Novel Transformation of Azabicyclothionocarbonate to Azaspirolactone

Shinya HARUSAWA, Norio SHIBATA, Naoki YAMAZAKI, Satomi SAKANOUE, Toshimasa ISHIDA, Ryuji YONEDA, and Takushi KURIHARA*

Osaka University of Pharmaceutical Sciences, 2-10-65, Kawai, Matsubara, Osaka 580, Japan. *Received March 23, 1989*

Treatment of azabicyclothionocarbonate (6a) with a catalytic amount of α,α′-azobisisobutyronitrile in refluxing benzene leads to the formation of a new azaspirolactone (8), whose structure was unambiguously established by an X-ray analysis. A mechanism is proposed for the formation of 8.

Keywords azabicyclothionocarbonate; azaspirolactone; α,α′-azobisisobutyronitrile; thiophosgene; cyclic carbonate; tributyltin hydride; radical reaction; 4-dimethylaminopyridine; macrocyclic ring; X-ray analysis

In connection with our program on anatoxin-a synthesis,[1] we were interested in the reactivity of azabicyclothionocarbonates (**6a,b**), containing a macrocyclic ring, and we now report a new transformation of **6a** to azaspiro[4.4]-nonanone (**8**). *cis*-Dihydroxypyrrolidines (**5a, b**) were synthesized as follows; according to the Parker, Raphael and Wilkinson procedure,[2] treatment of diethyl hexa-1,5-diyne-1,6-dicarboxylate (**1**), which was prepared from commercially available hexa-1,5-diyne[3] with benzylamine in hot EtOH, gave a high yield (>80%) of the pyrrolidine derivative (**2**), which was found to be a mixture of (*E*)-(=CH at δ 5.07) and (*Z*)-(=CH at δ 6.06) isomers by proton nuclear magnetic resonance (^{1}H-NMR) analysis. Catalytic hydrogenation of the ester (**2**) with 10% palladium on carbon (Pd–C) in acetic acid using a Skita apparatus under the initial hydrogen pressure of 5—6 kg/cm^2 at room temperature gave the saturated pyrrolidine diester (**3**) with hydrogenolysis of the benzyl group in quantitative yield. The structure was elucidated from the ^{1}H-NMR spectrum, in which symmetry can be observed, indicating the *cis*-stereochemistry. Alkylation of **3** with benzyl bromide or methyl iodide, followed by lithium aluminum hydride reduction of the *N*-alkylated product (**4a, b**) gave the corresponding *cis*-dihydroxypyrrolidine (**5a, b**) in good yield. Treatment of **5a** with thiophosgene and 4-dimethylaminopyridine (4-DMAP) in methylene chloride at 0 °C gave **6a** in 70% yield. It has been reported that cyclic thionocarbonates are deoxygenated by tributyltin hydride in the presence of α,α′-azobisisobutyronitrile (AIBN) to give the corresponding methylene derivatives, carbonates and thiolcarbonates.[4] With this in mind, when the thionocarbonate (**6a**) was refluxed with tributyltin hydride (1 mol eq) in benzene overnight, only the cyclic carbonate (**7**) was isolated in 16% yield, together with recovery of the starting material (**6a**) in 65% yield. On the other hand, refluxing the thionocarbonate (**6a**) (0.1 mmol) in degassed benzene (3 ml) in the presence of AIBN (0.01 mol) for 3.5 h under argon gave 2,5-*cis*-1-benzyl-2-(2-hydroxyethyl)-7-oxa-1-azaspiro[4.4]-nonan-6-one (**8**) as an oil in 65% yield (93% yield based on recovered **6a**), whose infrared (IR) spectrum showed the presence of OH and γ-lactone groups (3700—3100 and 1760 cm^{-1}, respectively). The tentative structure of **8** was supported by ^{1}H-NMR and MS data as well as carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrometry, which showed the presence of a quaternary carbon atom at δ 69.43. The product (**8**) was derived to the oily *tert*-butyldimethylsilyl ether (**9**), the chloride (**10**), and the crystalline *p*-bromobenzoate (**11**). Thus, in order to obtain definitive evidence for the structure and stereochemistry of spirolactone (**8**), an X-ray crystallographic analysis of **11** was carried out and its molecular structure is drawn in Fig. 1. The formation of **8**, which appears to be a novel azaspirocycle, is rather surprising and to our knowledge the conversion of thionocarbonates to spirocycles has not previously been reported.[5]

Several reactions, which serve to elucidate the reaction mechanism, are summarized in Table I. Without AIBN, the reaction does not proceed (run 1). AIBN may be replaced by a catalytic amount of di-*tert*-butyl peroxide and dibenzoyl peroxide (runs 3—5). On the other hand, *N*-methylthionocarbonate (**6b**) (runs 6, 7), which was obtained from **5b** with thiophosgene and 4-DMAP in 31% yield in a similar manner to that described for the preparation of **6a**,

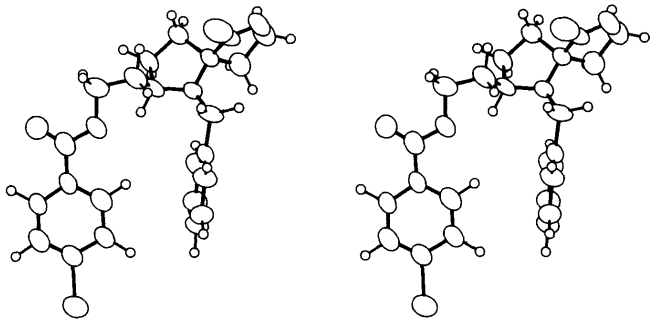
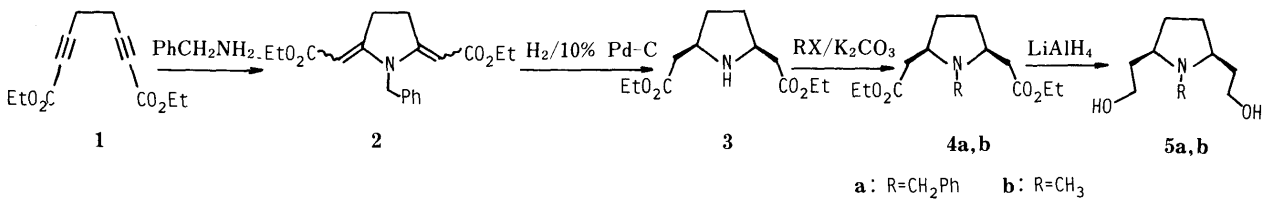


Fig. 1. Stereoscopic View of the Molecule of **11**



1 2 3 4a,b 5a,b

a: R=CH_2Ph b: R=CH_3

Chart 1

and *N*-benzylcarbonate (**7**) (runs 8, 9) do not give any corresponding azaspirocycles under similar reaction conditions. Thus, the *N*-benzyl and thiocarbonyl groups of azabicyclothinocarbonate (**6a**) play significant roles in this reaction.

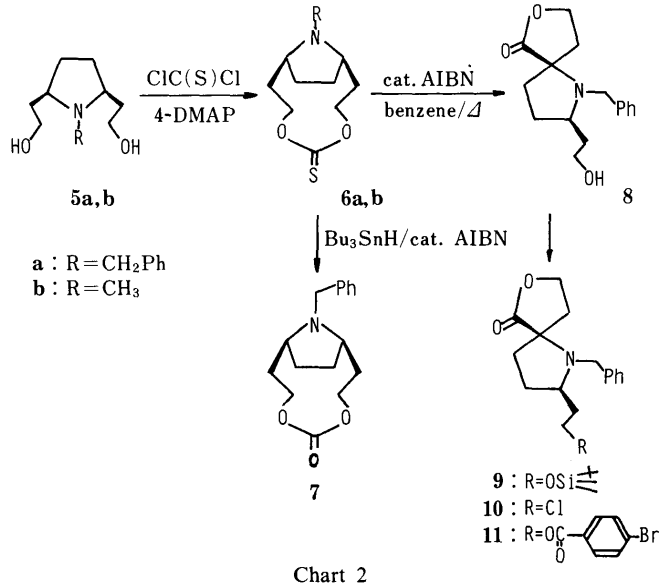
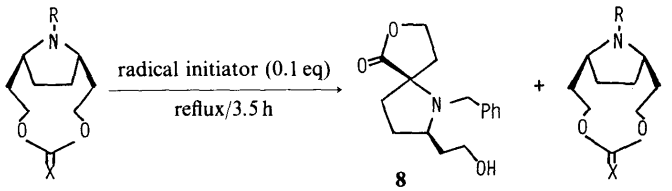


Chart 2

TABLE I. Transformation of Azabicyclothionocarbonate to Azaspirolactone



Run	R	X	Solvent	Initiator	Yield (%)[a] of **8**	Recovery yield (%)[a]
1	$PhCH_2$	S	B	None	—	Quant.
2	$PhCH_2$	S	B	AIBN	65	30
3	$PhCH_2$	S	B	(*tert*-BuO)$_2$	15	85
4	$PhCH_2$	S	T	(*tert*-BuO)$_2$	35	43
5	$PhCH_2$	S	B	$(PhCO)_2O_2$	25	73
6	CH_3	S	B	AIBN	—	35
7	CH_3	S	T	(*tert*-BuO)$_2$	—	20
8	$PhCH_2$	O	B	AIBN	—	Quant.
9	$PhCH_2$	O	B	$(PhCO)_2O_2$	—	Quant.

a) Isolated yield. Abbreviations: B=benzene, T=toluene.

These data lead to the mechanism proposed in Chart 3. We envision that a benzyl radical (A), which is generated by hydrogen abstraction by the initiator, undergoes a 1,3-hydrogen migration to form the radical (B). The radical (B) attacks the thiocarbonyl group to give a thiyl radical (C), which subsequently abstracts a hydrogen from **6a** to regenerate the starting radical (A). The resulting hemi-orthothiol ester intermediate (D) preferentially cleaves at the C–O* bond according to the principle of stereoelectronic effects[6] to yield the thionolactone (E), which is quickly hydrolyzed on silica gel with loss of hydrogen sulfide to give the product (**8**).

Experimental

No corrections were made for melting and boiling points. The IR and ultraviolet (UV) spectra were recorded on Shimadzu IR-435 and JASCO UVIDEC-505 spectrophotometers. Mass spectra (MS) were taken on Hitachi M-80 spectrometer. ^{1}H- and ^{13}C-NMR spectra were taken with tetramethylsilane as an internal standard on a Varian Gemini-200 spectrometer in $CDCl_3$. For column chromatography, SiO_2 (Merck 9385) was used. All reactions were carried out under a nitrogen atmosphere unless otherwise noted.

(1-Benzyl-2,5-bis-ethoxycarbonylmethylene)pyrrolidine (2) A solution of benzylamine (3.32 g, 31 mmol) in dry EtOH (10 ml) was added to a solution of diethyl hexa-1,5-diyne-1,6-dicarboxylate (**1**) (6.25 g, 28.2 mmol) in dry EtOH (60 ml) under ice-cooling. After stirring for 2 h at room temperature, the mixture was refluxed for a further 2 h. Removal of the solvent *in vacuo* afforded the crude mass, which was washed with cold EtOH–AcOH (10:1) to give the almost pure (*E*)-pyrrolidine (**2**) (7.41 g, 80%), which was recrystallized from EtOH to give colorless needles, mp 147—148 °C. High resolution (HR)-MS Calcd for $C_{19}H_{23}NO_4$: 329.1626. Found: 329.1633. The UV spectrum ($\lambda_{max}^{CHCl_3}$ 312 nm) was identical with that ($\lambda_{max}^{CHCl_3}$ 314 nm) of the corresponding *N*-methyl derivative.[2] IR ν_{max}^{KBr} cm^{-1}: 1695 (CO), 1575 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 1.23 (6H, t, J=9 Hz, 2×$CO_2CH_2C\underline{H}_3$), 3.29 (4H, s, CH_2CH_2), 4.10 (4H, q, J=9 Hz, 2×$CO_2C\underline{H}_2CH_3$), 4.68 (2H, s, N–CH_2), 5.07 (2H, s, 2×=CH), 7.24 (5H, br s, Ar-H). MS *m/z*: 329 (M^+). *Anal.* Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.47; H, 7.02; N, 4.25. Evaporation of the filtrate *in vacuo* gave a crude viscous oil (1.77 g), whose ^{1}H-NMR spectrum showed the presence of the (*Z*)-pyrrolidine (**2**) [^{1}H-NMR ($CDCl_3$) δ: 1.16 (6H, t, J=9 Hz, 2×$CO_2CH_2C\underline{H}_3$), 3.47 (4H, s, CH_2CH_2), 5.16 (2H, s, N–CH_2), 6.06 (2H, s, 2×=CH), 7.02 (5H, br s, Ar-H). Without purification, this was submitted to the following reaction.

Diethyl 2,5-*cis*-Pyrrolidinyldiacetate (3) A solution of **2** (500 mg, 1.5 mmol) in AcOH (20 ml) was hydrogenated over 10% Pd–C (200 mg) under the initial pressure of 5.3 kg/cm^2 for 17 h. After removal of the catalyst by filtration with the aid of a celite pad, the filtrate was concentrated *in vacuo*. The residue was neutralized by addition of saturated sodium bicarbonate

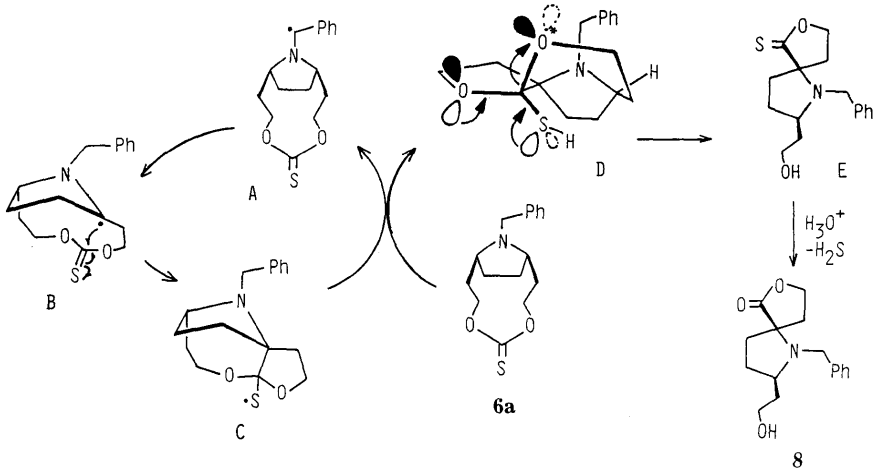


Chart 3

solution and extracted with EtOAc–hexane (3 : 1) (30 ml). The extract was dried over Na_2SO_4 and evaporated to give the almost pure oil (362 mg, 99%), bp 110 °C (bath temp.)/0.2 mmHg. IR ν_{max}^{film} cm^{-1}: 3350 (NH), 1722 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (6H, t, J=8 Hz, 2 × $CO_2CH_2C\underline{H}_3$), 1.40 and 1.85 (each 2H, each m, CH_2CH_2), 2.43 (4H, d, J=8 Hz, 2 × CH_2CO), 2.65 (1H, s, NH), 3.45 (2H, br s, 2 × CH), 4.10 (4H, q, J=8 Hz, 2 × $CO_2C\underline{H}_2CH_3$). MS m/z: 243 (M^+). *Anal.* Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.03; H, 8.66; N, 5.72.

Diethyl 1-Benzyl-2,5-*cis*-pyrrolidinyldiacetate (4a) A suspension of **5** (340 mg, 1.4 mmol), benzyl bromide (263 mg, 1.54 mmol), and potassium carbonate (386 mg, 2.8 mmol) in acetone (2 ml) was vigorously stirred at room temperature for 2 h. After removal of the solvent, the residue was extracted with EtOAc (50 ml) and the extract was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The oily residue was purified by column chromatography using hexane–EtOAc (8 : 2) as the eluent to give pure **4a** (398 mg, 85%), bp 170 °C (bath temp.)/0.2 mmHg. IR ν_{max}^{film} cm^{-1}: 1725 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.20 (6H, t, J=7 Hz, 2 × $CO_2CH_2C\underline{H}_3$), 1.55 and 1.95 (each 2H, each m, CH_2CH_2), 2.17 and 2.39 (each 1H, each dd, J=19, 10 Hz and J=19, 5 Hz, CH_2CO), 3.13 (2H, m, 2 × CH), 3.77 (2H, s, N–CH_2), 4.05 (4H, q, J=7 Hz, 2 × $CO_2C\underline{H}_2CH_3$), 7.26 (5H, br s, Ar-H). MS m/z: 333 (M^+). *Anal.* Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.34; H, 8.15; N, 4.20.

Diethyl 1-Methyl-2,5-*cis*-pyrrolidinyldiacetate (4b) A suspension of **3** (200 mg, 0.823 mmol), methyl iodide (0.077 ml, 1.235 mmol) and potassium carbonate (1.137 g, 8.23 mmol) was refluxed for 15 min. Work-up as described for the preparation of **4a** gave the almost pure oil (168 mg, 79%), which was purified by column chromatography using hexane–EtOAc (7 : 3) as the eluent to give pure **4b** (141 mg, 67%), bp 145 °C (bath temp.)/0.2 mmHg. IR ν_{max}^{film} cm^{-1}: 1725 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.22 (6H, t, J=8 Hz, 2 × $CO_2CH_2C\underline{H}_3$), 1.50 and 1.90 (each 2H, m, CH_2CH_2), 2.1—2.3 (2H, m, 2 × CH), 2.24 (3H, s, CH_3), 2.45—2.75 (4H, m, 2 × CH_2CO), 4.10 (4H, q, J=8 Hz, 2 × $CO_2C\underline{H}_2CH_3$). MS m/z: 257 (M^+). *Anal.* Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.68; H, 9.11; N, 5.56.

General Procedure for Reduction of Diesters (4a, b) A solution of a diester (**4a**, **b**) (3.0 mmol) in dry Et_2O (8 ml) was added dropwise to a suspension of $LiAlH_4$ (9.0 mmol) in dry Et_2O (7 ml) at 0 °C. After stirring for 5 min, the reaction mixture was acidified by addition of 6 N HCl (12 ml) and then made alkaline with 6 N NaOH (16 ml). The mixture was extracted with Et_2O, dried over $MgSO_4$, and evaporated to give the almost pure diol in quantitative yield. This product was used for the following reaction without further purification.

1-Benzyl-2,5-*cis*-pyrrolidinyldiethanol (**5a**): Viscous oil. IR ν_{max}^{film} cm^{-1}: 3700—3200 (OH). ^{1}H-NMR ($CDCl_3$) δ: 1.65—1.87 (8H, m, C_3-H_2, C_4-H_2, 2 × CH_2CH_2OH), 3.02 (2H, br s, 2 × CH), 3.20 and 3.90 (each 1H, each br s, 2 × OH), 3.55—3.70 (4H, m, 2 × $C\underline{H}_2OH$), 3.76 (2H, s, N–CH_2), 7.32 (5H, s, Ar-H). MS m/z: 249 (M^+). HR-MS Calcd for $C_{15}H_{23}NO_2$: 249.1728. Found: 249.1730.

1-Methyl-2,5-*cis*-pyrrolidinyldiethanol (**5b**): Viscous oil. IR ν_{max}^{film} cm^{-1}: 3700—3200 (OH). ^{1}H-NMR ($CDCl_3$) δ: 1.50—2.0 (8H, m, C_3-H_2, C_4-H_2, 2 × CH_2CH_2OH), 2.32 (3H, s, CH_3), 2.57 (2H, br, 2 × CH), 3.10 (2H, br, 2 × OH), 3.62 and 3.82 (2H, each m, 2 × $C\underline{H}_2OH$). MS m/z: 173 (M^+). HR-MS Calcd. for $C_9H_{19}NO_2$: 173.1415. Found: 173.1417.

General Procedure for Preparation of Azabicyclothionocarbonates (6a, b) Thiophosgene (0.052 mmol) was added to a solution of a diol (**5a**, **b**) (0.048 mmol) and 4-DMAP (0.125 mmol) in CH_2Cl_2 (0.4 ml) at 0 °C. The mixture was stirred for 30 min, then SiO_2 (80 mg) was added, and the whole was concentrated under reduced pressure to give an SiO_2 mass, which was submitted to column chromatography using hexane–EtOAc (9 : 1) as the eluent for **6a** and hexane–EtOAc (7 : 3) as the eluent for **6b** to give the pure azabicyclothionocarbonate.

12-Benzyl-4,6-dioxa-12-azabicyclo[7.2.1]dodecane-5-thione (**6a**): Viscous oil. 64%. ^{1}H-NMR ($CDCl_3$) δ: 1.30 and 2.28 (each 2H, each dd, J=18, 3 Hz and J=18, 5 Hz, C_2- and C_8-H_2), 1.88 (4H, m, C_{11}- and C_{12}-H_2), 3.23 (2H, br s, C_1- and C_9-H), 3.70 (2H, s, N–CH_2), 4.60 and 4.70 (each 2H, each br, C_3- and C_7-H_2), 7.30 (5H, m, Ar-H). MS m/z: 291 (M^+). HR-MS Calcd for $C_{16}H_{21}NO_2S$: 291.1292. Found: 291.1293.

12-Methyl-4,6-dioxa-12-azabicyclo[7.2.1]dodecane-5-thione (**6b**): Crystals (mp 66—67 °C). 31% ^{1}H-NMR ($CDCl_3$) δ: 1.30 and 2.50 [each 2H, br d (J=16 Hz) and m, C_2- and C_8-H_2], 1.88 (4H, br s, C_{11}- and C_{12}-H_2), 2.25 (3H, s, CH_3), 2.86 (2H, br s, C_1- and C_9-H), 4.50 and 4.70 [each 2H, br and t (J=12 Hz), C_3- and C_7-CH_2]. MS m/z: 215 (M^+). HR-MS Calcd for $C_{10}H_{17}NO_2S$: 215.0979. Found: 215.0979.

12-Benzyl-4,6-dioxa-12-azabicyclo[7.2.1]dodecan-5-one (7) A solution of **6a** (20 mg, 0.069 mmol) and tributyltin hydride (18.9 μl, 0.069 mmol) in benzene (3 ml) in the presence of AIBN (1 mg, 0.007 mmol) was refluxed overnight without using an N_2 stream. After evaporation of the solvent under reduced pressure, the residue was submitted to column chromatography, hexane–EtOAc (9.3 : 0.7) being used for elution. From the first fraction, the starting material (**6a**) (13 mg, 65%) was recovered. Further elution with the same solvent system gave the carbonate (**7**) (3 mg, 16%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.22 and 2.10 [each 2H, br d (J=15 Hz) and m, C_2- and C_8-H_2], 1.7—2.1 (4H, br, C_{11}- and C_{12}-H_2), 3.23 (2H, br s, C_1- and C_9-H), 3.70 (2H, s, N–CH_2), 4.11 and 4.44 (each 2H, br d and t, J=12 Hz, C_3- and C_7-H_2). MS m/z: 275 (M^+). HR-MS Calcd for $C_{16}H_{21}NO_3$: 275.1520. Found: 275.1522.

General Procedure for Reaction of Thionocarbonate (6a, b) with AIBN A solution of **6a** (29 mg, 0.1 mmol) in benzene (3 ml) was bubbled through with Ar for 10 min, then AIBN (1.6 mg, 0.01 mmol) was added. The mixture was refluxed for 3.5 h under an Ar atmosphere. After evaporation of the solvent, the residue was purified by column chromatography using hexane–EtOAc (7 : 3) as the eluent to give **6a** (10 mg, 35%) from the earlier fraction and 2,5-*cis*-1-benzyl-2-(2-hydroxyethyl)-7-oxa-1-azaspiro[4.4]-nonan-6-one (**8**) (8 mg, 65%) from the later fraction. IR ν_{max}^{film} cm^{-1}: 3700—3100 (OH), 1760 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.56 (2H, m, $C\underline{H}_2CH_2OH$), 1.86 (3H, m, C_4-H_2 and C_9-H), 2.09 (2H, m, C_3-H_2), 2.50 (1H, dd, J=22, 10 Hz, C_9-H), 3.0 (1H, br s, OH), 3.22 (1H, br s, C_2-H), 3.56 and 3.71 (each 1H, each m, $C\underline{H}_2OH$, sharpened by the addition of D_2O), 3.80 (2H, s, N–CH_2), 4.10 (1H, m, C_8-H), 4.25 (1H, dd, J=16, 7 Hz, C_8-H), 7.25 (5H, m, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 28.66 (t), 29.41 (t), 35.05 (t), 35.97 (t), 52.96 (t), 60.26 (t), 61.86 (d), 65.19 (t), 69.43 (s), 127.83 (d), 128.88 (2C, d), 129.21 (2C, d), 139.22 (s), 180.32 (s). MS m/z: 275 (M^+). HR-MS Calcd for $C_{16}H_{21}NO_3$: 275.1520. Found: 275.1523.

Reaction of **6b** as described for the reaction of **6a** with AIBN resulted in the recovery of only the starting material (**6b**) in 35% yield.

2,5-*cis*-1-Benzyl-2-(2-*tert*-butyldimethylsilyloxyethyl)-7-oxa-1-azaspiro-[4.4]nonan-6-one (9) *tert*-Butyldimethylsilyloxy trifluoromethanesulfonate (8.3 μl, 0.036 mmol) was added to a solution of **8** (5 mg, 0.018 mmol) in dry pyridine (0.2 ml) at −10 °C, and the mixture was stirred for 10 min. The reaction mixture was quenched by the addition of H_2O, and extracted with EtOAc–hexane (1 : 1) (30 ml). The extract was washed with brine, dried over anhydrous Na_2SO_4, and then evaporated under reduced pressure. The residue was purified by column chromatography using hexane–EtOAc (9 : 1) for elution to give **9** (4 mg, 57%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: −0.11 [6H, s, $Si(CH_3)_2$], 0.85 [9H, s, $SiC(CH_3)_3$], 1.50—1.90 (6H, br m, $C\underline{H}_2CH_2O$ and C_3- and C_4-H_2), 2.05 and 2.38 (each 1H, each q, J=13 Hz, C_9-H_2), 3.05 (1H, br s, C_2-H), 3.47 (2H, t, J=7 Hz, OCH_2), 3.63 and 3.85 (each 1H, each d, J=16 Hz, N–CH_2), 4.06 and 4.16 (each 1H, each m, C_8-H_2), 7.25 (5H, m, Ar-H). MS m/z: 389 (M^+). HR-MS Calcd for $C_{22}H_{35}NO_3Si$: 389.2384. Found: 389.2404

2,5-*cis*-1-Benzyl-2-(2-chloroethyl)-7-oxa-1-azaspiro[4.4]nonan-6-one (10) A solution of **8** (5 mg, 0.018 mmol) and triphenylphosphine (5 mg, 0.0198 mmol) in CCl_4 (1.5 ml) was refluxed for 36 h. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography using hexane–EtOAc (7 : 3) as the eluent to give **10** (3 mg, 58%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.70 (2H, m, $C\underline{H}_2CH_2Cl$), 1.93—2.42 (6H, m, C_3-, C_4-, and C_9-H_2), 3.17 (1H, C_2-H), 3.41 (2H, m, $ClCH_2$), 3.56 and 3.87 (each 1H, each d, J=15 Hz, N–CH_2), 4.15 (2H, m, OCH_2), 7.26 (5H, m, Ar-H). MS m/z: 293 (M^+). HR-MS Calcd for $C_{16}H_{20}NO_2Cl$: 293.1181. Found: 293.1194.

2,5-*cis*-1-Benzyl-2-(2-*p*-bromobenzoyloxyethyl)-7-oxa-1-azaspiro[4.4]-nonan-6-one (11) A solution of **8** (27 mg, 0.098 mg) and *p*-bromobenzoyl chloride (43 mg, 0.196 mmol) in dry pyridine (1.5 ml) in the presence of 4-DMAP (12 mg, 0.098 mmol) was stirred at room temperature for 42 h. The reaction mixture was quenched by the addition of H_2O, and extracted with EtOAc–hexane (1 : 1) (100 ml). The extract was washed with H_2O, saturated sodium bicarbonate solution and brine, dried over anhydrous Na_2SO_4, and then evaporated under reduced pressure. The residue was purified by column chromatography using hexane–EtOAc (7 : 3) as the eluent to give **11** (34 mg, 76%), which solidified on standing. Recrystallization from 10% EtOAc in hexane gave colorless needles, mp 93—95 °C. IR ν_{max}^{Nujol} cm^{-1}: 1760, 1710 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.67—2.18 (7H, m, C_3- and C_4-H_2, C_9-H, and $OCH_2C\underline{H}_2$), 2.47 (1H, dd, J=20, 10 Hz, C_9-H), 3.18 (1H, br s, C_2-H), 3.71 and 3.96 (each 1H, each d, J=15 Hz, N–CH_2), 4.21 (4H, m, C_8-H_2 and OCH_2), 7.3 (5H, m, N–CH_2Ar-H), 7.51 and 7.70 (each 2H, d, J=8 Hz, benzoyl-H). MS m/z: 457 (M^+). HR-MS Calcd for $C_{23}H_{24}NO_4Br$: 457.0889. Found: 457.0865.

X-Ray Determination of 2,5-*cis*-1-Benzyl-2-(2-*p*-bromobenzoyloxyethyl)-7-oxa-1-azaspiro[4.4]nonan-6-one (11) Transparent, colorless, plate-like crystals were obtained from MeOH solution. Crystal data: $C_{23}H_{24}NO_4Br$,

monoclinic, space group $P2_{n/1}$, $a=10.153$ (1), $b=16.105$ (2), $c=14.051$ (2) Å, $\beta=110.74$ (1)°, $U=2148.6$ (5) Å, $Z=4$, $D_c=1.417\,g\cdot cm^{-3}$, $(CuK_\alpha)=28.43\,cm^{-1}$, $F(000)=944$. In total, 2328 independent observed reflections ($F^2 \geqq 4\sigma(F^2)$) were measured on a Rigaku AFC automatic four-circle diffractometer using graphite-monochromated CuK_α radiation ($\lambda=1.5418$ Å). Observed data were corrected for Lorentz and polarization effects and for absorption using the empirical ϕ scanning method at $\times=90°$. The structure was solved by the usual heavy atom method. Anisotropic refinement was carried out for nonhydrogen atoms. Ideal positions of hydrogen atoms were calculated and included only for the calculation of structure factors. The present R value is 0.12 ($R_\omega=0.14$). This value is rather high, because of the relatively poor crystallinity and small crystal size of this compound. Atomic coordinates of nonhydrogen atoms, bond lengths and angles, and anisotropic thermal parameters have been deposited at the Cambridge Crystallographic Data Center (see Notice to Authors, Issue No. 1, 1988).

Acknowledgement We thank Ueo Chikuenkai of Kyoto for financial supoort.

References and Notes

1) G. Fodor and R. Dharanipragada, *Nat. Prod. Rep.*, **5**, 67 (1988).
2) W. Parker, R. A. Raphael, and D. I. Wilkinson, *J. Chem. Soc.*, **1959**, 2433.
3) 1,5-Hexadiyne was purchased from Tokyo Kasei Kogyo Co., Ltd.
4) Y. Tsuda, K. Kanemitsu, K. Kakimoto, and T. Kikuchi, *Chem. Pharm. Bull.*, **35**, 2148 (1987).
5) For reviews of the preparation of spiro compounds, see A. P. Krapcho, *Synthesis*, **1974**, 383, **1976**, 425 and **1978**, 77.
6) P. Deslongchamps "Steroelectronic Effects in Organic Chemistry," Pergamon Press, 1983.