

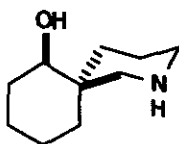
**SYNTHESIS OF ($\pm$)-NITRAMINE AND ($\pm$)-ISONITRAMINE
BY UTILIZING STEREOSELECTIVE REDUCTION OF ETHYL
1-(3-BROMOPROPYL)-2-OXOCYCLOHEXANECARBOXYLATE**

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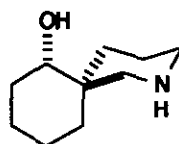
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Abstract - Formal synthesis of ($\pm$)-nitramine (**1**) and ($\pm$)-isonitramine (**2**) was achieved. Thus, the reduction of ethyl 1-(3-bromopropyl)-2-oxocyclohexanecarboxylate (**6**) with NaBH_4 in MeOH gave the corresponding cyclohexanol (**7**) having *cis* geometry between hydroxyl and ester groups, predominantly. On the other hand, the *trans* located isomer (**8**) was preferentially obtained by reduction with $\text{LiAl}(\text{OBu})_3\text{H}$ in THF. Treatment of the former reduction product (**7**) having *cis* geometry with benzylamine at 60 °C gave *cis* located ethyl 1-(3-(*N*-benzylamino)-propyl)-2-hydroxycyclohexanecarboxylate (**9**), which was further treated with BuLi to give a spirolactam, 2-benzyl-7-hydroxy-2-azaspiro[5.5]undecan-1-one (**11**) in 84 % yield. Reduction of the lactam (**11**) with $\text{BH}_3\cdot\text{SMe}_2$ in THF gave *N*-benzyl-nitramine (**13**). In a similar manner, *N*-benzylisonitramine (**14**) was synthesized from *trans* located hydroxyaminoester (**10**).

Piperidine alkaloids nitramine (**1**) and isonitramine (**2**), isolated from plants of the genus *Nitraria*,¹ are of interest due to their unique structure of a 2-azaspiro[5.5]undecan-7-ol skeleton, which resembles that of neurotoxic alkaloids histrionicotoxins.² Various strategies and approaches to the synthesis of azaspiro-alkaloids have been reported: *via* Michael addition,^{3a,b,c} Mannich reaction,^{3d} Diels-Alder reaction,^{3e} Birch reductive alkylation,^{3f} intramolecular addition of nitrile oxide,^{3g} intramolecular addition of nitron,^{3b} $\text{S}_\text{N}2'$ intramolecular alkylation of lactam enolate,³ⁱ radical cyclization,^{3j} intramolecular ring-opening of the chiral epoxy sulfone,^{3k} and others.^{3l-o} We were able to achieve a synthesis of the 2-azaspiro[5.5]undecane skeleton by means of an intramolecular spirolactam formation between amine and ester functions. We describe herein a new and stereoselective formal synthesis of nitramine (**1**) and isonitramine (**2**).

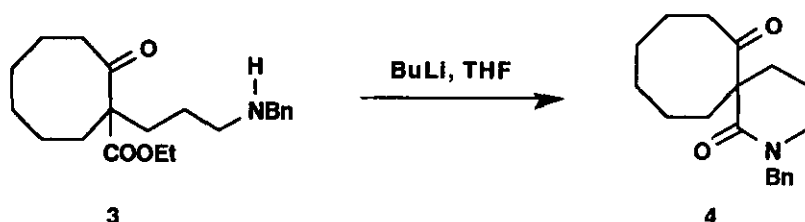


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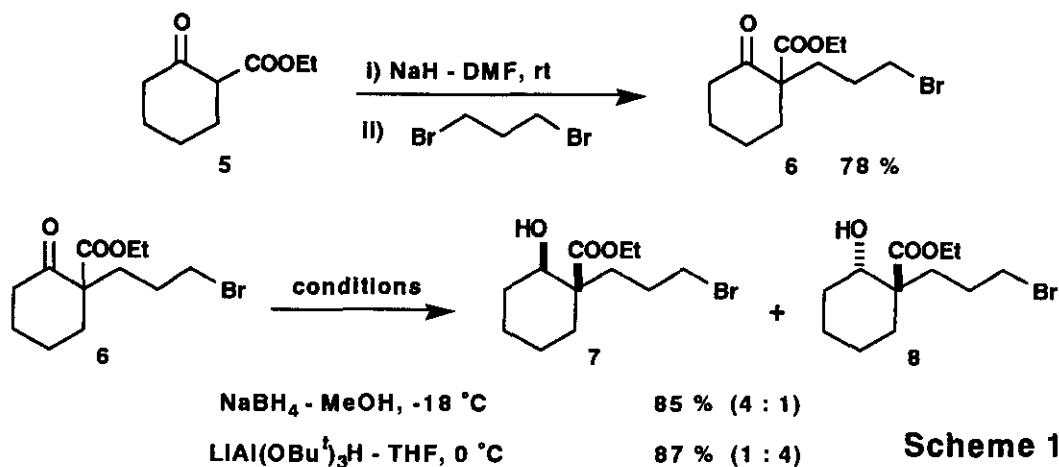


2

In the course of our studies on a synthesis of nitrogen heterocycles, we found that treatment of cyclic amino- β -keto ester (**3**) with BuLi failed to afford ring expansion products *via* retro-aldol reaction but gave spirolactam (**4**) in 48% yield. Spirolactam (**4**) could readily be transformed into 2-azaspiro compounds. Therefore, we applied this transformation to a synthesis of nitramine (**1**) and isonitramine (**2**).



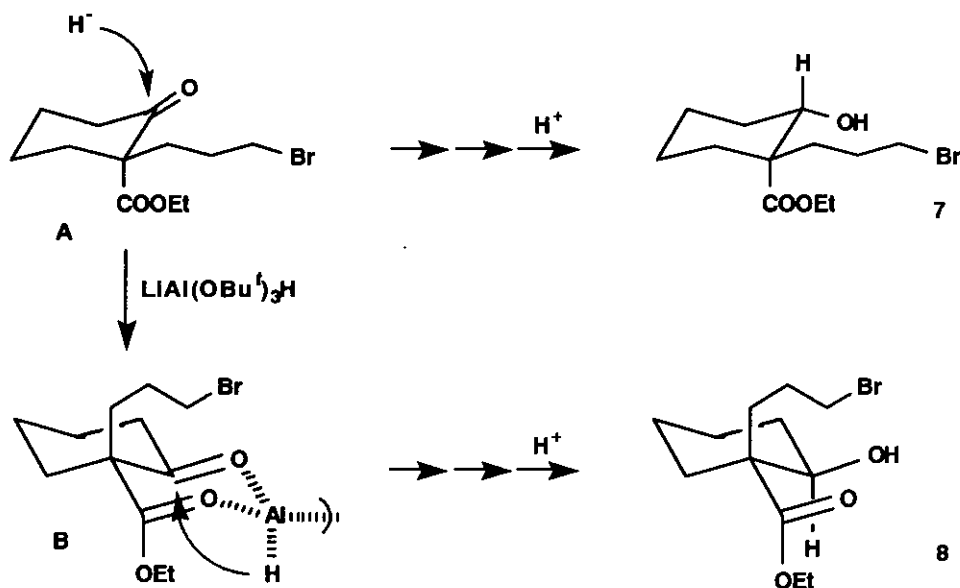
Treatment of ethyl 2-oxocyclohexanecarboxylate (**5**) with NaH in DMF followed by the reaction with 1,3-dibromopropane afforded ethyl 1-(3-bromopropyl)-2-oxocyclohexanecarboxylate (**6**) in 78 % yield. The yield of **6** was better than that by previously reported procedures.⁴ Reduction of cyclohexanone moiety of **6** with NaBH₄ in MeOH⁵ at -18 °C gave a *ca.* 4 : 1 mixture of two stereoisomeric cyclohexanols (**7** and **8**) in 85 % yield. Various methods for the reduction of **6** were examined in order to obtain cyclohexanol (**7**) and (**8**) in a stereoselective manner. As a result, we found that the reduction of **6** with LiAl(OBu^t)₃H in THF⁶ at 0 °C gave a *ca.* 1 : 4 mixture of **7** and **8** in 87 % yield (Scheme 1). The ¹H NMR spectrum of the mixture of isomers (**7**) and (**8**) exhibited two doublet of doublets at δ 3.44 ($J=3.6$ and 10.2 Hz) and 3.97 ($J=3.6$ and 8.6 Hz), which were assignable to the C₂ methine protons carrying a hydroxyl group in two isomers (**7** and **8**). The large coupling constants of **7** ($J=10.2$ Hz) and **8** ($J=8.6$ Hz) indicated that both methine protons of **7** and **8** were located in the axial positions of the cyclohexane ring. Stereochemical assignment of the products was finally established by a transformation of **7** or **8** into the precursors of nitramine (**1**) or isonitramine (**2**). The isomers (**7**) and (**8**) were transformed respectively into *N*-benzyl nitramine (**13**) and *N*-benzyl isonitramine (**14**), which were confirmed to be completely identical with those of published results^{3c,d,f,g} (*vide infra*). Therefore, it was determined that the isomer (**7**) had a *cis* relationship and the isomer (**8**) had a *trans* relationship between the hydroxyl group and ester group. Moreover, a comparison of



Scheme 1

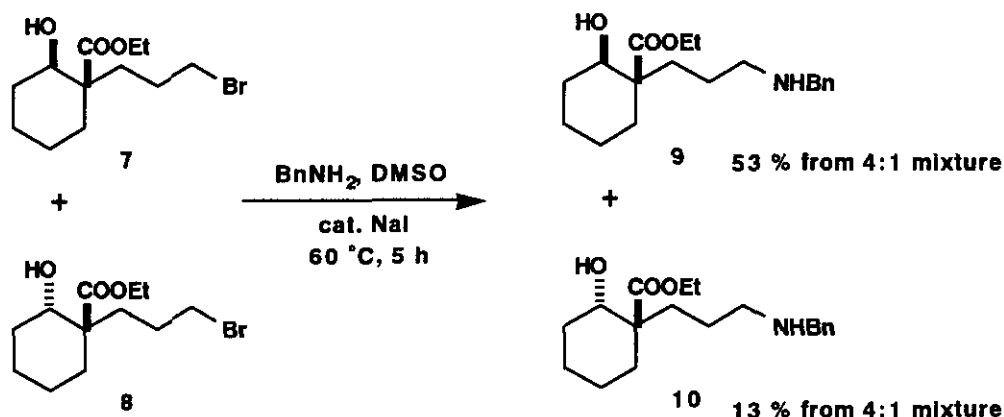
our results of NaBH_4 reduction with those reported by Hellberg and Beeson^{3a} and by Fráter⁵ also supports our assignment.

The stereochemical outcome of these reductions could be explained as shown in Scheme 2. When NaBH_4 is used as a reducing agent, axial hydride approach antiperiplanar to the dipolar electron withdrawing carboxylate substituent⁷ gives the *cis* located isomer (**7**) predominantly. On the other hand, in the case of reduction with $\text{LiAl}(\text{OBu}^t)_3\text{H}$, the conformation of the cyclohexane ring is probably flipped because of a chelation between aluminum and two carbonyl groups of **6** (conformation **B**). An axial attack of the hydride to the cyclohexanone carbonyl would result in a preferential formation of the *trans* cyclohexanol (**8**).



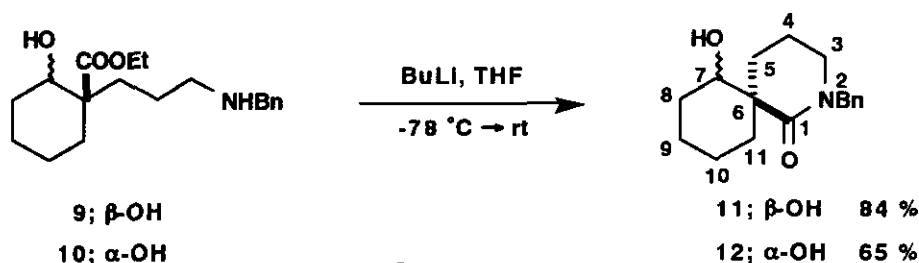
Scheme 2

Displacement of bromo atom in the reduction products to the *N*-benzylamino group was carried out according to the procedure of Arnold⁸ as shown in Scheme 3. Thus, a solution of the *ca* 4 : 1 mixture of **7** and **8** in DMSO was heated at 60 °C for 5 h with benzylamine in the presence of a catalytic amount of NaI to give a mixture of amino alcohols (**9**) and (**10**), which were separated by tlc to afford **9** (53 %) and **10** (13 %). A similar result was obtained by the reaction of *ca* 1 : 4 mixture of **7** and **8**. If keto ester (**6**) was treated with benzylamine at 60 °C, **6** gave the expected displacement product but underwent a further nucleophilic addition of the benzylamino group to cyclohexanone carbonyl to afford a bicyclic enamine.^{3d,9} Amino esters obtained were subjected to a spirolactam formation reaction. Treatment of the amino ester (**9**) in THF with BuLi at -78 °C gave spirolactam (**11**) in 84 % yield (Scheme 4). Elemental analysis and mass spectrometry indicated that it had a molecular formula of $\text{C}_{17}\text{H}_{23}\text{NO}$. The IR spectrum exhibited two bands at 3284 and 1596 cm^{-1} , due to a hydroxyl group and a lactam carbonyl group. The ^1H NMR spectrum of **11** exhibited one broad singlet at δ 3.76 (1H), assignable to C_7 methine proton carrying a hydroxyl group; two doublets at δ 4.50 (1H, $J=14.5$ Hz) and 4.65 (1H, $J=14.5$ Hz), assignable to methylene protons of *N*-benzyl group; and one broad singlet at δ 6.02 (1H), assignable to an OH proton. The ^{13}C NMR spectrum of



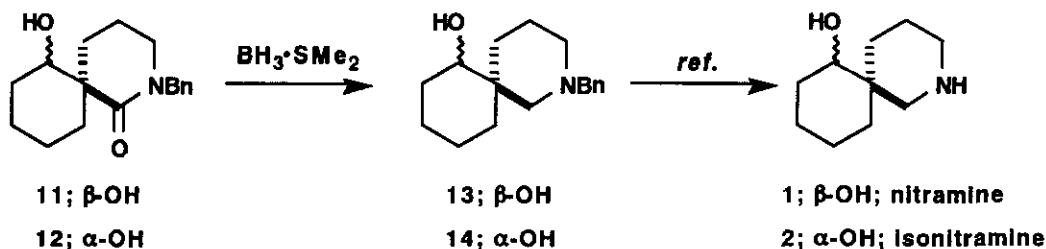
Scheme 3

11 exhibited eight methylene carbons at δ 18.74, 18.92, 19.89, 27.51, 28.34, 28.43, 47.53 and 50.51; one methine carbon at δ 71.81, assignable to C_7 carbon; two quaternary carbons at δ 44.02 and 176.87, assignable to spiro carbon at C_6 and C_1 lactam carbonyl carbon respectively; and signals assignable to aromatic carbons at δ 127.44, 127.71, 128.70, and 136.91. These spectral results are in good accordance with the assigned structure of spirolactam (**11**). In a similar reaction of **10**, spirolactam (**12**) was also obtained in 65 % yield. The spectral data of **12** were identical with those of previous reports.^{3f}



Scheme 4

Reduction of the spirolactams (**11**) and (**12**) with $\text{BH}_3 \cdot \text{SMe}_2$ according to the procedure of Brown¹⁰ gave *N*-benzyl nitramine (**13**) and *N*-benzyl isonitramine (**14**) in 99 % and 72 % yields. The spectral data were identical with those of previous reports.^{3c,d,f} The transformation of *N*-benzyl nitramine (**13**) and *N*-benzyl isonitramine (**14**) into nitramine (**1**) and isonitramine (**2**) has already been reported.^{3c,d,f}



Scheme 5

EXPERIMENTAL

Mps were determined with a Yanagimoto mp apparatus and are uncorrected. Unless otherwise stated, the IR spectra were determined in a neat form with a JASCO IR-810 infrared spectrophotometer. The ^1H and ^{13}C NMR spectra were determined in CDCl_3 (SiMe_4 as an internal reference) with a JEOL JNM EX-270 high-resolution spectrometer. The J -values are in Hz. The mass spectra were recorded using a JEOL JMS-DX303 or JMS-HX110 spectrometer (70 eV). Elemental analyses were performed by the staff of the analytical laboratory of the Faculty of Pharmaceutical Science. Preparative tlc was carried out with Merck Kiesel gel 60PF₂₅₄.

Ethyl 1-(3-bromopropyl)-2-oxocyclohexanecarboxylate (6).

To a suspension of NaH (2.37 g, 59 mmol; 40 % suspension in mineral oil) in DMF (55 mL), ethyl 2-oxocyclohexanecarboxylate (5) (10.05 g, 59 mmol) was slowly added at rt under a nitrogen atmosphere. The reaction mixture was stirred for 2 h until the generation of hydrogen ceased, and then 1,3-dibromopropane (18 mL, 177 mmol) was added to the mixture. After the reaction mixture was stirred overnight, it was poured into ice-water and extracted with ether. The organic layer was washed with water and brine successively, and was dried over anhydrous MgSO_4 . Evaporation of the solvent followed by distillation under reduced pressure gave ethyl 1-(3-bromopropyl)-2-oxocyclohexanecarboxylate (6) (13.4 g, 78 %): bp 112-117 °C / 0.15 Torr (lit.^{4a} 102-108 °C / 0.1 Torr); ^1H NMR δ_{H} 1.28 (3H, t, $J=7.26$), 1.40-2.07 (9H, m), 2.41-2.55 (3H, m), 3.39 (2H, m), 4.22 (2H, q, $J=7.26$); IR 1715, 1450, 1309, 1242, 1217, 1199, 1094, 1025 cm^{-1} .

Reduction of Ethyl 1-(3-bromopropyl)-2-oxocyclohexanecarboxylate (6).

i) with NaBH_4 in MeOH. To a stirred solution of ethyl 1-(3-bromopropyl)-2-oxocyclohexanecarboxylate (6) (3.4 g, 11.7 mmol) in MeOH (100 mL), sodium borohydride (0.9 g, 23.8 mmol) was slowly added at -18 °C (in an ice-salt bath) under a nitrogen atmosphere. After stirring for 1 h, the reaction mixture was allowed to warm to rt. MeOH was removed under reduced pressure, and ether and 2N HCl were added to the residue. The resulting mixture was extracted with ether. The ethereal solution was washed with water and brine successively, and was dried over anhydrous MgSO_4 . Evaporation of the solvent followed by distillation under reduced pressure gave a 4 : 1 mixture of stereoisomeric ethyl 1-(3-bromopropyl)-2-hydroxycyclohexanecarboxylates (7) and (8) (3.38 g, 85 %): bp 120-123 °C / 0.2 Torr; ^1H NMR δ_{H} 1.29 (3H, t, $J=7.25$, *trans*-isomer), 1.30 (3H, t, $J=7.25$, *cis*-isomer), 1.1-2.0 (12H, m), 2.1-2.2 (1H, m), 3.3-3.4 (2H, m), 3.44 (1H, dd, $J=3.6$ and 10.2, *cis*-isomer), 3.97 (1H, dd, $J=3.6$ and 8.6, *trans*-isomer), 4.1-4.3 (2H, m); ^{13}C NMR δ_{C} 14.22 (CH_3), 22.52 (CH_2), 23.78 (CH_2), 27.78 (CH_2), 31.75 (CH_2), 32.26 (CH_2), 33.71 (CH_2), 35.80 (CH_2), 51.07 (C), 60.63 (CH_2), 74.90 (CH), 176.71 (C=O); IR 3496, 1725, 1451, 1230, 1137, 1024 cm^{-1} ; MS (EI) m/z 294 (M^+ , 5.1), 292 (M^+ , 5.3), 276 [$(\text{M}-\text{H}_2\text{O})^+$, 2.0], 274 [$(\text{M}-\text{H}_2\text{O})^+$, 1.9], 266 [$(\text{M}-\text{CO})^+$, 22.9], 264 [$(\text{M}-\text{CO})^+$, 23.8], 248 [$(\text{M}-\text{EtOH})^+$, 19.0], 246 [$(\text{M}-\text{EtOH})^+$, 19.0], 223 (21.0), 221 (31.4), 212 [$(\text{M}-\text{Br})^+$, 18.3], 139 (91.2), 121 (28.5), 95 (38.0), 81 (31.5), 67 (69.2), 55 (63.4), 41 (100 %); HRMS Calcd for $\text{C}_{12}\text{H}_{21}\text{O}_3\text{Br}$ 292.0674. Found 292.0700.

ii) with $\text{LiAl}(\text{O}i\text{Bu})_3\text{H}$ in THF. To a vigorously stirred solution of ethyl 1-(3-bromopropyl)-2-oxocyclohexanecarboxylate (**6**) (3.09 g, 10.6 mmol) in THF (50 mL), $\text{LiAl}(\text{O}i\text{Bu})_3\text{H}$ (10.6 mL; 1.0 M solution in THF) was slowly added at 0 °C under a nitrogen atmosphere. After 15 min, water and crushed ice were added, followed by the addition of sufficient 10 % H_2SO_4 to dissolve the precipitate. The aqueous layer was extracted with ether, and then the organic layer was washed with 10% NaHCO_3 , water and brine successively, and dried over anhydrous MgSO_4 . After evaporation of the solvent, the crude product was distilled under reduced pressure to give a 1 : 4 mixture of **7** and **8** (2.59 g, 87 %): bp 125-127 °C / 0.2 Torr; ^1H NMR δ_{H} 1.29 (3H, t, $J=7.25$, CH_3 of *trans*-isomer), 1.30 (3H, t, $J=7.25$, CH_3 of *cis*-isomer), 1.1-2.0 (12H, m), 2.1-2.2 (1H, m), 2.77 (1H, br s, OH), 3.3-3.5 (3H, m, CHOH of *cis*-isomer and CH_2Br), 3.97 (1H, dd, $J=3.6$ and 8.6, CHOH of *trans*-isomer), 4.1-4.3 (2H, m, COOCH_2); ^{13}C NMR δ_{C} 14.22 (CH_3), 21.19 (CH_2), 22.48 (CH_2), 27.77 (CH_2), 29.31 (CH_2), 29.38 (CH_2), 29.69 (CH_2), 34.00 (CH_2), 50.12 (C), 60.70 (CH_2), 71.57 (CH), 176.78 (C=O); IR 3440, 1724, 1449, 1236, 1145, 1036 cm^{-1} ; MS (EI) m/z 294 (M^+ , 1.4), 292 (M^+ , 1.4), 276 [$(\text{M}-\text{H}_2\text{O})^+$, 1.6], 274 [$(\text{M}-\text{H}_2\text{O})^+$, 1.6], 266 [$(\text{M}-\text{CO})^+$, 6.0], 264 [$(\text{M}-\text{CO})^+$, 6.0], 248 [$(\text{M}-\text{EtOH})^+$, 4.5], 246 [$(\text{M}-\text{EtOH})^+$, 4.6], 223 (6.5), 221 (11.9), 171 (19.2), 157 (5.6), 139 (33.0), 111 (12.6), 95 (18.3), 81 (19.9), 67 (50.8), 55 (51.3), 41 (100 %); HRMS Calcd for $\text{C}_{12}\text{H}_{21}\text{O}_3\text{Br}$ 292.0674. Found 292.0664.

Ethyl 1-(3-benzylaminopropyl)-2-hydroxycyclohexanecarboxylate (**9**) and (**10**).

To a solution of a 4:1 mixed **7** and **8** (149 mg, 0.51 mmol) in DMSO (2 mL) were added benzylamine (0.17 mL, 1.53 mmol) and a catalytic amount of NaI (9 mg). The resulting solution was heated at 60 °C for 5 h under a nitrogen atmosphere. The reaction mixture was poured into 1% aqueous NaOH, and the resulting mixture was extracted with ether. The organic layer was washed with water and brine. After drying the layer over anhydrous MgSO_4 , evaporation of the solvent followed by TLC separation on silica gel (CH_2Cl_2 / MeOH / 25 % aqNH₃; 200 / 10 / 1) gave ethyl *cis*-1-(3-benzylaminopropyl)-2-hydroxycyclohexanecarboxylate (**9**) (86.4 mg, 53 %) and *trans*-isomer (**10**) (21.4 mg, 13 %). **9**: ^1H NMR δ_{H} 1.28 (3H, t, $J=7.26$, CH_3), 1.1-1.8 (9H, m), 1.8-2.0 (2H, m), 2.0-2.4 (3H, br m, NH, OH and CH), 2.61 (2H, t, $J=7.26$ Hz, CH_2N), 3.43 (1H, dd, $J=3.63$ and 9.89 Hz, CHOH), 3.78 (2H, s, CH_2Ph), 4.19 (2H, m), 7.2-7.35 (5H, m, Ph); ^{13}C NMR δ_{C} 14.23 (CH_3), 22.59 (CH_2), 23.87 (CH_2), 24.66 (CH_2), 31.56 (CH_2), 32.37 (CH_2), 34.68 (CH_2), 49.72 (CH_2), 51.32 (C), 53.96 (CH_2), 60.49 (CH_2), 74.81 (CH), 126.88 (CH), 128.09 (CH), 128.37 (CH), 140.36 (C), 177.14 (C=O); IR 3490, 3302, 1723, 1454, 1226, 1183, 1132; MS (EI) m/z 319 (M^+ , 2.5), 290 (1.3), 274 (5.4), 256 (6.2), 246 (21.2), 211 (32.2), 120 (100), 106 (53.1), 91 (95.7 %); HRMS Calcd. for $\text{C}_{19}\text{H}_{29}\text{NO}_3$ 319.2148. Found 319.2148. **10**: ^1H NMR δ_{H} 1.26 (3H, t, $J=7.26$, CH_3), 1.2-1.9 (12H, m), 2.29 (2H, br s, NH and OH), 2.59 (1H, dt, $J=6.6$ and 11.55 Hz, CH_2N), 2.70 (1H, dt, $J=6.6$ and 11.55 Hz, CH_2N), 3.79 (2H, s, CH_2Ph), 4.03 (1H, dd, $J=3.63$ and 6.26 Hz, CHOH), 4.16 (2H, q, $J=7.26$ Hz), 7.2-7.4 (5H, m, Ph); ^{13}C NMR δ_{C} 14.23 (CH_3), 21.75 (CH_2), 21.96 (CH_2), 23.97 (CH_2), 29.60 (CH_2), 29.67 (CH_2), 29.92 (CH_2), 49.36 (CH_2), 50.60 (C), 53.82 (CH_2), 60.38 (CH_2), 69.90 (CH), 127.08 (CH), 128.25 (CH), 128.45 (CH), 139.60 (C), 176.77 (C=O); IR 3382, 3306, 1720, 1454, 1180, 1144, 1028, 994 cm^{-1} ; MS (EI) m/z 319 (M^+ , 2.1), 290 (1.2), 274 (3.3), 256 (5.9), 246 (18.7), 211 (18.7), 120 (100), 106 (42.7), 91 (88.3 %); HRMS Calcd for $\text{C}_{19}\text{H}_{29}\text{NO}_3$ 319.2148. Found 319.2178.

1-Oxo-*N*-benzyl nitramine (*cis*-2-Benzyl-7-hydroxy-2-azaspiro[5.5]undecan-1-one) (11).

To a solution of ethyl *cis*-1-(3-benzylaminopropyl)-2-hydroxycyclohexanecarboxylate (**9**) (55 mg, 0.17 mmol) in THF (8.5 mL), 1.6M *n*-BuLi (0.1 mL, 0.16 mmol) was slowly added at -78 °C under an argon atmosphere. After stirring for 1 h at -78 °C, the solution was allowed to warm to rt. Saturated NH₄Cl and 2N HCl were then added to the reaction mixture. The resulting mixture was extracted with ether. The organic layer was washed with water and brine successively, and then dried over anhydrous MgSO₄. Evaporation of the solvent followed by recrystallization from hexane/CH₂Cl₂ gave *cis*-2-benzyl-2-azaspiro[5.5]undecan-1-one-7-ol (**11**) (38.5 mg, 84 %): mp 89-91 °C (hexane-CH₂Cl₂); Anal. Calcd for C₁₇H₂₃NO₂ C, 74.69; H, 8.48; N, 5.12. Found C, 74.84; H, 8.58; N, 5.12; ¹H NMR δ_H 1.3-1.9 (10H, m), 2.04 (1H, m), 2.27 (1H, m), 3.21 (2H, m, C₃-H), 3.76 (1H, br s, C7-H), 4.50 (1H, d, *J*=14.5, PhCH₂), 4.65 (1H, d, *J*=14.5, PhCH₂), 6.02 (1H, br s, OH), 7.18-7.35 (5H, m, Ph); ¹³C NMR δ_C 18.74 (CH₂), 18.92 (CH₂), 19.89 (CH₂), 27.51 (CH₂), 28.34 (CH₂), 28.43 (CH₂), 44.02 (C), 47.53 (CH₂), 50.51 (CH₂), 71.81 (CH), 127.44 (CH), 127.71 (CH), 128.70 (CH), 136.90 (C), 176.87 (C=O); IR 3284, 1596, 1496, 1271, 1250, 1204, 1167, 1077, 1037, 1018 cm⁻¹; MS (EI) *m/z* 273 (M⁺, 24.2), 255 [(M-H₂O)⁺, 44.4], 245 [(M-CO)⁺, 18.6], 218 (13.1), 202 (100), 91 (77.1 %).

1-Oxo-*N*-benzyl isonitramine (*trans*-2-Benzyl-7-hydroxy-2-azaspiro[5.5]undecan-1-one) (12).

A solution of ethyl *trans*-1-(3-benzylaminopropyl)-2-hydroxycyclohexanecarboxylate (**10**) (16.3 mg, 0.051 mmol) in THF (2.6 mL) was treated with BuLi (0.05 mL, 0.08 mmol) in the same manner as that of **9**. After the usual work-up, recrystallization from hexane-CH₂Cl₂ gave a pure *trans*-2-benzyl-2-azaspiro[5.5]undecan-1-one-7-ol (**12**) (9.0 mg, 65 %). The spectral data were identical with those of previous reports.^{3f} **12**: mp 104-106 °C (hexane-CH₂Cl₂) (lit.,^{3f} 91-92 °C); Anal. Calcd for C₁₇H₂₃NO₂ C, 74.69; H, 8.48; N, 5.12. Found C, 74.80; H, 8.57; N, 5.28; ¹H NMR δ_H 1.2-1.9 (11H, m), 1.9-2.1 (1H, m), 2.23 (1H, br s, OH), 3.1-3.3 (2H, m, C₃-H), 4.35 (1H, dd, *J*=11.21 and 4.29, CHOH), 4.48 (1H, d, *J*=14.9, PhCH₂), 4.73 (1H, d, *J*=14.9, PhCH₂), 7.2-7.35 (5H, m, Ph); ¹³C NMR δ_C 19.12 (CH₂), 19.80 (CH₂), 21.37 (CH₂), 24.39 (CH₂), 29.00 (CH₂), 32.58 (CH₂), 47.26 (CH₂), 48.43 (C), 50.78 (CH₂), 73.32 (CH), 127.10 (CH), 127.60 (CH), 128.52 (CH), 137.39 (C), 175.18 (C=O); IR (nujol) 3378, 1609, 1492, 1266, 1247, 1208, 1197, 1135, 1061, 980 cm⁻¹; MS (EI) *m/z* 273 (M⁺, 36.4), 255 [(M-H₂O)⁺, 29.9], 245 [(M-CO)⁺, 8.4], 218 (15.32), 202 (55.4), 182 (20.0), 91 (100 %).

***N*-Benzyl nitramine (13).**

To a refluxed solution of 1-oxo-*N*-benzyl nitramine (**11**) (7.8 mg, 0.029 mmol) in THF (1.0 mL), 10M BH₃·SMe₂ solution in THF (0.1 mL, 1 mmol) was dropwise added under a nitrogen atmosphere. The reaction mixture was refluxed additionally for 30 min. The reaction mixture was cooled to rt, and then the solvent and dimethyl sulfide were evaporated. After an addition of 6N HCl (1.0 mL) to the residue, the solution was heated at 100 °C for 30 min and then cooled to rt. The mixture was neutralized with 6N NaOH and then extracted with ether. The organic layer was washed with brine and dried over anhydrous MgSO₄. Evaporation of the solvent gave an almost pure *N*-benzyl nitramine (**12**) (7.4 mg, 99 %). The spectral data were identical with those of previous reports.^{3d,n}

***N*-Benzylisonitramine (14).**

A solution of 1-oxo-*N*-benzylisonitramine (**13**) (12.9 mg, 0.047 mmol) in THF (1.0 mL) was subjected to similar treatment as that of **13** to give an almost pure *N*-benzylisonitramine (**14**) (8.8 mg, 72 %). The spectral data were identical with those of previous reports.^{3c,d}

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