An Approach to the Stereoselective Synthesis of Nidifocene. III.[1] Total Syntheses of the Stereoisomers of (±)-Nidifocene from (±)-Dehalogenonidifocene

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Two stereoisomers, 6 and 15, of nidifocene (1) were synthesized in a regio- and stereoselective manner by means of direct addition of "BrCl", generated from *N*-bromosuccinimide and ammonium chloride, to dehalogenonidifocene (3) and by means of displacement of the hydroxyl group of the chlorohydrin 21, stereoselectively prepared from 3, with bromine.

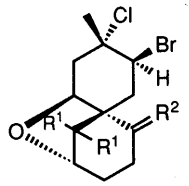
Keywords nidifocene; dehalogenonidifocene; chlorohydrin; bromochlorocyclohexane ring system; stereoselective synthesis; regioselective synthesis

A number of mono- and sesquiterpenes containing a *vic-trans*-bromochlorocyclohexane ring system have been isolated from marine organisms.[2] In these compounds, the regio- and stereochemistries of the bromochlorocyclohexane moiety are known to be closely related with their biological activities,[3] so it is of interest to synthesize the bromochlorocyclohexane ring system of not only the natural type but also the unnatural type in a regio- and stereoselective manner. However, only a few examples of direct addition reaction of bromonium chloride (BrCl) to olefinic precursors have been reported and it has been found that this type of reaction does not afford a satisfactory result as regards the regio- and stereoselectivity.[4]

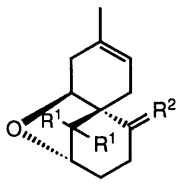
Nidifocene (**1**) is one such compound having a characteristic spiro[5.5]undecane skeleton, and it was isolated from *Laurencia nidifica* by Erickson and coworkers.[5] In the previous papers, we have reported the synthesis of the nidifocene model compound **2** and its regio- and stereoisomers by means of regio- and stereoselective introduction of "BrCl" *via* the bromohydrin starting from **4**[6] and we achieved an efficient synthesis of dehalogenonidifocene (**3**).[1] In this paper, we describe the selective direct addition of "BrCl" generated from halonium ion sources and ammonium halides to the dehalogenonidifocene (**3**) as well as the construction of a bromochlorocyclohexane ring system *via* halohydrins prepared from dehalogenonidifocene (**3**).

Synthesis of the Stereoisomers, 6 and 7, of (±)-Nidifocene (1) by Direct Addition of "BrCl" to (±)-Dehalogenonidifocene (3) Dehalogenonidifocene (**3**) was reacted with "BrCl", generated from halonium ion sources, such as *N*-bromosuccinimide (NBS) and *N*-chlorosuccinimide (NCS), and halide salts; the results are summarized in Table I. In every case, two *trans*-isomers, **6** and **7**, of the four possible *trans*-isomers were obtained in good yields and the reaction products with the *exo*-methylene moiety could not be detected. The best result was predominant formation of **6** when ammonium chloride was used as a Cl^- source, and the bulkiness of the alkylammonium group did not affect the regioselectivity. In these reactions (runs 1—5), it seems that the bromonium ion is attacked from the less-hindered side, that is, *trans* attack against the methyl group at the C-10 position to form the bromonium ion intermediate **5** selectively. Subsequent nucleophilic attack of Cl^- at the C-7 position is stereoelectronically favored but is inhibited by the steric hindrance of the equatorial methyl group at the C-10 position to afford **6** as a major product. Direct addition initiated by Cl^+ was also examined (run 6), but two *trans*-isomers, **6** and **7**, were obtained in the ratio of *ca.* 1:1, as in the case of run 1. In this reaction, halonium ion exchange ($Cl^+ + Br^- \rightarrow Br^+ + Cl^-$) may occur before attack of Cl^+ on **3** takes place.

This stereochemical consideration was confirmed by the following experiment. Epoxidation of **3** with *m*-chloroperbenzoic acid (MCPBA) stereoselectively afforded the epoxide **8**, which is a product attacked in the same mode as the bromonium ion, in 60% yield and no isomer could be detected. The stereochemistry of **8** was apparent from a



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

TABLE I. Direct Addition of "BrCl" to Dehalogenonidifocene (**3**)

Run	Reagents	Time (h)	Ratio (**6**:**7**)
1	NBS, BTEACl	19	59:41
2	NBS, NH_4Cl	18	90:10
3	NBS, Me_4NCl	18	67:33
4	NBS, LiCl	18	75:25
5	NBS, BEDIACl	24	80:20
6	BTEABr, NCS	22	56:44

BTEACl, benzyltriethylammonium chloride; BEDIACl, benzylethyldiisopropylammonium chloride; BTEABr, benzyltriethylammonium bromide.

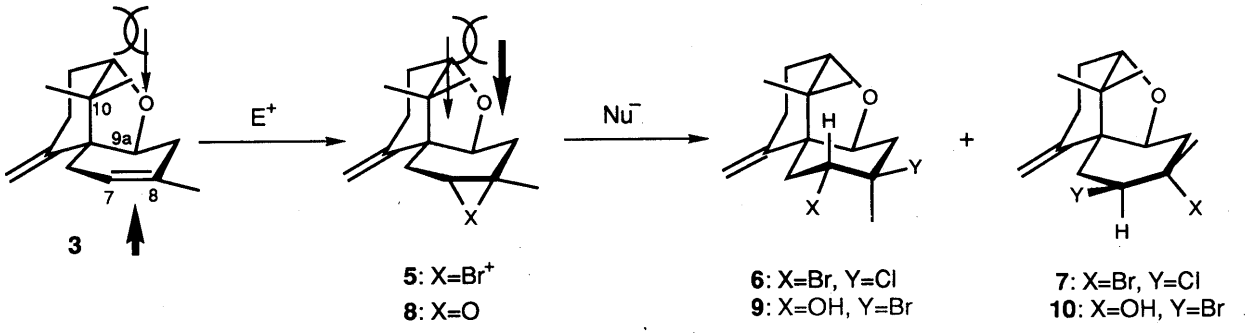
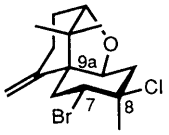
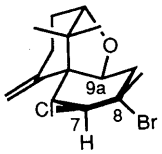
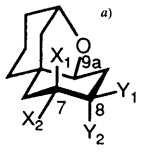


Chart 1

TABLE II. 500 MHz ^{1}H-NMR Data Measured in C_6D_6 for Bromochloro Derivatives

Compound	C_7-H	C_{9a}-H	C_8-Me
 **6**	4.60 (dd, J=5.5, 12.8 Hz)	4.21 (dd, J=7.9, 10.4 Hz)	1.60 (s)
 **7**	4.48 (dd, J=2.4, 13.4 Hz)	4.31 (dd, J=4.6, 12.5 Hz)	1.87 (s)
 a) **11**: X_1=H, X_2=Br, Y_1=Cl, Y_2=Me	4.45 (dd, J=4.9, 12.8 Hz)	3.91 (dd, J=6.7, 10.4 Hz)	1.61 (s)
12: X_1=Cl, X_2=H, Y_1=Me, Y_2=Br	4.39 (ddd, J=1.8, 2.4, 4.3 Hz)	4.21 (dd, J=6.1, 9.8 Hz)	1.92 (s)
13: X_1=H, X_2=Cl, Y_1=Br, Y_2=Me	4.59 (dd, J=4.9, 12.8 Hz)	3.92 (dd, J=6.7, 10.4 Hz)	1.81 (s)
14: X_1=Br, X_2=H, Y_1=Me, Y_2=Cl	4.38 (ddd, J=1.8, 2.4, 4.3 Hz)	4.21 (dd, J=6.1, 9.8 Hz)	1.77 (s)

a) Taken from ref. 6.

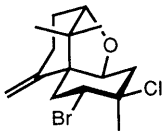
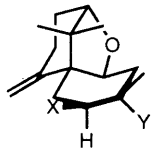
consideration of a molecular model of **3** and, furthermore, it was spectroscopically confirmed by comparison of the proton nuclear magnetic resonance (^{1}H-NMR) spectrum with that of the *cis*-isomer prepared by the method described below. Subsequent nucleophilic ring opening of the epoxide **8** mainly occurred at the C-8 position on treatment with dilithium tetrabromonickelate (Li_2NiBr_4), known as a soft Br^- source,[7] to afford **9** accompanied with **10** in the ratio of 4 : 1.

The stereochemistries of the bromochloro derivatives, **6** and **7**, were determined by comparison of the ^{1}H-NMR spectra with that of natural nidifocene (**1**)[8] and those of the model compounds **11**—**14** reported previously.[6] As shown in Table II, the chemical shift of the C-8 methyl group measured in C_6D_6 gives important information on the regiochemistry of the halogen substituents. The fact that the C-8 methyl signal of the major isomer **6** and that of the minor isomer **7** are observed at 1.60 and 1.87 ppm, each as a singlet, confirms that chlorine and bromine are bonded at the C-8 position, respectively. The values of the coupling constants (J) of the hydrogens at both the C-9a and C-7 positions of **6** correspond well with those of the model compounds **11** and **13**, indicating that the A ring of this compound has a chair form as in the model compounds, **11** and **13**, and thus **6** should be a stereoisomer of nidifocene (**1**) concerning both the C-7 and C-8 positions. In contrast, as shown in Table III, the J values of the C-9a and C-7 hydrogens of the minor isomer **7** agree well with those of nidifocene (**1**), though chemical shifts of some hydrogens differ from those of nidifocene (**1**). Thus, the structure of **7** was assigned as the regioisomer of nidifocene (**1**).

The structures of the bromohydrins, **9** and **10** were also confirmed from their ^{1}H-NMR spectra. The ^{1}H-NMR spectrum of **9** shows the C-9a hydrogen signal at 4.20 ppm as a doublet of doublets (J=8.2, 10.7 Hz) and the C-7 hydrogen signal at 4.24 ppm as a doublet of doublets of doublets (J=2.1, 6.7, 10.7 Hz), being coupled with the hydrogen of the hydroxyl group. This indicates that the A ring of **9** has a boat form and that the hydroxyl group is attached at the C-7 position. Thus, the structure of the minor isomer **10** was concomitantly determined to be as shown.

As described above, it was found that compound **6**, the stereoisomer of (±)-nidifocene (**1**), was stereoselectively and easily obtained by the direct addition of "BrCl" prepared from NBS and ammonium chloride to dehalogenonidifocene (**3**), and that the regio- and stereoselectivity

TABLE III. ^{1}H-NMR Data Measured in $CDCl_3$ for Bromochloro Derivatives, **6** and **7**, and Nidifocene (**1**)[8]

Compound	C_7-H	C_{9a}-H	C_8-Me	C_{10}-Me_2
 **6**[a]	4.61 (dd, J=6.4, 11.9 Hz)	3.96 (dd, J=7.9, 10.6 Hz)	1.42 (s)	0.40, 0.78 (each s)
 **7**: X=Cl, Y=Br[a]	4.69 (dd, J=3.3, 12.3 Hz)	4.41 (dd, J=4.4, 12.5 Hz)	1.70 (s)	0.52, 0.83 (each s)
Nidifocene (**1**): X=Br, Y=Cl	4.70 (dd, J=3, 13 Hz)	4.45 (dd, J=5, 13 Hz)	1.65 (s)	0.53, 0.87 (each s)

a) Measured in 90 MHz.

of the addition reaction to the C_7–C_8 double bond of **3** is greatly affected by the steric bulkiness of the C-10 methyl group.

Stereoselective Synthesis of (±)-7-Epinidifocene (15) *via* the Chlorohydrin From the results of the direct addition reaction, we selected the chlorohydrin **16** as a key intermediate, from which both nidifocene (**1**) and 7-epinidifocene (**15**) might be synthesized by stereoselective displacement of the hydroxyl group. Synthesis of **16** was achieved as follows (Chart 2, route A). On treatment of **3** with 1 eq of NBS in aqueous tetrahydrofuran (THF), the bromohydrin **17** was obtained as a major product accompanied with the bromomethyl derivative **18**. On the other hand, when excess NBS was used under the same conditions, the bromomethyl derivative **18** was obtained as a sole product and could be easily reduced to **17** by treatment with zinc–acetic acid. The structure of **18** was apparent from the presence of the olefinic proton signal at 5.87 ppm (1H, m) and the bromomethyl group signal at 4.03 ppm (2H, s) and from its mass spectrum (MS) showing $M^+ - Me$ peaks at m/z: 387, 389, 391 (1.2, 1.8, 1.2). Reaction of **17** in alcoholic KOH solution afforded the *cis*-epoxide **19**, the stereochemistry of which was confirmed by comparison of the ^{1}H-NMR spectrum with that of the *trans*-isomer **8** prepared above. In the case of the *cis*-epoxide **19**, the signal of hydrogen at the C-9a position was observed at 4.07 ppm, while that of the *trans*-epoxide **8** was shifted to lower field due to the deshielding effect of the oxygen of the epoxy ring and was observed at 4.19 ppm. Cleavage of the epoxy ring of **19** with dilithium tetrachlorocuprate (Li_2CuCl_4)[9] afforded **16** and **20** in 77% yield and in the ratio of *ca.* 2:1, while, in the presence of 1 eq of *tert*-butyldimethylsilyl chloride (TBDMSCl), **16** was selectively obtained in 93% yield. In this reaction, TBDMSCl may act as a weak Lewis acid to assist the cleavage of the C_8–O bond. The structure of **16** is supported by the following observations. From its ^{1}H-NMR spectrum, it was found that the hydroxyl group is attached equatorially to the C-7 position, because the C-7 hydrogen (4.12 ppm) is coupled with the hydrogen of the hydroxyl group with the J value of 4.3 Hz and with the neighboring methylene hydrogens with J values of 3.1 and 12.8 Hz, respectively, which suggests that the A ring should have a boat form.

Many attempts to displace the hydroxyl group of **16** with bromine under various conditions[10] resulted in failure; the bromomethyl derivative **22** could be obtained, as an unstable oil in low yield (16%), only when **16** was reacted with phosphorus pentabromide (PBr_5) in the presence of calcium carbonate and pyridine as acid scavengers. A lower field shift of the C_7-hydrogen signal was observed on going from **16** to **22** (4.12 to 4.63 ppm), suggesting the displacement of the hydroxyl group of **16** by bromine. The stereochemistry of bromine at the C-7 position could be assumed to be equatorial, as shown in Chart 2, by analogy with the examples reported before[10,11] but this could not be spectroscopically confirmed. From the J values of the C-7 hydrogen signal at 4.63 ppm (J=8.6, 9.8 Hz), the bromine substituent was found to be equatorially oriented, but the conformation of the A ring could not be determined at this stage. The signals of the olefinic proton at 5.87 ppm and the bromomethyl group at 4.01 ppm show that the *exo*-methylene group was converted to an allyl bromide moiety as in the reaction of **3** with excess NBS. Conversion of the *exo*-methylene group of **16** to the bromomethyl moiety of **22** was expected to be caused by Br_2 generated by decomposition of PBr_5, so we examined the reaction of **16** with Br_2. As expected, **21** was obtained in 69% yield and its structure was confirmed from its ^{1}H-NMR spectrum. Treatment of **21** with PBr_5 afforded **22** as a sole product in 60% yield (41%, overall yield from **16**), and this was identical with the product obtained by direct treatment of **16** with PBr_5. Although the stereochemistry at the C-7 position could not be determined at this stage, it was found that the substitution reaction proceeds stereospecifically with retention or inversion of stereochemistry at the C-7 position, because the stereoisomer could not be detected.

As it was found that, in the reaction of the bromomethyl derivative **21**, the displacement of the C-7 hydroxyl group could be achieved in better yield than in that of the *exo*-methylene derivative **16**, we next examined the synthesis of **22** from **18** (route B). Treatment of **18** with potassium *tert*-butoxide (*tert*-BuOK) in THF afforded the epoxide **24** in 83% yield. When **24** was allowed to react with Li_2CuCl_4 in the presence of TBDMSCl, both cleavage of the epoxy ring and substitution of the bromomethyl group to the chloromethyl group occurred to afford **23**. Without purification, the chloromethyl group was con-

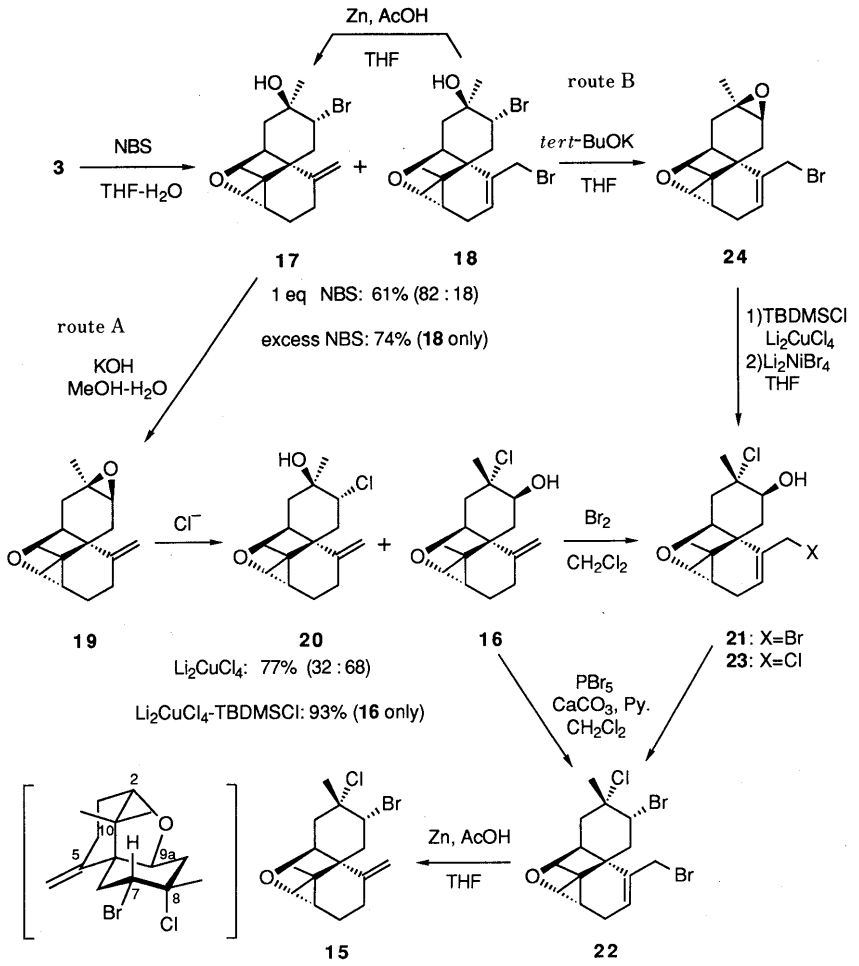


Chart 2

verted to the bromomethyl group by treatment with Li_2NiBr_4 to give **21**. The ^{1}H-NMR spectrum and the MS of **21**, thus obtained, were identical with those of **21** prepared according to the procedure described above. As mentioned above, the route to **22** could be shortened and the overall yield could also be improved. Conversion of the allyl bromide moiety of **22** to the *exo*-methylene group was easily achieved by treatment with zinc–acetic acid to afford **15** as a sole product. The ^{1}H-NMR spectrum of **15** is apparently not identical with that of nidifocene (**1**): the signals of two hydrogens of the *exo*-methylene group are observed at 4.79 ppm (d, $J=1.8$ Hz) and 4.65 ppm (d, $J=1.8$ Hz) and that of the C-7 hydrogen is observed at 4.56 ppm as a doublet of doublets ($J=6.1$, 12.2 Hz), which indicates that the bromine at the C-7 position is equatorially oriented. Furthermore, good agreement of the J values of the C-9a hydrogen (4.20 ppm, $J=7.9$, 10.4 Hz) with those of the C-9a hydrogen of **6** (4.21 ppm, $J=7.9$, 10.4 Hz) was observed, indicating that ring A of **15** has a chair form like that of **6**, and so the structure of **15** can be assigned as (±)-7-epinidifocene (**15**), as shown in Chart 2.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 260-10 spectrometer. ^{1}H-NMR spectra were recorded on a Hitachi R-22 (90 MHz), a JEOL JNM-FX90Q (90 MHz), or a JEOL JNM GX-500 spectrometer with tetramethylsilane (TMS) as an internal standard. 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. The capillary gas chromatography (GC) was carried out on a Shimadzu GC-14A with a HiCap CBP5-M25-025 capillary column and with nitrogen as a carrier gas. High-performance liquid chromatography (HPLC) was carried out on a Waters Associates HPLC system with an M6000A pump, a U6K septumless injector, an R401 differential refractometer, and a μBondapak™/C_{18} column. For column chromatography, Merck Kieselgel 60 (0.063—0.200 mm) was used.

Examination of Direct Addition of "BrCl" The halogen anion source (X^- source, *ca.* 10 eq) was added to a stirred THF (1 ml) solution of **3** (*ca.* 2 mg, *ca.* 0.009 mmol) and subsequently a halogen cation source (NBS or NCS, *ca.* 1.2 eq) was added to the reaction mixture. Stirring was continued at room temperature until **3** was no longer detectable on TLC, then the reaction mixture was diluted with ether, filtered through a short silica gel column and concentrated under reduced pressure to afford a mixture of **6** and **7**, which was analyzed by capillary GC (column temperature; 200 °C, gas flow rate; 20 ml/min). The retention time of **7** was 11.9 min and that of **6** was 14.2 min. The results were summarized in Table I.

Preparation of 6 and 7 by Direct Addition of "BrCl" to 3 with NBS and BTEACl Benzyltriethylammonium chloride (BTEACl, 100 mg, 0.44 mmol) and then NBS (9.4 mg, 0.053 mmol) were added to a stirred solution of **3** (9.6 mg, 0.044 mmol) in THF (4.3 ml). The mixture was stirred for 15 h at room temperature, then NBS (9.4 mg, 0.053 mmol) was added and stirring was continued until the starting material disappeared on TLC (*ca.* 19 h). The reaction mixture was diluted with Et_2O, 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) to give a mixture of **6** and **7** (12.5 mg) in 85% yield. This mixture was separable by reversed phase HPLC (acetonitrile : $H_2O=5:1$; flow rate, 3 ml/min) to

afford **7** (5.0 mg) in 34% yield and **6** (7.2 mg) in 49% yield. **6**: mp 85.0—87.0 °C (colorless crystals). IR (CCl_4): 2945, 2870, 1645, 1120, 900 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.84, 1.26 (each 3H, s, C_{10}-Me_2), 1.60 (3H, s, C_8-Me), 3.92 (1H, br d, J=3.1 Hz, C_2-H), 4.21 (1H, dd, J=7.9, 10.4 Hz, C_{9a}-H), 4.60 (1H, dd, J=5.5, 12.8 Hz, C_7-H), 4.66, 4.80 (each 1H, d, J=2.1 Hz, C_5=CH_2). MS m/z: 332, 334, 336 (M^+, 2.6, 3.2, 4.8). High MS m/z: 336.0516 (M^+, Calcd for $C_{15}H_{22}{}^{81}Br^{37}ClO$: 336.0491). **7**: mp 80.0—82.0 °C (colorless crystals). IR (CCl_4): 2945, 2870, 1640, 1110, 895 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.86, 1.15 (each 3H, s, C_{10}-Me_2), 1.87 (3H, s, C_8-Me), 3.91 (1H, br d, J=2.5 Hz, C_2-H), 4.31 (1H, dd, J=4.6, 12.5 Hz, C_{9a}-H), 4.48 (1H, dd, J=2.4, 13.8 Hz, C_7-H), 4.71, 4.89 (each 1H, d, J=2.4 Hz, C_5=CH_2). MS m/z: 332, 334, 336 (M^+, 0.5, 0.8, 0.2). High MS m/z: 336.0460 (M^+, Calcd for $C_{15}H_{22}{}^{81}Br^{37}ClO$: 336.0491).

(2*RS*,5a*RS*,7*SR*,8*RS*,9a*RS*)-7,8-Epoxy-2,3,4,5,5a,6,7,8,9,9a-decahydro-2,5a-methano-8,10,10-trimethyl-5-methylene-1-benzoxepin (8) MCPBA (80%, 7.7 mg, 0.036 mmol) was added to a stirred mixture of $NaHCO_3$ (20 mg, 0.24 mmol) and a CH_2Cl_2 (2.6 ml) solution of **3** (7.8 mg, 0.036 mmol) at 0 °C and stirring was continued for 2 h at the same 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 (AcOEt) to give **8** (5.0 mg) as a colorless oil in 60% yield. ^{1}H-NMR ($CDCl_3$) δ: 0.81, 1.14 (each 3H, s, C_{10}-Me_2), 1.32 (3H, s, C_8-Me), 3.04 (1H, d, J=3.7 Hz, C_7-H), 3.81 (1H, t-like, J=2.8 Hz, C_2-H), 4.19 (1H, dd, J=7.3, 11.0 Hz, C_{9a}-H), 4.75, 4.78 (each 1H, d, J=2.4 Hz, C_5=CH_2). MS m/z: 234 (M^+, 6.5). High MS m/z: 234.1630 (M^+, Calcd for $C_{15}H_{22}O_2$: 234.1620).

Cleavage of the Epoxy Ring of 8 with Li_2NiBr_4 Under a nitrogen atmosphere, a THF solution of Li_2NiBr_4 (*ca.* 0.4 M solution in THF, 1 ml, *ca.* 0.4 mmol) was added to a stirred solution of **8** (8.4 mg, 0.036 mmol) in THF (0.5 ml). After being stirred for 55 h at room temperature, the reaction mixture was diluted with ether, 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 to give **10** (1.2 mg) in 11% yield and **9** (4.7 mg) in 42% yield. **9**: colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.84, 1.22 (each 3H, s, C_{10}-Me_2), 1.66 (3H, s, C_8-Me), 3.92 (1H, br d, J=2.4 Hz, C_2-H), 4.20 (1H, dd, J=8.2, 10.7 Hz, C_{9a}-H), 4.24 (1H, ddd, J=2.1, 6.7, 10.7 Hz, C_7-H), 4.68, 4.77 (each 1H, d, J=2.1 Hz, C_5=CH_2). MS m/z: 314, 316 (M^+, 1.0, 1.0). **10**: colorless oil. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 0.80, 1.12 (each 3H, s, C_{10}-Me_2), 1.42 (3H, s, C_8-Me), 3.80—4.35 (3H, m, C_2-H, C_7-H, and C_{9a}-H), 4.70, 4.84 (each 1H, d, J=2 Hz, C_5=CH_2). MS m/z: 314, 316 (M^+, 0.1, 0.1).

(2*RS*,5a*RS*,7*SR*,8*SR*,9a*RS*)-7-Bromo-2,3,4,5,5a,6,7,8,9,9a-decahydro-8-hydroxy-2,5a-methano-8,10,10-trimethyl-5-methylene-1-benzoxepin (17) NBS (11.3 mg, 0.063 mmol) was added to a stirred solution of **3** (11.6 mg, 0.053 mmol) in THF (1.5 ml) and water (0.5 ml) and stirring was continued for 1 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 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 **17** (8.5 mg) in 51% yield and **18** (2.0 mg) in 10% yield. **17**: mp 145—147 °C (colorless crystals). IR ($CHCl_3$): 3570, 1130 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.84, 1.23 (each 3H, s, C_{10}-Me_2), 1.56 (3H, s, C_8-Me), 3.91 (1H, br d, J=3.1 Hz, C_2-H), 4.25 (1H, dd, J=8.2, 10.7 Hz, C_{9a}-H), 4.51 (1H, dd, J=5.5, 12.8 Hz, C_7-H), 4.67, 4.79 (each 1H, d, J=2.4 Hz, C_5=CH_2). MS m/z: 314, 316 (M^+, 4.2, 3.7). High MS m/z: 314.0881 (M^+, Calcd for $C_{15}H_{23}{}^{79}BrO$: 314.0881).

Reduction of 18 with Zn–AcOH AcOH (0.014 ml, 0.24 mmol) was added to a stirred suspension of zinc powder (27.0 mg, 0.41 mgatm) in a THF (1 ml) solution of **18** (11.4 mg, 0.028 mmol) and stirring was continued for 30 min. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with ether. The ethereal phase 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 = 3 : 1) to afford **17** (6.1 mg) in 67% yield.

(2*RS*,5a*RS*,7*SR*,8*SR*,9a*RS*)-7-Bromo-5-bromomethyl-2,3,5a,6,7,8,9,9a-octahydro-8-hydroxy-2,5a-methano-8,10,10-trimethyl-1-benzoxepin (18) NBS (47.0 mg, 0.26 mmol) was added to a stirred solution of **3** (23.2 mg, 0.13 mmol) in THF (2.8 ml) and water (0.02 ml) and stirring was continued for 2 h at room temperature. After further addition of NBS (30.0 mg, 0.17 mmol), the reaction mixture was stirred for 4.5 h at room temperature, 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 afford **18** (31.0 mg) in 74% yield. **18**: mp 160—164 °C (colorless crystals). IR ($CHCl_3$): 3575, 1135 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.02, 1.32 (each 3H, s, C_{10}-Me_2), 1.42 (3H, s, C_8-Me), 3.87 (1H, br d, J=1.2 Hz, C_2-H), 4.03 (2H, s, C_5-CH_2–Br), 4.35 (1H, dd, J=7.9, 11.0 Hz, C_{9a}-H), 4.51 (1H, dd, J=6.1, 12.2 Hz, C_7-H), 5.87 (1H, m, C_4-H). MS m/z: 387, 389, 391 (M^+ − Me, 1.2, 1.8, 1.2).

(2*RS*,5a*RS*,7*RS*,8*SR*,9a*RS*)-7,8-Epoxy-2,3,4,5,5a,6,7,8,9,9a-decahydro-2,5a-methano-8,10,10-trimethyl-5-methylene-1-benzoxepin (19) A 2 N KOH solution (0.14 ml, 0.28 mmol) was added to a stirred solution of **17** (5.2 mg, 0.017 mmol) in MeOH (1 ml) and stirring was continued for 70 min at room temperature. After further addition of 2 N KOH solution (0.14 ml), the reaction mixture was stirred for 15 min and diluted with ether. The ethereal solution 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 = 5 : 1) to give **19** (3.2 mg) as a colorless oil in 85% yield. IR ($CHCl_3$): 1645, 1100, 875 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.80, 1.08 (each 3H, s, C_{10}-Me_2), 1.32 (3H, s, C_8-Me), 2.94 (1H, dd, J=4.9, 6.1 Hz, C_7-H), 3.90 (1H, t-like, J=2.4 Hz, C_2-H), 4.07 (1H, dd, J=5.5, 13.4 Hz, C_{9a}-H), 4.71, 4.76 (each 1H, d, J=2.4 Hz, C_5=CH_2). MS m/z: 234 (M^+, 64.5). High MS m/z: 234.1603 (M^+, Calcd for $C_{15}H_{22}O_2$: 234.1618).

Cleavage of the Epoxy Ring of 19 with Li_2CuCl_4 Under a nitrogen atmosphere, a solution of Li_2CuCl_4 (0.1 M in THF, 1.8 ml, 0.18 mmol) was added to a stirred solution of **19** (4.2 mg, 0.018 mmol) in THF (0.1 ml). After being stirred for 24 h at room temperature, the reaction mixture was diluted with ether, 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 to give **16** (2.5 mg) in 52% yield and **20** (1.2 mg) in 25% yield. **16**: mp 137—139 °C (colorless crystals). IR ($CHCl_3$): 3600, 1090, 900 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.86, 1.15 (each 3H, s, C_{10}-Me_2), 1.55 (3H, s, C_8-Me), 3.89 (1H, br t-like, J=2.4 Hz, C_2-H), 4.12 (1H, ddd, J=3.1, 4.3, 12.8 Hz, C_7-H), 4.28 (1H, dd, J=4.9, 12.8 Hz, C_{9a}-H), 4.75, 4.86 (each 1H, d, J=2.8 Hz, C_5=CH_2). MS m/z: 270, 272 (M^+, 4.8, 1.9). High MS m/z: 270.1385 (M^+, Calcd for $C_{15}H_{23}{}^{35}ClO_2$: 270.1387). **20**: IR ($CHCl_3$): 3500, 1045 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.85, 1.13 (each 3H, s, C_{10}-Me_2), 1.54 (3H, s, C_8-Me), 3.87 (1H, m, C_2-H), 4.08 (1H, dd, J=2.8, 12.5 Hz, C_{9a}-H), 4.27 (1H, dd, J=4.9, 12.8 Hz, C_7-H), 4.89, 4.96 (each 1H, d, J=2.5 Hz, C_5=CH_2). MS m/z: 270, 272 (M^+, 7.9, 2.0). High MS m/z: 270.1398 (M^+, Calcd for $C_{15}H_{23}{}^{35}ClO_2$: 270.1387).

Cleavage of the Epoxy Ring of 19 with Li_2CuCl_4 in the Presence of TBDMSCl Under a nitrogen atmosphere, a solution of Li_2CuCl_4 (0.1 M in THF, 2.3 ml, 0.23 mmol) was added to a stirred solution of **19** (5.3 mg, 0.023 mmol) and TBDMSCl (4.1 mg, 0.027 mmol) in THF (0.1 ml). After being stirred for 4.5 h at room temperature, the reaction mixture was worked up as described above to give **16** (5.8 mg) in 93% yield.

(2*RS*,5a*RS*,7*SR*,8*RS*,9a*RS*)-7-Bromo-5-bromomethyl-8-chloro-2,3,5a,6,7,8,9,9a-octahydro-2,5a-methano-8,10,10-trimethyl-1-benzoxepin (22) Under a nitrogen atmosphere, a CH_2Cl_2 (1 ml) solution of **16** (3.7 mg, 0.014 mmol) was added dropwise to a stirred suspension of $CaCO_3$ (13.7 mg, 0.14 mmol) in a CH_2Cl_2 (1 ml) solution of PBr_5 (*ca.* 7 mg, *ca.* 0.016 mmol) under ice cooling. This mixture was stirred for 5 min, then a 2% pyridine solution in CH_2Cl_2 (0.04 ml) was added, and the whole was stirred for 15 min at 0 °C, poured into saturated aqueous $NaHCO_3$, and extracted with ether. 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) to give **22** (0.9 mg) as an unstable colorless oil in 16% yield. IR ($CHCl_3$): 1640 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.01, 1.32 (each 3H, s, C_{10}-Me_2), 1.54 (3H, s, C_8-Me), 3.88 (1H, br s, C_2-H), 4.01 (2H, s, C_5-CH_2–Br), 4.32 (1H, dd, J=7.6, 10.7 Hz, C_{9a}-H), 4.63 (1H, dd, J=8.6, 9.8 Hz, C_7-H), 5.87 (1H, m, C_4-H).

(2*RS*,5a*RS*,7*RS*,8*RS*,9a*RS*)-5-Bromomethyl-8-chloro-2,3,5a,6,7,8,9,9a-octahydro-7-hydroxy-2,5a-methano-8,10,10-trimethyl-1-benzoxepin (21) Bromine (0.01 ml, 0.19 mmol) was added to a stirred solution of **16** (10.3 mg, 0.038 mmol) in dry CH_2Cl_2 (2 ml) and stirring was continued

for 15 min. After being diluted with ether, the reaction mixture was washed with saturated aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl and dried over $MgSO_4$. Evaporation under reduced pressure and purification by silica gel column chromatography (C_6H_6 : AcOEt = 3 : 1) afforded **21** (9.1 mg) as a colorless oil in 69% yield. IR ($CHCl_3$): 3600, 1645, 1100 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.03, 1.24 (each 3H, s, C_{10}-Me_2), 1.55 (3H, s, C_8-Me), 3.83 (1H, br s, C_2-H), 4.12, 4.20 (each 1H, d, J = 10.1 Hz, C_5-CH_2-Br), 4.42 (1H, dd, J = 6.1, 11.6 Hz, C_{9a}-H), 5.89 (1H, t-like, J = 3.0 Hz, C_9-H). MS m/z: 348, 350, 352 (M^+, 1.1, 1.9, 0.7). High MS m/z: 348.0520 (M^+, Calcd for $C_{15}H_{22}{}^{79}Br^{35}ClO_2$: 348.0492).

(2*RS*,5a*RS*,7*SR*,8*RS*,9a*RS*)-7-Bromo-5-bromomethyl-8-chloro-2,3,5a,6,7,8,9,9a-octahydro-2,5a-methano-8,10,10-trimethyl-1-benzoxepin (22) from 21 Under a nitrogen atmosphere, a solution of **21** (4.5 mg, 0.013 mmol) in CH_2Cl_2 (1 ml) was added dropwise to an ice-cooled suspension of $CaCO_3$ (10.3 mg, 0.10 mmol) in a solution of PBr_5 (*ca.* 7 mg, 0.016 mmol) in CH_2Cl_2 (2.5 ml) and stirring was continued for 5 min at the same temperature. A 2% pyridine solution in CH_2Cl_2 (0.06 ml) was added to the reaction mixture and the whole was stirred for a further 15 min under ice cooling then worked up as described above to give **22** (3.2 mg) in 60% yield.

(2*RS*,5a*RS*,7*RS*,8*SR*,9a*RS*)-5-Bromomethyl-7,8-epoxy-2,3,5a,6,7,8,9,9a-octahydro-2,5a-methano-8,10,10-trimethyl-1-benzoxepin (24) *tert*-BuOK (*ca.* 10 mg, *ca.* 0.089 mmol) was added to a stirred solution of **18** (5.0 mg, 0.013 mmol) in THF (1.5 ml) and stirring was continued for 6 h at room temperature. After being diluted with ether, the reaction mixture 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 = 5 : 1) to give **24** (3.3 mg) as a colorless oil in 83% yield. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 0.94, 1.13 (each 3H, s, C_{10}-Me_2), 1.38 (3H, s, C_8-Me), 3.19 (1H, dd, J = 4.0, 6.4 Hz, C_7-H), 3.84 (1H, m, C_2-H), 3.88—4.25 (2H, AB type, C_5-CH_2-Br), 4.26 (1H, dd, J = 5.9, 10.2 Hz, C_{9a}-H), 5.90 (1H, m, C_4-H). MS m/z: 312, 314 (M^+, 1.0, 1.1).

(2*RS*,5a*RS*,7*RS*,8*RS*,9a*RS*)-5-Bromomethyl-8-chloro-2,3,5a,6,7,8,9,9a-octahydro-7-hydroxy-2,5a-methano-8,10,10-trimethyl-1-benzoxepin (21) *via* 23 Under a nitrogen atmosphere, a mixture of **24** (3.3 mg, 0.011 mmol) and TBDMSCl (2.0 mg, 0.013 mmol) in a Li_2CuCl_4 solution (0.1 M in THF, 1.0 ml, 0.1 mmol) was stirred for 7 h at room temperature. After being diluted with ether, the reaction mixture was washed with saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure to afford **23** as a colorless oil. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 0.97, 1.17 (each 3H, s, C_{10}-Me_2), 1.54 (3H, s, C_8-Me), 3.77 (1H, m, C_2-H), 3.92—4.30 (2H, AB type, C_5-CH_2-Br), 4.36 (1H, dd, J = 6.8, 11.2 Hz, C_{9a}-H), 5.78 (1H, m, C_4-H). MS m/z: 304, 306, 308 (M^+, 2.8, 0.8, 0.1). Without purification, the chloromethyl derivative **23** was treated with Li_2NiBr_4 and worked up according to the same procedure as described above and purified by silica gel column chromatography (C_6H_6 : AcOEt = 10 : 1) to give **21** (2.0 mg) in 54% yield. The physical properties (TLC, ^{1}H-NMR) of the product were identical with those of **21** obtained by route A.

(±)-7-Epinidifocene (15) Zinc powder (10 mg, 0.15 mgatm) and AcOH (0.01 ml, 0.17 mmol) were added to a solution of **22** (1.6 mg, 0.0039 mmol) in THF (2 ml) and stirring was continued for 1.5 h at room temperature. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with ether. 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) to give **15** (1.0 mg) as a colorless oil. IR (CCl_4): 2950, 1645 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.84, 1.25 (each 3H, s, C_{10}-Me_2), 1.75 (3H, s, C_8-Me), 3.92 (1H, br d, J = 3.1 Hz, C_2-H), 4.20 (1H, dd, J = 7.9, 10.4 Hz, C_{9a}-H), 4.56 (1H, dd, J = 6.1, 12.2 Hz, C_7-H), 4.65, 4.79 (each 1H, d, J = 1.8 Hz, C_5=CH_2). MS m/z: 332, 334, 336 (M^+, 1.4, 1.7, 0.7). High MS m/z: 332.0549 (M^+, Calcd for $C_{15}H_{22}{}^{79}Br^{35}ClO$: 332.0544).

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References and Notes

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