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An Efficient and Enantioselective Approach to the Azaspirocyclic Core of Alkaloids: Formal Synthesis of Halichlorine and Pinnaic Acid

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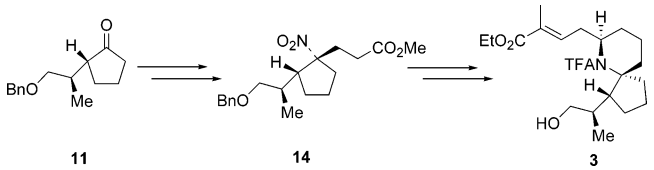
Received November 30, 2004



A novel, highly stereoselective synthesis of an azaspirocyclic core, which contains four stereogenic carbons consistent with structures of natural halichlorine and pinnaic acid, is presented. Lipase PS-catalyzed selective acylation, asymmetric methylation on the α-methylene of the bicyclic lactone, and an asymmetric Michael addition of the tertiary nitro cyclopentane were concisely used to conquer the challenging problem of successfully constructing the *C9* quarternary carbon center with complete stereocontrol. The spiropiperidine ring was formed by reduction of the *δ*-nitroketone, intramolecular condensation, and then highly stereoselective reduction of the cyclic nitrone with $NaBH_4$. This spirocyclic core is a key intermediate in Danishefsky's synthesis of pinnaic acid and halichlorine.

Introduction

The naturally occurring marine alkaloids halichlorine **1** and pinnaic acid **2** (Figure 1) are found in *halichondria okadai kadota* and *pinna muricata*, respectively.[1,2] Because of their biological activity and unique structure, **1** and **2** have garnered much attention from the synthetic community. Halichlorine **1** is a potent inhibitor of VCAM-1, which is a potential target for the treatment of inflammation and coronary heart disease.[3] Pinnaic acid *2* is an inhibitor of *c*PLA_2, and so has potential for treatment of inflammatory disease.[4] To date, considerable effort has been directed toward the total synthesis of the two compounds.[5] Among others, Danishefsky's group has reported the total synthesis of halichlorine and pinnaic acid and assigned simultaneously the stereochemistry at C13 and C17 of pinnaic acid in a communication.[6] Recently, Heathcock's group reported their total syntheses of (±)-halichlorine, (±)-pinnaic acid, and (±)-tauropinnaic acid.[7] Stimulated by the novel structures and biological activity of these compounds, and with the aim

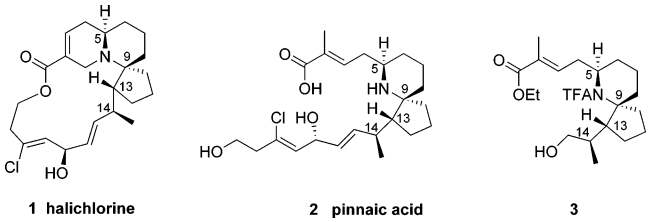


FIGURE 1. Structures of halichlorine and pinnaic acid.

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10.1021/jo047882v CCC: $30.25
Published on Web 05/26/2005

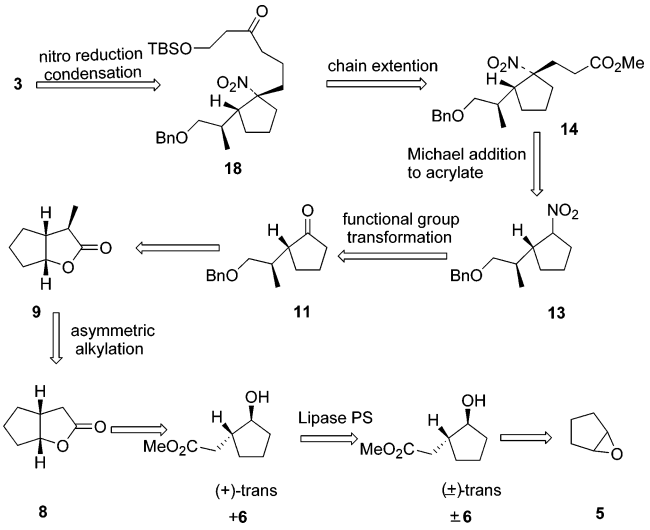


FIGURE 2. Retrosynthetic analysis of azaspirocyclic core **3**.

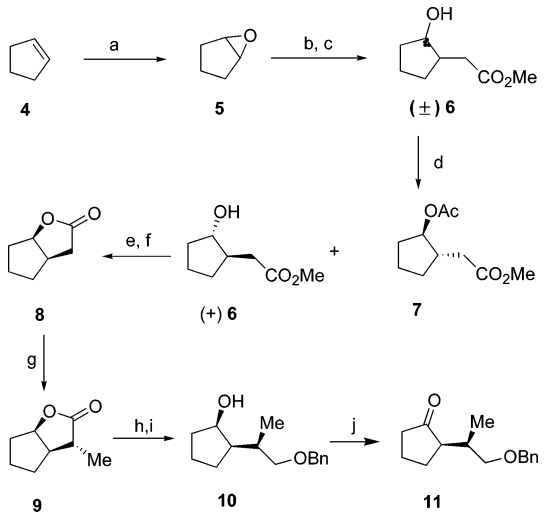
to further confirm the absolute configuration in pinnaic acid and to contribute a more efficient route to it, we initiated a program to synthesize these two alkaloids with complete stereocontrol. The key in the total synthesis of halichlorine and pinnaic acid is the construction of the azaspirocyclic core **3**.

Three contiguous stereogenic carbons C9, C13, and C14 make the synthesis challenging, particularly the C9 which is a spirochiral center. We report herein the methods we have developed for concisely dealing with this challenge. The retrosynthetic scheme is shown in Figure 2. Our strategy involves Lipase PS-catalyzed irreversible transesterification to prepare the optical intermediate (+) **6**[8] with the desired configuration at C13; asymmetric methylation of the bicyclic lactone **8** to introduce the chiral center at C14; and asymmetric Michael addition of the nitrocyclopentane **13** to install the chiral spirocenter C9. Finally, the spiropiperidine ring can be constructed through nitro reduction of **18**, followed by intramolecular condensation with simultaneous formation of the stereogenic C5.

Results and Discussion

The cyclopentene **4** (Scheme 1) was treated with *N*-bromosuccinimide (NBS) in water and then with aqeous NaOH at 2−10 °C to afford the epoxide **5** in 65% yield.[8] The epoxide **5** was opened with sodium malonic ester to give the trans-diester,[9] which was decarboxlated in the presence of LiCl and water in DMSO at 140 °C to give (±) **6** in 82% yield.[10] Selective acylation of (±) **6** under the control of Lipase PS in vinyl acetate produced

SCHEME 1[a]



[a] Reaction conditions: (a) (i) NBS, H_2O, rt, 2.5 h, (ii) NaOH, H_2O, 2−10 °C, 3 h, 65% over two steps; (b) Na, $CH_2(CO_2Me)_2$, MeOH, reflux, 6 h, 89%; (c) 2 eq. LiCl, 1 eq. H_2O, DMSO, 140 °C, 3 h, 82%; (d) 5% Lipase PS, 2 eq. vinyl acetate, rt, 48 h, 43% for (+) 6, 99.5% ee for (+) 6, 48% for 7; (e) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to room temperature; (f) 5% aqueous NaOH, THF, 0 °C, 24 h, 89% over two steps; (g) LDA, MeI, THF, −78 °C, 6 h, 77%; (h) $LiAlH_4$, THF, reflux, 4 h; (i) 1.2 eq. BnBr, 1.3 eq. NaH, THF, rt, 10 h, 80% over two steps; (j) PCC, CH_2Cl_2, rt, 4 h, 90%.

the desired product (+) **6** (43% yield, 99.5% ee),[11] which was converted to the bicyclolactone **8** (89% yield) through mesylation, hydrolysis, and cyclization.

Substrate-induced asymmetric methylation of the bicyclolactone **8** using LDA as base at −78 °C led to **9** in 77% yield. Reduction of **9** with $LiAlH_4$, followed by regioselective protection of the primary alcohol with benzylbromide, provided **10** (80% over two steps), which was directly oxidized in 90% yield to the cyclopentanone **11** using PCC in CH_2Cl_2. Thus, the construction of two stereogenic carbons *C13* and *C14* was completed. This method for the preparation of optical cyclopentanone **11** with two adjacent stereocenters is very efficient and the cyclopentanone can be prepared in large scale.

To construct the piperidine ring with a chiral spirocenter, the strategy of intramolecular condensation between the amine and the carbonyl group was adopted. The synthesis of the key intermediate **18**, which is the precursor for the intramolecular condensation and the piperidine ring formation, is shown in Scheme 2. The cyclopentanone **11** was transformed to a pair of nitro cyclopentane **13** diastereoisomers through oxime **12** in 74% yield (two steps). *m*-CPBA was used for the oxidation of oxime **12** instead of 90% hydrogen peroxide to avert a potential explosion danger,[12] although the yield might be lower. The nitro cyclopentane **13** is a good donor for Michael addition and did add successfully to methyl acrylate. It is interesting that the nitroester **14** is produced as a single diastereoisomer in high yield.[13] The

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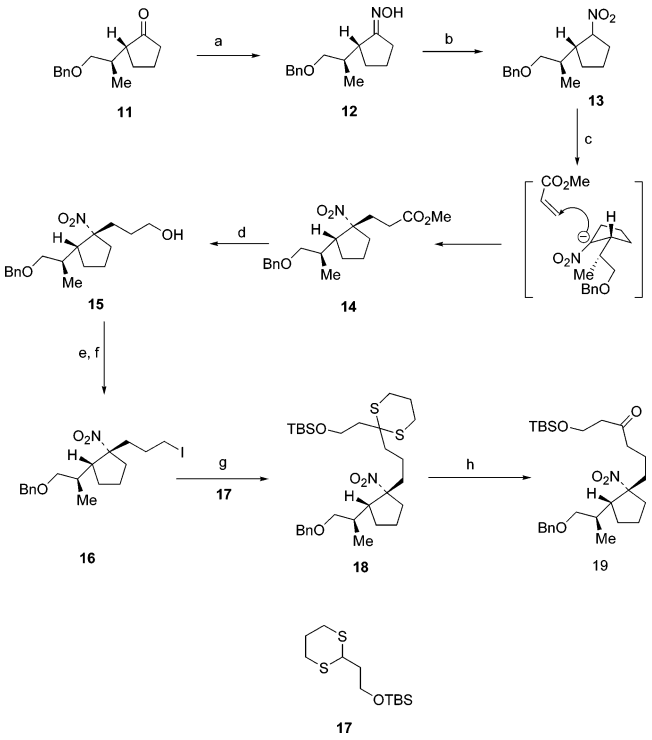
SCHEME 2[a]

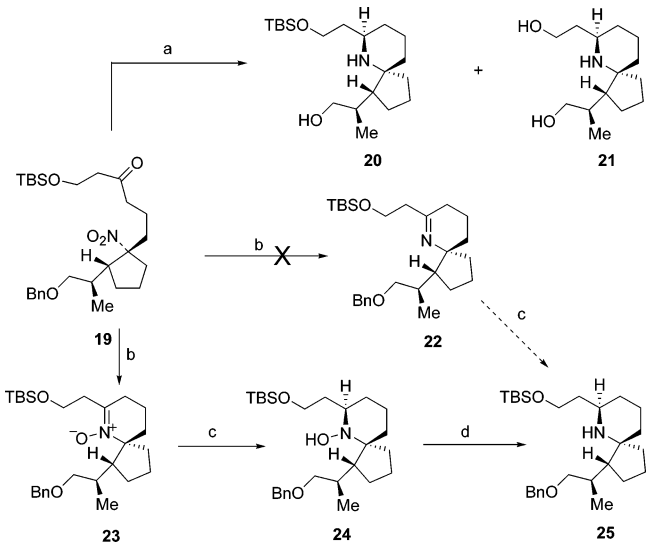


[a] Reaction conditions: (a) $NH_2OH{\bullet}HCl$, K_2CO_3, MeOH, rt, 4 h, 97%; (b) *m*-CPBA, Na_2HPO_4, crushed urea, MeCN, 80 °C, 76%; (c) methyl acrylate, Triton B, *t*-BuOH, THF, rt, 48 h, 95%; (d) $NaBH_4$, dioxane/H_2O 1:1, rt, 24 h, 84%; (e) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to room temperature, 2 h; (f) NaI, $NaHCO_3$, acetone, rt, 24 h, 77% over two steps; (g) **17**, 1.5 eq. *t*-BuLi, 3 eq. HMPA, −78 °C, 40 min, 99%; (h) MeI, $CaCO_3$, MeCN/H_2O 4:1, rt, 24 h, 91%.

stereochemistry of the newly formed quarternary carbon in **14** has tentatively been assigned and its structure is depicted in Scheme 2, in view of the likelihood of the acrylate approaching from the less hindered side of **13**. This stereochemical assignment was later confirmed by NOE and by X-ray crystallography. Reduction of the nitroester **14** with $NaBH_4$ to give the nitro alcohol **15** in 84% yield, followed by mesylation and iodination, led to the iodide **17** (77% over two steps). Metalation of the dithiane **17**[14] with *t*-BuLi and alkylation with the iodide **16** afforded **18** in high yield,[15] but when *n*-BuLi was used as a base, the reaction was reluctant to proceed. Removal of the dithiolane by exposure of **18** to MeI and $CaCO_3$ in MeCN/H_2O (4:1) gave the ketone **19** that is the critical precursor for the piperidine ring cyclization.

To form the piperidine ring by intramolecular condensation of δ-aminoketone, the tertiary nitro group in **19** has to be reduced to an amino group. When **19** was hydrogenated in the presence of Pd/C, the nitro group was intact, but both the benzyl and TBS groups were cleaved. Although Raney-Ni could reduce the nitro group and gave the desired spiropiperidine core structure as

SCHEME 3[a]



[a] Reaction conditions: (a) Raney-Ni, MeOH, 5 atm H_2; (b) Ni_2B, $NH_2NH_2{\cdot}H_2O$, EtOH, refux, 2 h, 72%; (c) $NaBH_4$, MeOH, 0 °C to room temperature, 96%; (d) $TiCl_3$, NaOAc, MeOH, H_2O, rt, 1.5 h, 79%.

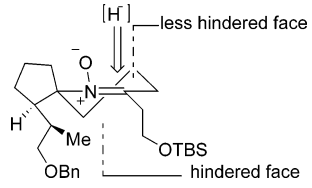


FIGURE 3. Stereoselectivity of cyclic nitrone **23** reduction with $NaBH_4$.

shown in Scheme 3, TBS was also partially cleaved, and two benzyl deprotected products **20** and **21** were obtained. To avoid these deprotection problems, **19** was reduced using freshly prepared Ni_2B as the catalyst and hydrazine hydrate as the hydrogen donor in EtOH,[16] but surprisingly only spiro-2,3,4,5-tetrahydropyridine *N*-oxide **23** was produced instead of the expected spiropiperidine **22**. This may be because the intramolecular condensation to cyclonitrone **23** occurred more quickly than reduction of the nitro group. Although we optimized the reaction conditions, compound **23** was still the only product.

Reduction of the cyclic nitrone **23** with $NaBH_4$ in MeOH gave the desired diastereoisomer **24** exclusively.[17] We think the excellent selectivity was mainly attributed to hydride attack from the less hindered face as shown in Figure 3. Therefore, although compound **19** was not directly reduced to product **22**, compounds **23** and **24** could be obtained in high yield, and the reaction conditions (for the reduction of **23**) are mild and very simple. The hydroxyl group in **24** was reduced with $TiCl_3$[18] to afford the desired product **25**. Notably, in this case, the TBS and benzyl protecting groups were not attacked.

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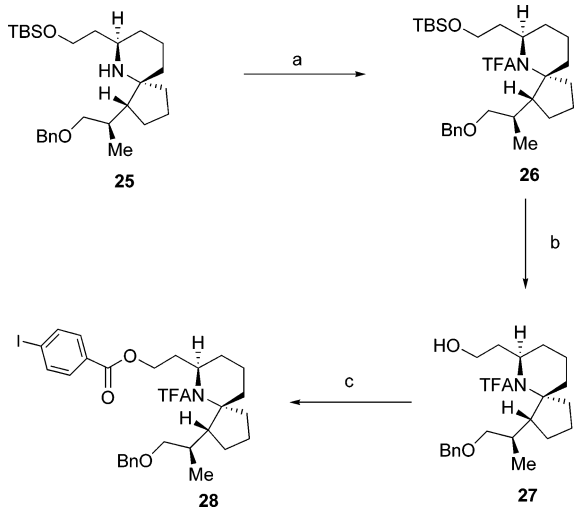
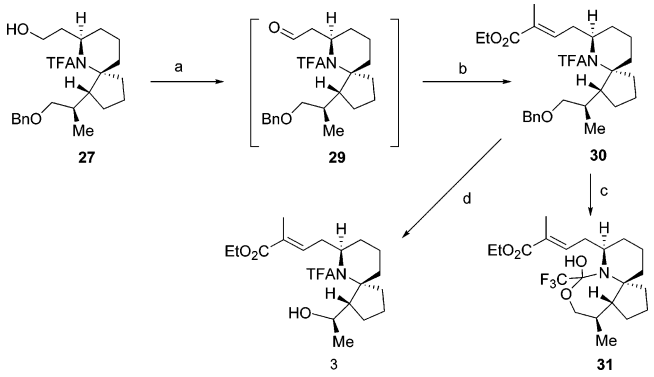
SCHEME 4[a]



[a] Reaction conditions: (a) $(CF_3CO)_2O$, $(^iPr)_2NEt$, CH_2ClCH_2Cl, 0 °C, 40 min, 84%; (b) HF·Py, THF, rt, 24 h, 88%; (c) *p*-iodobenzoic acid, DCC, DMAP, CH_2Cl_2, rt, 71%.

SCHEME 5[a]



[a] Reaction conditions: (a) PCC, Celite, CH_2Cl_2, rt, 93%; (b) triethyl-2-phosphonopropionate, NaH, THF, 0 °C to room temperature, 90%; (c) TMSI, CH_2Cl_2, rt, 83%; (d) BBr_3, CH_2Cl_2, −78 °C, 91%.

The stereochemistry of **27** was established by single-crystal X-ray structure analysis of its *p*-iodo-benzoate **28** (its ORTEP drawing of the X-ray structure is shown in the Supporting Information), which was prepared by N-acylation with trifluoroacetic anhydride, deprotection of the TBS group, and transformation to derivative 28 (Scheme 4).[19]

With substrate **27** in hand, we extended its upper side chain by olefination. The (*E*)-C2−C3 double bond could be easily constructed by a Horner−Wadworth−Emmons reaction, and the yield reached 90%. Subsequent removal of the benzyl group using TMSI in CH_2Cl_2 at room temperature resulted in an undesired product in high yield, which was proven to be a seven-membered semiketal, **31** (^{1}HNMR, IR, ^{19}FNMR). Its easy formation could be attributed to the high elecrophilicity of the trifluoroacetyl group. By using BBr_3 in CH_2Cl_2 at −78 °C instead of TMSI, the desired compound **3** was obtained smoothly (Scheme 5).

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Since intermediate **3** has already been transformed into pinnaic acid[6d,e] and compound **27** can be transformed to halichlorine,[5q,6a] the formal synthesis of pinnaic acid and halichlorine is complete.

Summary

In conclusion, we have presented herein an efficient and highly stereoselective synthesis of an azaspirocyclic core, which contains four stereogenic carbons consistent with the structure of natural halichlorine and pinnaic acid. Mild conditions, excellent stereoselectivity, and high yields in construction of four stereogenic carbons are featured in this synthesis. A formal synthesis of halichlorine and pinnaic acid was completed.

Experimental Section

Cyclopentene oxide (**5**) and (±)-(*trans*-2-hydroxy-cyclopentyl)-acetic acid methyl ester (±) **6** were prepared according to the previously described procedure.[8−11]

(1*R*, 2*S*)-(*trans*-2-Hydroxy-cyclopentyl)-1-acetic Acid Methyl Ester (+6).[11] A solution of (±) 6 (35.0 g, 221 mmol) in vinyl acetate (41 mL, 442 mmol) was incubated with Lipase PS (1.8 g, 0.05 mass eq.) at room temperature with stirring for 48 h. Filtration and evaporation in vacuo furnished the crude product, which was purified by column chromatography (silica gel, EtOAc/Hexanes 1:3) to give the acetate **7** (21.3 g, 48%) and the alcohol (+) **6** (15 g, 43%, 99.5% ee, analytical sample was converted to benzoate and determined by HPLC on Chiralcel OD column, eluent: V_{hexane}:V_{i-PrOH} 10:1) as colorless oil.

$[\alpha]^{20}_D$ + 43.5 (*c* 1.12, MeOH); R_f 0.66 (EtOAc/Hexanes 1:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.84 (q, J = 6.3 Hz, 1H), 3.69 (s, 3H), 3.32 (s, 1H), 2.44 (d, J = 2.5 Hz, 1H), 2.42 (s, 1H), 2.08 (dd, J = 7.5, 15.8 Hz, 1H), 2.01−1.91 (m, 2H), 1.77−1.55 (m, 3H), 1.22 (ddd, J = 8.1, 12.5, 16.5 Hz, 1H).

(4*R*, 8*S*)-Hexahydro-cyclopenta[b]furan-2-one (8). The alcohol (+) **6** (5.6 g, 35.3 mmol), Et_3N (9.8 mL, 70.6 mmol), and DMAP (100 mg) were dissolved in CH_2Cl_2 (60 mL) at 0 °C, and methanesulfonyl chloride (4.2 mL, 52.9 mmol) was added dropwise with stirring. The reaction mixture was stirred at 0 °C for 1 h, allowed to warm to room temperature, and poured into 5% aqueous $NaHCO_3$. Extraction with CH_2Cl_2 and removal of solvent gave the crude mesylate, which was then directly dissolved in THF (180 mL) at 0 °C without further purification, and then 5% aqueous sodium hydroxide (90 mL) was added dropwise. After stirring for 24 h at 0 °C, concentrated hydrochloric acid was added to acidify to pH = 3, the organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo, and the crude product was purified by column chromatography (silica gel, EtOAc/Hexanes 2:5) to give the bicyclolactone **8** (3.9 g, 89%) as colorless oil.

$[\alpha]^{20}_D$ + 59.7 (*c* 1.28, MeOH); R_f 0.64 (EtOAc/Hexanes 1:2); IR (film) ν_{max} 2961, 2872, 1773, 1177, 984 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.01 (t, J = 5.3 Hz, 1H), 2.92−2.82 (m, 1H), 2.79, (d, J = 10.3 Hz, 1H), 2.29 (d, J = 17.5 Hz, 1H), 2.07−2.02 (m, 1H), 1.90−1.66 (m, 4H), 1.58−1.51 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 86.3, 37.8, 35.9, 33.4, 33.3, 23.3; MS (EI) *m/z* 126 (M^+, 12.94%), 98 (49.59), 97 (58.75), 80 (42.07), 67 (100), 54 (68.47); HRMS (EI) calcd for $C_7H_{10}O_2$ (M^+) 126.0681, found 126.0677.

(3*R*, 4*R*, 8*S*)-3-Methyl-hexahydro-cyclopenta[b]furan-2-one (9). To a solution of lithium diisopropylamide, prepared from a solution of diisopropylamine(4.9 mL, 35.1 mmol) in 120 mL of THF and *n*-BuLi (1.6 M in hexanes, 20 mL, 32.4 mmol) at −78 °C, was added a solution of lactone **8** (3.4 g, 27 mmol) in THF (10 mL). After stirring for an additional 30 min at −78 °C, MeI (1.8 mL, 28.4 mmol) was added. The reaction mixture

was stirred at −78 °C for 6 h, quenched with water, and acidified with concentrated hydrochloric acid to pH = 3−4; the organic layer was separated and the aqueous layer was extracted with EtOAc. The combined extracts were dried (Na_2SO_4), concentrated, and purified by flash chromatography (silica gel, EtOAc/Hexanes 2:5) to afford **9** (2.9 g, 77%) as colorless oil.

$[\alpha]^{20}_D$ = +68.6 (*c* = 1.64, in MeOH); R_f = 0.69 (EtOAc/Hexanes 2:5); IR (film) ν_{max} 2964, 2874, 1767, 1191, 984 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 4.98 (t, *J* = 5.5 Hz, 1H), 2.53 (ddd, *J* = 3.5, 7.3, 11.1 Hz, 1H), 2.36 (qd, *J* = 4.1, 7.8 Hz, 1H), 2.04−1.99 (m, 1H), 1.87−1.57 (m, 5H), 1.32 (d, *J* = 7.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.8, 84.3, 46.7, 42.4, 33.4, 32.7, 23.4, 17.4; MS (ESI): *m/z* (%): 141.1 $[M + H]^+$; HRMS (ESI) calcd for $C_8H_{12}O_2Na$ 163.0730, found 163.0736 $[M + Na]^+$.

(1*S*, 2*R*, 1′*R*)-2-(2′-Benzyloxy-1′-methyl-ethyl)-1-cyclopentanol (10). To a stirred cold slurry of lithium aluminum hydride (1.0 g, 26.3 mmol) in THF (100 mL) was added a solution of lactone **9** (3.0 g, 21.4 mmol) in THF (10 mL). The mixture was refluxed for 4 h, quenched with saturated aqueous ammonium chloride solution (5 mL) under cooling, and concentrated. The residue was diluted with water (15 mL) and extracted with EtOAc, dried (Na_2SO_4), concentrated to afford crude alcohol, which was dissolved in THF (50 mL) at 0 °C without purification, and sodium hydride (60%, 1.1 g, 26.2 mmol) was added. After stirring 30 min, benzyl bromide (2.9 mL, 24.1 mmol) was added dropwise. The resulting solution was stirred at room temperature for 10 h, quenched with saturated aqueous ammonium chloride solution (5 mL), extracted with ethyl acetate, dried (Na_2SO_4), concentrated, and purified by flash chromatography (silica gel, EtOAc/Hexanes 1:5) to afford **10** (4 g, 80%) as colorless oil.

$[\alpha]^{20}_D$ + 13.8 (*c* 1.22, $CHCl_3$); R_f 0.60 (EtOAc/Hexanes 1:5); IR (film) ν_{max} 3448, 2958, 1454, 1093, 737, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.25 (m, 5H), 4.53 (s, 2H), 4.24 (s, 1H), 3.44 (dd, *J* = 3.1, 9.0 Hz, 1H), 3.37 (t, *J* = 9.0 Hz, 1H), 3.17 (s, 1H), 1.92−1.71 (m, 5H), 1.54−1.38 (m, 3H), 0.91 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 128.5, 127.8, 127.7, 77.0, 73.7, 73.5, 53.3, 34.5, 33.9, 28.7, 21.9, 17.3; MS (EI) *m/z* 234 (M^+, 0.14%), 133 (0.13), 125 (19.81), 110 (16.64), 91 (100), 67 (27.83); Anal. Calcd for $C_{15}H_{22}O_2$ (234.16): C, 76.88; H, 9.46. Found: C, 76.71; H, 9.35.

(2*R*, 1′*R*)-2-(2′-Benzyloxy-1′-methyl-ethyl)-cyclopentanone (11). The alcohol **10** (4 g, 17.1 mmol) in CH_2Cl_2 (15 mL) was added to a mixture of PCC (8 g, 37.2 mmol) and Celite (8 g) in CH_2Cl_2 (150 mL). After stirring at room temperature for 4 h, the mixture was diluted with hexanes (100 mL) and filtered through a short silica gel column. The filtrate was concentrated and purified by flash chromatography (silica gel, EtOAc/Hexanes 1:5) to afford cyclopentanone **11** (3.6 g, 90%) as colorless oil.

$[\alpha]^{20}_D$ + 115.6 (*c* 1.10, $CHCl_3$); R_f 0.71 (EtOAc/Hexanes 1:5); IR (film) ν_{max} 2962, 2876, 1735, 1098, 737, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.25 (m, 5H), 4.53 (d, *J* = 12.4 Hz, 1H), 4.46 (d, *J* = 11.9 Hz, 1H), 3.40 (dd, *J* = 6.0, 9.3 Hz, 1H), 3.35 (dd, *J* = 7.8, 9.3 Hz, 1H), 2.47−2.26 (m, 3H), 2.05−1.94 (m, 3H), 1.73−1.60 (m, 2H), 0.78 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 221.0, 138.6, 128.4, 127.6, 127.5, 73.8, 72.8, 50.9, 39.0, 32.3, 24.2, 20.7, 12.9; MS (EI) *m/z* 232 (M^+, 2.76%), 190 (5.25), 174 (5.76), 141 (9.18), 91 (100), 84 (26.96), 55 (27.75); Anal. Calcd for $C_{15}H_{20}O_2$ (232.15): C, 77.55; H, 8.68. Found: C, 77.43; H, 8.49.

(2*R*, 1′*R*)-2-(2′-Benzyloxy-1′-methyl-ethyl)-cyclopentanone oxime (12). To a solution of cyclopentanone **11** (3.57 g, 15.4 mmol) in MeOH (50 mL) at room temperature was added hydroxylamine hydrochloride (1.6 g, 23.1 mmol) and K_2CO_3 (3.2 g, 23.1 mmol). The resulting mixture was stirred at room temperature for 4 h, diluted with water, and extracted with EtOAc. The extracts were dried (Na_2SO_4) and concentrated in vacuo to give a residue, which was subjected to column chromatography (silica gel, EtOAc/Hexanes 2:5) to give oxime 12 (3.7 g, 97%) as colorless oil.

$[\alpha]^{20}_D$ + 53.6 (*c* 1.41, $CHCl_3$); R_f 0.67 (EtOAc/Hexanes 2:5); IR (film) ν_{max} 3313, 2960, 1454, 1092, 914, 736, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.28 (br, 1H), 7.34−7.23 (m, 5H), 4.52 (d, *J* = 11.9 Hz, 1H), 4.46 (d, *J* = 12.2 Hz, 1H), 3.39 (qd, *J* = 7.5, 9.3 Hz, 2H), 2.79−2.61 (m, 2H), 2.39−2.21 (m, 2H), 1.86−1.71 (m, 2H), 1.59−1.45 (m, 2H), 0.86 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 140.6, 130.3, 129.5, 129.4, 76.2, 74.8, 46.6, 35.6, 29.8, 28.2, 24.5, 14.6; MS (EI) *m/z* 247 (M^+, 3.19%), 230 (5.69), 189 (9.85), 156 (16.83), 126 (26.69), 99 (83.51), 91 (100), 67 (10.55); Anal. Calcd for $C_{15}H_{21}NO_2$ (247.16): C, 72.84; H, 8.56; N, 5.66. Found: C, 72.77; H, 8.66; N, 5.46.

(1*R*, 1′*R*)-1-(2′-Benzyloxy-1′-methyl-ethyl)-2-nitro-cyclopentane (13). A mixture of oxime **12** (3.7 g, 14.9 mmol), anhydrous dibasic sodium phosphate (17.7 g, 124.6 mmol), crushed urea (4.8 g, 81.5 mmol), and dry MeCN (200 mL) was refluxed for 0.5 h under Ar. Portions of *m*-CPBA (70−75%, 6.7 g, 28.1 mmol) were then added at intervals of 15 min. After refluxing for 2 h, the reaction mixture was cooled to room temperature, filtered, and concentrated to a solid residue, which was then dissolved in CH_2Cl_2 (150 mL). The CH_2Cl_2 solution was washed with saturated aqueous $NaHCO_3$, aqueous $Na_2S_2O_3$ and water, and dried (Na_2SO_4). After removal of the solvent in vacuo, the residue was purified by flash chromatography (silica gel, EtOAc/Hexanes 1:10) to afford **13** (3 g, 76%) as yellow oil.

R_f 0.68 (EtOAc/Hexanes 1:10); IR (film) ν_{max} 2964, 2876, 1546, 1454, 1373, 1098, 738, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36−7.24 (m, 5H), 4.93 (t, *J* = 5.5 Hz, 0.13H), 4.80 (ddd, *J* = 1.8, 4.3, 8.5 Hz, 0.87H), 4.49 (s, 0.3H), 4.42 (s, 1.7H), 3.34 (dd, *J* = 2.7, 9.2 Hz, 2H), 2.64 (dq, *J* = 7.5, 9.9 Hz, 1H), 2.20 (dq, *J* = 4.3, 17.2 Hz, 1H), 2.12−1.61 (m, 5H), 1.38−1.27 (m, 1H), 1.01 (d, *J* = 6.8 Hz, 0.4H), 0.96 (d, *J* = 6.8 Hz, 2.6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 128.5, 128.4, 127.8, 127.7, 127.6, 89.8, 89.5, 74.4, 73.9, 73.2, 73.1, 49.1, 49.0, 36.5, 34.2, 33.4, 32.1, 29.2, 28.1, 24.3, 22,5, 16.9, 14.7; MS (ESI) 264.2 (M^+ + H); Anal. Calcd for $C_{15}H_{21}NO_3$ (263.15): C, 68.42; H, 8.04; N, 5.32. Found: C, 68.47, H, 7.85; N, 5.38.

(1*R*, 2*S*, 1′*R*)-1-(2′-benzyloxy-1′-methyl-ethyl)-2-Nitro-2-(2″-methoxycarbonyl-ethyl)- cyclopentane (14). Methyl acrylate (1.1 mL, 12.2 mmol) and Triton B (40% in MeOH, 0.6 mL) were added to a solution of **13** (3 g, 11.4 mmol) in dry THF (25 mL) and *t*-BuOH (50 mL), and the mixture was stirred under Ar atmosphere at room temperature for 48 h. The solution was evaporated to a residue, which was subjected to column chromatography (silica gel, EtOAc/Hexanes 1:5) to give nitroester **14** (3.8 g, 95%) as colorless oil.

$[\alpha]^{20}_D$ + 27.6 (*c* 0.98, $CHCl_3$); R_f 0.44 (EtOAc/Hexanes 1:5); IR (film) ν_{max} 2952, 2877, 1740, 1532, 738, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.27 (m, 5H), 4.52 (d, *J* = 11.9 Hz, 1H), 4.44 (d, *J* = 12.0 Hz, 1H), 3.66 (s, 3H), 3.40 (dd, *J* = 5.0, 9.4 Hz, 1H), 3.24 (dd, *J* = 6.8, 9.3 Hz, 1H), 2.85−2.75 (m, 1H), 2.52 (ddd, *J* = 5.7, 9.1, 14.4 Hz, 1H), 2.35 (t, *J* = 8.0 Hz, 2H), 2.20 (ddd, *J* = 4.2, 7.3, 11.7 Hz, 1H), 2.11−1.60 (m, 7H), 0.75 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 138.4, 128.4, 127.6, 127.5, 99.2, 74.6, 72.9, 51.8, 51.7, 35.7, 32.8, 32.1, 29.9, 26.2, 22.1, 13.7; MS (ESI) 372.3 (M^+ + Na); Anal. Calcd for $C_{19}H_{27}NO_5$ (349.19): C, 65.35; H, 7.79; N, 4.01. Found: C, 65.42; H, 7.65; N, 3.91.

(1*R*, 2*S*, 1′*R*)-1-(2′-Benzyloxy-1′-methyl-ethyl)-2-(3″-hydroxypropyl)-2-nitro-cyclopentane (15). To a stirred solution of the nitroester **14** (299 mg, 0.86 mmol) in dioxane−water (1:1, 10 mL) was added $NaBH_4$ (0.46 g, 12 mmol) in small portions, and stirring was continued for 24 h at room temperature. The mixture was acidified with HCl (18%) under ice cooling and extracted with ether. The combined ether extracts were concentrated to a residue, which was treated with a solution of NaOH (100 mg) in EtOH/H_2O (10 mL/3 mL). The mixture was heated to reflux for 2 h. After removal of the solvents, water was added and the mixture was extracted with

EtOAc. The organic phase was washed with water and brine and then dried (Na_2SO_4), concentrated, and purified by flash chromatography (silica gel, EtOAc/Hexanes 1:2) to afford nitro alcohol **15** (230 mg, 84%) as colorless oil.

$[\alpha]^{20}_D$ + 36.2 (*c* 1.26, $CHCl_3$); R_f 0.38 (EtOAc/Hexanes 1:2); IR (film) ν_{max} 3395, 2958, 2875, 1530, 1097, 738, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.26 (m, 5H), 4.51 (d, J = 12.1 Hz, 1H), 4.46 (d, J = 12.0 Hz, 1H), 3.64−3.54 (m, 2H), 3.39 (dd, J = 5.0, 9.3 Hz, 1H), 3.24 (dd, J = 7.2, 9.2 Hz, 1H), 2.61−2.42 (m, 2H), 2.20 (ddd, J = 3.9, 7.5, 11.7 Hz, 1H), 2.08−1.98 (m, 3H), 1.91−1.81 (m, 1H), 1.77−1.45 (m, 6H), 0.74 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 128.3, 127.5, 127.4 99.8, 74.7, 72.7, 62.3, 51.3, 35.5, 33.9, 31.7, 28.0, 25.7, 22.0, 13.4; MS (ESI) 344.2 (M^+ + Na); Anal. Calcd for $C_{18}H_{27}NO_4$ (321.19): C, 67.26; H, 8.47; N, 4.36. Found. C, 67.05; H, 8.41; N, 4.29.

(1*R*, 2*S*, 1′*R*)-1-(2′-Benzyloxy-1′-methyl-ethyl)-2-(3″-iodopropyl)-2-nitro-cyclopentane (16). The above nitro alcohol **15** (1 g, 3.12 mmol) and Et_3N (0.8 mL, 5.7 mmol) and DMAP (50 mg) were dissolved in CH_2Cl_2 (60 mL) at 0 °C, and methanesulfonyl chloride (0.4 mL, 5.16 mmol) was added dropwise with stirring. The reaction mixture was stirred at 0 °C for 1 h, allowed to warm to room temperature, and poured into a solution of 5% aqueous $NaHCO_3$. The methanesulfonate ester was isolated by extraction with CH_2Cl_2 and the solvent was removed. The crude mesylate was then stirred with sodium iodide (4.2 g, 28 mmol) and $NaHCO_3$ (500 mg, 6 mmol) in acetone (50 mL) for 24 h at room temperature. After the solvent was removed in vacuo, the residue was redissolved in water and extracted with ethyl acetate. The combined organic phase was dried (Na_2SO_4), concentrated, and purified by flash chromatography (silica gel, EtOAc/Hexanes 1:10) to give iodide **16** (1.03 g, 77%) as yellow oil.

$[\alpha]^{20}_D$ + 32.5 (*c* 1.02, $CHCl_3$); R_f 0.69 (EtOAc/Hexanes 1:10); IR (film) ν_{max} 2960, 2874, 1530, 1096, 737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39−7.26 (m, 5H), 4.55 (d, J = 12.1 Hz, 1H), 4.47 (d, J = 11.7 Hz, 1H), 3.44 (dd, J = 5.0, 9.4 Hz, 1H), 3.28−3.19 (m, 2H), 3.10 (q, J = 7.5 Hz, 1H), 2.60−2.47 (m, 2H), 2.20 (ddd, J = 4.1, 7.3, 11.8 Hz, 1H), 2.06−1.96 (m, 2H), 1.91−1.59 (m, 7H), 0.75 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 128.6, 127.8, 127.7, 99.6, 74.8, 73.1, 51.7, 38.9, 36.0, 32.2, 29.0, 26.2, 22.2, 13.9, 6.2; MS (ESI) 453.9 (M^+ + Na); HRMS (ESI) calcd for $C_{18}H_{26}INO_3Na$ (M^+ + Na) 454.0849, found 454.0846.

(1*R*, 2*S*, 1′R)-1-(2′-benzyloxy-1′-methyl-ethyl)-2-nitro-2-(6″-*tert*-butyldimethylsilanyloxy-4″-[1,3] dithian-hexyl)-cyclopentane (18). To a solution of dithiane **17**[14] (1 g, 3.6 mmol) in 100 mL of THF at −78 °C was added *t*-BuLi (2.4 mL, 3.6 mmol) and HMPA (1.25 mL, 7.2 mmol). After stirring for an additional 20 min at −78 °C, iodide **15** (1.03 g, 2.4 mmol) in THF (10 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 40 min, quenched with saturated aqueous ammonium chloride solution (5 mL), and extracted with EtOAc and dried (Na_2SO_4), concentrated, and purified by flash chromatography (silica gel, EtOAc/Hexanes 1:10) to give **18** (1.37 g, 99%) as a colorless oil.

$[\alpha]^{20}_D$ + 18.5 (*c* 1.03, $CHCl_3$); R_f 0.74 (EtOAc/Hexanes 1:5); IR (film) ν_{max} 2953, 2856, 1532, 1095, 837, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29−7.19 (m, 5H), 4.46 (d, J = 12.2 Hz, 1H), 4.40 (d, J = 12.2 Hz, 1H), 3.70 (t, J = 7.2 Hz, 2H), 3.33 (dd, J = 5.4, 9.3 Hz, 1H), 3.17 (dd, J = 7.0, 9.6 Hz, 1H), 2.76−2.69 (m, 4H), 2.50 (ddd, J = 5.4, 9.2, 14.4 Hz, 1H), 2.34 (dd, J = 10.6, 13.6 Hz, 1H), 2.09−2.03 (m, 3H), 1.98−1.36 (m, 13H), 0.82 (s, 9H), 0.66 (d, J = 6.9 Hz, 3H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 128.5, 127.7, 127.6, 100.1, 74.8, 72.9, 59.8, 51.8, 51.7, 40.8, 39.6, 38.1, 35.7, 32.1, 26.24, 26.17, 26.1, 25.4, 22.2, 20.1, 18.5, 13.7, −5.1; MS (ESI) 604.1 (M^+ + Na); Anal. Calcd for $C_{30}H_{51}NO_4S_2Si$ (581.30): C, 61.92; H, 8.83; N, 2.41. Found: C, 61.64; H, 8.70; N, 2.25.

(1*R*, 2*S*, 1′*R*)-1-(2′-benzyloxy-1′-methyl-ethyl)-2-nitro-2-(6″-*tert*-butyldimethylsilanyloxy-4″-oxo-hexyl)-cyclopentane (19). To a solution of **18** (1.37 g, 2.36 mmol) in MeCN/H_2O (4:1, 150 mL) at room temperature was added MeI (25 mL, 394.5 mmol) and $CaCO_3$ (2.63 g, 26.3 mmol). The resulting mixture was stirred at room temperature for 24 h. The organic phase was separated, the aqueous phase was extracted with EtOAc, and the combined extracts were dried (Na_2SO_4) and concentrated in vacuo to give a residue, which was subjected to column chromatography (silica gel, EtOAc/Hexanes 1:5) to give **19** (1.06 g, 91%) as a colorless oil.

$[\alpha]^{20}_D$ + 23.9 (*c* 0.91, $CHCl_3$); R_f 0.53 (EtOAc/Hexanes 1:5); IR (film) ν_{max} 2955, 2856, 1716, 1532, 1096, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31−7.22 (m, 5H), 4.46 (d, J = 12.3 Hz, 1H), 4.41 (d, J = 11.9 Hz, 1H), 3.82 (t, J = 6.3 Hz, 2H), 3.33 (dd, J = 5.0, 9.2 Hz, 1H), 3.19 (dd, J = 7.1, 9.5 Hz, 1H), 2.54−2.30 (m, 6H), 2.10 (ddd, J = 3.6, 7.4, 11.7 Hz, 1H), 2.00−1.89 (m, 3H), 1.70−1.47 (m, 6H), 0.83 (s, 9H), 0.68 (d, J = 6.9 Hz, 3H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.2, 138.5, 128.4, 127.6, 127.5, 99.9, 74.8, 72.8, 58.9, 51.5, 45.6, 43.5, 37.1, 35.5, 31.9, 25.9, 25.8, 22.1, 18.8, 18.3, 13.5, −5.4; MS (ESI) 514.2 (M^+ + Na); Anal. Calcd for $C_{27}H_{45}NO_5Si$ (491.31): C, 65.95; H, 9.22; N, 2.85. Found: C, 66.01; H, 8.85; N, 2.75.

(1*R*, 5*S*, 7*R*, 1′*R*)-1-(2′-*tert*-butyldimethylsilanyloxy -1′-methyl-ethyl)-7-(2″-benzyloxy-1″-methyl-ethyl)-6-aza-5-spiro[4.5]dec-6-ene-6-oxide (23). Ni_2B catalyst was prepared according to literature.[16] To a solution of **19** (400 mg, 0.81 mmol) in ethanol (16 mL) was added Ni_2B (207 mg, 1.62 mmol), and the mixture was heated at 80 °C and then NH_2-NH_2·H_2O (85%, 1.5 mL) was added and stirred at 80 °C for 2 h. The catalyst was filtered off and the filtrate was then concentrated and purified by flash chromatography (silica gel, EtOAc/Hexanes 1:2) to give **23** (270 mg, 72%) as a colorless oil.

$[\alpha]^{20}_D$ − 68.3 (*c* 0.95, $CHCl_3$); R_f 0.42 (EtOAc/Hexanes 1:2); IR (film) ν_{max} 3046, 3030, 2954, 2858, 1455, 1255, 1088, 837, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.28 (m, 5H), 4.50 (d, J = 11.9 Hz, 1H), 4.43 (d, J = 12.4 Hz, 1H), 3.95 (dt, J = 6.1, 9.9 Hz, 1H), 3.80 (dt, J = 5.5, 9.8 Hz, 1H), 3.37 (dd, J = 4.4, 9.1 Hz, 1H), 3.26 (dd, J = 4.5, 9.3 Hz, 1H), 2.64−2.38 (m, 5H), 2.25 (ddd, J = 5.7, 10.6, 19.1 Hz, 1H), 2.01−1.45 (m, 9H), 1.42 (m, 1H), 1.04 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 138.4, 128.1, 127.5, 127.3, 76.5, 74.4, 72.8, 58.7, 53.4, 40.1, 37.7, 36.1, 33.9, 32.2, 31.2, 25.8, 24.3, 18.0, 17.3, 17.2, −5.5, −5.6; MS (ESI) 460.3 (M^+ + H); HRMS (ESI) calcd for $C_{27}H_{45}NO_3SiNa$ (M^+ + Na) 482.3061, found 482.3062.

(1*R*, 5*S*, 7*R*, 1′*R*)-1-(2′-*tert*-butyldimethylsilanyloxy-1′-methyl-ethyl)-7-(2″- benzyloxy-1″-methyl-ethyl)-6-hydroxy-6-aza-5-spiro[4.5]decane (24). To nitrone **23** (285 mg, 0.62 mmol) in MeOH (10 mL), $NaBH_4$ (152 mg, 4 mmol) was added at 0 °C and stirred overnight. The solution was evaporated and the residue was diluted with water and extracted with EtOAc. The extracts was washed with water and brine and dried (Na_2SO_4), concentrated, and purified by flash chromatography (silica gel, EtOAc/Hexanes 1:10) to afford **23** (275 mg, 96%) as a colorless oil.

$[\alpha]^{20}_D$ − 24.7 (*c* 1.05, $CHCl_3$); R_f 0.41 (EtOAc/Hexanes 1:10); IR (film) ν_{max} 3416, 2931, 2859, 1255, 1092, 836, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.26 (m, 5H), 5.63 (br, 1H), 4.54 (d, J = 12.2 Hz, 1H), 4.47 (d, J = 12.2 Hz, 1H), 3.75 (ddd, J = 4.3, 7.6, 10.3 Hz, 1H), 3.66 (d, J = 5.4 Hz, 3H), 2.68 (ddd, J = 2.9, 5.8, 8.8 Hz, 1H), 2.11 (dd, J = 11.4, 20.0 Hz, 2H), 1.87−1.25 (m, 14H), 1.02 (d, J = 6.9 Hz, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.8, 129.9, 129.4, 129.0, 76.9, 74.7, 72.2, 61.8, 61.7, 55.7, 40.9, 38.8, 36.2, 34.2, 33.1, 29.9, 27.7, 25.9, 23.6, 20.0, 19.5, −3.6, −3.8; MS (ESI) 462.4 (M^+ + 1); HRMS (ESI) calcd for $C_{27}H_{48}NO_3Si$ (M^+ + H) 462.3398, found 462.3377.

(1*R*, 5*S*, 7*R*, 1′*R*)-1-(2′-*tert*-butyldimethylsilanyloxy-1′-methyl-ethyl)-7-(2″-benzyloxy-1″-methyl-ethyl)-6-aza-5-spiro[4.5]decane (25). 24 (1.2 g, 2.6 mmol) was dissolved in MeOH (16 mL), and sodium acetate (3.2 g, 39.0 mmol) and water (9.6 mL) were added. The mixture was stirred under Ar atmosphere for 10 min, and $TiCl_3$ (30% in 2 N HCl, 4 mL,

10.3 mmol) was added dropwise. After stirring for 1.5 h at room temperature, the suspension was poured into a solid mixture of Na_2SO_4 and Na_2CO_3 containing water; when the black solid turned to white, the solid was filtered and washed with EtOAc. The filtrate was then concentrated and purified by flash chromatography (silica gel, MeOH/$CHCl_3$ 1:10) to afford **25** (910 mg, 79%) as a yellow oil.

$[\alpha]^{20}_D$ −29.4 (*c* 1.14, $CHCl_3$); R_f 0.50 (MeOH/$CHCl_3$ 1:20); IR (film) ν_{max} 3342, 2931, 2858, 1255, 1095, 836, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36−7.25 (m, 5H), 4.50 (d, J = 1.2 Hz, 2H), 3.66 (q, J = 5.9 Hz, 2H), 3.51 (dd, J = 5.9, 9.0 Hz, 1H), 3.33 (t, J = 8.1 Hz, 1H), 2.76−2.73 (m, 1H), 2.05 (m, 1H), 1.77−1.22 (m, 16H), 0.96 (d, J = 6.9 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 129.6, 128.9, 128.7, 77.9, 77.5, 74.1, 64.4, 62.3, 53.2, 50.5, 41.8, 38.0, 37.3, 34.5, 33.5, 28.7, 27.4, 24.2, 23.9, 19.7, 17.5, −3.93, −3.95; MS (ESI) 446.3 (M^+ + H); HRMS (ESI) calcd for $C_{27}H_{48}NO_2Si$ (M^+ + H) 446.3449, found 446.3445.

(1*R*, 5*S*, 7*R*, 1′*R*)-1-(2′-*tert*-butyldimethylsilanyloxy-1′-methyl-ethyl)-7-(2″-benzyloxy-1″-methyl-ethyl)-6-trifluoroacetyl-6-aza-5-spiro[4.5] decane (26). The secondary amine **25** (770 mg, 1.73 mmol) and diisopropylethylamine (6.2 mL, 34.6 mmol) were dissolved in CH_2ClCH_2Cl (30 mL) at 0 °C, and trifluoro acetic anhydride (4.8 mL, 34.6 mmol) was added dropwise with stirring. The reaction mixture was stirred at 0 °C for 40 min, quenched with saturated aqueous $NaHCO_3$, and diluted with CH_2Cl_2 (150 mL); the organic phase was washed with brine and dried (Na_2SO_4), concentrated, and purified by flash chromatography (silica gel, EtOAc/Hexanes 1:10) to afford **26** (790 mg, 84%) as a colorless oil.

$[\alpha]^{20}_D$ − 36.0 (*c* 1.10, $CHCl_3$); R_f 0.64 (EtOAc/Hexanes 1:10); IR (film) ν_{max} 2954, 2859, 1687, 1199, 1143, 1100, 836, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30−7.29 (m, 5H), 4.49 (d, J = 12.0 Hz, 1H), 4.38 (d, J = 12.1 Hz, 1H), 4.04 (d, J = 13.3 Hz, 1H), 3.50 (ddd, J = 5.7, 10.5, 19.7 Hz, 2H), 3.35 (dd, J = 4.0, 8.9 Hz, 1H), 3.29 (dd, J = 5.6, 8.9 Hz, 1H), 2.18 (dd, J = 6.5, 12.9 Hz, 1H), 2.10 (dd, J = 7.6, 12.9 Hz, 1H), 1.90−1.45 (m, 13H), 1.31−1.22 (m, 1H), 0.91 (d, J = 6.6 Hz, 3H), 0.85 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0 (q, $J_{F,C=O}$ =34 Hz), 139.4, 128.9, 128.4, 128.1, 117.6 (q, $J_{F,C}$ = 287 Hz), 76.1, 73.6, 69.6, 60.9, 55.1, 52.3 (d, $J_{F,C}$ = 3 Hz), 38.1, 36.4, 34.8, 33.9, 31.5, 26.4, 25.2, 23.7, 18.8, 17.5, 14.7, −4.9, −5.0; MS (ESI) 542.3 (M^+ + H); HRMS (ESI) calcd for $C_{29}H_{46}F_3NO_3SiNa$ (M^+ + Na) 564.3091, found 564.3097.

(1*R*, 5*S*, 7*R*, 1′*R*)-1-(2′-hydroxy-1′-methyl-ethyl)-7-(2″-benzyloxy-1″-methyl-ethyl)-6-trifluoroacetyl-6-aza-5-spiro [4.5]decane (27). To a solution of **26** (780 mg, 1.44 mmol) in THF (10 mL) was added HF·Py (1 M, 1.8 mL, 1.8 mmol). The mixture was stirred for 24 h at room temperature and diluted with EtOAc (200 mL). The organic layer was washed with brine and dried (Na_2SO_4), concentrated, and purified by flash chromatography (silica gel, EtOAc/Hexanes 1:2) to afford **27** (540 mg, 88%) as a syrup.

$[\alpha]^{20}_D$ − 29.9 (*c* 1.07, $CHCl_3$); R_f 0.50 (EtOAc/Hexanes 1:2); IR (film) ν_{max} 3460, 2947, 2872, 1686, 1194, 1142 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.29 (m, 5H), 4.53 (d, J = 12.1 Hz, 1H), 4.44 (d, J = 12.0 Hz, 1H), 4.03−3.99 (m, 1H), 3.53 (dt, J = 5.8, 11.7 Hz, 2H), 3.37 (dd, J = 4.1, 8.6 Hz, 1H), 3.31 (dd, J = 5.7, 8.6 Hz, 1H), 2.24−2.15 (m, 2H), 1.98 (m, 1H), 1.88−1.49 (m, 12H), 1.34(m, 1H), 1.18 (m, 1H), 0.96 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ157.9 (q, $J_{F,C=O}$ = 34 Hz), 139.4, 128.9, 128.5, 128.1, 117.5 (q, $J_{F,C}$ = 287 Hz), 76.3, 73.6, 69.7, 60.8, 55.2, 52.0 (q, $J_{F,C}$ = 3 Hz), 38.4, 36.3, 34.7, 33.9, 31.3, 25.1, 24.1, 17.3, 14.6; MS (ESI) 428.1 (M^+ + H); HRMS (ESI) calcd for $C_{23}H_{32}F_3NO_3Na$ (M^+ + Na) 450.2226, found 450.2226.

(1*R*, 5*S*, 7*R*, 1′*R*)-1-(2′-*p*-iodobenzoyloxy-1′-methyl-ethyl)-7-(2″-benzyloxy-1″-methyl -ethyl)-6-trifluoroacetyl-6-aza-5-spiro[4.5]decane (28). *p*-iodobenzoic acid (200 mg, 0.80 mmol) and DMAP (50 mg) were added to a solution of alcohol 27 (100 mg, 0.22 mmol) in CH_2Cl_2 (8 mL), DCC (250 mg, 1.20 mmol) in two portions was added within a 15-min interval, and the reaction mixture was stirred at room temperature overnight and then stirred for 1 h with water (2 mL) and filtered. The precipitate was washed with ether. The combined organic phase was concentrated and purified by flash chromatography (silica gel, EtOAc/ Hexanes 1:10) to give **28** (110 mg, 71%) as a white solid.

Mp 153.9 ± 0.5 °C; $[\alpha]^{20}_D$ − 26.2 (*c* 0.82, $CHCl_3$); R_f 0.73 (EtOAc/Hexanes 1:5); IR (KBr) ν_{max} 1715, 686, 1196, 1275, 1134 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, J = 8.6 Hz, 2H), 7.70 (d, J = 9.0 Hz, 2H), 7.34−7.25 (m, 5H), 4.54 (d, J = 11.9 Hz, 1H), 4.26 (d, J = 12.1 Hz, 1H), 4.20 (t, J = 5.8 Hz, 1H), 4.17 (dd, J = 4.4, 9.2 Hz, 1H), 4.06 (d, J = 11.3 Hz, 1H), 3.34 (d, J = 3.8 Hz, 2H), 2.23 (dd, J = 6.3, 13.0 Hz, 1H), 2.16 (dd, J = 7.9, 13.0 Hz, 1H), 2.00 (dd, J = 8.8, 14.2 Hz, 2H), 1.91−1.52 (m, 11H), 1.39−1.30 (m, 1H), 0.96 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 159.1 (q, $J_{F,C=O}$ = 34 Hz), 140.0, 139.2, 132.3, 130.7, 129.7, 129.4, 129.0, 120.4 (q, $J_{F,C}$ = 287 Hz), 102.3, 77.0, 74.6, 70.5, 63.6, 56.0, 52.6 (d, $J_{F,C}$ = 3 Hz), 37.2, 35.2, 35.1, 34.7, 32.1, 25.9, 24.3, 18.1, 15.3; MS (ESI) 680.1 (M^+ + Na); Anal. Calcd for $C_{30}H_{35}F_3INO_4$ (657.16): C, 54.80; H, 5.37; N, 2.13. Found: C, 54.85; H, 5.36; N, 2.11.

(1′*R*, 5′*S*, 7′*R*, 1″*R*)-4-{1′-[2″-benzyloxy-1″-methyl-ethyl]-6′-trifluoroacetyl-6′-aza-5′-spiro [4.5]dec-7′-yl}-2-methyl-but-2*E*-enoic Acid Ethyl Ester (30). The alcohol **27** (140 mg, 0.33 mmol) in CH_2Cl_2 (18 mL) was added to a mixture of PCC (355 mg, 1.65 mmol) and Celite (500 mg). After stirring at room temperature for 2 h, the mixture was diluted with hexanes (50 mL) and filtered through a short silica gel column. The filtrate was concentrated and purified by flash chromatography (silica gel, EtOAc/Hexanes 1:2) to afford aldehyde 29 (130 mg, 93%) as a colorless oil. To sodium hydride (60%, 25 mg, 0.61 mmol) was added triethyl-2-phosphonopropionate (183 mg, 0.76 mmol) in THF (5 mL) at 0 °C. After stirring for 30 min, aldehyde **29** (130 mg, 0.30 mmol) in THF (2 mL) was added. After 20 min, the mixture was warmed to room temperature and reacted for 1 h and saturated ammonium chloride was added to the solution and extracted with ethyl acetate. The extract was washed with water and brine, and dried (Na_2SO_4), concentrated, and purified by flash chromatography (silica gel, EtOAc/Hexanes 1:10) to afford **30** (141 mg, 90%) as a colorless oil.

$[\alpha]^{20}_D$ − 21.6 (*c* 0.95, $CHCl_3$); R_f 0.70 (EtOAc/Hexanes 2:10); IR (film) ν_{max} 1712, 1690, 1652, 1260, 1200, 1139 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.32 (m, 5H), 6.54 (t, J = 7.2 Hz, 1H), 4.48 (q, J = 12.6 Hz, 2H), 4.22 (q, J = 7.1 Hz, 2H), 3.92 (d, J = 9.3 Hz, 1H), 3.40−3.32 (t, J = 4.8 Hz, 2H), 2.59−2.37 (m, 2H), 2.25−2.05 (m, 3H), 1.86−1.57 (m, 14H), 1.28 (t, J = 7.2 Hz, 3H), 0.96 (d, J = 6.3 Hz, 3H); ^{19}F NMR(200 MHz, $CDCl_3$): δ −69.02; ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 162.4, 157.4 (q, $J_{F,C=O}$ = 34 Hz), 138.6, 136.6, 130.2, 128.3, 127.6, 117.0 (q, $J_{F,C}$ = 287 Hz), 75.8, 73.2, 69.2, 60.7, 54.6, 53.1 (t, $J_{F,C}$ = 3.5 Hz), 35.6, 34.8, 34.3, 33.4, 30.6, 24.5, 23.3, 16.7, 14.3, 14.1, 12.7; MS (ESI) 532.3 (M^+ + Na); HRMS (ESI) calcd for $C_{28}H_{38}F_3NO_4Na$ (M^+ + Na) 532.2645, found 532.2647.

(11*R*, 1′*S*, 5′*R*, 6′*R*)-4-(6′-Methyl-9′-hydroxy-9′-trifluoromethyl-8′-oxa-10′-aza-1′-tricyclo[8.4. 0.0$^{1',5'}$]tetradec-11′-yl)-2-methyl-but-2*E*-enoic Acid Ethyl Ester (31). TMSI (0.53 mL, 2.60 mmol) was added dropwise to a solution of **30** (1.02 g, 2.00 mmol) in CH_2Cl_2 (20 mL) at room temperature. After 40 min, MeOH (0.8 mL) was added to the orange-red solution. The mixture was diluted with EtOAc and washed with saturated $Na_2S_2O_3$, saturated $NaHCO_3$, and brine and dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography (silica gel, EtOAc/Hexanes 2:5) to give **31** (700 mg, 83%) as a yellow oil.

$[\alpha]^{20}_D$ + 26.8 (*c* 0.35, $CHCl_3$) R_f 0.32 (EtOAc/hexanes 2:10); IR (film) ν_{max} 3311, 2954, 2869, 1709, 1651, 1553, 1182 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.69 (t, J = 7.1 Hz, 1H), 6.44 (d, J = 8.7 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 4.07 (m, 1H), 3.87 (dd, J = 8.7, 6.6 Hz, 1H), 3.21 (t, J = 8.7 Hz, 1H), 2.45 (q, J = 7.2 Hz, 2H), 2.34 (t, J = 7.5 Hz, 1H), 1.85 (s, 3H), 1.82−1.41

(m, 13H), 1.27 (t, $J = 7.2$ Hz, 3H), 1.02 (d, $J = 6.9$ Hz, 3H);^{19}F NMR(200 MHz, $CDCl_3$) δ −76.25; MS (ESI) 442.2 ($M^+ + Na$); HRMS (ESI) calcd for $C_{21}H_{32}F_3NO_4Na$ ($M^+ + Na$) 442.2175, found 442.2162.

(1′*R*, 5′*S*, 7′*R*, 1″*R*)-4-[7′-(2″-hydroxy-1″-methyl-ethyl)-6′-trifluoroacetyl-6′-aza-5′-spiro[4.5] dec-1′-yl]-2-methyl-but-2*E*-enoic Acid Ethyl Ester (3). A solution of BBr_3 (0.36 mL, 2 M in CH_2Cl_2, 0.72 mmol) was added rapidly via syringe to a stirred solution of the ester **30** (183 mg, 0.36 mmol) in CH_2Cl_2 (15 mL) at −78 °C. After 20 min, saturated $NaHCO_3$ and $Na_2S_2O_3$ were added sequentially to stirred solution. The organic layer was washed with saturated $NaHCO_3$ and water, dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography (silica gel, EtOAc/Hexanes 2:5) to give **3** (138 mg, 91%) as a colorless oil.

$[\alpha]^{20}_D$ − 7.2 (*c* 1.01, $CHCl_3$); R_f 0.29 (EtOAc/Hexanes 2:5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.61 (t, $J = 7.5$ Hz, 1H), 4.20 (q, $J = 7.1$ Hz, 2H), 4.02 (d, $J = 11.0$ Hz, 1H), 3.65 (dd, $J = 10.2$, 3.1 Hz, 1H), 3.51 (dd, $J = 10.4$, 5.1 Hz, 1H), 2.88−2.76 (m, 1H), 2.59 (m, 1H), 2.20 (m, 3H), 1.91−1.61 (m, 15H), 1.30 (t, $J = 7.1$ Hz, 3H), 0.95 (d, $J = 6.2$ Hz, 3H); ^{19}F NMR(200 MHz, $CDCl_3$) δ −69.02; ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 157.1 (q, $J_{F,C=O} = 34$ Hz), 136.0, 130.1, 116.6 (q, $J_{F,C} = 287$ Hz), 68.8, 67.6, 60.5, 53.7, 52.9 (dd, $J_{F,C} = 3.9$, 6.8 Hz), 35.3, 35.1, 34.5, 34.1, 30.4, 24.2, 22.9, 15.9, 13.9, 13.8, 12.4; IR (film) ν_{max} 3518, 2953, 2873, 1711, 1691, 1652, 1263, 1201, 1138 cm^{-1}; MS (ESI) 442.2 ($M^+ + Na$); HRMS (ESI) calcd for $C_{21}H_{32}F_3NO_4Na$ ($M^+ + Na$) 442.2176, found 442.2177.

Acknowledgment. We thank the National Natural Sciences Foundation for support of this research.

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra and data of single-crystal X-ray structure analysis of *p*-iodo-benzoate **28**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO047882V