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An Approach to the Stereoselective Synthesis of Nidifocene: Regio- and Stereoselective Synthesis of *vic-trans*-Bromochlorocyclohexane Ring System

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(±)-(2*R**,5a*S**,7*R**,8*R**,9a*R**)- and (2*R**,5a*S**,7*S**,8*S**,9a*R**)-7-Bromo-8-chloro-decahydro-2,5a-methano-1-benzoxepin (**1** and **2**), the 11,11-dedimethyl-7-demethylene derivative of nidifocene and its isomer, were stereoselectively synthesized *via* the bromohydrin **3** and **4** starting from the *exo*-diene **14**.

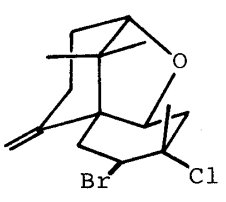
Keywords——halogenated sesquiterpene; nidifocene; *vic-trans*-bromochlorocyclohexane ring system; tricyclic skeleton; regioselective synthesis; stereoselective synthesis; bromohydrin

Nidifocene, which is one of the halogenated chamigrane-type sesquiterpenes,[1] was isolated from *Laurencia nidifica* in 1976.[2] In connection with our synthetic studies toward chamigrane-type sesquiterpenes,[3] we became interested in the stereoselective construction of its unique tricyclic skeleton and the regio- and stereoselective introduction of the *vic-trans*-bromochlorocyclohexane ring system. The *vic*-bromochlorocyclohexane ring system is usual in not only chamigrane-type sesquiterpenes but also mono- and sesquiterpenes isolated from marine organisms. González and co-workers have reported some relation between the regio- and stereochemistry of these *vic*-dihaloterpenes and their biological activity.[4] But, to our knowledge, a successful regio- and stereoselective synthesis of these natural products has not been reported.

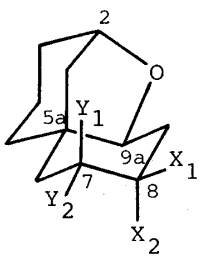
We now describe an efficient and stereoselective route to the diaxial bromochloro derivative **1** and diequatorial bromochloro derivative **2**, corresponding to 11,11-dedimethyl-7-demethylenenidifocene and its isomer, *via* the bromohydrins **3** and **4** which were stereoselectively prepared from the common olefin **12**.

Synthesis of the Olefin 12

We planned that the regioselective synthesis of the olefin **12** would be carried out by the 1,4-reduction of the *endo*-diene **7** or the *exo*-diene **14**. The *endo*-diene **7** was synthesized as follows: the hydroxyspirodienone **5**[5] was treated with methyllithium in tetrahydrofuran (THF) to give the dienol **6**, which was so unstable that the crude product was used



nidifocene



1: X_1=Me, X_2=Cl, Y_1=Br, Y_2=H
2: X_1=Cl, X_2=Me, Y_1=H, Y_2=Br
3: X_1=Me, X_2=OH, Y_1=Br, Y_2=H
4: X_1=OH, X_2=Me, Y_1=H, Y_2=Br

Fig. 1

immediately for the next reaction without purification. Although the dienol **6** was easily decomposed to aromatic compounds by a catalytic amount of acid (dienol–benzene rearrangement), treatment with magnesium perchlorate in THF afforded the *endo*-diene **7** in 74% yield from **5**.[6] The structure of **7** was confirmed by the ^{1}H-nuclear magnetic resonance (NMR) signals of the C_9-olefinic proton at 5.27 ppm (m), the C_6- and C_7-olefinic protons at 5.48—5.78 ppm (AB type), and the C_2- and C_{9a}-protons at 4.67 ppm (m) and 4.11 ppm (t-like, $J=5$ Hz), and an absorption maximum in the ultraviolet (UV) spectrum due to an *endo*-diene at 261 nm. Catalytic hydrogenation of **7** over palladium–barium sulfate (Pd–$BaSO_4$) in benzene afforded a mixture of **11**, **12**, and **13** in the ratio of 2 : 3 : 1 in 91% yield. The reduction mixture could be separated into the desired olefin **12** and a mixture of **11** and **13** by silver nitrate-impregnated silica gel column chromatography. Alternative attempts to reduce **7** (catalytic hydrogenation, metal–ammonia reduction) did not give good results in terms of regioselectivity and yield.

The *exo*-diene **14** was synthesized in 62% yield from the tricyclic enone **8**[5] by methylenation of **8** under the conditions reported by Nozaki *et al.* (CH_2I_2–Zn–$TiCl_4$).[7] The structure of **14** was confirmed by the ^{1}H-NMR signals of the *exo*-methylene protons at 4.62—5.11 ppm (AB type), the C_6- and C_7-olefinic protons at 6.04 ppm (d, $J=10$ Hz) and 5.57 ppm (1H, d, $J=10$ Hz), and the C_{9a}- and C_2-protons at 3.97 ppm (1H, dd, $J=11$, 6 Hz) and 4.42 ppm (1H, t-like, $J=5$ Hz), and an absorption maximum in the UV spectrum due to an *exo*-diene at 232 nm. Reduction of **14** with lithium in liquid ammonia afforded the desired olefin **12** in 74% yield accompanied with the isomer **13** in 9% yield.

Alternatively the isomeric olefin **11** was regioselectively synthesized starting from the enone **9**[5] as follows: the enone **9** was treated with methyllithium in THF and dehydrated with

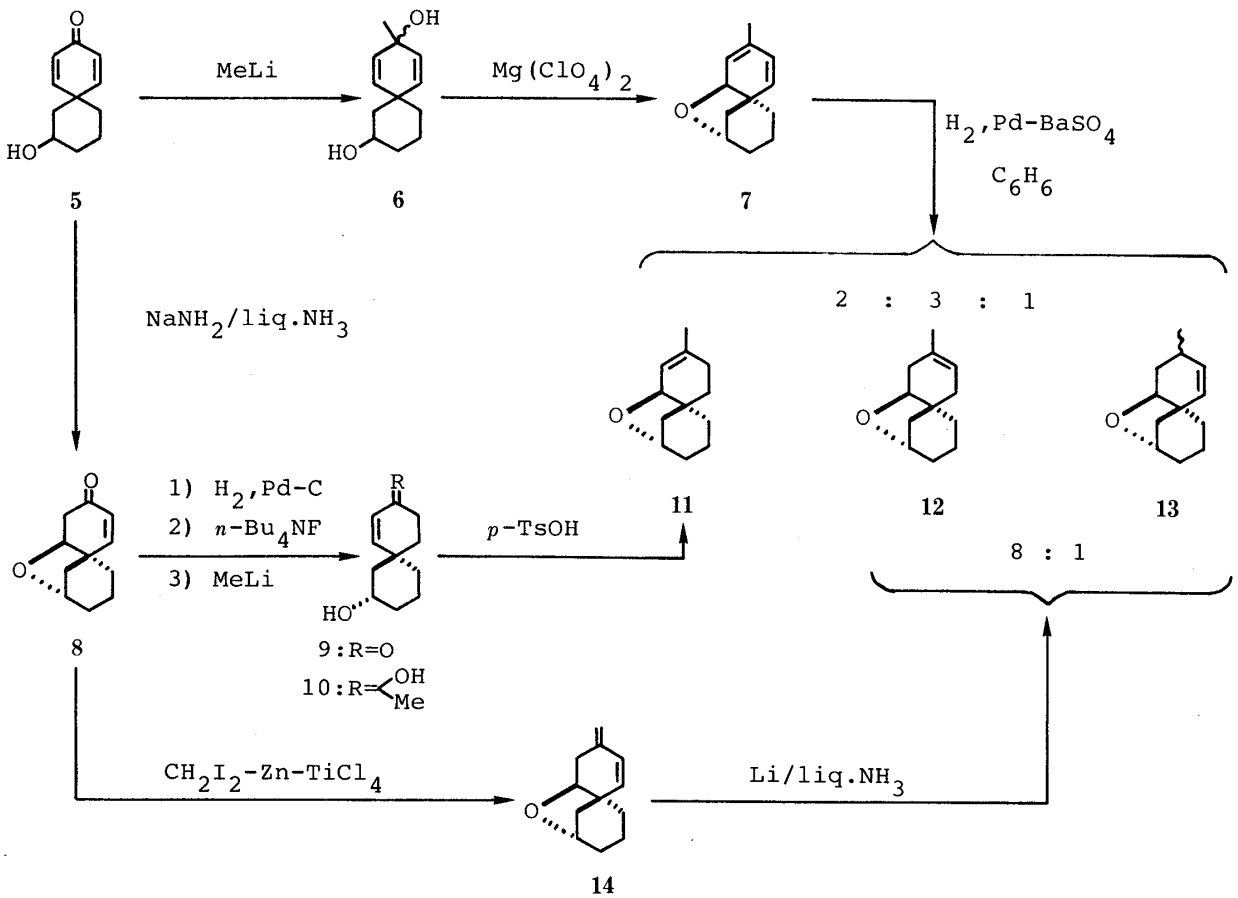


Chart 1

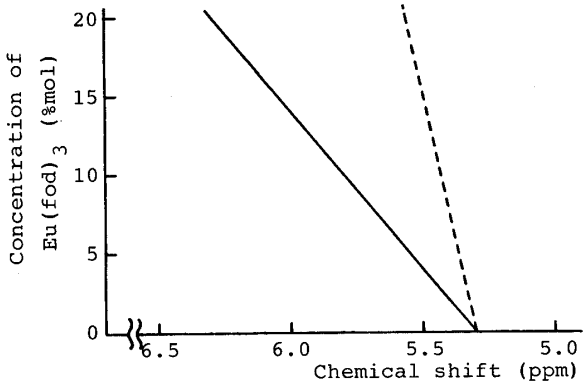
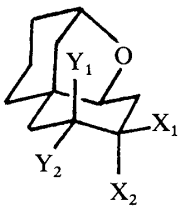


Fig. 2. $Eu(fod)_3$-Induced Shift of the Olefinic Proton Signal of **11** (------) and **12** (——)

TABLE I. Direct Addition of "BrCl" to **12**



15: X_1=Me, X_2=Br, Y_1=Cl, Y_2=H
16: X_1=Br, X_2=Me, Y_1=H, Y_2=Cl
17: X_1=Me, X_2=Br, Y_1=Br, Y_2=H
18: X_1=Br, X_2=Me, Y_1=H, Y_2=Br
19: X_1=Me, X_2=Cl, Y_1=Cl, Y_2=H
20: X_1=Cl, X_2=Me, Y_1=H, Y_2=Cl

Run	Reagents	Solvent	Conditions Temp. °C (Time h)	Isolated Yield (%)	Ratio (%)[a]						Ref.
					1	**2**	**15**	**16**	**17**	**18**	
1	$CuCl_2$, KBr	MeCN	r.t. (24)→refl. (5.5)	79	9	59	23	9	—	—	8
2	Amberlyst A-26 Cl_2Br	CH_2Cl_2	r.t. (20)	95	18	32	43	7	—	—	9
3	BrCl	CCl_4	r.t. (0.25)	Quant.	<1	6	<1	31	31	31	10
4	$SbCl_5$, Br_2	CCl_4	r.t. (0.25)	81	19	23	42	8	8	—	11
5	DMSO, *tert*-BuBr, BTEACl	—	80 (2.5)	54	50	25	—	25	—	—	12
6	NCS, LiBr	THF	0 (2)→r.t. (41)	Quant.	<1	<1	<1	<1	>96	—	13
7	NBA, LiCl	THF	r.t. (21)	Quant.	41[b]	13	41[b]	5	—	—	14
8	NBS, LiCl	THF	r.t. (1)	Quant.	38[b]	6	50[b]	6	—	—	—
9	NBS, LiCl	CH_2Cl_2	r.t. (3)	56	18	37	18	27	—	—	—
10	NBS, LiCl	MeCN	r.t. (0.25)	73	22	<1	44	33	—	—	—
11	NBS, BTEACl	THF	r.t. (40)	82	44	<1	22	<1	33	—	—

a) Determined by ^{1}H-NMR. *b*) Determined from isolated yield.

p-toluenesulfonic acid in benzene at room temperature to afford **11** in 87% overall yield.

Although the regiochemistries of the olefin **11** and **12** are synthetically apparent, a shift reagent study further confirmed the structures of **11** and **12**. The ^{1}H-NMR signal of the olefinic proton in **11** was shifted to lower field than that of the olefinic proton in **12** by addition of $Eu(fod)_3$ as shown in Fig. 2.

Introduction of "BrCl"

Initial efforts concentrated upon the introduction of "BrCl" into the olefin **12** directly using the methods already reported[8-14] (runs 1—7), but direct addition to the olefin **12** did not result in satisfactory regio- and stereoselectivity as shown in Table I.

Faulkner has reported the introduction with *N*-bromoacetoamide and lithium chloride in THF[14] according to the concept of biogenesis.[15] The diaxial derivatives **1** and **15** were

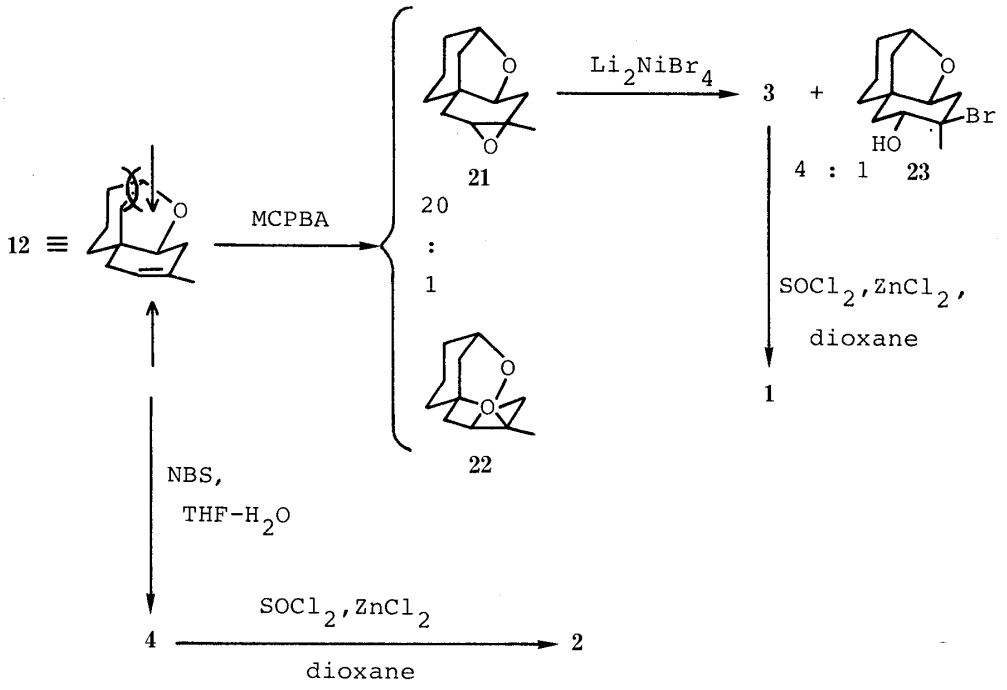


Chart 2

stereoselectively obtained under the same conditions, but regioselectivity was not observed (run 7). Further investigation based on the same concept indicated that the conditions of run 11 (*N*-bromosuccinimide–lithium chloride–THF) afforded the best result, but the regioselectivity is not high (**1** : **15** = 2 : 1).

Inspection of the molecular model of the olefin **12** indicates that the approach of the reagent to the double bond would be from the less hindered bottom face. As expected, the olefin **12** was stereoselectively epoxidized with *m*-chloroperbenzoic acid (MCPBA) in methylene chloride at 0 °C to afford the epoxide **21** in 84% yield (**21** : **22** = 20 : 1). Cleavage of the epoxide **21** with lithium tetrabromonickelate in THF[16] afforded the bromohydrin **3** as a major product in 76% yield (**3** : **23** = 4 : 1). Treatment of **3** with thionyl chloride and zinc chloride in dioxane[17] afforded the desired diaxial bromochloro derivative **1** with retention of C-8 stereochemistry in 58% yield.

Alternatively, direct bromohydrination of the olefin **12** by treatment with *N*-bromosuccinimide in THF–H_2O afforded the diequatorial bromohydrin **4** exclusively in 74% yield, and this could also be transformed to the diequatorial bromochloro derivative **2** under the same conditions as described for the preparation of **1**, with retention of C-8 stereochemistry, in 62% yield.

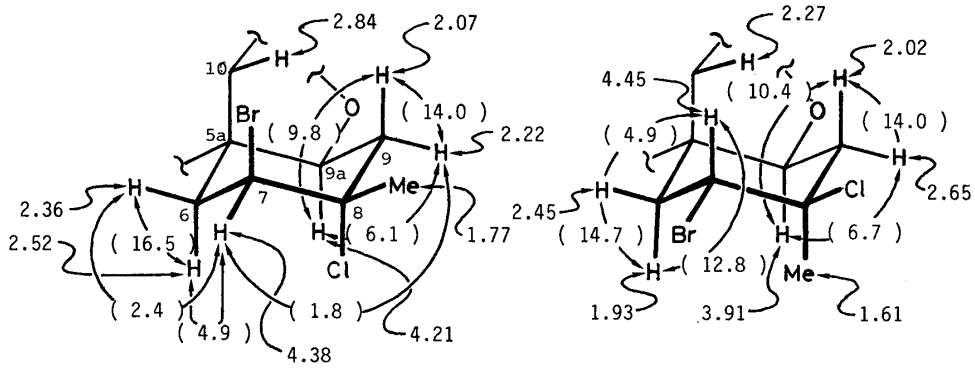
Regio- and Stereochemistry of the Bromochloro Derivatives

The stereochemistries of the halogenated derivatives were confirmed by detailed analysis of the 500 MHz ^{1}H-NMR spectra as shown in Table II and Fig. 3. The coupling constants $J_{6ax\text{-}7}$ (4.3—4.9 Hz) and $J_{6eq\text{-}7}$ (2.4—3.7 Hz) and the long-range coupling constants $J_{7\text{-}9eq}$ (1.8 Hz) in the diaxial derivatives are consistent with the axial configuration of the C_7-halogens. The values of $J_{6ax\text{-}7}$ (11.6—13.4 Hz) and $J_{6eq\text{-}7}$ (4.9—5.5 Hz) in the diequatorial derivatives are consistent with the equatorial configuration of the C_7-substituents. The chemical shifts for the C_{9a}-protons (4.14—4.24 ppm) and for the C_{10}-equatorial protons (2.69—2.85 ppm) in the diaxial derivatives appear at lower field than those for C_{9a}-protons (3.91—3.94 ppm) and for the C_{10}-equatorial protons (2.25—2.28 ppm) in the diequatorial derivatives due to the effects of the C_8-axial and C_7-axial halogens or hydroxyl groups,

TABLE II. ^{1}H-NMR (500 MHz) Data for Halogenated Derivatives

Compd. No.	Chemical shift (ppm)									Coupling constant J (Hz)							
	2	6ax	6eq	7	9ax	9eq	9a	10eq	Me	2	6ax-7	6eq-7	6ax-eq	7-9eq	9ax-9a	9eq-9a	9ax-eq
1	4.32	2.52	2.36	4.38	2.07	2.22	4.21	2.84	1.77	4.9	4.3	2.4	15.9	1.8	9.8	6.1	14.0
	dd	dd	dd	ddd	dd	ddd	dd	m	s	6.1							
15	4.30	2.48	2.33	4.39	1.96	2.25	4.21	2.69	1.92	5.5	4.3	2.4	16.5	1.8	9.8	6.1	14.7
	dd	dd	dd	ddd	dd	ddd	dd	m	s	6.1							
17	4.32	2.63	2.45	4.56	1.99	2.28	4.24	2.85	1.97	4.9	4.9	2.4	16.5	1.8	9.2	6.1	14.7
	dd	dd	dd	ddd	dd	ddd	dd	m	s	6.1							
19	4.30	2.37	2.25	4.22	2.02	2.19	4.19	2.69	1.72	5.5	4.3	2.5	15.9	1.8	9.8	6.1	14.0
	dd	dd	dd	ddd	dd	ddd	dd	m	s	6.1							
3	4.33	2.32	2.19	4.05	1.86	1.96	4.14	2.69	1.43	5.5	4.3	3.7	15.3	*ca.* 1	11.0	4.9	14.0
	t-like	dd	dd	ddd	dd	ddd	dd	m	s								
2	4.38	1.93	2.45	4.45	2.02	2.65	3.91	2.27	1.61	5.5	12.8	4.9	14.7	—	10.4	6.7	14.0
	dd	dd	dd	dd	dd	dd	dd	m	s	6.1							
16	4.38	1.93	2.40	4.59	1.97	2.85	3.92	2.27	1.81	5.5	12.8	4.9	14.7	—	10.4	6.7	14.0
	dd	dd	dd	dd	dd	dd	dd	m	s	6.1							
18	4.37	1.97	2.40	4.59	2.27	2.84	3.92	2.28	1.81	4.9	13.4	5.5	14.7	—	10.4	6.1	14.0
	dd	dd	dd	dd	dd	dd	dd	m	s	6.1							
20	4.38	1.74	2.33	4.30	1.98	2.59	3.91	2.26	1.57	4.9	12.8	4.9	14.7	—	10.4	6.1	14.0
	dd	dd	dd	dd	dd	dd	dd	m	s	6.1							
4	4.37	1.87	2.42	4.31	1.57	2.30	3.94	2.25	1.24	5.5	13.4	4.9	14.7	—	10.4	6.7	13.4
	t-like	dd	dd	dd	dd	dd	dd	m	s								
23	4.36	1.40	2.04	4.13	2.19	2.68	3.92	2.27	1.68	5.5	11.6	5.5	14.6	—	10.4	6.7	13.4
	dd	dd	dd	dd	dd	dd	dd	m	s	6.1							

The measurements were made on a JNM-GX500 in $CDCl_3$ with TMS as an internal standard.



1 **2**

Fig. 3. ^{1}H-NMR Data for Bromochloro Derivatives **1** and **2** (δ ppm, J in Hz)

TABLE III. ^{13}C-NMR (22.5 MHz) Data for Halogenated Derivatives

Compd. No.	Chemical shift (ppm)											
	C-2	C-3	C-4	C-5[a)]	C-5a	C-6[a)]	C-7	C-8	C-9[a)]	C-9a	C-10[a)]	Me
1	75.2	31.7	19.3	39.2	40.4	40.0	55.7	72.1	39.3	78.3	41.6	33.3
15	75.1	31.6	19.3	39.1	40.0	40.4	64.2	67.3	39.4	79.3	41.9	33.3
17	75.1	31.7	19.3	39.2	40.3	40.9	56.8	68.2	40.4	79.4	41.8	35.3
19	75.3	31.7	19.3	38.5	40.1	39.5	63.5	71.7	39.2	78.3	41.8	31.5
3	75.6	31.7	19.2	38.8	41.5	39.5	56.1	74.0	39.2	78.4	41.2	30.1
2	75.6	31.6	19.0	38.5	44.4	47.7	59.0	70.2	39.5	77.9	42.8	23.3
16	75.8	31.7	19.1	38.6	44.5	49.2	65.8	66.0	39.5	77.7	42.3	24.8
18	75.7	31.6	19.0	38.5	44.4	49.1	59.9	66.1	39.4	77.5	42.1	24.8
20	76.0	31.7	19.1	38.7	43.8	48.2	65.3	70.6	39.8	78.0	41.7	22.0
4	75.7	31.7	19.1	38.7	44.7	42.6	62.0	71.9	39.8	78.8	44.0	21.3

The measurements were made on a JEOL FX90Q in $CDCl_3$ with TMS as an internal standard and multiplicities were assigned based on the INEPT sequence. *a*) Assignments may be reversed.

respectively.

The configuration of the C_8-position is confirmed by the ^{13}C-NMR signals of the C_8-methyl group, as shown in Table III. The ^{13}C-NMR chemical shifts for the C_8-methyl groups (21.3—24.8 ppm) in the diequatorial derivatives appear at higher field than those for the C_8-methyl groups (30.1—35.3 ppm) in the diaxial derivatives due to the γ-effect.[18)]

The regiochemistries of the bromochloro derivatives **1**, **2**, **15**, and **16** were confirmed by comparison of the ^{13}C-NMR spectra with those of the dihalogeno derivatives **17**—**20**, prepared from **12** by direct addition of Br_2 or by treatment with *N*-chlorosuccinimide and lithium chloride. Good agreement exists in the ^{13}C-NMR chemical shifts of C-7 and C-8 between the halogenated derivatives **1**, **2**, **3**, **4**, **15**, and **16** and the dibromo and dichloro derivatives **17**—**20**. For example, the chemical shift for C-7 (55.7 ppm) in the diaxial bromochloro derivative **1** agrees well with that for C-7 (56.8 ppm) in the diaxial dibromo derivative **17**, and that for C-8 (72.1 ppm) in **1** agrees with that for C-8 (71.7 ppm) in the diaxial dichloro derivative **19**.

This sequential transformation from the olefin to the bromochloro derivatives, *via* the bromohydrin, is highly regio- and stereoselective and has proved to be a useful method for the stereoselective synthesis of the mono- and sesquiterpenes which contain the *vic-trans*-bromochlorocyclohexane ring system characteristic of halogenated terpenes isolated from marine organisms.

Experimental

Melting points were determined on a Yanagimoto micromelting point apparatus, and boiling points and melting points are uncorrected. UV spectra were recorded on a Hitachi 124 spectrophotometer. Infrared (IR) spectra were recorded on a Hitachi EPI G-3 and/or a Hitachi 260-10 spectrometer. ^{1}H-NMR spectra were recorded on a Hitachi R-22 (90 MHz), a JEOL JNM-FX90Q (90 MHz), and/or a JEOL JNM-GX 500 (500 MHz) with tetramethylsilane as an internal standard. The following abbreviations are used; s = singlet, d = doublet, t = triplet, m = multiplet, and br = broad. The frequency of measurement is 90 MHz unless otherwise stated. ^{13}C-NMR spectra were recorded on a JEOL JNM-FX90Q (22.5 MHz). Mass spectra (MS) were obtained with a JEOL JMS-D300 and/or a Shimadzu GCMS-QP1000 mass spectrometer. High-resolution mass spectra (High MS) were obtained with a JEOL JMS-D300 mass spectrometer. For preparative thin layer chromatography (PTLC) and column chromatography, Merck Kieselgel PF_{254} and Merck Kieselgel 60 (70—230 mesh or 230—400 mesh) were used, respectively. High pressure liquid chromatography (HPLC) was carried out on a Waters Associates high-pressure liquid chromatography with an M6000A pump, a U6K septumless injector, and a Series R401 differential refractometer. Two silica packed columns [Waters Associates, μ-Porasil (7.8 mm i.d. × 30 cm length)] were connected and used at a flow rate of 5 ml/min.

(2*R,5a*S**,9a*R**)-2,3,4,5,5a,9a-Hexahydro-2,5a-methano-8-methyl-1-benzoxepin (7) *via* 6**——An ethereal solution of methyllithium (1.26 M, 11.5 ml) was added dropwise to a stirred THF solution of **5** (515.2 mg) at 0 °C. After being stirred for 1.5 h at 0 °C, the reaction mixture was diluted with ether saturated with water, washed with water and brine, dried (Na_2SO_4), and concentrated *in vacuo* to give **6** (577.3 mg) as a viscous oil, which was immediately used for the next reaction without purification. This was dissolved in dry THF (10 ml), and magnesium perchlorate (*ca.* 5 mg) was added to the THF solution. After being stirred for 4 h at room temperature, the reaction mixture was poured into saturated sodium bicarbonate solution containing crushed ice, and extracted with ether. The extract was washed with water and brine, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (benzene) to give **7** (375.5 mg) in 74% yield as a colorless oil. IR ($CHCl_3$): 2990, 2940, 2850, 1090 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.71 (3H, m, C_8-CH_3), 4.11 (1H, t-like, J = 5 Hz, C_2-H), 4.67 (1H, m, C_{9a}-H), 5.27 (1H, m, C_9-H), 5.48—5.78 (2H, AB type, C_6- and C_7-H). UV λ_{max}^{EtOH} nm (ε): 261 (7240). MS *m/z*: 176 (M^+, 55.2). High MS *m/z*: 176.119 (M^+, Calcd for $C_{12}H_{16}O$: 176.120).

Catalytic Hydrogenation of 7——Compound **7** (200 mg) in benzene (5 ml) was hydrogenated in the presence of 5% Pd–$BaSO_4$ (200 mg) for 30 min at ordinary pressure. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo* and purified by silica gel column chromatography (benzene) to give a mixture of **11**, **12**, and **13** (183.3 mg) in 91% yield (**11** : **12** : **13** = 2 : 3 : 1 based on gas chromatography (GC) analysis). Further purification of this mixture using silver nitrate-impregnated silica gel column chromatography gave **12** (59.7 mg) in 30% yield and a mixture of **11** and **13** (62.3 mg) in 31% yield.

12: bp 85—90 °C (bath temperature)/1 mmHg. IR ($CHCl_3$): 2990, 2940, 2850, 1100 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.64 (3H, br s, C_8-H), 3.91 (1H, t-like, J = 7 Hz, C_{9a}-H), 4.27 (1H, t-like, J = 6 Hz, C_2-H), 5.26 (1H, m, C_7-H). MS *m/z*: 178 (M^+, 37.3). *Anal.* Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.57; H, 10.12.

(2*R,5a*S**,9a*R**)-9*H*-2,3,4,5,5a,9a-Hexahydro-2,5a-methano-8-methylene-1-benzoxepin (14)**——Methylene iodide (1.49 ml) was added to a stirred suspension of zinc powder (2.17 g) in THF (30 ml) at room temperature, and the reaction mixture was stirred for 30 min at room temperature. A 10% CH_2Cl_2 solution of titanium tetrachloride (4.1 ml) was added dropwise to this reaction mixture at 0 °C, and the resulting reaction mixture was stirred for 30 min at room temperature. A dry THF solution (5 ml) of **8** (658.1 mg) was added dropwise to the reaction mixture. After being stirred for 15 min at room temperature, the reaction mixture was poured into ether, and filtered. The filtrate was washed with saturated ammonium chloride solution, water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (benzene) to give **14** (403.3 mg) as a colorless oil in 62% yield. IR ($CHCl_3$): 2985, 2940, 2850, 1640, 1600, 1095 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.97 (1H, dd, J = 6, 11 Hz, C_{9a}-H), 4.42 (1H, t-like, J = 5 Hz, C_2-H), 4.62—5.11 (2H, AB type, *exo*-methylene protons), 5.57 (1H, d, J = 10 Hz, C_6-H), 6.04 (1H, d, J = 10 Hz, C_7-H). UV λ_{max}^{EtOH} nm (ε): 232 (22300). MS *m/z*: 176 (M^+, 61.0). High MS *m/z*: 176.120 (M^+, Calcd for $C_{12}H_{16}O$: 176.120).

(2*R,5a*R**,9a*R**)-9*H*-2,3,4,5,5a,9a-Hexahydro-2,5a-methano-8-methyl-1-benzoxepin (12)**——A THF solution (5 ml) of **14** (387.3 mg) was added dropwise to a stirred solution of lithium (1.67 g) in liquid ammonia (*ca.* 400 ml) at −78 °C. The mixture was stirred for 2 h with reflux, then powdered dry ammonium chloride (*ca.* 2 g) was added portionwise, and ammonia was evaporated off at room temperature. Water and ether were added to the residue, and the ether extract was washed with saturated sodium bicarbonate solution, water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (benzene) to give a mixture of **12** and **13** (328.2 mg) in 84% yield, which was further purified by silver nitrate-impregnated silica gel column chromatography (hexane : ethyl acetate = 80 : 1) to give **12** (288.7 mg) in 74% yield and **13** (35.4 mg) in 9% yield.

13: Colorless oil. IR ($CHCl_3$): 2990, 2940, 2875, 2850, 1085 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.99 (3H, d, J = 7 Hz, C_8-CH_3), 3.91 (1H, dd, J = 5, 12 Hz, C_{9a}-H), 4.33 (1H, t-like, J = 5 Hz, C_2-H), 5.14—5.67 (2H, AB type, C_6- and C_7-H). MS *m/z*: 178 (M^+, 26.6). High MS *m/z*: 178.137 (M^+, Calcd for $C_{12}H_{18}O$: 178.136).

(2*R,5a*R**,9a*R**)-7*H*-2,3,4,5,5a,9a-Hexahydro-2,5a-methano-8-methyl-1-benzoxepin (11)**——An ethereal so-

lution of methyllithium (1.26 M, 2.0 ml) was added dropwise to a stirred THF solution (10 ml) of **9** (126.7 mg) at 0 °C. After being stirred for 30 min, the reaction mixture was diluted with ether saturated with water, washed with water and brine, dried (Na_2SO_4), and concentrated to give crude **10** (127.0 mg). This was dissolved in dry benzene (10 ml), and *p*-toluenesulfonic acid (123.1 mg) was added to the solution. The reaction mixture was stirred for 5 h at room temperature and then diluted with benzene. The benzene solution was washed with saturated sodium bicarbonate solution, water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (benzene) to give **11** (78.0 mg) as a colorless oil in 87% yield. **11**, bp 105—108 °C (bath temperature)/1 mmHg. IR ($CHCl_3$): 2940, 2870, 2850, 1100 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.65 (3H, br s, C_8-CH_3), 4.17 (1H, m, C_{9a}-H), 4.29 (1H, t-like, J=5 Hz, C_2-H), 5.28 (1H, m, C_9-H). MS *m/z*: 178 (M^+, 14.3). *Anal.* Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.70; H, 9.89.

Direct Addition of "BrCl" to the Olefin 12——Runs 1—6 were carried out according to the literature,[8-13] and the ratio of the reaction products was determined from the ^{1}H-NMR data. A typical procedure for the direct addition using *N*-bromoamides and chloride salts (runs 7—11) is as follows. *N*-Bromosuccinimide (66.3 mg) was added to a stirred mixture of **12** (44.3 mg) and lithium chloride (105.1 mg) in THF (3 ml) at room temperature. The reaction mixture was stirred for 1 h at room temperature and then diluted with ether. The ethereal solution was washed with saturated sodium bicarbonate solution, water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give a mixture of **1** and **15** (62.9 mg) in 86% yield (**1** : **15** = 1 : 1.3 based on ^{1}H-NMR), and a mixture of **2** and **16** (9.1 mg) in 13% yield (**2** : **16** = 1 : 1 based on ^{1}H-NMR). A former mixture was separable by HPLC (hexane : ethyl acetate = 50 : 1) to give **1** (16.5 mg) in 26% yield and **15** (25.2 mg) in 40% yield. **1**, mp 69—70 °C (colorless crystals from hexane). IR ($CHCl_3$): 2945, 2860, 1085 cm^{-1}. MS *m/z*: 292, 294, 296 (M^+, 3.8, 5.9, 1.3). High MS *m/z*: 292.022 (M^+, Calcd for $C_{12}H_{18}{}^{79}Br^{35}ClO$: 292.023).

15: mp 77—78 °C (colorless crystals from hexane). IR ($CHCl_3$): 2945, 2860, 1085 cm^{-1}. MS *m/z*: 292, 294, 296 (M^+, 6.3, 7.4, 2.6). *Anal.* Calcd for $C_{12}H_{18}BrClO$: C, 49.09; H, 6.18; Br+Cl, 39.28. Found: C, 48.81; H, 6.16; Br+Cl, 39.39. ^{1}H- and ^{13}C-NMR data for **1** and **15** are summarized in Tables II and III.

(2*R,5a*S**,7*R**,8*R**,9a*R**)- and (2*R**,5a*S**,7*S**,8*S**,9a*R**)-7,8-Dibromo-decahydro-2,5a-methano-8-methyl-1-benzoxepin (17 and 18)**——A CCl_4 solution (1 ml) of bromine (0.02 ml) was added dropwise to a stirred solution of **12** (49.4 mg) in CCl_4 (5 ml) at 0 °C. After being stirred for 5 min at 0 °C, the reaction mixture was diluted with ether and washed with 10% sodium thiosulfate solution, water and brine. The solution was dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 10 : 1) to give **17** (29.6 mg) in 32% yield and **18** (59.8 mg) in 64% yield. **17**, mp 57—58 °C (colorless crystals from hexane). IR ($CHCl_3$): 2945, 2855, 1084 cm^{-1}. MS *m/z*: 336, 338, 340 (M^+, 3.4, 6.3, 3.4). *Anal.* Calcd for $C_{12}H_{18}Br_2O$: C, 42.63; H, 5.37; Br, 47.27. Found: C, 42.66; H, 5.27; Br, 46.84.

18: mp 106.5—107.5 °C (colorless crystals from hexane). IR ($CHCl_3$): 2940, 2850, 1083 cm^{-1}. MS *m/z*: 336, 338, 340 (M^+, 1.2, 2.3, 1.1). *Anal.* Calcd for $C_{12}H_{18}Br_2O$: C, 42.63; H, 5.37; Br, 47.27. Found: C, 42.40; H, 5.28; Br, 47.04. ^{1}H- and ^{13}C-NMR data for **17** and **18** are summarized in Tables II and III.

(2*R,5a*S**,7*R**,8*R**,9a*R**)- and (2*R**,5a*S**,7*S**,8*S**,9a*R**)-7,8-Dichloro-decahydro-2,5a-methano-8-methyl-1-benzoxepin (19 and 20)**——Lithium chloride (16.7 mg) and *N*-chlorosuccinimide (26.2 mg) were added to a stirred THF solution (1 ml) of **12** (7 mg). The reaction mixture was stirred for 2 h at room temperature and poured into a saturated sodium bicarbonate solution. After extraction with ether, the ethereal phase was washed with water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (benzene) to give **19** (3.7 mg) in 38% yield and **20** (2.8 mg) in 29% yield. **19**, mp 39—41 °C (colorless crystals from hexane). IR ($CHCl_3$): 2990, 2855, 1085 cm^{-1}. MS *m/z*: 248, 250, 252 (M^+, 4.6, 2.9, 0.5). High MS *m/z*: 248.072 (M^+, Calcd for $C_{12}H_{18}{}^{35}Cl_2O$: 248.074).

20: mp 103.5—104 °C (colorless crystals from hexane). IR ($CHCl_3$): 2950, 2875, 1090 cm^{-1}. MS *m/z*: 248, 250, 252 (M^+, 7.6, 4.6, 0.8). High MS *m/z*: 248.071 (M^+, Calcd for $C_{12}H_{18}{}^{35}Cl_2O$: 248.074). ^{1}H- and ^{13}C-NMR data for **19** and **20** are summarized in Tables II and III.

(2*R,5a*S**,7*S**,8*R**,9a*R**)-7,8-Epoxy-decahydro-2,5a-methano-8-methyl-1-benzoxepin (21)**——MCPBA (121.7 mg) was added to a stirred mixture of **12** (104.8 mg) and sodium bicarbonate (493.9 mg) in dry CH_2Cl_2 (5 ml) at 0 °C. After being stirred for 1 h at 0 °C, the reaction mixture was poured into saturated sodium bicarbonate solution, and extracted with ethyl acetate. The extract was washed with saturated sodium bicarbonate solution, water, and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (benzene : ethyl acetate = 10 : 1) to give **21** (90.6 mg) as a colorless oil in 79% yield and **22** (4.9 mg) as a colorless oil in 4% yield. **21**, IR ($CHCl_3$): 3000, 2950, 2860, 1117 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.32 (3H, s, C_8-CH_3), 1.63 (1H, dd, J=14.0, 11.0 Hz, C_{9ax}-H), 1.85 (1H, m, C_{10eq}-H), 2.00 (1H, dd, J=15.9, 2.4 Hz, C_6-H), 2.07 (1H, dd, J=15.9, 1.8 Hz, C_6-H), 2.21 (1H, dd, J=14.0, 6.1 Hz, C_{9eq}-H), 2.90 (1H, dd, J=2.4, 1.8 Hz, C_7-H), 4.06 (1H, dd, J=11.0, 6.1 Hz, C_{9a}-H), 4.22 (1H, t-like, J=5.5 Hz, C_2-H). MS *m/z*: 194 (M^+, 16.1). High MS *m/z*: 194.131 (M^+, Calcd for $C_{12}H_{18}O_2$: 194.131).

22: IR ($CHCl_3$): 3000, 2950, 2860, 1100 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.30 (3H, s, C_8-CH_3), 1.75 (1H, dd, J=15.9, 3.1 Hz, C_6-H), 1.87 (1H, dd, J=15.9, 6.7 Hz, C_{9eq}-H), 2.13 (1H, dd, J=15.9, 2.4 Hz, C_6-H), 2.20 (1H, dd, J=15.9, 8.5 Hz, C_{9ax}-H), 2.30 (1H, m, C_{10eq}-H), 2.99 (1H, dd, J=3.1, 2.4 Hz, C_7-H), 3.87 (1H, dd, J=8.5, 6.7 Hz,

C_{9a}-H), 4.30 (1H, dd, J=6.1, 5.5 Hz, C_2-H). MS m/z: 194 (M^+, 19.0). High MS m/z: 194.129 (M^+, Calcd for $C_{12}H_{18}O_2$: 194.131).

(2*R,5a*S**,7*R**,8*R**,9a*R**)-7-Bromo-decahydro-2,5a-methano-8-methyl-1-benzoxepin-8-ol (3)**——A THF solution of lithium tetrabromonickelate (*ca.* 0.4 M, 0.64 ml) was added to a stirred THF solution (2 ml) of **21** (15.5 mg) at room temperature, and the reaction mixture was stirred for 60 h. The resulting reaction mixture was diluted with ether and washed with saturated sodium bicarbonate solution, water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (benzene : ethyl acetate = 3 : 1) to give **3** (12.9 mg) in 59% yield and **23** (3.7 mg) in 17% yield. **3**, mp 130—131 °C (colorless crystals from ether). IR ($CHCl_3$): 3580, 2985, 2940, 2875, 2850, 1096 cm^{-1}. MS m/z: 274, 276 (M^+, 0.9, 0.9). *Anal.* Calcd for $C_{12}H_{19}BrO_2$: C, 52.38; H, 6.96; Br, 29.04. Found: C, 52.34; H, 6.73; Br, 28.56.

23: mp 97.0—98.5 °C (colorless crystals from hexane). IR ($CHCl_3$): 3000, 2940, 2855, 1090 cm^{-1}. MS m/z: 274, 276 (M^+, 0.4, 0.4). *Anal.* Calcd for $C_{12}H_{19}BrO_2$: C, 52.38; H, 6.96. Found: C, 52.37; H, 7.00. ^{1}H-NMR data for **3** and **23** are summarized in Table II, and ^{13}C-NMR data for **3** in Table III.

(2*R,5a*S**,7*R**,8*R**,9a*R**)-7-Bromo-8-chloro-decahydro-2,5a-methano-1-benzoxepin (1)**——Thionyl chloride (0.06 ml) was added to a stirred mixture of **3** (42.3 mg) and zinc chloride (2.1 mg) in dry dioxane (2 ml) at room temperature and under nitrogen. The reaction mixture was stirred for 12.5 h at room temperature and diluted with ether. The ethereal solution was washed with saturated sodium bicarbonate solution, water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (benzene) to give **1** (26.3 mg) in 58% yield.

(2*R,5a*S**,7*S**,8*S**,9a*R**)-7-Bromo-decahydro-2,5a-methano-8-methyl-1-benzoxepin-8-ol (4)**——*N*-Bromosuccinimide (42.5 mg) was added to a stirred solution of **12** (38.7 mg) in THF (2 ml) and water (2 ml), and the reaction mixture was stirred for 1 h at room temperature, poured into saturated sodium bicarbonate solution and extracted with ethyl acetate. The extract was washed with water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (benzene : ethyl acetate = 3 : 1) to give **4** (43.9 mg) in 74% yield. mp 158 °C (sublimed, colorless crystals from ethyl acetate). IR ($CHCl_3$): 3555, 2945, 2875, 2855, 1123 cm^{-1}. MS m/z: 274, 276 (M^+, 8.5, 7.8). *Anal.* Calcd for $C_{12}H_{19}BrO_2$: C, 52.38; H, 6.96; Br, 29.04. Found: C, 52.15; H, 6.95; Br, 28.60. ^{1}H- and ^{13}C-NMR data for **4** are summarized in Tables II and III.

(2*R,5a*S**,7*S**,8*S**,9a*R**)-7-Bromo-8-chloro-decahydro-2,5a-methano-8-methyl-1-benzoxepin (2)**——Compound **2** (16.3 mg) was obtained in 60% yield from **4** (25.4 mg) by the same method as described for the preparation of **1**. Thionyl chloride (0.03 ml), zinc chloride (1.3 mg), and dioxane (2 ml) were used, and the reaction time was 17 h. **2**, mp 75—76 °C (colorless crystals from hexane). IR ($CHCl_3$): 2995, 2950, 2875, 2855, 1088 cm^{-1}. MS m/z: 292, 294, 296 (M^+, 5.4, 7.7, 1.7). High MS m/z: 292.023 (M^+, Calcd for $C_{12}H_{18}{}^{79}Br^{35}ClO$: 292.023). ^{1}H- and ^{13}C-NMR data for **2** are given in Tables II and III.

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