ENANTIOSELECTIVE TOTAL SYNTHESES OF SIBIRINE, NITRAMINE, AND ISONITRAMINE†

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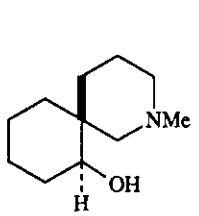
Abstract — The stereoselective Birch reductive alkylation strategy has provided total syntheses and configurational assignments for the 1-azaspiro[5.5]undecane alkaloids sibirine (1), isonitramine (2), and nitramine (3).

Sibirine (1), isolated from Nitraria sibirica, is a member of the relatively new 1-azaspiro-[5.5]undecane group of alkaloids.[1] The structures of related substances, isonitramine (2) and nitramine (3), isolated from Nitraria Schobere, have been confirmed by X-ray crystallographic studies of their corresponding hydrochloride salts;[1b] however, the absolute configurations of all of these alkaloids have not been reported.[1a]



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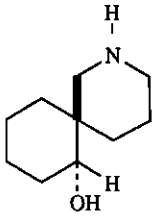

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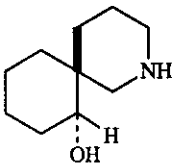

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Kozikowski and Yuen[2] have described total syntheses of racemic 1 and 2 by the nitrile oxide cycloaddition route.[3] Furthermore, Snider and Cartaya-Marin[4] have published a total synthesis of racemic nitramine (3) by an intramolecular nitrone cycloaddition.[5] In this paper, we report efficient enantioselective syntheses of 1-3, which provide unambiguous configurational assignments for all of these alkaloids.

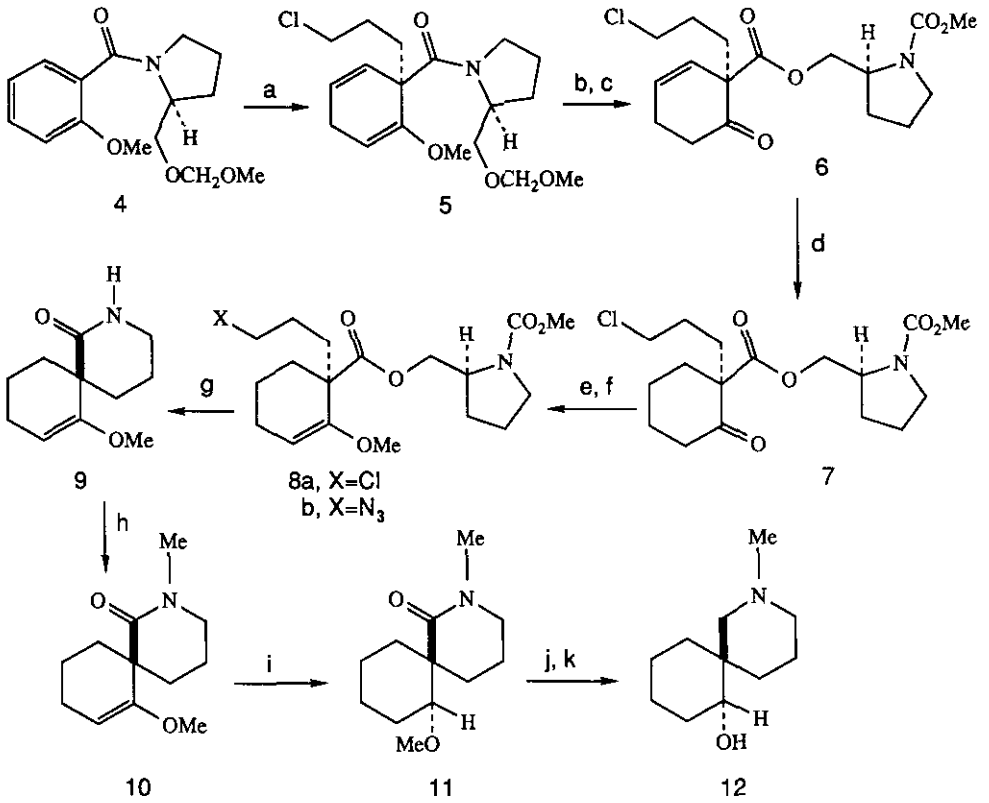
The synthesis of (+)-sibirine (Scheme 1) began by the stereoselective Birch reductive alkylation of anisic acid derivative 4[6] with 1-bromo-3-chloropropane to give 5 in 78% isolated yield. In

†Dedicated to Professor Gilbert Stork on the occasion of his 65th birthday.

an earlier study, we found that the diastereoselectivity of reductive methylation of 4 was 260:1.[6] We presume that 5 is obtained with comparable stereoselectivity.

The chiral auxiliary, L-prolinol, was activated for removal by treatment of 5 with hydrochloric acid in refluxing methanol, which effected enol ether and MOM group hydrolysis, followed by N to O acyl migration; acylation with methyl chloroformate provided β-ketoester 6 (protected from probable rearrangement back to the amide)[7] in 87% yield after flash chromatography on silica gel.

Scheme 1



(a) K, NH_3, t-BuOH, 1-bromo-3-chloropropane; (b) HCl, MeOH; (c) $ClCO_2Me$, $NaHCO_3$, CH_2Cl_2; (d) H_2, Pd/C, EtOAc; (e) $HC(OMe)_3$, H_2SO_4, MeOH; (f) NaN_3, PTC, H_2O; (g) $NaBH_4$, PTC, H_2O; (h) NaH, THF, MeI; (i) H_2, $[Ir(cod)pyPCy_3]PF_6$, CH_2Cl_2; (j) EtSH, $AlCl_3$, CH_2Cl_2; (k) $LiAlH_4$, THF.

After some experimentation it was found that the double bond in 6 imparted serious instability to subsequent transformation products. Hydrogenation of the troublesome unsaturation with 5% Pd/C gave 7 in 97% yield. Reformation of the enol ether gave 8a (93% yield), which was subjected to chloride displacement by sodium azide under phase transfer conditions[8] to give azide 8b. Azide reduction with sodium borohydride under the same phase transfer conditions[9] was followed by cyclization of the resulting amino ester. The expected spirocyclic lactam 9 was obtained in 70%

overall yield from 8a after flash chromatographic separation of 9 from the chiral auxiliary, recovered as the N-methoxycarbonyl derivative. Other methods of azide reduction proved to be less effective.[10] N-methylation was effected by treatment of 9 with sodium hydride-methyl iodide to give 10.

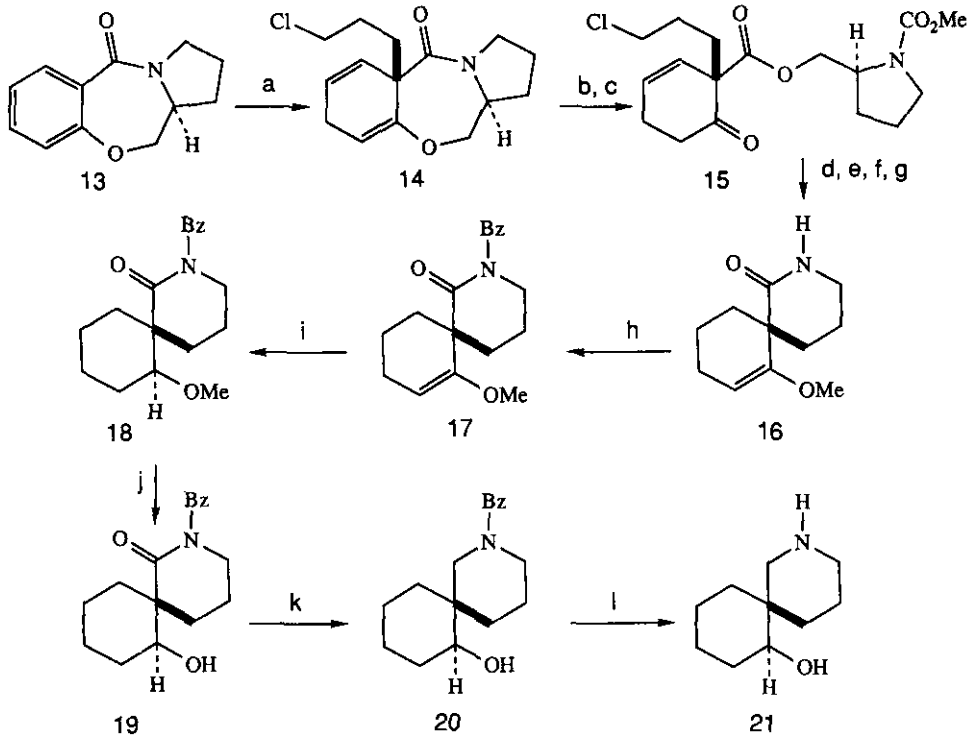
The proper relative configuration at C(7) was obtained by utilization of the carboxamide group directed stereoselective iridium-catalyzed homogeneous enol ether hydrogenation.[11] Using standard hydrogenation conditions[12] of ~5 mole % of $[Ir(cod)py(PCy_3)]PF_6$ in methylene chloride[13] at atmospheric pressure, 10 was converted to diastereoisomerically pure 11 in ~ quantitative overall yield from 9. Methyl ether cleavage with ethanethiol and $AlCl_3$[14] gave the corresponding hydroxy lactam in 91% yield and this was converted to (+)-sibirine (12) by lithium aluminum hydride reduction (93% yield).

The optical rotation of 12 was found to be $[\alpha]^{24}_D$ +25.0°, while the literature value for the natural product was $[\alpha]^{24}_D$ -22.5°.[15] The configuration of natural (-)-sibirine, therefore, must be that shown as structure 1.[16] A formal total synthesis of (-)-sibirine (1) was carried out (Scheme 2) via Birch reductive alkylation of benzoxazepinone 13 to give 14 in 91% isolated yield. On the basis of earlier studies,[7,17] we estimate that the diastereoselectivity for the conversion 13 → 14 must be >99:1. Conversion of 14 to 16, the enantiomer of the (+)-sibirine intermediate, 9, was accomplished by methods similar to those presented in Scheme 1.

Enol ether 16 failed to undergo iridium-catalyzed hydrogenation. However, conversion of 16 to the N-benzyl derivative 17 (Scheme 2) followed by hydrogenation with the iridium catalyst system gave 18 as a single diastereoisomer. Methyl ether cleavage, lithium aluminum hydride reduction, and debenzylation gave 21, the enantiomer of natural isonitramine (2), in ~50% overall yield from 16.

After stereorational syntheses of 12 and 21 were completed, a more rapid construction of 21 and a highly stereoselective synthesis of nitramine (3) were developed by experimentation with a variety of conditions for ketone carbonyl group reduction (Scheme 3). Enol ether hydrolysis of 16 gave the versatile keto lactam 22 (94% yield). While reduction of the ketone group in 22 with sodium borohydride or lithium aluminum hydride proceeded with low stereoselectivity, treatment of 22 with two equivalents of diisobutylaluminum hydride (DIBAL) gave a mixture of 23 and 24 (94% yield) in a ratio of 13:1 in favor of isomer 23. Conversion of 23 to isonitramine (21) was accomplished by lithium aluminum hydride reduction. Thus, 21 is available in enantiomerically pure form in ten steps from benzoxazepinone 13 (~50% overall yield).

Scheme 2

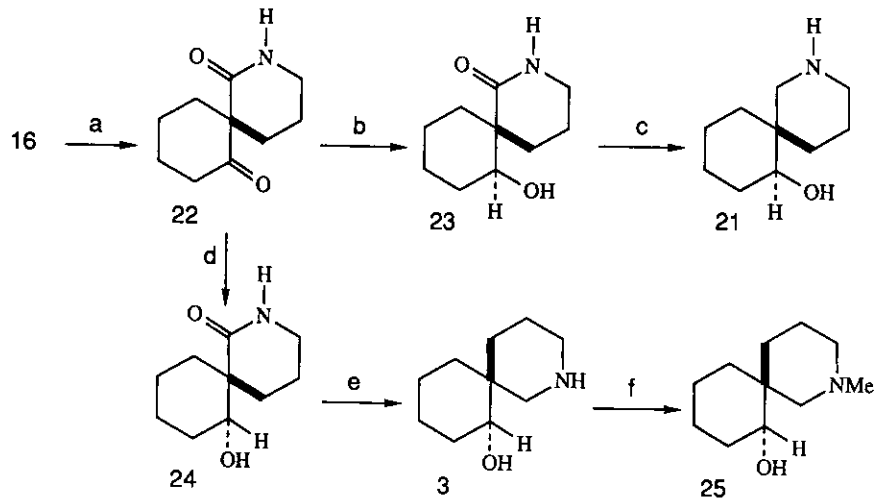


(a) K, NH_3, t-BuOH, 1-bromo-3-chloropropane; (b) HCl, MeOH; (c) $ClCO_2Me$, $NaHCO_3$, CH_2Cl_2; (d) H_2, Pd/C, EtOAc; (e) $HC(OMe)_3$, H_2SO_4, MeOH; (f) NaN_3, PTC, H_2O; (g) $NaBH_4$, PTC, H_2O; (h) NaH, THF, BzBr; (i) H_2, [Ir(cod)PyPCy$_3$]PF_6, CH_2Cl_2; (j) EtSH, $AlCl_3$, CH_2Cl_2; (k) $LiAlH_4$, THF; (l) H_2, Pd/C, MeOH.

Reduction of 22 *with sodium borohydride in methanol gave a 1:2 mixture of* 24 and 23, respectively. This ratio could be dramatically changed by addition of cerium chloride (1.1 equiv) to the borohydride reduction mixture to give 24 and 23 in a 4:1 ratio. Ytterbium chloride was an even more effective additive, producing 24 and 23 in a ratio of 13:1.[18] Lithium aluminum hydride reduction of 24 provided nitramine (3) in 95% yield.[19]

Spectral data for synthetic 3 were identical to those described for the natural product;[1c] unfortunately, a rotation for 3 has not been reported. For this reason, we converted[20] synthetic 3 to the N-methyl derivative 25; colorless oil: $[\alpha]^{22}_D$ +17.6° (c 1.23, $CHCl_3$); Lit. $[\alpha]_D$ +17.0° (c 0.43, $CHCl_3$).[1c] Thus, the configuration of natural nitramine must be that shown in structure 3.

Scheme 3



(a) HCl, MeOH; (b) DIBAL, THF, -78°C; (c) $LiAlH_4$, THF; (d) $NaBH_4$, $YbCl_3$, MeOH; (e) $LiAlH_4$, THF; (f) MeI, EtOH, reflux.

EXPERIMENTAL

(6R)-6-[(Methoxymethyl)-(S)-prolinolcarboxamido]-6-(3-chloropropyl)-1-methoxy-1,4-cyclohexadiene (5). Prepared by procedures described elsewhere; Birch reduction with potassium, exchange with lithium bromide, and alkylation with 1-bromo-3-chloropropane (1.3 equiv).[6] Flash chromatography on silica gel (EtOAc-Hexane 4:1) gave 5 as a colorless oil (78%); IR (film) 3.37, 6.15, 9.45 μm; ^1H NMR δ 1.42-2.00 (m, 7H), 2.12 (m, 1H), 2.89 (m, 2H), 3.28 (m, 2H), 3.36 (s, 3H), 3.51 (s, 3H), 3.51 (t, 2H), 3.61 (m, 1H), 3.73 (dd, 1H, J=10, 4 Hz), 4.30 (br s, 1H), 4.16 (q, 2H), 4.78 (t, 1H), 5.35 (dt, 1H, J=10 Hz), 5.94 (dt, 1H, J=10 Hz); $[\alpha]^{27}_D$ -33.8° (c 1.1, $CHCl_3$); chemical ionization mass spectrum m/z (relative intensity) M+1 (62), 322 (100), 172 (65); anal. calcd for $C_{18}H_{28}ClNO_4$: C, 60.42; H, 7.88. Found: C, 60.20; H, 7.95.

(2R)-2-[(N-Carbomethoxy-(S)-prolinol)carbalkoxy]-2-(3-chloropropyl)cyclohex-3-ene-1-one (6). To a solution of 5 (4.53 mmol) in methanol (10 ml) was added concentrated HCl (1 ml). The resulting solution was heated to reflux for 4 h, cooled to room temperature, concentrated to one-half the reaction volume, and was neutralized with solid sodium bicarbonate. Extraction with methylene chloride, drying the organic layer over anhydrous $MgSO_4$, and solvent evaporation gave a yellow oil that was immediately redissolved in methylene chloride. Addition of $NaHCO_3$ (1.1 equiv) and cooling to ice-bath temperature was followed by addition of methyl chloroformate. After stirring for 3 h at room temperature, water (5 ml) was added, and the reaction mixture was extracted with methylene chloride. The organic phase was washed with dilute HCl solution, dried ($MgSO_4$), and evaporated; flash chromatography on silica gel (EtOAc-Hexane, 4:1) gave 6 as a colorless oil (87%); IR (film) 3.38, 5.76, 5.82, 5.93, 6.92, 7.14 μm; ^1H NMR δ 1.40-2.06 (m, 7H), 2.16 (dt, 1H, J=6 Hz), 2.30-2.82 (m, 4H), 3.32 (m, 2H), 3.51 (dt, 2H, J=2 Hz), 3.71 (s, 3H), 3.96-4.36 (m, 3H), 5.66 (d, 1H), 6.15 (br d, 1H); $[\alpha]^{27}_D$ -95.9° (c 1.1, $CHCl_3$); chemical ionization mass spectrum m/z (relative intensity) M+1 (86), 322 (38), 160 (100); anal. calcd for $C_{17}H_{24}ClNO_5$: C, 57.07; H, 6.75. Found: C, 56.92; H, 6.66.

(2R)-2-[(N-Carbomethoxy-(S)-prolinol)carbalkoxy]-2-(3-chloropropyl)cyclohexanone (7). A solution of 6 (1 mmol) in 3 ml of ethyl acetate and 5% Pd/C was stirred under hydrogen (1 atm) for 2 h. The catalyst was removed by filtration through Celite, and the solvent was evaporated; flash chromatography on silica gel (EtOAc-Hexane, 3:1) gave 7 as a colorless oil (97%); IR (film) 3.37, 5.71-5.95 (broad), 6.94, 7.24 μm; ^{1}H NMR δ 1.26-2.10 (m, 13H), 2.30-2.54 (m, 3H), 3.36 (m, 2H), 3.50 (t, 2H), 3.68 (s, 3H), 3.94-4.38 (m, 3H); $[\alpha]^{32}_D$ -95.0° (c 0.42, $CHCl_3$); chemical ionization mass spectrum m/z (relative intensity) M+1 (90), 324 (100), 201 (55), 160 (36); anal. calcd for $C_{17}H_{26}ClNO_5$: C, 56.75; H, 7.28. Found: C, 56.65; H, 7.19.

(6R)-6-[(N-Carbomethoxy-(S)-prolinol)carboalkoxy]-6-(3-chloropropyl)-1-methoxycyclohex-1-ene (8a). A solution of 7 (1 mmol) in 1 ml of dry methanol, 2 ml of trimethylorthoformate, and several drops of concentrated sulfuric acid was stirred overnight at room temperature. The reaction mixture was concentrated, saturated $NaHCO_3$ was added, and the resulting mixture was extracted with methylene chloride. The organic layers were combined, dried over $MgSO_4$, and concentrated to give 8a as a light yellow oil. Flash chromatography on silica gel (EtOAc-Hexane, 70:30) gave a colorless oil (93%); IR (film) 3.39, 5.80, 5.98, 6.89, 7.20 μm; ^{1}H NMR δ 1.40-2.20 (m, 14H), 3.38 (br m, 2H), 3.45 (s, 3H), 3.53 (d, 2H), 3.68 (br s, 3H), 4.10 (m, 3H), 4.78 (br t, 1H); $[\alpha]^{24}_{365nm}$ +38.7° (c 0.58, $CHCl_3$); chemical ionization mass spectrum m/z (relative intensity) M+1 (70), 338 (49), 187 (100), 160 (74); anal. calcd for $C_{18}H_{28}ClNO_5$: C, 57.83; H, 7.54. Found: C, 57.82; H, 7.57.

(6R)-6-[(N-Carbomethoxy-(S)-prolinol)carbalkoxy]-6-(3-azidopropyl)-1-methoxycyclohex-1-ene (8b). Prepared from 8a by procedures described elsewhere.[8] Flash chromatography on silica gel (EtOAc-Hexane, 70:30) gave 8b as a colorless oil (92%); IR (film) 3.42, 4.80, 5.82, 5.90 μm; ^{1}H NMR δ 1.32-2.14 (m, 14H), 3.24 (t, 2H), 3.36 (m, 2H), 3.46 (s, 3H), 3.70 (s, 3H), 4.10 (m, 3H), 4.80 (br t, 1H); $[\alpha]^{24}_D$ +11.0° (c 1.94, $CHCl_3$); chemical ionization mass spectrum m/z (relative intensity) 353 (70), 177 (100), 142 (90); anal. calcd for $C_{18}H_{28}N_4O_5$: C, 56.83; H, 7.41. Found: C, 56.91; H, 7.50.

2-Oxopiperidine-3(R)-spiro-2'-(1-methoxycyclohex-1-ene) (9). A mixture of 8b (1 mmol) in 2 ml of water and hexadecyltri-N-butylphosphonium bromide (PTC, 0.1 mmol) was heated to 80°C, then $NaBH_4$ was added in portions over 30 min.[8] The resulting mixture was heated for 24 h, then cooled and extracted with methylene chloride (3 x 10 ml). The organic layers were combined, dried over $MgSO_4$, and concentrated. Flash chromatography on silica gel (EtOAc-MeOH, 95:5) gave 9 as a colorless oil (73%), R_f = 0.28; IR (film) 3.05, 3.12, 3.40, 6.60 μm; ^{1}H NMR δ 1.34-2.30 (m, 10H), 3.29 (m, 2H), 3.50 (s, 3H), 4.81 (dd, 1H, J=6, 3 Hz), 6.40 (br s, 1H); $[\alpha]^{23}_D$ +36.4° (c 1.1, $CHCl_3$); chemical ionization mass spectrum m/z (relative intensity) M+1 (100).

N-Methyl-2-oxopiperidine-3(R)-spiro-2'-(1-methoxycyclohex-1-ene) (10). Sodium hydride (1.2 mmol) was added to a solution of 9 (1 mmol) in 2 ml of dry THF, and the resulting mixture was stirred for 1.5 h, after which methyl iodide (2 equiv) was added. After 2 h, the reaction mixture was quenched with water and extracted with methylene chloride (2 x 10 ml). The combined organic layers were dried over $MgSO_4$ and concentrated to give 10 as a light yellow oil (quantitative). An analytical sample was prepared by Kugelrohr distillation; bp 79-80°C (0.5 mm Hg); IR (film) 3.40, 6.11, 8.33 μm; ^{1}H NMR δ 1.36-2.30 (m, 10H), 2.96 (s, 3H), 3.20 (m, 1H), 3.38 (m, 1H), 3.48 (s, 3H), 4.77 (dd, 1H, J=5, 3 Hz); $[\alpha]^{27}_D$ +28.3° (c 0.38, $CHCl_3$); chemical ionization mass

spectrum m/z (relative intensity) M+1 (100); a satisfactory analysis could not be obtained. Hydrolysis using HCl in methanol provided the ketone derivative; mp 82°C; anal. calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78. Found: C, 67.73; H, 8.72.

N-Methyl-2-oxopiperidine-3(R)spiro-2'-[1(R)-methoxycyclohexane] (11). Prepared from 10 by procedures described elsewhere[11,13] (quantitative). An analytical sample was prepared by Kugelrohr distillation: colorless oil; bp 79-80°C (0.5 mm Hg); IR (film) 3.40, 6.14, 9.15 μm; ^{1}H NMR δ 1.02-1.96 (m, 12H), 2.92 (s, 3H), 3.14 (m, 1H), 3.26 (s, 3H), 3.32 (m, 1H), 3.78 (dd, 1H, J=12, 4 Hz); $[\alpha]^{31}_D$ -65.7° (c 1.02, $CHCl_3$); chemical ionization mass spectrum m/z (relative intensity) M+1 (100), 180 (65); anal. calcd for $C_{12}H_{21}NO_2$: C, 68.22; H, 10.01. Found: C, 68.34; H, 9.91.

N-Methyl-2-oxopiperidine-3(R)-spiro-2'-[1(R)-hydroxycyclohexane]. To a solution of 11 (1 mmol) in 4 ml of dry methylene chloride was added ethanethiol (5 mmol) and $AlCl_3$ (3 mmol).[14] The reaction mixture was stirred for 3 h at room temperature, then quenched slowly with water (2 ml), followed by dilution with methylene chloride (5 ml). The organic layer was separated, dried over $MgSO_4$, and concentrated. Flash chromatography on silica gel (EtOAc-MeOH, 95:5) gave a colorless solid (91%); mp 109-110°C; IR (KBr) 2.94, 3.42, 6.20 μm; ^{1}H NMR δ 1.16-2.04 (m, 13H), 2.94 (s, 3H), 3.18 (m, 1H), 3.33 (m, 1H), 4.30 (m, 1H); $[\alpha]^{27}_D$ -87.7° (c 0.32, $CHCl_3$); chemical ionization mass spectrum m/z (relative intensity) M+1 (100), 180 (60); anal. calcd for $C_{11}H_{19}NO_2$: C, 66.98; H, 9.70. Found: C, 66.89; H, 9.62.

(+)-Sibirine (12). To a suspension of $LiAlH_4$ (1.6 mmol) in 2 ml of dry THF was added a solution of N-methyl-2-oxopiperidine-3(R)-spiro-2'(R)-hydroxycyclohexane (obtained from the preceding experiment) in 2 ml of THF. The resulting mixture was stirred for 12 h, then quenched with 20% KOH. The precipitate was removed by filtration and was washed with additional THF. The organic layers were combined and concentrated to give 12 as a colorless oil (95%); ^{1}H NMR δ 0.80-2.24 (m, 15H), 2.24 (s, 3H), 2.63 (d, 1H, J=11 Hz), 2.79 (br d, 1H), 3.58 (dd, 1H, J=10, 4 Hz); ^{13}C ($CHCl_3$) δ 79.27, 69.69, 56.47, 46.53; 37.29, 37.07, 29.60, 27.60, 24.39, 23.96, 20.36; $[\alpha]^{22}_D$ +25.0° (c 0.73, $CHCl_3$); chemical ionization mass spectrum m/z (relative intensity) 184 (100), 166 (32). The ^{1}H and ^{13}C NMR data correspond closely to those reported for the natural product.[1] The hydrochloride salt was prepared by dissolving 12 in ethanol followed by addition of a few drops of concentrated HCl. Solvent evaporation gave a colorless gum, which, when triturated with acetone, gave colorless cubes, mp 194-195°C (Lit.[1] 191-192°C).

1,2,3,8,11,11a(S)-6a(S)-(3-Chloropropyl)-hexahydro-5H-[2,1-c]benzoxazapin-5-one (14). Prepared from 13 by procedures described elsewhere.[6] Flash chromatography on silica gel (EtOAc-$CHCl_3$, 4:1) gave 14 as a colorless oil (91%). IR (film) 3.38, 3.47, 5.95, 6.20 μm; ^{1}H NMR δ 1.44-2.16 (m, 8H), 2.80 (d, 2H), 3.54 (q, 4H), 3.88 (dd, 1H, J=12, 11 Hz), 4.12 (dd, 1H, J=11, 2 Hz), 4.30 (q, 1H), 5.56 (t, 1H), 5.84 (s, 2H); $[\alpha]^{24}_D$ +101.4° (c 0.57, $CHCl_3$); chemical ionization mass spectrum m/z (relative intensity) M+1 (67), 246 (100). A satisfactory elemental analysis could not be obtained.

(2S)-2-[(N-Carbomethoxy-(S)-prolinol)carbalkoxy-2-(3-chloropropyl)cyclohex-3-ene-1-one (15). Prepared from 14 as described for 6. Flash chromatography on silica gel (EtOAc-Hexane, 70:30) gave 15 as a colorless oil (84%); IR (film) 3.38, 5.75, 5.82, 5.90, 6.94, 7.25 μm; ^{1}H NMR δ 1.48-

2.04 (m, 7H), 2.18 (dt, 1H), 2.28-2.82 (m, 4H), 3.38 (m, 2H), 3.52 (dt, 2H), 3.71 (s, 3H), 3.96-4.24 (m, 3H), 5.66 (d, 1H), 6.16 (br d, 1H); $[\alpha]^{27}_D$ +45.0° (c 0.96, $CHCl_3$); chemical ionization mass spectrum m/z (relative intensity) M+1 (29), 322 (37), 171 (23), 160 (100); anal. calcd for $C_{17}H_{24}ClNO_5$: C, 57.07; H, 6.75. Found: C, 56.93; H, 6.70.

(2S)-2-[(N-Carbomethoxy-(S)-prolinol)carbalkoxy]-2-(3-chloropropyl)cyclohexanone. Prepared from 15 as described for 7 (quantitative). An analytical sample was prepared by flash chromatography on silica gel (EtOAc-Hexane, 70:30) to give a colorless oil; IR (film) 3.38, 5.85 (broad), 6.94, 7.24 μm; ^1H NMR δ 1.60-2.10 (m, 13H), 2.46 (m, 3H), 3.38 (m, 2H), 3.53 (br t, 2H), 3.71 (br s, 3H), 4.00-4.36 (m, 3H); $[\alpha]^{22}_D$ +18.2° (c 1.47, $CHCl_3$); chemical ionization mass spectrum m/z (relative intensity) M+1 (45), 324 (100), 201 (95); anal. calcd for $C_{17}H_{26}ClNO_5$: C, 56.75; H, 7.28. Found: C, 56.69; H, 7.20.

(6S)-6-[(N-Carbomethoxy-(S)-prolinol)carboalkoxy]-6-(3-chloropropyl)-1-methoxycyclohexene. Prepared as described for 8a. Flash chromatography on silica gel (EtOAc-Hexane, 4:1) gave a colorless oil (91%): IR (film) 3.38, 5.86 (broad), 6.92, 7.24 μm; ^1H NMR δ 1.50-2.16 (m, 17H), 3.36 (m, 2H), 3.48 (s, 3H), 3.52 (t, 2H), 3.96-4.30 (m, 3H), 4.80 (br s, 1H); $[\alpha]^{22}_D$ -65.2° (c 0.75, $CHCl_3$); chemical ionization mass spectrum m/z (relative intensity) M+1 (40), 338 (40), 187 (100), 160 (90).

(6S)-6-[(N-Carbomethoxy-(S)-prolinol)carbalkoxy]-6-(3-azidopropyl)-1-methoxycyclohexene. Prepared by procedures described elsewhere.[8] Flash chromatography on silica gel (EtOAc-Hexane; 70:30) gave a colorless oil (91%); IR (film) 3.38, 4.77, 5.78, 5.88, 6.90, 7.24 μm; ^1H NMR δ 1.36-2.10 (m, 14H), 3.26 (t, 2H), 3.36 (m, 2H), 3.48 (s, 3H), 3.71 (s, 3H), 3.92-4.30 (m, 3H), 4.81 (br s, 1H); $[\alpha]^{23}_D$ -59.1° (c 0.93, $CHCl_3$); chemical ionization mass spectrum m/z (relative intensity) 353 (4), 194 (22), 142 (100); anal. calcd for $C_{18}H_{28}N_4O_5$: C, 56.83; H, 7.41. Found: C, 56.81; H, 7.48.

2-Oxopiperidine-3(S)-spiro-2'-(1-methoxycyclohex-1-ene) (16). Prepared as described for 9: colorless oil; $[\alpha]^{23}_D$ -35.3° (c 1.38, $CHCl_3$); a satisfactory analysis could not be obtained.

2-Oxopiperidine-3(S)-spiro-2'-cyclohexan-1-one (22). A solution of 16 (1 mmol) in 2 ml of 95% methanol and several drops of concentrated HCl was stirred for 1 h at room temperature. The solution was concentrated, saturated $NaHCO_3$ was added to the residue, and the resulting mixture was extracted with methylene chloride (3 x 5 ml). The combined organic layers were dried over $MgSO_4$ and concentrated to give 22 (97%). Recrystallization from ethyl acetate gave colorless crystals; mp 184-185°C (dec); IR (KBr) 3.12, 3.38, 5.93, 6.05 μm; ^1H NMR δ 1.52-2.10 (m, 8H), 2.28-2.76 (m, 4H), 3.32 (m, 2H), 5.92 (brs, 1H); $[\alpha]^{23}_D$ -50.8° (c 1.16, $CHCl_3$); chemical ionization mass spectrum m/z (relative intensity) M+1 (100); anal. calcd for $C_{10}H_{15}NO_2$: C, 66.28; H, 8.34. Found: C, 66.35; H, 8.31.

2-Oxopiperidine-3(S)-spiro-2'-[1(S)-hydroxycyclohexane] (24). A mixture of 22 (0.22 mmol) and anhydrous $YbCl_3$ (0.24 mmol) in 1 ml of dry methanol was stirred at room temperature for 30 min. To the resulting suspension was added $NaBH_4$ (0.33 mmol) in several portions over 5 min. After 1 h, saturated NH_4Cl was added and the mixture was extracted with methylene chloride (3 x 5 ml). The combined organic layers were dried ($MgSO_4$) and concentrated to give a 92:8 mixture of 24 and

23. Flash chromatography on silica gel (EtOAc-MeOH, 9:1) gave 24 as a colorless solid (69%, higher R_f). Recrystallization from ethyl acetate gave colorless crystals; mp 108-109°C; IR (KBr) 3.05, 3.12, 3.40, 6.13 μm; ^{1}H NMR δ 1.20-2.30 (m, 12H), 3.30 (m, 2H), 3.76 (br t, 1H), 5.72 5.72 (br s, 1H), 6.28 (br s, 1H); $[\alpha]^{22}_D$ +37.2° (c 0.20, $CHCl_3$); chemical ionization mass spectrum m/z (relative intensity) M+1 (100), 166 (87); anal. calcd for $C_{10}H_{17}NO_2$: C, 65.55; H, 9.34. Found: C, 65.49; H, 9.46.

(+)-Nitramine (3). Prepared from 24 as described for 12: colorless oil (91%); ^{1}H NMR δ 0.90-1.98 (m, 11H), 2.12 (m, 1H), 2.42 (d, 1H, J=12 Hz), 2.61 (dt, 1H), 3.00 (m, 1H), 3.48 (d, 1H, J=12 Hz), 3.54 (dd, 1H); ^{13}C δ (C_6D_6) 77.86, 52.68, 47.27, 38.43, 36.94, 36.35, 32.88, 24.50, 24.01, 21.50; $[\alpha]^{25}_D$ +23.0° (c 1.58, CH_2Cl_2); chemical ionization mass spectrum m/z (relative intensity) M+1 (100). Nitramine hydrochloride was prepared as described for the hydrochloride salt of 12; recrystallization from acetone gave colorless cubes, mp (sealed capillary) 230°C (dec).

2-Oxopiperidine-3(S)-spiro-2'-[1(R)-hydroxycyclohexane] (23). To a solution of 22 (1 mmol) in 5 ml of dry THF cooled to -78°C was added DIBAL (1.0 M in hexane, 2.1 mmol) slowly via syringe. The solution was stirred for 2 h at -78°C, then quenched with saturated $NaHSO_4$ (5 ml). The mixture was diluted with methylene chloride, separated, then extracted with additional methylene chloride (2 x 10 ml). The organic layers were combined, dried over $MgSO_4$, and concentrated to give a 13:1 mixture of 23 and 24 (94%). Flash chromatography on silica gel (EtOAc-MeOH, 8:1) gave 23 as a colorless solid (lower R_f); mp 148-149°C; IR (KBr) 3.05, 3.12, 3.42, 3.50, 6.16 μm; ^{1}H NMR δ 1.16-2.22 (m, 13H), 3.29 (m, 2H), 4.29 (dd, 1H, J=12, 5 Hz), 5.97 (br s, 1H); $[\alpha]^{23}_D$ +73.9° (c 0.50, $CHCl_3$); chemical ionization mass spectrum m/z (relative intensity) M+1 (36), 166 (100); anal. calcd for $C_{10}H_{17}NO_2$: C, 65.55; H, 9.34. Found: C, 65.47; H; 9.39.

(-)-Isonitramine (21). Prepared from 23 as described for 12: colorless solid (93%). Sublimation gave colorless needles, mp 103-104°C (Lit.,[1a] 101-103°C); ^{1}H NMR δ 0.84-2.20 (m, 7H), 2.15 (br d, 1H), 2.50 (d, 1H, J=11 Hz), 2.59 (dt, 1H), 2.91 (d, 1H), 3.04 (m, 1H), 3.66 (dd, 1H, J=11, 4 Hz); ^{13}C δ (C_6D_6) 79.64, 60.59, 47.56, 36.53, 30.40, 29.44, 24.49, 23.46, 20.87; $[\alpha]^{24}_D$ -3.5° (c 1.61, $CHCl_3$); chemical ionization mass spectrum m/z (relative intensity) M+1 (100), 152 (83).[21]

N-Benzyl-2-oxopiperidine-3(S)-spiro-2'-[1-methoxycyclohex-1-ene] (17). Prepared from 16 and benzyl bromide as described for 10. Flash chromatography on silica gel (EtOAc-Hexane, 3:2) gave 17 as a colorless oil (67%); IR (film) 3.42, 6.14, 6.94 μm; ^{1}H NMR δ 1.40-2.30 (m, 10H), 3.00-3.32 (m, 2H), 3.50 (s, 3H), 4.45 (d, 1H, J=14 Hz), 4.78 (d, 1H, J=14 Hz), 4.80 (overlapping m, 1H), 7.28 (m, 5H); $[\alpha]^{22}_D$ -50.8° (c 0.86, CH_2Cl_2); chemical ionization mass spectrum m/z (relative intensity) M+1 (100); anal. calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12. Found: C, 75.79; H, 8.00.

N-Benzyl-2-oxopiperidine-3(S)-spiro-2'-[1(R)-methoxycyclohexane] (18). Prepared from 17 as described for 11 (quantitative); Kugelrohr distillation gave a colorless oil; bp 82°C (0.5 mm Hg); IR (film) 3.40, 6.20, 6.93 μm; ^{1}H NMR δ 1.04-2.00 (m, 16H), 3.00-3.34 (m, 2H), 3.32 (s, 3H), 3.84 (dd, 1H, J=12, 5 Hz), 4.40 (d, 1H, J=15 Hz), 4.84 (d, 1H, J=15 Hz), 7.28 (m, 5H); $[\alpha]^{22}_D$

-18.8° (c 1.20, $CHCl_3$); chemical ionization mass spectrum m/z (relative intensity) M+1 (100), 256 (54).

N-Benzyl-2-oxopiperidine-3(S)-spiro-2'-[1(R)-hydroxycyclohexane] (19). Prepared from 18 as described for 11b. Flash chromatography on silica gel (EtOAc-Hexane, 10:1) gave 19 as a color-solid (84%); mp 91-92°C; IR (KBr) 2.95, 3.42, 6.25 μm; ^1H NMR δ 1.10-1.90 (m, 13H), 3.00-3.28 (m, 2H), 4.32 (br s, 1H), 4.44 (d, 1H, J=16 Hz), 4.70 (d, 1H, J=16 Hz), 7.28 (m, 5H); $[\alpha]^{23}_D$ +53.3° (c 0.69, $CHCl_3$); chemical ionization mass spectrum m/z (relative intensity) M+1 (100), 256 (53); anal. calcd for $C_{27}H_{23}NO_2$: C, 74.70; H, 8.47. Found: C, 74.80; H, 8.38.

Second Synthesis of (-)-Isonitramine (21). To a suspension of $LiAlH_4$ (1.5 mmol) in 3 ml of THF was added 19 (1 mmol) in 2 ml of THF. The resulting mixture was stirred at room temperature for 24 h, followed by workup as previously described to give 20 as a colorless oil. Hydrogenation of 20 (1 atm) over 5% Pd/C in methanol for 24 h, filtration through Celite, followed by evaporation of solvent gave 21 as a colorless solid (76%).

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REFERENCES

1. a) A. A. Ibragimov, Z. Osmanov, B. Tashkhodzhaev, N. D. Abdullaev, M. R. Yagudaev, and S. Yu. Yunusov, Chem. Nat. Prod., 1981, 17, 458; b) B. Tashkhodzhaev, Chem. Nat. Prod., 1982, 18, 70; c) Z. Osmanov, A. A. Ibragimov, and S. Yu. Yunusov, Chem. Nat. Prod., 1982, 18, 206.
2. A. P. Kozikowski and P.-W. Yuen, J. Chem. Soc., Chem. Commun., 1985, 847.
3. It should be noted that the numbering for nitramine and isonitramine in the text of reference 2 has been inverted. Structure 1 is, in fact, isonitramine and structure 2 is nitramine. As noted in the title of the paper, a total synthesis of racemic isonitramine was accomplished.
4. B. B. Snider and C. P. Cartaya-Marin, J. Org. Chem., 1984, 49, 1688.
5. For additional enantioselective syntheses of the nitramine alkaloids, see D. S. Grierson, J.-C. Quirion, H.-P. Husson, "Abstracts of the 10th International Congress of Heterocyclic Chemistry" University of Waterloo, Ontario, Canada, August, 1985, P7-179; H.-P. Husson, J. Nat. Prod., 1985, 48, 894.
6. A. G. Schultz, P. Sundararaman, M. Macielag, F. P. Lavieri, and M. Welch, Tetrahedron Lett., 1985, 26, 4575.
7. A. G. Schultz and S. Puig, J. Org. Chem., 1985, 50, 915.
8. F. Rolla, J. Org. Chem., 1982, 47, 4327.

9. The azide could not be reduced in the absence of the phase transfer catalyst, hexadecyltri-n-butylphosphonium bromide (PTC).

10. a) H. Suzuki and K. Takaoka, Chem. Lett., 1984, 1733; b) E. J. Corey, K. C. Nicolaou, R. D. Balanson, and Y. Machida, Synthesis, 1975, 590.

11. A. G. Schultz and P. J. McCloskey, J. Org. Chem., 1985, 50, 5905.

12. R. H. Crabtree and M. W. Davis, Organometallics, 1983, 2, 681.

13. In early experiments with carboxamide group directed enol ether hydrogenations, we sometimes found that trace to significant quantities of ketones resulting from enol ether hydrolysis were obtained. Enol ether hydrolysis could be eliminated or, in certain cases, suppressed by passing the reaction solvent, methylene chloride, through basic alumina prior to hydrogenation.

14. M. Node, K. Nishide, M. Sai, K. Ichikawa, K. Fuji, and E. Fujita, Chem. Lett., 1979, 97.

15. The compound shown as 12 also has been prepared by N-methylation of natural isonitramine (2); see reference 1c. The rotation of the literature material was reported to be $[\alpha]^{24}_D$ +25.0°, identical to synthetic (+)-sibirine (12).

16. For an explanation of configurational assignments for products resulting from Birch reductive alkylation of 4 and 13, see reference 6.

17. A. G. Schultz and P. Sundararaman, Tetrahedron Lett., 1984, 25, 4591.

18. For other stereoselective β-dicarbonyl group reductions, see T. Nakata and T. Oishi, Tetrahedron Lett., 1980, 21, 1641; T. Nakata, T. Kuwabara, Y. Tani, and T. Oishi, Tetrahedron Lett., 1982, 23, 1015; R. DiPardo and M. G. Bock, Tetrahedron Lett., 1983, 24, 4805; Y. Ito and M. Yamaguchi, Tetrahedron Lett., 1983, 24, 5385; D. A. Evans, M. D. Ennis, and T. Le, J. Am. Chem. Soc., 1984, 106, 1154.

19. The more direct conversion of 22 to 3 with lithium aluminum hydride resulted in only modest stereoselectivity at C(7).

20. The procedure described by Snider and Cartaya-Marin was used; see reference 4.

21. Ibragimov and co-workers report that a rotation for natural isonitramine is $[\alpha]^{25}_D$ -30° (c 1.36, $CHCl_3$).[1a] As noted in reference 15, natural isonitramine was converted to N-methylisonitramine. A rotation for this material, $[\alpha]^{24}_D$ +25.0°, is identical to that determined by us for synthetic sibirine (12). We do not understand why there is a discrepancy between the literature rotation and our rotation for isonitramine, but believe that the rotation for natural isonitramine should be closer to $[\alpha]^{24}_D$ +3.5° than that reported in reference 1a.

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