings, α,β-unsaturated ketones, and alkynes with ytterbium in liquid ammonia.[15] However this is the first example of difference of the reduction behavior between lithium and ytterbium and the effectiveness of ytterbium for reduction of compounds which are sensitive to base. The ^{1}H-NMR and IR spectra of thus obtained dehalogenonidifocene (**3**) were identical with those of an authentic sample prepared from natural nidifocene.[8a]

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Experimental

All melting points are uncorrected. Infared (IR) spectra were recorded on a Hitachi 260-10 spectrometer. The 90 MHz ^{1}H-NMR spectra were recorded on a Hitachi R-22 or a JEOL JNM-FX90Q spectrometer and 500 MHz ^{1}H-NMR spectra on a JEOL GX-500 spectrometer with tetramethylsilane (TMS) as an internal standard. ^{1}H-NMR data described here were recorded at 90 MHz unless otherwise stated. Low-resolution mass spectra (MS) were obtained with a Shimadzu GCMS-QP1000 or a JEOL JMS-D300 instrument, and high-resolution mass spectra (High MS) with a JEOL JMS-D300 instrument. UV spectra were recorded on a Hitachi 124 spectrometer. For column chromatography and preparative thin layer chromatography (PTLC), Merck Kieselgel 60 (0.063—0.200 mm) and Kieselgel 60 PF_{254} were used, respectively.

1,5,5-Trimethylspiro[5.5]undecane-2,9-dione (11) A solution of **5**[4a] (1.44 g, 6.61 mmol) in AcOEt (50 ml) was hydrogenated over 10% Pd–C (350 mg) according to the usual method under atmospheric pressure and at room temperature until **5** was no longer detectable on TLC (C_6H_6: AcOEt = 3 : 1). After removal of the catalyst by filtration, the solvent was evaporated off under reduced pressure and the resultant residue was purified by silica gel column chromatography to give **11** (1.45 g) in 99% yield, mp 100.5—101.0 °C (colorless crystals from Et_2O–petroleum ether). IR ($CHCl_3$): 1710, 1715 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (3H, s, C_5-CH_3), 1.16 (3H, d, J = 7 Hz, C_1-CH_3), 1.20 (3H, s, C_5-CH_3), 2.87 (1H, q, J = 7 Hz, C_1-H). MS *m/z*: 222 (M^+, 82.8). *Anal.* Calcd for $C_{14}H_{22}O_2$: C 75.63; H 9.97. Found: C 75.71; H 10.25.

1,5,5-Trimethylspiro[5.5]undecane-2,9-dione 9-(2,2-Dimethylpropylidene) Acetal (12) A mixture of **11** (3.31 g, 14.9 mmol), 2,2-dimethyl-1,3-propanediol (1.55 g, 14.9 mmol), and a catalytic amount of *p*-TsOH was stirred and refluxed using a Dean–Stark trap for 2 h. After cooling to room temperature, the reaction mixture was washed with saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl and dried over Na_2SO_4. The solvent was evaporated off under reduced pressure and the residue was purified by silica gel column chromatography to afford **12** (3.39 g) in 74% yield, mp 113.5—114.5 °C (colorless crystals from Et_2O–petroleum ether). IR ($CHCl_3$): 1703, 1100 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.94, 0.96, 1.00, 1.18 (each 3H, s, acetal methyl protons and C_5-$(CH_3)_2$), 1.20 (3H, d, J = 9 Hz, C_1-CH_3), 3.37—3.55 (4H, m, acetal protons). MS *m/z*: 308 (M^+, 0.5). *Anal.* Calcd for $C_{19}H_{32}O_3$: C 73.98; H 10.46. Found: C 73.84; H 10.36.

(7*RS*,8*SR*)-8-Hydroxy-7,11,11-trimethylspiro[5.5]undecan-3-one (2,2-Dimethylpropylidene) Acetal (14) The hydroxyspiroketone **13**[4a] (264 mg, 1.18 mmol) was acetalized with 2,2-dimethyl-1,3-propanediol (278 mg, 2.67 mmol) by the same method as described above to give **14** (340 mg) in quantitative yield. IR ($CHCl_3$): 3610, 1102 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.81, 0.96 (each 3H, 9H, s, acetal methyl protons and C_{11}-$(CH_3)_2$), 1.00 (3H, d, J = 6 Hz, C_7-CH_3), 3.42—3.53 (4H, m, acetal protons), 3.72—4.10 (1H, m, C_8-H). MS *m/z*: 310 (M^+, 0.2). High MS *m/z*: 310.2499 (M^+, Calcd for $C_{19}H_{34}O_3$: 310.2505).

PCC Oxidation of 14 Sodium acetate (27 mg, 0.33 mmol) and then PCC (1.18 g, 5.47 mmol) were added to a stirred solution of **14** (340 mg, 1.10 mmol) in CH_2Cl_2 (15 ml) and stirring was continued at room temperature for 1.5 h. After being diluted with Et_2O, the reaction mixture was filtered through a short alumina column and the column was eluted with Et_2O. The eluate was evaporated under reduced pressure and the residue was purified by alumina PTLC (Et_2O : petroleum ether = 1 : 3) to give **12** (220 mg) in 79% yield. Physical properties (TLC, IR, and ^{1}H-NMR) of this compound were identical with those of **12** prepared by direct acetalization of **11**.

1,5,5-Trimethylspiro[5.5]undec-3-ene-2,9-dione 9-(2,2-Dimethyl-1,3-propylidene) Acetal (15) Under a nitrogen atmosphere, *n*-BuLi (15% in hexane, 3.40 ml, 5.50 mmol) was added dropwise to a stirred solution of diisopropylamine (0.66 ml, 4.72 mmol) in THF (1 ml) at −78 °C and the whole was stirred at 0 °C for 15 min and then cooled to −78 °C. A solution of **12** (1.31 g, 4.25 mmol) in THF (3 ml) was added dropwise to the solution of LDA prepared above with stirring at −78 °C, and stirring was continued at the same temperature for 1 h. A solution of bromine (0.24 ml, 4.70 mmol) in CH_2Cl_2 (2 ml) was added slowly to the above reaction mixture at −78 °C and stirring was continued for 3 h at the same temperature. After addition of water, the reaction mixture was extracted with Et_2O and the combined ethereal layers were washed with saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure to give the crude bromide as an yellow oil (2.29 g). Without purification, a mixture of the crude product, Li_2CO_3 (1.09 g, 14.8 mmol), and LiBr (0.77 g, 8.87 mmol) in DMF (30 ml) was stirred and warmed under nitrogen at 120 °C for 5 h. After being cooled to room temperature, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with hexane. The combined organic layers were washed with water and saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (C_6H_6 : AcOEt = 5 : 1) to give **15** (0.91 g) in 70% yield, mp 115.5—117.0 °C (colorless crystals from AcOEt–petroleum ether). IR ($CHCl_3$): 1675, 1626, 1102 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.93, 0.98, 1.05, 1.17 (each 3H, s, acetal methyl protons and C_5-$(CH_3)_2$), 1.22 (3H, d, J = 8 Hz, C_1-CH_3), 2.87 (1H, q, J = 8 Hz, C_1-H), 3.40—3.50 (4H, m, acetal protons), 5.74 (1H, d, J = 10 Hz, C_3-H), 6.34 (1H, d, J = 10 Hz, C_4-H). UV λ_{max}^{MeCN} nm (ε): 229 (9500). MS *m/z*: 306 (M^+, 4.2). *Anal.* Calcd for $C_{19}H_{30}O_3$: C 74.47; H 9.87. Found: C 74.35; H 10.14.

(1*RS*,3*RS*,4*RS*)-3,4-Epoxy-1,5,5-trimethylspiro[5.5]undecane-2,9-dione 9-(2,2-Dimethylpropylidene) Acetal (16) Hydrogen peroxide (30%, 2.95 ml, 26.0 mmol) was added dropwise to a stirred solution of **15** (1.46 g, 4.77 mmol) in a mixture of MeOH (18 ml) and 10% aqueous NaOH (0.98 ml, 2.45 mmol) and stirring was continued for 2 h at room temperature. After addition of water, the reaction mixture was extracted with Et_2O. The ethereal extract was washed with water and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (C_6H_6 : AcOEt = 10 : 1) to give the enone **15** (607 mg, 42% recovery) and the epoxide **16** (732 mg) as colorless crystals in 50% yield (80% based on the consumed starting material), mp 110.0—114.5 °C. IR ($CHCl_3$): 1717, 1102 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.93, 0.95, 1.21 (each 3H, 3H, 6H, s, acetal methyl protons and C_5-$(CH_3)_2$), 1.04 (3H, d, J = 7.5 Hz, C_1-CH_3), 3.03 (1H, q, J = 7.5 Hz, C_1-H), 3.05—3.31 (2H, AB type, J = 4 Hz, C_3-H and C_4-H), 3.43 (4H, m, acetal protons). MS *m/z*: 322 (M^+, 0.1). High MS *m/z*: 322.2154 (M^+, Calcd for $C_{19}H_{30}O_4$: 322.2144).

(1*RS*,4*SR*)-4-Hydroxy-1,5,5-trimethylspiro[5.5]undecane-2,9-dione 9-(2,2-Dimethylpropylidene) Acetal (17) Under a nitrogen atmosphere, a solution of **16** (84 mg, 0.26 mmol) in THF (5 ml) was added in one portion to a solution of lithium (4.0 mg, 0.58 mgatm) in liquid ammonia (*ca.* 30 ml) with vigorous stirring. After 1 min, powdered NH_4Cl (*ca.* 200 mg) was added and ammonia was evaporated off at room temperature. The residue was extracted with Et_2O and water and the ethereal layer was washed with saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure to give **17** (83 mg) as colorless crystals in 98% yield, mp 142.0—144.0 °C. IR ($CHCl_3$): 3550, 1700, 1094 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.96, 1.09, 1.15 (each 6H, 3H, 3H, s, acetal methyl protons and C_5-$(CH_3)_2$), 1.19 (3H, d, J = 7 Hz, C_1-CH_3), 2.36 (1H, dd, J = 13, 8 Hz, C_{3ax}-H), 2.80 (1H, dd, J = 13, 5 Hz, C_{3eq}-H), 2.82 (1H, q, J = 7 Hz, C_1-H), 3.38—3.53 (4H, m, acetal protons), 3.83 (1H, dd, J = 8, 5 Hz, C_4-H). MS *m/z*: 324 (M^+, 0.1). High MS *m/z*: 324.2285 (M^+, Calcd for $C_{19}H_{32}O_4$: 324.2298).

(1*RS*,4*SR*)-4-(1-Ethoxyethoxy)-1,5,5-trimethylspiro[5.5]undecane-2,9-dione 9-(2,2-Dimethylpropylidene) Acetal (18) Ethyl vinyl ether (0.01 ml, 0.10 mmol) and PPTS (2.3 mg, 0.009 mmol) were added to a stirred solution of **17** (30 mg, 0.093 mmol) in CH_2Cl_2 (2 ml) and the whole was stirred for 2 h at room temperature and then diluted with Et_2O. The reaction mixture was washed with saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure to give **18** (35 mg) as a colorless oil in 94% yield. IR ($CHCl_3$): 1700, 1095 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.74 (1H, dd, J = 8, 4.5 Hz, C_4-H), 4.49—4.78 (1H, m, C_4-O–CH). MS *m/z*: 396 (M^+, <0.1), 350 (M^+ − EtOH, 0.1). High MS *m/z*: 396.2852 (M^+, Calcd for $C_{23}H_{40}O_5$: 396.2873).

(8*RS*,10*RS*,11*SR*)-8-(1-Ethoxyethoxy)-10-hydroxy-7,7,11-trimethylspiro[5.5]undecan-3-one (2,2-Dimethylpropylidene) Acetal (19) Sodium borohydride (64 mg, 1.7 mmol) was added portionwise to a stirred solution of **18** (615 mg, 1.55 mmol) in MeOH (41 ml) with cooling at −15 °C and stirring was continued for 20 min at the same temperature. The reaction mixture was poured into saturated aqueous $NaHCO_3$ containing ice and extracted with AcOEt. The organic phase was washed with water and saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give **19** (574 mg) as a colorless oil in 93% yield. IR ($CHCl_3$): 3340, 1095 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.05—4.38 (1H, m, C_8-H), 4.45—4.81 (1H, m, C_8-O–CH). MS *m/z*: 398 (M^+, <0.1), 352 (M^+ − EtOH, 0.1). High MS *m/z*: 398.3039 (M^+, Calcd for $C_{23}H_{42}O_5$: 398.3032).

8-(1-Ethoxyethoxy)-7,7,11-trimethylspiro[5.5]undec-10-en-3-one (2,2-Dimethylpropylidene) Acetal (20) Methanesulfonyl chloride (1.10 ml, 14.2 mmol) was added to a stirred solution of **19** (1.13 g, 2.84 mmol) in pyridine (29 ml) at 0 °C. After being stirred for 3 h at 0 °C, the reaction mixture was poured into saturated aqueous $NaHCO_3$ containing ice and

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extracted with Et_2O. The ethereal phase was washed with saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. Without purification, the crude mesylate thus obtained was dissolved in C_6H_6 (34 ml) containing DBU (1.26 ml, 8.43 mmol) and refluxed for 6 h. After being cooled to room temperature, the reaction mixture was washed with saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (C_6H_6 : AcOEt = 20 : 1) to give **20** (943 mg) as a colorless oil in 87% overall yield. IR ($CHCl_3$): 1100 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.86 (3H, br s, C_{11}-CH_3), 4.52—4.86 (1H, m, C_8-O-CH), 5.20 (1H, m, C_{10}-H). MS *m/z*: 380 (M^+, <0.1), 334 ($M^+ - EtOH$, 2.9). High MS *m/z* 380.2910 (M^+, Calcd for $C_{23}H_{40}O_4$: 380.2925).

8-Hydroxy-7,7,11-trimethylspiro[5.5]undec-10-en-3-one (2,2-Dimethylpropylidene) Acetal (22) PPTS (0.3 mg, 0.001 mmol) was added to a stirred solution of **20** (14.3 mg, 0.038 mmol) in dry acetone (1 ml). After being stirred at room temperature for 24 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic phase was washed with water and saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (C_6H_6 : AcOEt = 5 : 1) to give **22** (11.0 mg) as colorless crystals in 95% yield, mp 128.5—130.0 °C. IR ($CHCl_3$): 3610, 2960, 2870, 1100 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.77, 0.96, 0.98, 1.04 (each 3H, s, acetal methyl protons and C_7-$(CH_3)_2$), 1.88 (3H, m, C_{11}-CH_3), 3.48, 3.52 (each 2H, s, acetal protons), 3.87 (1H, m, C_8-H), 5.21 (1H, m, C_{10}-H). MS *m/z*: 308 (M^+, 7.1). High MS *m/z*: 308.2372 (M^+, Calcd for $C_{19}H_{32}O_3$: 308.2353).

8-Acetoxy-7,7,11-trimethylspiro[5.5]undec-10-en-3-one (2,2-Dimethylpropylidene) Acetal (23) Acetic anhydride (0.55 ml, 5.8 mmol) was added dropwise to a stirred solution of **22** (538 mg, 1.75 mmol) in pyridine (50 ml) containing DMAP (259 mg, 2.12 mmol). After being stirred for 2 h at room temperature, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic phase was washed with saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give **23** (611 mg) in quantitative yield, mp 88.0—89.0 °C (colorless crystals from hexane). IR ($CHCl_3$): 1720, 1105 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.86, 0.92, 0.94, 1.01 (each 3H, s, acetal methyl protons and C_7-$(CH_3)_2$), 1.89 (3H, m, C_{11}-CH_3), 2.04 (3H, s, C_8-$OCOCH_3$), 3.32—3.68 (4H, m, acetal protons), 5.09 (1H, dd, *J* = 10, 7 Hz, C_8-H), 5.22 (1H, m, C_{10}-H). MS *m/z*: 350 (M^+, 0.2). High MS *m/z*: 350.2451 (M^+, Calcd for $C_{21}H_{34}O_4$: 350.2458).

8-Acetoxy-7,7-dimethyl-11-methylenespiro[5.5]undecan-3-one (2,2-Dimethylpropylidene) Acetal (24) A C_6H_6 (20 ml) solution of **23** (115 mg, 0.328 mmol) in a quartz tube was degassed under reduced pressure, purged with Ar, and irradiated using a low-pressure Hg lamp at 10 °C for 42 h. The solvent was evaporated off under reduced pressure and the resultant residue was purified by silica gel column chromatography to give a mixture of **23** and **24** (106 mg), which was separated by means of medium-pressure liquid chromatography [Merck Lobar LiChroprep Si60 (40—63 μm), hexane : AcOEt = 12 : 1] to give **23** (5.0 mg; 4% recovery) and **24** (100 mg) as a colorless oil in 87% yield (91% based on the consumed starting material). IR ($CHCl_3$): 1725, 1640, 1104 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.84, 0.90, 0.92, 0.99 (each 3H, s, acetal methyl protons and C_7-$(CH_3)_2$), 2.03 (3H, s, C_8-$OCOCH_3$), 3.46 (4H, br s, acetal protons), 4.80 (1H, d, *J* = 1 Hz, C_{11}=CH_2), 4.99 (1H, dd, *J* = 10, 5 Hz, C_8-H), 5.13 (1H, m, C_{11}=CH_2). MS *m/z*: 350 (M^+, 3.7). High MS *m/z*: 350.2445 (M^+, Calcd for $C_{21}H_{34}O_4$: 350.2458).

8-Acetoxy-7,7-dimethyl-11-methylenespiro[5.5]undecan-3-one (27) A catalytic amount of *p*-TsOH was added to a stirred solution of **24** (297 mg, 0.849 mmol) in 70% aqueous acetone (60 ml) and the whole was stirred for 12 h at room temperature. After being poured into saturated aqueous $NaHCO_3$, the reaction mixture was extracted with AcOEt. The organic phase was washed with saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (C_6H_6 : AcOEt = 5 : 1) to give **27** (220 mg) as a colorless oil in 98% yield. IR ($CHCl_3$): 1721, 1711, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.90, 0.92 (each 3H, s, C_7-$(CH_3)_2$), 2.06 (3H, s, C_8-$OCOCH_3$), 4.89 (1H, d, *J* = 1 Hz, C_{11}=CH_2), 5.03 (1H, dd, *J* = 11, 5 Hz, C_8-H), 5.21 (1H, d, *J* = 1 Hz, C_{11}=CH_2). MS *m/z*: 264 (M^+, 43.8). High MS *m/z*: 264.1730 (M^+, Calcd for $C_{16}H_{24}O_3$: 264.1725).

8-Acetoxy-7,7-dimethyl-11-methylenespiro[5.5]undeca-1,4-dien-3-one (28) Under a nitrogen atmosphere, a solution of **27** (103 mg, 0.390 mmol), *m*-iodoxybenzoic acid (654 mg, 2.48 mmol), and diphenyl diselenide (40 mg, 0.13 mmol) in dry toluene (47 ml) was stirred and refluxed for 13 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic phase was washed with saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : Et_2O = 1 : 1) to give **28** (96 mg) as a colorless oil in 95% yield. IR ($CHCl_3$): 1730, 1665, 1625 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.91, 1.01 (each 3H, s, C_7-$(CH_3)_2$), 2.09 (3H, s, C_8-$OCOCH_3$), 4.76, 4.92 (each 1H, br s, C_{11}=CH_2), 5.07 (1H, dd, *J* = 8, 4 Hz, C_8-H), 6.24—7.40 (4H, ABCD type, C_1-H, C_2-H, C_4-H, and C_5-H). MS *m/z*: 260 (M^+, 11.1). High MS *m/z*: 260.1431 (M^+, Calcd for $C_{16}H_{20}O_3$: 260.1413).

8-Hydroxy-7,7-dimethyl-11-methylenespiro[5.5]undeca-1,4-dien-3-one (6) Aqueous KOH solution (5%, 13.9 ml) was added dropwise to a stirred solution of **28** (102 mg, 0.392 mmol) in THF (13.9 ml). After being stirred for 65 min at room temperature, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic phase was washed with water and saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (C_6H_6 : AcOEt = 3 : 1) to give **6** (81 mg) as a colorless oil in 95% yield. IR ($CHCl_3$): 3610, 1660, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.95, 0.99 (each 3H, s, C_7-$(CH_3)_2$), 3.86 (1H, dd, *J* = 8, 4 Hz, C_8-H), 4.73 (1H, br s, C_{11}=CH_2), 4.89 (1H, m, C_{11}=CH_2), 6.20—7.46 (4H, ABCD type, C_1-H, C_2-H, C_4-H, and C_5-H). MS *m/z*: 218 (M^+, 7.5). High MS *m/z*: 218.1304 (M^+, Calcd for $C_{14}H_{18}O_2$: 218.1307).

(2*RS*,5a*RS*,9a*RS*)-9*H*-2,3,4,5,5a,9a-Hexahydro-2,5a-methano-10,10-dimethyl-5-methylene-1-benzoxepin-8-one (8) A solution of **6** (115 mg, 0.528 mmol) in dry THF (7.9 ml) was added dropwise to a stirred solution of $NaNH_2$ in liquid ammonia (*ca.* 85 ml), prepared from Na (24 mg, 10 mgatm) according to the procedure reported previously,[9] at −78 °C. The whole mixture was stirred and refluxed for 5 h and then powdered NH_4Cl was added. After evaporation of the ammonia at room temperature, the residue was extracted with water and Et_2O. The ethereal phase was washed with saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting oil was purified by silica gel column chromatography (C_6H_6 : AcOEt = 5 : 1) to give **6** (23 mg) in 20% recovery and **8** (89 mg) as colorless crystals in 77% yield (96% based on the consumed starting material), mp 110.0—112.0 °C. IR ($CHCl_3$): 1680 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.99, 1.16 (each 3H, s, C_{10}-$(CH_3)_2$), 4.05 (1H, t-like, *J* = 3 Hz, C_2-H), 4.54 (1H, dd, *J* = 9, 8 Hz, C_{9a}-H), 4.60, 4.81 (each 1H, d, *J* = 2 Hz, C_5=CH_2), 6.13—6.94 (2H, AB type, C_6-H, C_7-H). MS *m/z*: 218 (M^+, 4.2). High MS *m/z*: 218.1314 (M^+, Calcd for $C_{14}H_{18}O_2$: 218.1307).

(2*RS*,5a*RS*,9a*RS*)-2,5a-Methano-10,10-dimethyl-5,8-dimethylene-2,3,4,5,5a,8,9,9a-octahydro-1-benzoxepin (9) Diiodomethane (0.30 ml, 3.7 mmol) was added dropwise to a stirred suspension of zinc dust (428 mg, 6.55 mgatm) in THF (3.5 ml). Stirring was continued for 30 min, then the mixture was diluted with THF (3.5 ml). A 10% $TiCl_4$ solution in CH_2Cl_2 (0.80 ml, 0.42 mmol) was added dropwise to the reaction mixture, which was further stirred at room temperature for 30 min. A solution of **8** (38 mg, 0.17 mmol) in THF (2 ml) was next added dropwise to the above reaction mixture and stirring was continued for 15 min at room temperature. The whole was diluted with Et_2O and filtered, then the filtrate was washed with saturated aqueous NH_4Cl, water, and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel PTLC (Et_2O : petroleum ether = 1 : 5) to give **9** (32 mg) as a colorless oil in 90% yield. IR ($CHCl_3$): 1640, 1610, 1115, 895 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.92, 1.08 (each 3H, s, C_{10}-$(CH_3)_2$), 3.96 (1H, t-like, *J* = 1.6 Hz, C_2-H), 4.60 (1H, d, *J* = 1.2 Hz, C_5=CH_2), 4.69 (1H, d, *J* = 1.2 Hz, C_5=CH_2), 4.91, 4.95 (each 1H, s, C_8=CH_2), 5.81 (1H, d, *J* = 9.8 Hz, C_7-H), 6.35 (1H, d, *J* = 9.8 Hz, C_6-H). MS *m/z*: 216 (M^+, 9.0). High MS *m/z*: 216.1521 (M^+, Calcd for $C_{15}H_{20}O$: 216.1514).

(±)-Dehalogenonidifocene (3) A solution of **9** (30.6 mg, 0.142 mmol) in THF (3 ml) was added to a stirred solution of Yb[16] (122 mg, 0.705 mgatm) in liquid ammonia (*ca.* 90 ml) at −78 °C and powdered NH_4Cl (*ca.* 100 mg) was added immediately to the reaction mixture. Stirring was continued for 30 min at −78 °C, then the ammonia was evaporated off and the resultant residue was extracted with water and Et_2O. The ethereal phase was washed with saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (C_6H_6 : AcOEt = 10 : 1) to give a mixture of dehalogenonidifocene (**3**) and **29** (26.7 mg) in 87% yield (**3** : **29** = *ca.* 9 : 1 from ^{1}H-NMR spectrum). The mixture was separable by means of MPLC [Merck Lobar LiChroprep

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Si60 (40—63 μm), hexane : AcOEt = 25 : 1]. (±)-Dehalogenonidifocene (**3**), colorless oil. IR ($CHCl_3$): 1620, 1105 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.82, 1.03 (each 3H, s, C_{10}-$(CH_3)_2$), 1.55 (3H, s, C_8-CH_3), 3.90 (1H, t-like, J = 2.4 Hz, C_2-H), 4.18 (1H, t-like, J = 7.6 Hz, C_{9a}-H), 4.71 (1H, d, J = 2.4 Hz, C_5=CH_2), 4.76 (1H, d, J = 2.4 Hz, C_5=CH_2), 5.45 (1H, br s, C_7-H). MS *m/z*: 218 (M^+, 7.5). High MS *m/z*: 218.1685 (M^+, Calcd for $C_{15}H_{22}O$: 218.1670). **29**, colorless oil. IR ($CHCl_3$): 1635, 1105, 910 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.88, 1.04 (each 3H, s, C_{10}-$(CH_3)_2$), 1.04 (3H, d, J = 6.7 Hz, C_8-H), 3.89 (1H, t-like J = 1.8 Hz, C_2-H), 4.16 (1H, dd, J = 6.1. 9.6 Hz, C_{9a}-H), 4.58 (1H, s, C_5=CH_2), 4.64 (1H, s, C_5=CH_2), 5.63 (1H, dd, J = 3.1, 10.4 Hz, C_7-H), 5.70 (1H, d, J = 10.4 Hz, C_6-H). MS *m/z*: 218 (M^+, 4.3). High MS *m/z*: 218.1665 (M^+, Calcd for $C_{15}H_{22}O$: 218.1670).

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