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Neighboring Hydroxyl Group Participation in Metal–Ammonia Reduction of Spirocyclic Dienones[1)]

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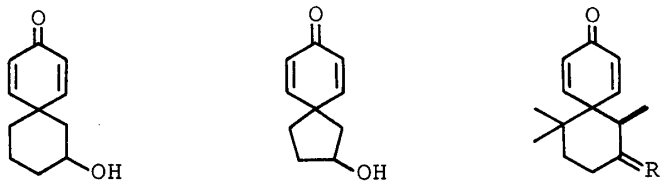
In connection with our synthetic work on spirocyclic sesqui- and diterpenes, neighboring hydroxyl group participation in metal–ammonia reduction of hydroxyspirodienones was studied. The role of the hydroxyl group in the regioselective metal–ammonia reduction was clearly established.

Keywords——metal–ammonia reduction; neighboring hydroxyl group participation; regioselective reduction; hydroxyspirodienone; tricyclic ketone; β-elimination; catalytic hydrogenation

Although metal–ammonia reductions of α,β-unsaturated carbonyl compounds are well known, the influence of the neighboring functional groups on the stereochemistry of the β-protonation has not been explored in detail. In some instances, hydroxyl groups in proximity to the β-position have been found to influence the stereochemistry of metal–ammonia reductions of α,β-unsaturated carbonyl compounds.[2)] For example, recently, McMurry and co-workers have reported the stereochemical influence of the lithium carboxylate function in the metal–ammonia reduction of an octalone derivative.[2d)] However, present evidence allows only speculation concerning the role of the hydroxyl groups.[3)]

In connection with our synthetic work on spirocyclic sesqui- and diterpenes, we studied the metal–ammonia reductions of the cross-conjugated hydroxyspirodienones **1**, **2**, **3a**, and **3b**. It was found that the hydroxyspirodienones **2** and **3b** were reduced in a highly regioselective manner owing to the influence of the neighboring hydroxyl group.

The hydroxyspirodienone **1** was prepared by the Meerwein–Ponndorf reduction[4)] of the spirodienone **4**[5)] in 87% yield. Reduction of **1** with alkali metal in liquid ammonia afforded a mixture of the hydroxyenones **5a** and **5b** in the ratio as shown in Table I. Upon changing the reducing metal from lithium or potassium to sodium, the ratio of **5a** increased. The stereochemistries of **5a** and **5b** were determined by the stereoselective synthesis of **5b** *via* an



1 2 3

a : R=H, OH

b : R=OH, H

Fig. 1

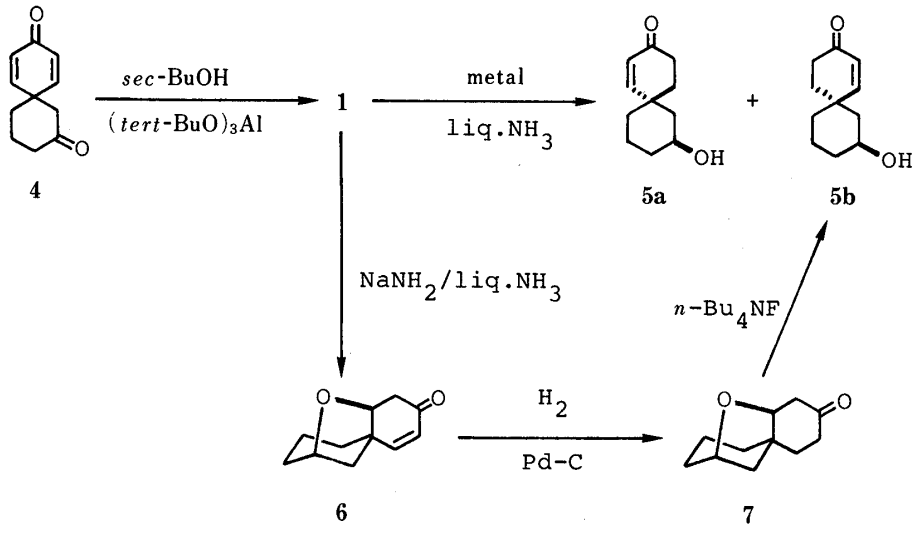


Chart 1

TABLE I. Metal–Ammonia Reduction of **1**

Metal	Yield (%)[a]	(**5a** : **5b**)[b]
Li	66	(3 : 2)
Na	57	(3 : 1)
K	62	(3 : 1.3)

a) Based on consumed starting material. *b*) Determined by ^{1}H-NMR.

TABLE II. Metal–Ammonia Reduction of **2**

Metal	Yield (%)[a]	(**9a** : **9b**)[b]
Li	52	(7 : 1)
Na	55	(**9a** only)
K	49	(7 : 1)

a) Based on consumed starting material. *b*) Determined by ^{1}H-NMR.

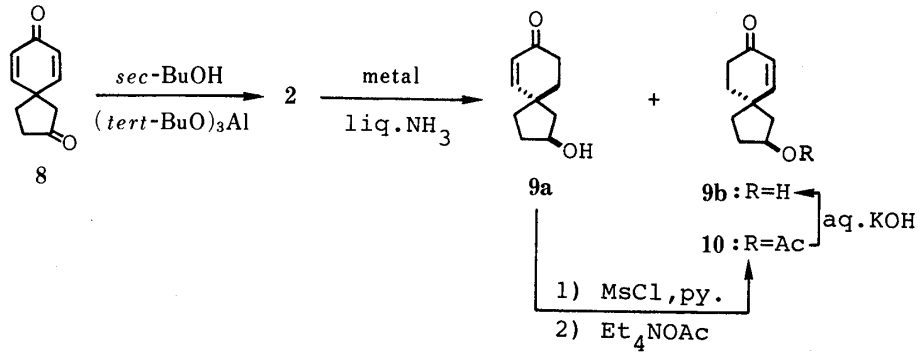


Chart 2

alternative route. Cyclization of **1** by treatment with sodium amide in liquid ammonia afforded the tricyclic enone **6** in 32% yield (57% yield based on consumed starting material **1**). Catalytic hydrogenation of **6** over palladium–carbon (Pd–C) afforded the tricyclic ketone **7** in 75% yield. Compound **7** was treated with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF) to afford the desired hydroxyenone **5b** in 38% yield (78% yield based on consumed starting material **7**); this product was identical with a minor component **5b** of the reduction mixture. Therefore, the stereochemistries of **5a** and **5b** were determined as shown.

The hydroxyspirodienone **2** was also prepared by the Meerwein–Ponndorf reduction of the spirodienone **8**[5] in 69% yield. Compound **2** was reduced regioselectively to the hydroxyenone **9a** as shown in Table II. The hydroxyenone **9b** could not be detected by proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy when sodium had been used. The

stereochemistries of **9a** and **9b** were confirmed by comparison of their ^{1}H-NMR spectra. The ^{1}H-NMR chemical shift of the C_6-olefinic proton in **9a** appears at 6.65 ppm, while that of **9b** appears at 6.95 ppm. This shift difference at C-6 between **9a** and **9b** is attributable to the effect of the C_2-hydroxyl group.[6] Further study using a shift reagent[7] confirmed the stereochemistries of **9a** and **9b** as shown in Fig. 2. The hydroxyenone **9a** could be transformed to **9b** as follows. After treatment of **9a** with methanesulfonyl chloride in pyridine at 0 °C, the crude methanesulfonate was refluxed in acetone with tetraethylammonium acetate[8] to afford the acetate **10** with inversion of stereochemistry. Hydrolysis of **10** with aqueous potassium hydroxide–THF afforded **9b** in 48% overall yield.

Based on the result of the metal–ammonia reduction of the hydroxyspirodienones **1** and **2**, it is suggested that there is a close correlation between the orientation of the hydroxyl group and the regioselectivity of reduction. We examined the metal–ammonia reduction of the hydroxyspirodienones **3a** and **3b**,[9] in which the hydroxyl groups have equatorial and axial configuration, respectively. Reduction of the equatorial alcohol **3a** with lithium afforded a mixture of the hydroxyenones **11a** and **11b** in the ratio of *ca.* 1 : 1. On the other hand, the reduction of the axial alcohol **3b** under the same conditions afforded the hydroxyenone **12a** regioselectively in a good yield. Change of the reducing metal and/or transformation of the hydroxyl group to the metal alkoxide by treatment with metal amide in liquid ammonia did not affect the regioselectivity, as shown in Table III.

The stereochemistry of **12a** was confirmed by comparison of the ^{1}H-NMR spectrum with that of the isomer **12b**, which was stereoselectively synthesized *via* two independent routes. The first one was as follows. Catalytic hydrogenation of **3b** over palladium–barium sulfate (Pd–$BaSO_4$) afforded a mixture of the saturated ketone and the hydroxyenone **12b** in *ca.* 10% yield. In the second route, **12b** was synthesized *via* the tricyclic ketone **14** by a method similar

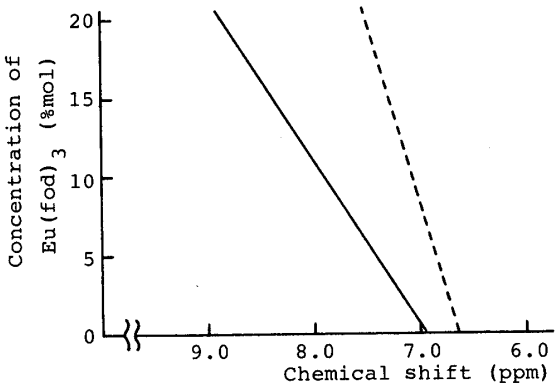
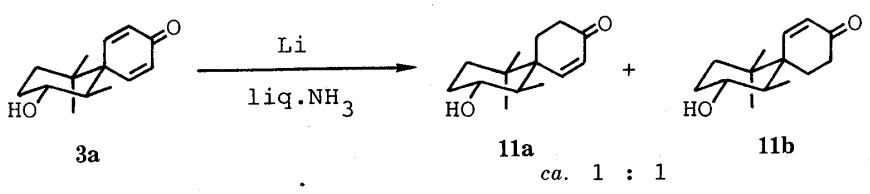
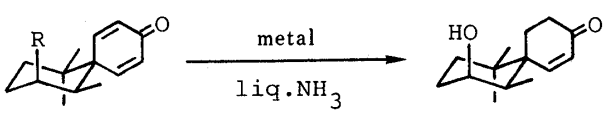


Fig. 2. Eu(fod)$_3$-Induced Shift of the C_5-Olefinic Proton Signal of **9a** (------) and **9b** (——)



3a **11a** **11b**

ca. 1 : 1



3b **12a**

Chart 3

TABLE III. Metal–Ammonia Reduction of **3b**

R	Metal	Yield (%)		R	Metal	Yield (%)	
		12a	**13**			**12a**	**13**
OH	Li	89	—	O^-Na^+	Li	77	19
	Na	87	Trace		Na	46	46
	K	87	Trace	O^-K^+	Li	87	Trace
O^-Li^+	Li	88	—		K	82	Trace

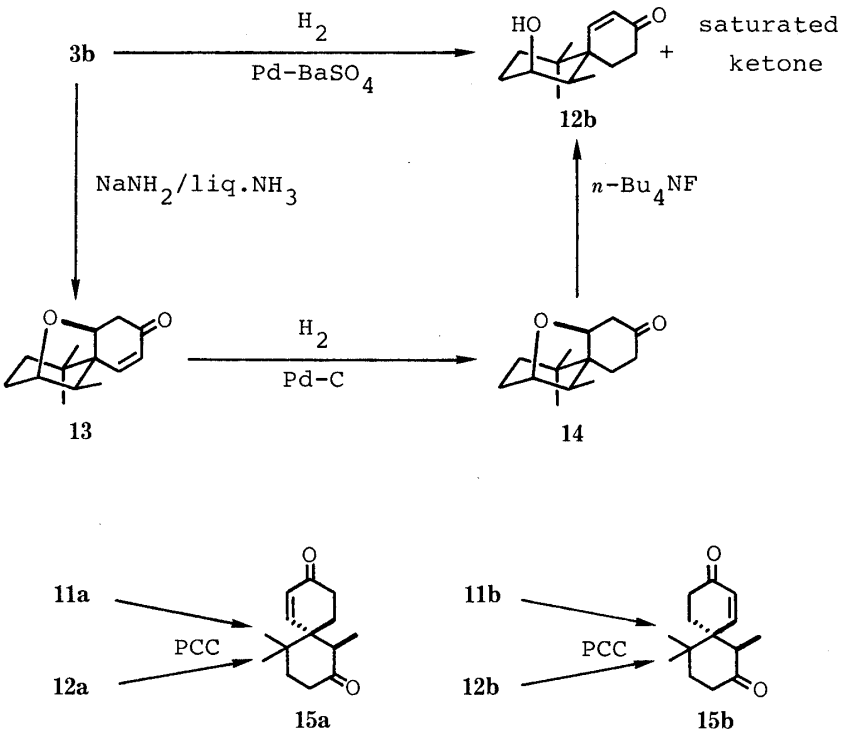
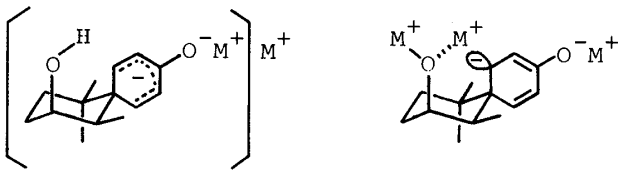


Chart 4

to that described for the synthesis of **5b**. Treatment of **3b** with sodium amide in liquid ammonia afforded the tricyclic ketone **13** in 48% yield (85% yield based on consumed starting material **3b**). Compound **13** was hydrogenated over Pd–C to afford **14** in 95% yield, and then **14** was treated with TBAF in THF to afford the desired hydroxyenone **12b** in 51% yield (81% yield based on consumed starting material **14**). The ^{1}H-NMR chemical shift of the C_1-olefinic proton in **12a** appears at 6.65 ppm in $CDCl_3$ and 6.60 ppm in pyridine-d_5, whereas that of **12b** appears at 7.30 ppm in $CDCl_3$ and 7.56 ppm in pyridine-d_5. The shift difference at C-1 between **12a** and **12b** and the solvent effect observed in **12b** are attributable to the C_{10}-axial hydroxyl group in **12b**.[10,11] The stereochemistries of the reduction products **11a** and **11b** were confirmed by the fact that the oxidation products of **11a** and **11b** (**15a** and **15b**) were identical with the oxidation products of **12a** and **12b**, respectively.

Results and Discussion

Concerning the reducing metal, although the reason is not clear, the best selectivity in the reduction of the hydroxyspirodienones **1** and **2** was observed when sodium was used as a reducing metal. Sarett and co-workers have reported a similar result in the reduction of



A B

Fig. 3

steroidal compounds with potassium as a reducing metal.[2a] It has been suggested that the presence of the metal amide influenced the stereochemistry of metal–ammonia reductions of the decalin derivatives,[3] but we could not observe such phenomena in the reduction of **3b**. It is evident that the proximity of the hydroxyl group strongly correlates with the rate of the regioselectivity of reduction (equatorially fixed cyclohexanol **3a** < flexible cyclohexanol **1** < cyclopentanol **2** < axially fixed cyclohexanol **3b**).

From the results mentioned above, these regioselective metal–ammonia reductions appear to occur *via* intramolecular protonation of an intermediate A and/or *via* a metal-chelated intermediate B.

This regioselective metal–ammonia reduction is useful for the syntheses of spirocyclic natural products. We have already reported total syntheses of spirocyclic sesqui- and diterpenes utilizing this method, and further synthetic studies on spirocyclic natural products are in progress.[12]

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded on a Hitachi EPI-G3 and/or a Hitachi 260-10 spectrometer, and ^{1}H-NMR spectra on a Hitachi R-22 (90 MHz) spectrometer with tetramethylsilane as an internal standard. Low- and high-resolution mass spectra (MS and High MS) were obtained with a JEOL JMS D-300 instrument. Ultraviolet (UV) spectra were recorded on a Hitachi 124 spectrophotometer. For preparative thin layer chromatography (PTLC), E. Merck Kieselgel 60 PF_{254} and Aluminiumoxide 150 PF_{254} (type T) were used. For column chromatography, Merck Kieselgel 60 (70—230 mesh) was used.

8-Hydroxyspiro[5.5]undeca-1,4-dien-3-one (1)——A mixture of aluminum tri-*tert*-butoxide (204 mg) and spirodienone **4** (100 mg) in *sec*-butanol (5.7 ml) and dry benzene (1.2 ml) was refluxed with stirring under nitrogen for 25 min, then allowed to cool to room temperature. Benzene (1 ml) was added, and the reaction mixture was poured into ice-water and extracted with ethyl acetate. The organic phase was dried (Na_2SO_4) and concentrated *in vacuo*, and the residue was purified by silica gel column chromatography (benzene : ethyl acetate = 3 : 1) to give **1** (87.7 mg) in 87% yield as colorless crystals, mp 135—137 °C (from ethyl acetate). IR ($CHCl_3$): 3620, 3440, 1670, 1627 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.00 (1H, m, C_8-H), 6.07—7.16 (4H, ABCD type, olefinic H). UV λ_{max}^{MeCN} nm (ε): 237 (14800). MS *m/z*: 178 (M^+, 3.7). *Anal.* Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.87; H, 8.14.

2-Hydroxyspiro[4.5]deca-6,9-dien-8-one (2)——The hydroxyspirodienone **2** was prepared from **8** by a method similar to that described for the hydroxyspirodienone **1**. Compound **2** (73.9 mg) was obtained from **8** (100 mg) in 73% yield, mp 93.5—94.0 °C (colorless crystals from hexane–ethyl acetate). IR ($CHCl_3$): 3610, 3440, 1665, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.60 (1H, m, C_2-H), 6.05—7.32 (4H, ABCD type, olefinic H). UV λ_{max}^{MeCN} nm (ε): 239 (11000). MS *m/z*: 164 (M^+, 7.2). High MS *m/z*: 164.083 (M^+, Calcd for $C_{10}H_{12}O_2$: 164.083).

Reduction of 1 with Lithium in Liquid Ammonia——A solution of **1** (130 mg, 0.73 mmol) in dry THF (10 ml) was added in one portion to a stirred solution of lithium (11.2 mg, 1.6 mg atom) in liquid ammonia (*ca.* 20 ml) at −78 °C under nitrogen. Immediately, dry ammonium chloride powder (*ca.* 300 mg) was added portionwise to the reaction mixture. After evaporation of ammonia, the residue was dissolved in brine and ethyl acetate. The organic phase was washed with saturated sodium bicarbonate solution, water and brine, then dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by silica gel PTLC (ether : petr. ether = 3 : 2, developed 5 times) to give a mixture of **5a** and **5b** (71.6 mg, **5a** : **5b** = 3 : 2 based on ^{1}H-NMR) in 55% yield (66% yield based on consumed starting material) with recovery of the starting material **1** (23.2 mg; 18%). **5a**, ^{1}H-NMR ($CDCl_3$) δ: 5.83 (1H, d, J = 10 Hz, C_2-H), 6.92 (1H, d, J = 10 Hz, C_1-H).

Reduction of 1 with Sodium or Potassium in Liquid Ammonia——The hydroxyspirodienone **1** (50 mg) was reduced with sodium (16.6 mg) or potassium (28.2 mg) in liquid ammonia (*ca.* 15 ml) by the same reaction and purification procedures as described above. Sodium gave the starting material **1** (6.6 mg) in 13% recovery and a

mixture of **5a** and **5b** (24.9 mg, **5a** : **5b** = 3 : 1 based on ^{1}H-NMR) in 49% yield (58% yield based on consumed starting material). Potassium gave **1** (4.2 mg) in 8% recovery and a mixture of **5a** and **5b** (28.7 mg, **5a** : **5b** = 3 : 1.3 based on ^{1}H-NMR) in 57% yield (62% yield based on consumed starting material).

(2*R,5a*S**,9a*R**)-9*H*-2,3,4,5,5a,9a-Hexahydro-2,5a-methano-1-benzoxepin-8-one (6)**——A solution of **1** (211 mg) in dry THF (5 ml) was added dropwise to a stirred solution of sodium amide in liquid ammonia, which was prepared by adding anhydrous ferric chloride (*ca.* 5 mg) to a stirred solution of sodium (60.2 mg) in liquid ammonia (*ca.* 15 ml) and stirring was continued until the blue color disappeared at −78 °C under nitrogen. After further stirring at −78 °C for 3 h, dry powdered ammonium chloride (*ca.* 500 mg) was added portionwise to the reaction mixture and ammonia was evaporated off. After the addition of water, the reaction mixture was extracted with ether. The combined ethereal phase was washed with saturated sodium bicarbonate solution, water and brine, then dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the crude product by silica gel PTLC (ether : petr. ether = 3 : 1) gave **6** (*Rf* ≒ 0.5, 68.4 mg) in 32% yield (57% yield based on consumed starting material) with partial recovery of the starting material **1** (*Rf* ≒ 0.1, 91.7 mg; 43%). IR ($CHCl_3$): 1677, 1615, 1093 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.23—3.00 (2H, AB in ABX, J_{AX} = 11 Hz, J_{BX} = 7 Hz, J_{AB} = 16 Hz, C_9-H), 4.32 (1H, dd, J = 7, 11 Hz, C_{9a}-H), 4.54 (1H, br t-like, J = 5 Hz, C_2-H), 5.84 (1H, br d, J = 10 Hz, C_7-H), 6.61 (1H, d, J = 10 Hz, C_6-H). UV λ_{max}^{MeCN} nm (ε): 238 (8130). MS *m/z*: 178 (M^+, 91.3). High MS *m/z*: 178.009 (M^+, Calcd for $C_{11}H_{14}O_2$: 178.009).

(2*R,5a*R**,9a*R**)-9*H*-Octahydro-2,5a-methano-1-benzoxepin-8-one (7)**——A solution of **6** (143 mg) in ethyl acetate (15 ml) was hydrogenated over 10% Pd–C (110 mg) in the usual manner and purified by silica gel PTLC (ether : petr. ether = 3 : 1) to give **7** (108 mg) in 75% yield. IR ($CHCl_3$): 2950, 1731, 1090 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.09 (1H, dd, J = 6, 9 Hz, C_{9a}-H), 4.38 (1H, br t-like, J = 5 Hz, C_2-H). MS *m/z*: 180 (M^+, 64.8). High MS *m/z*: 180.114 (M^+, Calcd for $C_{11}H_{16}O_2$: 180.115).

(6*R,8*R**)-8-Hydroxyspiro[5.5]undec-1-en-3-one (5b)**——A THF solution of TBAF (1 M, 0.73 ml) was added to a stirred solution of **7** (87.6 mg) in THF (5 ml) at 0 °C. After being stirred at 0 °C for 3 h, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic phase was washed with water and brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residual crude product was purified by silica gel PTLC (ether : petr. ether = 3 : 1) to give **5b** (33.5 mg) in 38% yield (78% yield based on consumed starting material) with partial recovery of the starting material **7** (44.8 mg, 51%), mp 40—41 °C (colorless crystals from ether–petr. ether). IR ($CHCl_3$): 3600, 3450, 1679 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 3.81 (1H, m, C_8-H), 5.80 (1H, d, J = 10 Hz, C_2-H), 6.66 (1H, d, J = 10 Hz, C_1-H). UV λ_{max}^{MeCN} nm (ε): 227 (7940). MS *m/z*: 180 (41.9, M^+). *Anal.* Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.14; H, 9.15.

Reduction of 2 with Lithium in Liquid Ammonia——The hydroxyspirodienone **2** (300 mg) was reduced with lithium (25.3 mg) in liquid ammonia (30 ml) by a procedure similar to that described for the reduction of **1** with lithium. The crude product was purified by silica gel PTLC (ether : petr. ether = 3 : 2, developed 3 times) and then alumina PTLC (ether : petr. ether = 3 : 2, developed 3 times) to give a mixture of **9a** and **9b** (102.5 mg, **9a** : **9b** = 7 : 1 based on ^{1}H-NMR) in 34% yield (52% yield based on consumed starting material) with recovery of the starting material **2** (105 mg, 35%).

Reduction of 2 with Sodium or Potassium in Liquid Ammonia——The hydroxyspirodienone **2** (50 mg) was reduced with sodium (14.5 mg) or potassium (24.6 mg) by the same reaction and purification procedures as described above. Sodium gave the starting material **2** (9.8 mg) in 20% recovery and **9a** (22.4 mg) in 44% yield (55% yield based on consumed starting material). Potassium gave **2** (7.0 mg) in 14% recovery and a mixture of **9a** and **9b** (21.2 mg, **9a** : **9b** = 7 : 1 based on ^{1}H-NMR) in 42% yield (49% yield based on consumed starting material). **9a**, colorless oil, bp 115—120 °C (bath temperature)/0.0025 mmHg. IR ($CHCl_3$): 3600, 3450, 1675, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.44 (1H, m, C_2-H), 5.79 (1H, d, J = 10 Hz, C_7-H), 6.65 (1H, d, J = 10 Hz, C_6-H). UV λ_{max}^{MeCN} nm (ε): 228 (7900). MS *m/z*: 166 (M^+, 1.5). *Anal.* Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.19; H, 8.62.

(2*R,5*R**)-2-Acetoxyspiro[4.5]dec-6-en-8-one (10)**——Methanesulfonyl chloride (0.1 ml) was added dropwise to a stirred solution of **9a** (45 mg) in pyridine (3 ml) at 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was poured into saturated sodium bicarbonate solution containing crushed ice and extracted with ethyl acetate. The organic phase was washed sequentially with water, saturated cupric sulfate solution, water, saturated sodium bicarbonate solution, water and brine, then dried (Na_2SO_4) and concentrated *in vacuo* at room temperature. The methanesulfonate was obtained as a pale yellow oil (65 mg) and used immediately without further purification.

An acetone solution (3 ml) of the methanesulfonate (65 mg) and tetraethylammonium acetate (166 mg) was refluxed for 2 h, then allowed to cool. Acetone was evaporated off *in vacuo* and the residue was purified by silica gel PTLC (ether : petr. ether = 3 : 2) to give the acetate **10** (36.5 mg) in 65% yield from **9a**. IR ($CHCl_3$): 1738, 1679, 1612 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.01 (3H, s, $-OCOCH_3$), 5.25 (1H, m, C_2-H), 5.83 (1H, d, J = 10 Hz, C_7-H), 6.82 (1H, d, J = 10 Hz, C_6-H). MS *m/z*: 208 (M^+, 1.5). High MS *m/z*: 208.109 (M^+, Calcd for $C_{12}H_{16}O_3$: 208.110).

Hydrolysis of the Acetate 10——A solution of **10** (30 mg) in 2% aqueous KOH (5 ml) and THF (5 ml) was stirred for 2 h at room temperature. After evaporation of the THF *in vacuo*, the aqueous phase was extracted with ether, and the combined ethereal phase was washed with water and brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residual oil was purified by silica gel PTLC (ether : petr. ether = 3 : 2) to give **9b** (17.2 mg) as a colorless oil in 74% yield, bp 123—128 °C (bath temperature)/0.006 mmHg. IR ($CHCl_3$): 3610, 3450, 1675, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$)

δ: 4.46 (1H, m, C_2-H), 5.79 (1H, d, J=10 Hz, C_7-H), 6.95 (1H, d, J=10 Hz, C_6-H). UV λ_{max}^{MeCN} nm (ε): 226 (7700). MS *m/z*: 166 (M^+, 1.5). *Anal.* Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.89; H, 8.81.

Reduction of 3a with Lithium in Liquid Ammonia——The hydroxyspirodienone **3a** (115 mg) was reduced with lithium (8.7 mg) in liquid ammonia (*ca.* 20 ml) by a method similar to that described for the reduction of **1** with lithium. The crude product was purified by silica gel PTLC (ether : petr. ether = 3 : 2, developed 3 times) to give **11a** (Rf=0.35, 23.4 mg) in 20% yield and **11b** (Rf=0.4, 22.6 mg) in 19% yield. **11a**, mp 117—119 °C (from ether–petr. ether). IR ($CHCl_3$): 3600, 3430, 1676, 1615 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, d, J=6 Hz, C_{11}-CH_3), 1.00, 1.09 (each 3H, s, C_7-CH_3), 3.41 (1H, m, C_{10}-H), 6.02—6.54 (2H, AB type, C_1- and C_2-H). UV λ_{max}^{MeCN} nm (ε): 230 (11300). MS *m/z*: 222 (M^+, 33.5). High MS *m/z*: 222.162 (M^+, Calcd for $C_{14}H_{22}O_2$: 222.158).

11b: mp 97—101 °C (from ether–petr. ether). IR ($CHCl_3$): 3600, 3430, 1672, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.85, 1.05 (each 3H, s, C_7-CH_3), 1.11 (3H, d, J=6 Hz, C_{11}-CH_3), 3.43 (1H, m, C_{10}-H), 6.14 (1H, d, J=12 Hz, C_2-H), 6.74 (1H, br d, J=12 Hz, C_1-H). UV λ_{max}^{MeCN} nm (ε): 230 (9900). MS *m/z*: 222 (M^+, 32.3). High MS *m/z*: 222.159 (M^+, Calcd for $C_{14}H_{22}O_2$: 222.158).

Reduction of 3b with Metals in Liquid Ammonia——The hydroxyspirodienone **3b** (50 mg) was reduced with metal (lithium 3.5 mg, sodium 11.6 mg, or potassium, 19.8 mg) by a method similar to that described for the reduction of **1**. The crude products were purified by PTLC (ether : petr. ether = 3 : 2, developed 3 times) to give **12a** (Rf=0.2). Lithium gave **12a** (45.3 mg) in 89% yield. Sodium and potassium gave **12a** (44.5 mg and 44.2 mg, respectively) in 87% yield, and the tricyclic ketone **13** (Rf=0.45, <1 mg) was obtained in each case.

12a: mp 155—158 °C (from ether). IR ($CHCl_3$): 3610, 3450, 1664, 1617 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.97, 1.03 (each 3H, s, C_7-CH_3), 1.01 (3H, d, J=7 Hz, C_{11}-CH_3), 3.88 (1H, m, C_{10}-H), 5.94—6.67 (2H, AB type, C_1- and C_2-H). (pyridine-d_5) δ: 0.87, 0.96 (each 3H, s, C_7-CH_3), 1.11 (3H, d, J=7 Hz, C_{11}-CH_3), 3.95 (1H, m, C_{10}-H), 5.96—6.70 (2H, AB type, C_1- and C_2-H). UV λ_{max}^{MeCN} nm (ε): 232 (9800). MS *m/z*: 222 (M^+, 38). *Anal.* Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.66; H, 9.72.

General Procedure for the Reduction of 3b with Metals in the Presence of Metal Amide——Anhydrous ferric chloride (*ca.* 3 mg) was added to a stirred solution of metal (lithium 3.5 mg, sodium 11.6 mg, or potassium 19.8 mg) in liquid ammonia (*ca.* 20 ml), and the reaction mixture was stirred under reflux until the blue color disappeared. A THF (7 ml) solution of the hydroxyspirodienone **3b** (50 mg) was added dropwise to a stirred metal amide solution at −78 °C. The mixture was stirred at −78 °C for 1 h, then a metal (lithium 3.5 mg, sodium 11.6 mg, or potassium 19.8 mg) was added and dissolved completely. Dry powdered ammonium chloride (*ca.* 100 mg) was added when the reaction mixture became slightly blue. Work-up and purification procedures were the same as described above, and yields are listed in Table III.

Catalytic Hydrogenation of 3b with Pd–$BaSO_4$——The hydroxyspirodienone **3b** (100 mg) in ethyl acetate (10 ml) was hydrogenated in the presence of Pd–$BaSO_4$ (200 mg) at ordinary pressure until the starting material was no longer detectable on thin layer chromatography (TLC). After separation of the catalyst by filtration, the filtrate was concentrated *in vacuo*, and the residue was purified by silica gel PTLC (ether : petr. ether = 3 : 2, developed 3 times) to give **12b** (Rf=0.22, 9.2 mg) in 9% yield. mp 132.5—133.0 °C (colorless crystals from ether–petr. ether). IR ($CHCl_3$): 3610, 3450, 1665, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88, 1.00 (each 3H, s, C_7-CH_3), 1.13 (3H, d, J=7 Hz, C_{11}-CH_3), 3.84 (1H, m, C_{10}-H), 6.11 (1H, d, J=11 Hz, C_2-H), 7.30 (1H, dd, J=11, 2 Hz, C_1-H); (pyridine-d_5) δ: 0.81, 0.91 (each 3H, s, C_7-CH_3), 1.18 (3H, d, J=7 Hz, C_{11}-CH_3), 4.83 (1H, m, C_{10}-H), 6.15 (1H, d, J=11 Hz, C_2-H), 7.56 (1H, d, J=11 Hz, C_1-H). UV λ_{max}^{MeCN} nm (ε): 234 (8300). MS *m/z*: 222 (M^+, 42). *Anal.* Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.50; H, 10.26.

(2*R,5a*R**,9a*R**,10*S**)-9*H*-2,3,4,5,5a,9a-Hexahydro-2,5a-methano-5,5,10-trimethyl-1-benzoxepin-8-one (13)**——Treatment of **3b** (100 mg) with sodium amide [prepared from sodium (26 mg)] and purification by silica gel PTLC according to the procedure described for the preparation of **6** gave **13** (48.4 mg) in 48% yield (85% yield based on consumed starting material) with partial recovery of the starting material **3b** (43.0 mg, 43%). IR ($CHCl_3$): 2940, 1681 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.80, 1.13 (each 3H, s, C_5-CH_3), 1.01 (3H, d, J=7 Hz, C_{10}-CH_3), 2.21 (1H, q, J=7 Hz, C_{10}-H), 2.22—2.95 (2H, AB in ABX, J_{AX}=10 Hz, J_{BX}=8 Hz, J_{AB}=17 Hz, C_9-H), 4.00 (1H, br d, J=4 Hz, C_2-H), 4.43 (1H, dd, J=10, 8 Hz, C_{9a}-H). UV λ_{max}^{MeCN} nm (ε): 232 (15100). MS *m/z*: 220 (M^+, 12.2). High MS *m/z*: 220.146 (M^+, Calcd for $C_{14}H_{20}O_2$: 220.146).

(2*R,5a*R**,9a*R**,10*S**)-9*H*-Octahydro-2,5a-methano-5,5,10-trimethyl-1-beozoxepin-8-one (14)**——A solution of **13** (45 mg) in ethyl acetate (10 ml) was hydrogenated over 10% Pd–C (50 mg) in the usual manner and purified by silica gel PTLC (ether : petr. ether = 3 : 2) to give **14** (42 mg) in 94% yield. IR ($CHCl_3$): 2990, 1735 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.96, 1.05 (each 3H, s, C_5-CH_3), 1.12 (3H, d, J=7 Hz, C_{10}-CH_3), 2.29—3.00 (2H, AB in ABX, J_{AX}=12 Hz, J_{BX}=7 Hz, J_{AB}=16 Hz, C_9-H), 4.05 (1H, br d, J=3 Hz, C_2-H), 4.30 (1H, dd, J=7, 12 Hz, C_{9a}-H). MS *m/z*: 222 (M^+, 52.1). High MS *m/z*: 222.161 (M^+, Calcd for $C_{14}H_{22}O_2$: 222.161).

10-Hydroxy-7,7,11-trimethylspiro[5.5]undec-1-en-3-one (12b)——Treatment of **14** (85 mg) with TBAF (1 M, 0.57 ml) as described for the preparation of **5b** and subsequent purification by silica gel PTLC (ether : petr. ether = 3 : 2) gave **12b** (Rf≒0.4, 43.5 mg) in 51% yield (81% yield based on consumed starting material) with partial recovery of the starting material **14** (Rf≒0.6, 31.5 mg, 37%).

(6*R,7*R**)-7,11,11-Trimethylspiro[5.5]undec-1-ene-3,8-dione (15a) from 12a**——A methylene chloride (1.5 ml)

solution of **12a** (25.2 mg) was added to a stirred suspension of pyridinium chlorochromate (PCC) (36.7 mg) in methylene chloride (2 ml). After being stirred for 1 h, the reaction mixture was diluted with ether and filtered through a short Florisil column. The filtrate was concentrated, and the residue was purified by silica gel PTLC (ether : petr. ether = 3 : 2) to give **15a** (19.4 mg) in 80% yield. mp 115—117 °C (colorless crystals from ether–petr. ether). IR ($CHCl_3$): 2970, 1716, 1684 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.99 (3H, d, J = 7 Hz, C_7-H), 1.06, 1.34 (each 3H, s, C_{11}-CH_3), 2.89 (1H, q, J = 7 Hz, C_7-H), 6.07—6.67 (2H, AB type, C_1- and C_2-H). UV λ_{max}^{MeCN} nm (ε): 227 (11700). MS m/z: 220 (M^+, 22.2). *Anal.* Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.30; H, 9.33.

(6*R,7*S**)-7,11,11-Trimethylspiro[5.5]undec-1-ene-3,8-dione (15b) from 12b**——Compound **12b** (50 mg) was oxidized with PCC (73 mg) by the same method as described above to give **15b** (46.0 mg) in 95% yield. mp 106—109 °C (colorless crystals from ether). IR ($CHCl_3$): 2950, 1716, 1685 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.97, 1.30 (each 3H, s, C_{11}-CH_3), 1.06 (3H, d, J = 7 Hz, C_7-CH_3), 2.83 (1H, q, J = 7 Hz, C_7-H), 6.01—6.39 (2H, AB type, C_1- and C_2-H). UV λ_{max}^{MeCN} nm (ε): 228 (12200). MS m/z: 220 (M^+, 28.6). *Anal.* Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.02; H, 9.28.

Oxidation of 11a and 11b with PCC——Compound **11a** (8.4 mg) was oxidized with PCC (10 mg) by the same method as described above to give **15a** (6.2 mg) in 74% yield. The product (**15a**) was identical with the oxidation product of **12a** on TLC, IR, and ^{1}H-NMR. On the other hand, **11b** (8.0 mg) was oxidized with PCC (15 mg). Work-up afforded **15b** (5.6 mg) in 71% yield, and this product was identical with the oxidation product of **12b** on TLC, IR, and ^{1}H-NMR.

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