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Enantioselective Total Syntheses of (–)-Isonitramine, (–)-Sibirine, and (+)-Nitramine by Ring-Closing Metathesis

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Concise enantioselective total syntheses of naturally occurring 2-azaspiro[5,5]undecan-7-ol (*Nitraria*) alkaloids viz. (–)-isonitramine, (–)-sibirine, and (+)-nitramine are accomplished in 42, 38, and 25 % overall yield, respectively, in six steps starting from enantiomerically pure (*S*)-methyl 3-allyl-2-oxo-1,2,3,6-tetrahydropyridine-3-carboxylate (>99 % *ee*). The key feature of the syntheses involves diastereoselective Hosomi–Sakurai allylation followed by ring-closing metathesis.

Introduction

The spiropiperidine structural subunit found in a variety of naturally occurring and synthetically derived products displays interesting biological properties. For instance, the 1-azaspiro[5, 5]undecane-8-ol alkaloid histrionicotoxin (**1**) isolated from the skin of the neotropical poisonous frog *Dendrobates histrionicus* is a very potent nicotinic receptor antagonist,[1a] whereas pinnaic acid (**2**), a novel polyketide containing a 6-azaspiro[4,5]decane subunit, isolated from Okinawan bivalve *Pinna muricata* has shown phospholipase A_2 (PLA_2) inhibitory activity.[1b] Similarly, synthetic spiro[piperidine-2,2′-adamantane] (**3**) has proved to be active against influenza viruses.[1c] The three structurally related spiropiperidine alkaloids, viz. (–)-isonitramine (**4**), (–)-sibirine (**5**), and (+)-nitramine (**6**), isolated[2] from *Nitraria sibrica* and *Nitraria Schoberi* have received considerable synthetic and pharmacological interest due to the potent biological activity in the class of γ-amino alcohols and due to their resemblance with the basic molecular framework of the neurotoxin histrionicotoxin (**1**, Figure 1). Generally, most of these alkaloids are isolated as racemates[3] despite the presence of many stereocenters. Although, several racemic[4] syntheses of one or more of these alkaloids have appeared since their isolation, only a few enantioselective[5] syntheses are known. Moreover, only a few general strategies enabling the production of all of these three alkaloids in the natural configurations have also appeared.[5a,5g]

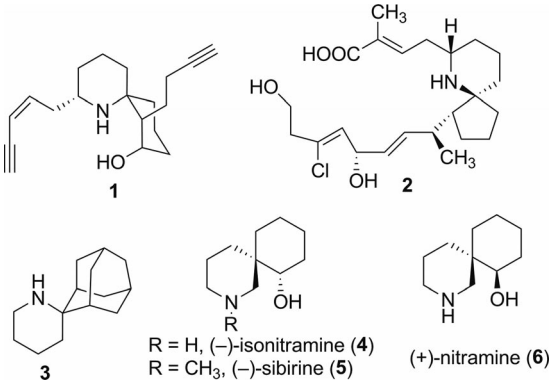

Figure 1. Representatives of azaspiroalkaloids.

The stereocontrolled construction of the secondary hydroxy and the adjacent all-carbon quaternary stereogenic center is difficult and poses a significant challenge for the syntheses of these deceptively simple-looking molecules. Existing synthetic routes[5] have generally relied on the formation of either a C–N or C–C bond of the spiro carbon atom, that is, C^1–C^6, C^5–C^6, or C^6–C^7. A plausible simpler strategy with the formation of the C^{10}–C^9 bond from a suitable precursor has remained unexplored. In this context,

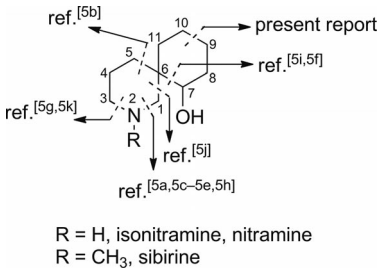

Figure 2. Existing key disconnections of the spiro skeleton.

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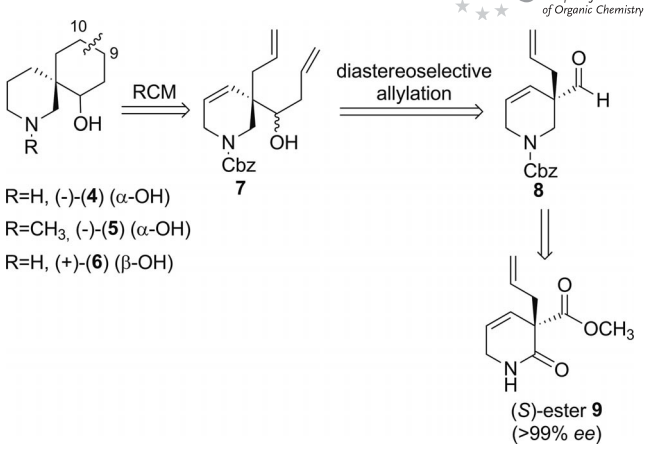
we have evaluated a ring-closing metathesis (RCM) strategy from **9** (>99%*ee*), recently synthesized for the construction of (+)-vincadifformine from our group,[6] and report herein a short enantioselective syntheses of all the three (i.e., **4**, **5**, and **6**) naturally occurring *Nitraria* alkaloids (Figure 2) in optically pure form.

Results and Discussion

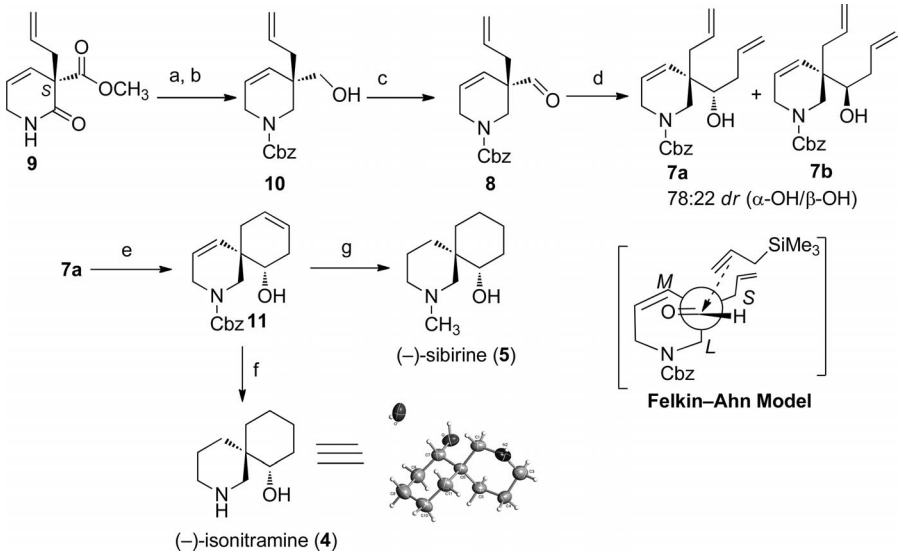
In continuation of our interest in the syntheses of *Aspidosperma* alkaloids,[6] we became interested in developing a new and concise route for the syntheses of *Nitraria* alkaloids from optically pure precursor **9** (>99%*ee*) and viewed their syntheses through the strategy depicted retrosynthetically in Scheme 1. The syntheses of (–)-isonitramine (**4**) and (–)-sibirine (**5**) commenced with the transformation of enantiopure **9** (>99%*ee*) into **10** by lithium aluminum hydride reduction followed by *N*-Cbz protection {81% yield, $[\alpha]_D^{26}$ = +1.16 (*c* = 1.21, $CHCl_3$)}. The oxidation of **10** by using 2-iodoxybenzoic acid (IBX) in ethyl acetate under reflux afforded **8** in 96% yield {$[\alpha]_D^{26}$ = +166.83 (*c* = 1.01, $CHCl_3$)}. Allylation of **8** with allylmagnesium bromide though gave desired **7** albeit in low yield (<15%). Therefore, we resorted to Hosomi–Sakurai's protocol involving the use of allyltrimethylsilane in the presence of $BF_3{\cdot}Et_2O$, which gave desired **7** in 92% yield [78:22 *dr* (α/β)]. The formation of the major diastereomer can possibly be explained through a Felkin–Anh model (Scheme 2). Fortunately, both diastereomers of **7** were separable by flash column chromatography.



Scheme 1. Retrosynthetic analysis of (–)-isonitramine, (–)-sibirine, and (+)-nitramine.

Our initial attempt at RCM[7] of **7a** by using Grubbs first generation catalyst failed to give expected product **11**. Therefore, we carried out this reaction with Grubbs second generation catalyst, which pleasingly afforded **11** in 85% yield. Hydrogenation of **11** over Pd/C (5%) in methanol gave **4** in 90% yield {$[\alpha]_D^{25}$ = –4.9 (*c* = 1.1, $CHCl_3$); ref.[5f] $[\alpha]_D^{25}$ = –4.5 (*c* = 0.24, $CHCl_3$)}. Similarly, reduction of **11** in the presence of aqueous formaldehyde[8] gave (–)-sibirine (**5**) in 82% yield {$[\alpha]_D^{25}$ = –23.1 (*c* = 0.76, $CHCl_3$); ref.[5g] $[\alpha]_D^{25}$ = –25.4 (*c* = 0.4, $CHCl_3$)}. The spectroscopic data of **4** and **5** were in good agreement with the literature data.[5e,5j] Finally, the absolute structure of **4** was also confirmed by X-ray diffraction analyses.[9]

Encouraged by these results, we envisaged synthesizing (+)-nitramine (**6**) also from corresponding **13a**, speculated to be formed by chelation-controlled allylation[10] of **12**. It



Scheme 2. Syntheses of (–)-isonitramine and (–)-sibirine. Reagents and conditions: (a) LAH, THF, reflux, 8 h; (b) CbzCl, $NaHCO_3$, dioxane/water, r.t., 5 h, 81%; (c) IBX, EtOAc, reflux, 8 h, 96%; (d) allyltrimethylsilane, CH_2Cl_2, $BF_3{\cdot}OEt_2$, –78 °C, 6 h, 92%; (e) Grubbs 2nd generation catalyst, CH_2Cl_2, reflux, 5 h, 85%; (f) Pd/C, MeOH, H_2, 5 h, 90%; (g) Pd/C, MeOH, aq. HCHO, H_2, MeOH, 30 h, 82%.

was visualized that reaction of **12** with allyltrimethylsilane in the presence of a Lewis acid (e.g., $SnCl_4$ and/or $TiCl_4$) may involve a hexacoordinate metal chelate complex directing the approach of the nucleophilic allyltrimethylsilane, possibly from the least-hindered face of the conformationally locked (Cram-chelate model) carbonyl group (Figure 3).

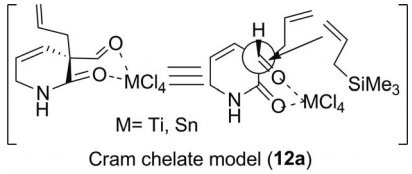
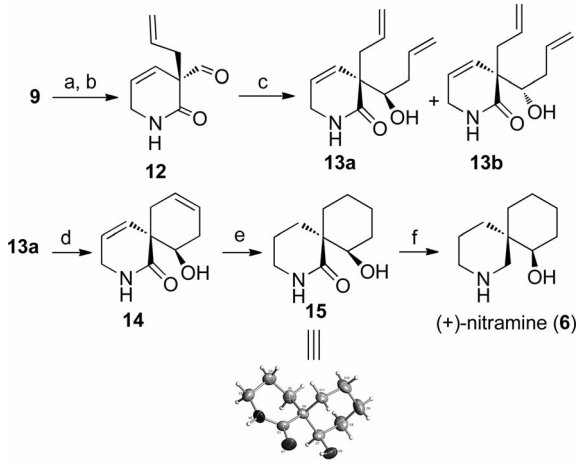


Figure 3. Speculative generation of **13a** through a Cram–chelate-type model.

In order to evaluate our proposed hypothesis, **12** obtained in 66% yield from **9** by simple functional group transformations was treated with allyltrimethylsilane in CH_2Cl_2 in the presence of $SnCl_4$ at –78 °C to give corresponding allylated product **13** in 87% yield [96:4 *dr* (β/α); HPLC, Chiralcel OD-H (250 × 4.6 mm) column, isopropanol/*n*-hexane = 15:85, 0.5 mL min^{-1} (25 Kgf), λ = 225 nm, 25 °C)].

To improve the yield as well as the diastereomeric ratio, the same reaction was also carried out by using $TiCl_4$; however, there was no significant improvement in the diastereomeric ratio [83% yield, 97.4:2.6 *dr* (β/α)].[11] RCM of **13a** under reaction conditions identical to those described above for **7a** afforded **14** (81%), which upon usual hydrogenation furnished **15** in 94% yield. X-ray diffraction analysis[9] of recrystallized **15** confirmed its absolute configuration. Lithium aluminum hydride reduction of **15** produced (+)-nitramine (**6**) in 60% yield {$[\alpha]_D^{25}$ = +21.4 (*c* = 0.3, CH_2Cl_2); ref.[5a] $[\alpha]_D^{25}$ = +23.0 (*c* = 1.58, CH_2Cl_2)} (Scheme 3). All the spectroscopic data were in good agreement with the literature report.[5h]



Scheme 3. Synthesis of (+)-nitramine and ORTEP diagram of **15**. Reagents and conditions: (a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, r.t., 48 h, 78%; (b) IBX, EtOAc, reflux, 8 h, 85%; (c) allyltrimethylsilane, $SnCl_4$/$TiCl_4$, CH_2Cl_2, –78 °C, 87%; (d) Grubbs 2nd generation catalyst, CH_2Cl_2, r.t., 3 h, 81%; (e) Pd/C, H_2, MeOH, r.t., overnight, 94%; (f) LAH, THF, r.t., 80 h, 60%.

Conclusions

In summary, we have developed an efficient enantioselective synthetic route to (–)-isonitramine, (–)-sibirine, and (+)-nitramine in 42, 38, and 25% overall yield, respectively. The key feature of the syntheses involved diastereoselective Hosomi–Sakurai allylation followed by ring-closing metathesis.

Experimental Section

General Remarks: All air- and moisture-sensitive reactions were performed under an atmosphere of argon with oven-dried (125 °C) glassware. Anhydrous tetrahydrofuran (THF) was distilled from sodium/benzophenone. Dichloromethane (DCM) was distilled from calcium hydride and stored over 4 Å molecular sieves. Solvents used for chromatography were distilled at their respective boiling points by using known procedures. All reagents and solvents were purchased from commercial sources. Reactions were monitored by thin-layer chromatography (TLC, 0.25 mm silica gel plates, $60F_{254}$) and visualized by UV light, ethanolic solution of phosphomolybdic acid, and iodine. Column chromatography was performed on silica gel 60–120/100–200/230–400 mesh obtained from commercial sources. Typical syringe and cannula techniques were used to transfer air- and moisture-sensitive reagents. Melting points were measured with a Thermonik melting point apparatus. ^1H and ^{13}C NMR spectra were recorded with Bruker AC-200, AV-400, and DRX 500 instruments in deuteriated solvents. ^{13}C NMR chemical shifts are reported in ppm relative to the central line of $CDCl_3$ (δ = 77.0 ppm). Electrospray ionization (ESI) mass spectrometry (MS) experiments were recorded with a Finnigan Mat-1020 spectrometer and were performed to obtain molecular mass of the compound. High-resolution mass spectrometric data were obtained by using an MSI Concept through direct insertion probe. Optical rotations were measured with a JASC P-1030 Polarimeter.

(*S*)-Benzyl 5-Allyl-5-(hydroxymethyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (10): To an ice-cooled stirred slurry of lithium aluminum hydride (0.47 g, 12.41 mmol) in anhydrous THF (12 mL) was added a solution of **9** (0.2 g, 1.03 mmol) in anhydrous THF (4 mL). The reaction mixture was warmed to room temperature and heated at reflux for 8 h. The reaction was cooled to room temperature, quenched carefully with moist Na_2SO_4, and filtered, and the residue was washed with DCM and concentrated. To a solution of the resulting crude amino alcohol dissolved in dioxane/water (1:1, 6 mL) was added sodium hydrogen carbonate (0.17 g, 2.06 mmol) followed by the slow addition of benzyl chloroformate (0.16 mL, 1.13 mmol) in dioxane (1 mL) under vigorous stirring at 0 °C. The reaction mixture was stirred for another 5 h at ambient temperature, and dioxane was evaporated. Water (20 mL) was poured into the residue, which was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried with Na_2SO_4, filtered, concentrated under reduced pressure, and purified by column chromatography (SiO_2; EtOAc/petroleum ether, 2:8) to afford **10** as a colorless oil (0.24 g, 81%). R_f = 0.28 (EtOAc/petroleum ether, 3:7). $[\alpha]_D^{26}$ = +1.16 (*c* = 1.21, $CHCl_3$). IR (film, $CHCl_3$): $\tilde{\nu}$ = 3434, 2925, 1683, 1434, 1237 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.30 (m, 5 H), 5.81–5.59 (m, 3 H), 5.15–5.06 (m, 4 H), 4.20–4.09 (m, 1 H), 3.93–3.68 (m, 2 H), 3.33 (app. s, 2 H), 3.12, 2.87 (2 d, *J* = 13.0 Hz, 1

H), 2.26–2.11 (m, 2 H), 1.87 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) (rotamers): δ = 156.51 (155.57), 136.6, 133.7, 130.6 (129.8), 128.6, 128.2, 128.0, 125.1 (125.7), 118.3, 67.5, 65.7 (65.8), 46.1 (46.4), 43.9 (43.7), 41.3, 36.9 ppm. HRMS (EI): calcd. for $C_{17}H_{21}NO_3$: 287.15214; found 287.14669.

(*S*)-Benzyl 5-Allyl-5-formyl-5,6-dihydropyridine-1(2*H*)-carboxylate (8): To a solution of **10** (0.1 g, 0.34 mmol) dissolved in ethyl acetate (7 mL) was added IBX (0.19 g, 0.68 mmol). The resulting suspension was heated at reflux for 8 h, cooled to room temperature, and filtered through a pad of Celite. The filtrate cake was washed with ethyl acetate (2 × 4 mL), and the combined filtrates were concentrated to give aldehyde **8** as a colorless sticky liquid (0.095 g, 96%). R_f = 0.38 (EtOAc/petroleum ether, 2:8). $[\alpha]_D^{26}$ = +166.83 (c = 1.01, $CHCl_3$). IR (film, $CHCl_3$): $\tilde{\nu}$ = 3017, 2849, 1722, 1702, 1431, 1238 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, rotamers): δ = 9.53 (9.50) (2 s, 1 H), 7.35–7.29 (m, 5 H), 5.99, 5.91 (2 app. d, J = 9.5 Hz, 1 H), 5.74–5.65 (m, 2 H), 5.15–5.09 (m, 4 H), 4.18–3.99 (m, 2 H), 3.85–3.78 (m, 1 H), 3.28,3.17 (2d, J = 13.3 Hz, 1 H), 2.37–2.33 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, rotamers): δ = 200.8, 155.7 (155.4), 141.8, 136.4, 133.8 (133.3), 131.7 (131.9), 128.6 (128.2), 128.1 (127.3), 125.5 (124.9), 119.6, 67.6, 51.5, 44.9, 43.2, 37.8 ppm. HRMS (EI): calcd. for $C_{17}H_{19}NO_3$ 285.13649; found 285.13631.

(*S*)-Benzyl 5-Allyl-5-[(*S*)-1-hydroxybut-3-enyl]-5,6-dihydropyridine-1(2*H*)-carboxylate (7): A solution of aldehyde **8** (0.287 g, 1 mmol) in anhydrous DCM (34 mL) at –78 °C under an argon atmosphere was treated with $BF_3{\cdot}OEt_2$ (0.31 mL, 2.51 mmol). After 15 min, allyltrimethylsilane (0.31 mL, 2 mmol) was added, and the resulting solution was stirred for 6 h at –78 °C. The reaction was poured into saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with DCM (3 × 30 mL). The extracts were combined, washed with brine (25 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue upon flash column chromatographic separation afforded major isomer **7a** (0.23 g) and minor isomer **7b** (0.067 g) as a colorless oil. Total yield: 0.3 g (92%). R_f = 0.5 (minor), 0.42 (major; acetone/DCM, 0.2:9.8; *p*-anisaldehyde staining solution). Data for major isomer **7a**: $[\alpha]_D^{26}$ = +20.49 (c = 1.18, $CHCl_3$). IR (film, $CHCl_3$): $\tilde{\nu}$ = 3454, 2912, 1698, 1435, 1240 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.28 (m, 5 H), 5.78–5.65 (m, 4 H), 5.13–5.03 (m, 6 H), 4.01–3.86 (m, 2 H), 3.75–3.65 (m, 1 H), 3.52 (d, J = 10.45 Hz, 1 H), 3.35–3.26 (m, 1 H), 2.34 (dd, J = 6.6, 13.75 Hz, 2 H), 2.11–2.03 (m, 2 H), 1.73 (br. s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, rotamers): δ = 155.6 (155.5), 136.6, 135.8 (135.7), 134.0, 130.2 (129.9), 128.4, 127.9, 124.8 (124.3), 118.0, 74.4 (73.8), 67.1, 45.3, 43.3, 42.4, 39.4, 36.6 ppm. HRMS (EI): calcd. for $C_{20}H_{25}NO_3$ 327.18344; found 327.18377. Data for minor isomer **7b**: $[\alpha]_D^{26}$ = +19.56 (c = 0.77, $CHCl_3$). IR (film, $CHCl_3$): $\tilde{\nu}$ = 3454, 2912, 1698, 1435, 1240 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.31 (m, 5 H), 5.89–5.59 (m, 4 H), 5.15–5.02 (m, 6 H), 4.19–4.10 (m, 1 H), 4.0 (3.85) (2 d, J = 13.48 Hz, 1 H), 3.77–3.70 (m, 1 H), 3.46–3.40 (m, 1 H), 3.10 (2.93) (2 d, J = 13.48 Hz, 1 H), 2.34–2.16 (m, 4 H), 1.82 (1.76) (app. br. s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, rotamers): δ = 156.4 (155.41), 136.5 (135.8), 134.15 (134.09), 131.7 (130.4), 128.58 (128.50), 128.17 (128.07), 127.8, 125.3 (124.8), 117.8 (117.7), 116.7, 73.8 (73.2), 67.3 (67.1), 45.8 (45.7), 43.7 (43.4), 43.15 (43.07), 36.9 (36.4), 35.7 (35.4) ppm. MS (ESI): m/z = 328.13 $[M + H]^+$, 350.11 $[M + Na]^+$, 366.11 $[M + K]^+$. $C_{20}H_{25}NO_3$ (327.42): calcd. C 73.37, H 7.70, N 4.28; found C 73.24, H 7.61, N 4.21.

(6*S*,11*S*)-Benzyl 11-Hydroxy-2-azaspiro[5,5]undeca-4,8-diene-2-carboxylate (11): To a degassed solution of **7a** (0.119 g, 0.36 mmol) in anhydrous DCM (10 mL) under an argon atmosphere at 20 °C was added Grubbs 2nd generation catalyst (21 mg, 7 mol-%). The solution was heated to reflux for 5 h, at which point TLC analysis indicated the reaction was complete. The reaction mixture was then concentrated. Purification by flash column chromatography (DCM/acetone, 10:0→9.8:0.2) afforded **11** (0.09 g, 85%). R_f = 0.3 (acetone/DCM, 0.3:9.7). $[\alpha]_D^{25}$ = +57.61 (c = 1.07, $CHCl_3$). IR (film, $CHCl_3$): $\tilde{\nu}$ = 3450, 3029, 2898, 1686, 1432, 1238 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.28 (m, 5 H), 5.87 (app. dt, J = 2.46, 10.24 Hz, 1 H), 5.76 (d, J = 8.53 Hz, 1 H), 5.59 (br. s, 2 H), 5.13 (br. s, 2 H), 3.95 (m, 2 H), 3.71 (br. s, 1 H), 3.56–3.25 (m, 2 H), 2.39–2.28 (m, 1 H), 2.08–1.93 (m, 4 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, rotamers): δ = 155.8, 136.5 130.0, 128.3, 127.9, 127.7, 124.6, 123.5 (122.9), 71.7 (71.0), 67.1, 48.6, 43.5, 38.8, 32.6, 31.4 ppm. HRMS (EI): calcd. for $C_{18}H_{21}NO_3$ 299.15214; found 299.15306.

(–)-Isonitramine (4): To a solution of **11** (0.108 g, 0.36 mmol) in anhydrous MeOH (10 mL) was added Pd/C (0.075 g). The suspension was allowed to stir for 5 h at room temperature under an atmosphere of hydrogen. The suspension was filtered through Celite and concentrated under reduced pressure. Purification by flash column chromatography ($CHCl_3$/MeOH/NH_3(aq.), 46:50:4; R_f = 0.3) afforded solid **4**, which upon crystallization with ethyl acetate/petroleum ether gave colorless crystals. M.p. 94.7–95.5 °C. $[\alpha]_D^{25}$ = –4.9 (c = 1.1, $CHCl_3$) {ref.[5f] $[\alpha]_D^{25}$ = –4.5 (c = 0.24, $CHCl_3$)}. IR (film, $CHCl_3$): $\tilde{\nu}$ = 3407, 2933, 1215 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.78–3.44 (br. s, 2 H), 3.62 (dd, J = 3.51, 11.29 Hz, 1 H), 3.01 (br. d, J = 10.8 Hz, 1 H), 2.91 (d, J = 11.29 Hz, 1 H), 2.57 (td, J = 3.26, 11.55 Hz, 1 H), 2.49 (d, J = 11.3 Hz, 1 H), 2.22 (d, J = 14 Hz, 1 H), 2.08–1.97 (m, 1 H), 1.72–1.66 (m, 2 H), 1.56–1.43 (m, 2 H), 1.39–1.32 (m, 2 H), 1.27–1.15 (m, 2 H), 1.08–1.03 (m, 1 H), 0.97–0.90 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 80.4, 60.6, 47.1, 36.6, 36.1, 29.6, 28.6, 24.2, 23.0, 20.2 ppm. HRMS (EI): calcd. for $C_{10}H_{19}NO$ 169.14666; found 169.14445.

(–)-Sibirine (5): Aqueous formaldehyde (37% solution, 0.1 mL, 1.1 mmol) was added to a stirred solution of carbamate **11** (0.033 g, 0.11 mmol) in distilled methanol (5 mL). The reaction mixture was stirred at room temperature under an atmosphere of hydrogen in the presence of a catalytic amount of Pd/C (0.02 g) for 30 h. After completion of the reaction, the reaction mixture was filtered through a pad of Celite, concentrated, and subjected to column to chromatography afford **5** as a colorless oil (0.016 g, 82%). $[\alpha]_D^{25}$ = –23.1 (c = 0.76, $CHCl_3$) {ref.[5g] $[\alpha]_D^{25}$ = –25.4 (c = 0.4, $CHCl_3$)}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84–1.0 (m, 2 H), 1.16–1.27 (m, 2 H), 1.33–1.40 (m, 2 H), 1.44–1.54 (m, 2 H), 1.68–1.74 (m, 2 H), 1.85–1.95 (m, 2 H), 2.07–2.17 (m, 2 H), 2.21 (s, 3 H), 2.60 (d, J = 11.3 Hz, 1 H), 2.79 (br. d, J = 7 Hz, 1 H), 3.58 (dd, J = 11.2, 3.2 Hz, 1 H), 3.21–3.86 (v. br., 1 H, OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.32, 23.0, 24.0, 27.5, 29.4, 37.0, 37.1, 46.4, 56.3, 69.8, 80.4 ppm. HRMS (EI): calcd. for $C_{11}H_{21}NO$183.16231; found 183.16196.

(*R*)-3-Allyl-3-(hydroxymethyl)-1,6-dihydropyridin-2(3*H*)-one (9a): To a suspension of $NaBH_4$ (390 mg, 10.03 mmol) and cerium chloride heptahydrate (529 mg, 1.42 mmol) in ethanol (6 mL) was added dropwise a solution of **9** (190 mg, 0.97 mmol) in ethanol (2 mL) over 1 h. The reaction mixture was stirred for 2 d at room temperature, then poured into a saturated aqueous NH_4Cl solution, and extracted with DCM (3 × 15 mL). The combined organic layers were dried with Na_2SO_4, filtered, and evaporated under reduced pressure. This residue was purified by column chromatography (acetone/petroleum ether, 1:1) to afford **9a** (126 mg, 78%) as a colorless liquid. R_f = 0.33 (acetone/petroleum ether, 6:4). $[\alpha]_D^{25}$ = –26.8050 ($CHCl_3$ c = 0.4). IR (film, $CHCl_3$): $\tilde{\nu}$ = 3400, 3020, 1697,

1215, 759 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.66 (br. s, 1 H), 5.96–5.90 (m, 1 H), 5.74–5.64 (m, 1 H), 5.46 (d, J = 10.29 Hz, 1 H), 5.12–5.05 (m, 2 H), 3.94 (br. s, 2 H), 3.71 (d, J = 10.79 Hz, 1 H), 3.57 (d, J = 10.79 Hz, 1 H), 2.76–2.68 (m, 2 H), 2.16 (dd, J = 7.03, 13.55 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.5, 132.7, 127.5, 122.7, 118.4, 68.0, 47.7, 43.2, 39.2 ppm. MS (ESI): m/z = 168.31 $[M + H]^+$, 190.25 $[M + Na]^+$. $C_9H_{13}NO_2$ (167.21): calcd. C 64.65, H 7.84, N 8.38; found C 64.51, H 7.78, N 8.26.

(*R*)-3-Allyl-2-oxo-1,2,3,6-tetrahydropyridine-3-carbaldehyde (12): To a solution of alcohol **9a** (100 mg, 0.598 mmol) in ethyl acetate (15 mL) was added IBX (217 mg, 0.778 mmol), and the resultant suspension was heated at reflux for 8 h. After cooling to room temperature, the reaction mixture was filtered through a pad of Celite and washed with ethyl acetate. The filtrate was concentrated and purified by column chromatography (ethyl acetate/petroleum ether, 4:6) to give **12** as a colorless liquid (84 mg, 85%). R_f = 0.5 (acetone/petroleum ether, 1:1). $[\alpha]_D^{25}$ = +12.92 ($CHCl_3$ c = 0.25). IR (film, $CHCl_3$): $\tilde{\nu}$ = 3288, 1726, 1681, 1654, 1494, 757 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.66 (s, 1 H), 7.62 (br. s, 1 H), 6.0 (d, J = 10.29 Hz, 1 H), 5.67–5.57 (m, 2 H), 5.12–5.06 (m, 2 H), 3.92 (m, 2 H), 2.82 (dd, J = 7.2, 13.5 Hz, 1 H), 2.40 (dd, J = 7.2, 13.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.9, 169.1, 131.2, 124.1, 122.9, 119.6, 58.4, 43.3, 38.5 ppm. MS (ESI): m/z = 166.13 $[M + H]^+$. $C_9H_{11}NO_2$ (165.19): calcd. C 65.44, H 6.71, N 8.48; found C 65.52, H 6.65, N 8.46.

Diastereoselective Allylation of Aldehyde 12: To a solution of aldehyde **12** (140 mg, 0.848 mmol) in anhydrous DCM (8 mL) at –78 °C under an argon atmosphere was added the Lewis acid ($SnCl_4$ or $TiCl_4$, 1 mmol). After 20 min, allyltrimethylsilane (3.392 mmol) was added dropwise and stirring was continued at –78 °C for 7 h. Upon complete consumption of the aldehyde, the reaction mixture was quenched with saturated aqueous sodium hydrogen carbonate solution and the temperature was allowed to attain room temperature. The aqueous phase was separated and extracted with DCM. The organic phase was washed with brine, dried with sodium sulfate, filtered, and concentrated to afford the homoallylic alcohol (152 mg). The diastereomeric ratio was determined by HPLC analysis {[Chiralcel OD-H (250 × 4.6 mm), isopropanol/*n*-hexane = 15:85, 0.5 mL min^{-1} (25 Kgf), λ = 225 nm, 25 °C]: t_R = 10.708 (for **13a**), 11.508 (for **13b**) min}. The diastereomeric mixture of homoallylic alcohols **13a/13b** was separated by flash column chromatography (acetone/petroleum ether, 3:7) to give 148 mg of **13a** and 4 mg of **13b**.

(*R*)-3-Allyl-3-[(*R*)-1-hydroxybut-3-enyl]-1,6-dihydropyridin-2(3*H*)-one (13a): R_f = 0.42 (acetone/petroleum ether, 4:6). $[\alpha]_D^{23}$ = +38.14 ($CHCl_3$, c = 1.1). IR (film, $CHCl_3$): $\tilde{\nu}$ = 3395, 1651, 1494, 1217, 758 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.33 (br. s, 1 H), 5.93–5.78 (m, 2 H), 5.72–5.63 (m, 2 H), 5.14–5.01 (m, 4 H), 3.95–3.89 (m, 3 H), 2.74 (dd, J = 7.53, 13.55 Hz, 1 H), 2.60 (br. s, 1 H), 2.39 (dd, J = 7.28, 13.56 Hz, 1 H), 2.31–2.26 (m, 1 H), 2.14–2.05 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2, 135.3, 133.8, 126.4, 122.0, 118.1, 117.9, 74.7, 50.6, 43.4, 39.5, 37.2 ppm. MS (ESI): m/z = 208.28 $[M + H]^+$, 230.27 [M + Na]. $C_{12}H_{17}NO_2$ (207.27): calcd. C 69.54, H 8.27, N 6.76; found C 69.66, H 8.15, N 6.67.

(*R*)-3-Allyl-3-[(*S*)-1-hydroxybut-3-enyl]-1,6-dihydropyridin-2(3*H*)-one (13b): R_f = 0.48 (acetone/petroleum ether, 4:6). $[\alpha]_D^{23}$ = –25.1876 ($CHCl_3$, c = 1.45). IR (film, $CHCl_3$): $\tilde{\nu}$ = 3401, 3019, 1642, 1215, 758 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.91 (br. s, 1 H), 5.94–5.86 (m, 2 H), 5.72–5.61 (m, 1 H), 5.40–5.38 (m, 1 H), 5.10–5.02 (m, 4 H), 4.15 (d, J = 10 Hz, 1 H), 3.89–3.86 (m, 2 H), 3.51–3.47 (m, 1 H), 2.91 (dd, J = 7.9, 13.7 Hz, 1 H), 2.34–2.30 (m, 1 H), 2.24 (dd, J = 7.33, 13.43 Hz, 1 H), 2.05–1.99 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.6, 135.7, 132.9, 127.7, 121.6, 118.7, 116.6, 76.2, 49.5, 43.0, 40.8, 38.3 ppm. MS (ESI): m/z = 208.27 $[M + H]^+$. $C_{12}H_{17}NO_2$ (207.27): calcd. C 69.54, H 8.27, N 6.76; found C 69.51, H 8.30, N 6.70.

(6*R*,11*R*)-11-Hydroxy-2-azaspiro[5,5]undeca-4,8-dien-1-one (14): To a degassed solution of **13a** (30 mg, 0.144 mmol) in anhydrous DCM (5 mL) under an argon atmosphere at room temperature was added Grubbs 2nd generation catalyst (8.6 mg, 7 mol-%). The solution was stirred at room temperature for 3 h, at which point TLC analysis indicated the reaction was complete. The reaction mixture was adsorbed over silica gel and purified by flash column chromatography (ethyl acetate/petroleum ether, 1:1) to afford **14** as a viscous liquid (21 mg, 81%). R_f = 0.36 (ethyl acetate). $[\alpha]_D^{25}$ = –86.0473 (c = 0.465, $CHCl_3$). IR (film, $CHCl_3$): $\tilde{\nu}$ = 3310, 1645, 1495, 1216, 757 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.7 (br. s, 1 H), 5.82–5.63 (m, 4 H), 4.94 (s, 1 H), 4.0–3.90 (m, 3 H), 2.96–2.93 (m, 1 H), 2.33–2.19 (m, 2 H), 1.91–1.87 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.1, 127.8, 123.4, 122.9, 121.0, 68.8, 43.2, 43.0, 30.0, 29.1 ppm. MS (ESI): m/z = 202.06 $[M + Na]^+$. $C_{10}H_{13}NO_2$ (179.22): calcd. C 67.02, H 7.31, N 7.82; found C 67.12, H 7.26, N 7.90.

(6*R*,7*R*)-7-Hydroxy-2-azaspiro[5,5]undecan-1-one (15): To a solution of **14** (20 mg, 0.111 mmol) in anhydrous MeOH (5 mL) was added Pd/C (20 mg), and the mixture was stirred overnight at room temperature under an atmosphere of hydrogen. The suspension was filtered through Celite and concentrated under reduced pressure. Purification by flash column chromatography (ethyl acetate/petroleum ether, 1:1) afforded solid **15** (19 mg, 94%), which upon crystallization with ethyl acetate/petroleum ether gave colorless crystals. M.p. 108–109 °C; R_f = 0.36 (ethyl acetate). $[\alpha]_D^{25}$ = +43.7706 (c = 0.625, $CHCl_3$). IR (film, $CHCl_3$): $\tilde{\nu}$ = 3219, 2932, 1638, 1446, 1046 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.47 (br. s, 1 H), 5.75 (br. s, 1 H), 3.72 (br. s, 1 H), 3.27–3.26 (m, 2 H), 2.18–2.12 (m, 1 H), 2.02–1.98 (m, 1 H), 1.84–1.68 (m, 4 H), 1.59–1.35 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.3, 71.5, 43.4, 42.1, 27.9, 27.9, 27.2, 19.6, 18.8, 18.5 ppm. MS (ESI): m/z = 184.44 $[M + H]^+$. $C_{10}H_{17}NO_2$ (183.25): calcd. C 65.54, H 9.35, N 7.64; found C 65.46, H 9.31, N 7.58.

(+)-Nitramine (6): To an ice-cooled stirred slurry of lithium aluminum hydride (0.034 g, 0.9 mmol) in anhydrous THF (3 mL) was added a solution of **15** (0.011 g, 0.06 mmol) in anhydrous THF (2 mL). The suspension was stirred at room temperature for 80 h, after which it was cooled to 0 °C and quenched with the slow alternative dropwise addition of saturated aqueous ammonium chloride solution and a 50% aqueous sodium hydroxide solution (each time a portion of 3 to 4 drops). The suspension was filtered, the precipitate was thoroughly washed with DCM, and the filtrate was dried with potassium carbonate, filtered, and concentrated to afford a yellow viscous liquid. Purification by column chromatography ($CHCl_3$/MeOH/25% NH_4OH, 46:50:4) gave pure **6** (0.006 g, 60%). R_f = 0.25 ($CHCl_3$/MeOH/25% NH_4OH), 46:50:4). $[\alpha]_D^{25}$ = +21.4 (c = 0.3, CH_2Cl_2). IR (film, $CHCl_3$): $\tilde{\nu}$ = 3350, 2940, 1175 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.62 (dd, J = 3.96, 9.15 Hz, 1 H), 3.50 (d, J = 12.2 Hz, 1 H), 3.65–3.45 (br. s, 2 H), 3.10–3.07 (m, 1 H), 2.68 (td, J = 3.35, 11.59 Hz, 1 H), 2.43 (d, J = 11.9 Hz, 1 H), 2.16–2.05 (m, 1 H), 1.84–1.78 (m, 2 H), 1.68–1.52 (m, 3 H), 1.43–1.24 (m, 5 H) 1.09–1.04 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 77.7, 51.8, 46.5, 37.3, 36.7, 35.3, 32.2, 24.0, 22.8, 21.3 ppm. MS (ESI): m/z = 170.25 $[M + H]^+$. $C_{10}H_{19}NO$ (169.27): calcd. C 70.96, H 11.34, N 8.28; found C 70.90, H 11.43, N 8.42.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H and ^{13}C NMR spectra, HPLC chromatograms, and X-ray crystallographic data.

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[9] The melting point of **4** is 94.7–95.5 °C. CCDC-837580 (for **4**) and -837578 (for **15**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[11] See the Experimental Section for HPLC conditions.

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