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Formal Synthesis of (−)-Perhydrohistrionicotoxin via Cyclic Amino Acid Ester−Enolate Claisen Rearrangement and Ring-Closing Metathesis

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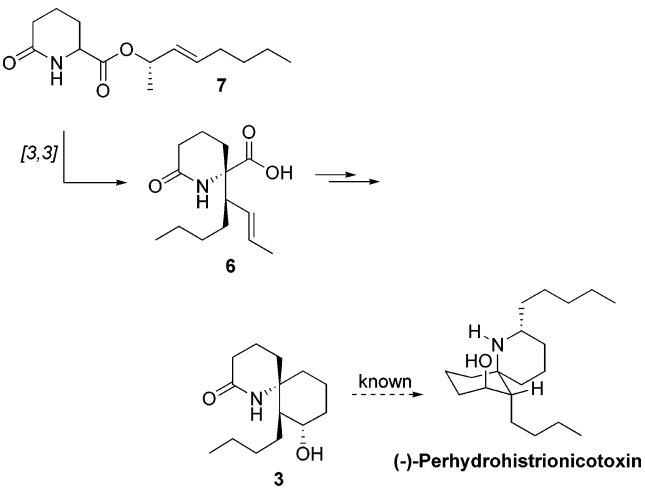

We have successfully synthesized an advanced synthetic intermediate, hydroxy lactam **3**, which has previously been converted to perhydrohistrionicotoxin. An important feature of this synthesis is the creation of stereogenic centers by using the cyclic amino acid ester−enolate Claisen rearrangement together with a ring-closing metathesis for azaspirocyclic skeleton construction.

In 1971, Witkop and co-workers reported the isolation and structure of a unique azaspirocyclic alkaloid designated (−)-histrionicotoxin (**1**, Figure 1).[1] Since its isolation, a further 15 alkaloids in this family have been identified, varying only in the length and degree of saturation present in the two side chains.[2] Due to their unique biological properties and challenging architecture, these alkaloids along with the nonnatural perhydrohistrionicotoxin (**2**) have been attractive and popular targets for synthetic chemists over the last few decades.[3] Indeed, more than 70 elegant synthetic approaches to histrionicotoxins have been reported to date. Despite these numerous approaches, the histrionicotoxins remain particularly attractive targets for organic synthesis, especially in developing new synthetic strategies for the stereoselective construction of the azaspiro[5.5]undecane framework of these alkaloids. Herein, we wish to report a novel formal stereoselective synthesis of (−)-perhydrohistrionicotoxin (**2**). Our strategy is based on the use of the cyclic amino acid ester−enolate Claisen rearrangement and a ring-closing metathesis (RCM) reaction[4] as presented in the retrosynthetic Scheme 1.

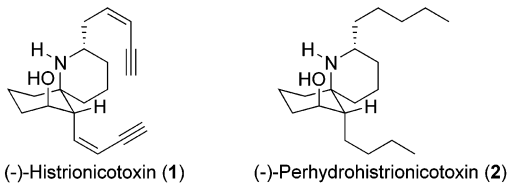

FIGURE 1. Chemical structures of compounds **1** and **2**.

Hydroxy lactam **3** (Scheme 1) is a key advanced intermediate in previous total syntheses of perhydrohistrionicotoxin, and several syntheses of **3** have been developed.[5] We envisioned that this intermediate **3** could be synthesized from the cyclohexene **4**. The azaspirocyclic skeleton of **4** was envisaged to be constructed by a RCM of diene **5**, which then would be accessible from the densely functionalized cyclic amino acid **6**. The presence of a γ,δ-unsaturated carbonyl unit in compound **6** suggested the use of a Claisen rearrangement of cyclic amino acid allylic ester **7**. This transformation could establish the relative stereochemistry of two contiguous stereocenters by controlling the enolate geometry and olefin configuration. Further analysis indicated the commercially available 6-oxopipecolic acid and the known (*S*)-(*E*)-3-octen-2-ol[6] as a source of chirality to be suitable synthetic precursors for the Claisen rearrangement substrate **7**.

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(1) Daly, J. W.; Karle, I.; Myers, C. W.; Tokuyama, T.; Waters, J. A.; Witkop, B. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1870.
(2) Daly, J. W. *J. Nat. Prod.* **1998**, *61*, 162.
(3) For recent leading references to histrionicotoxins and perhydrohistrionicotoxin syntheses, see: (a) Stockman, R. A.; Sinclair, A.; Arini, L. G.; Szeto, P.; Hughes, D. L. *J. Org. Chem.* **2004**, *69*, 1598. (b) McLaughlin, M. J.; Hsung, R. P.; Cole, K. P.; Hahn, J. M.; Wang, J. *Org. Lett.* **2002**, *4*, 2017. (c) Luzzio, F. A.; Fitch, R. W. *J. Org. Chem.* **1999**, *64*, 5485.
(4) For precedents in the construction of azaspirocyclic skeleton of histrionicotoxins using RCM, see: (a) Tanner, D.; Hagberg, L.; Poulsen, A. *Tetrahedron* **1999**, *55*, 1427. (b) Wybrow, R. A. J.; Stevenson, N. G.; Harrity, J. P. A. *Synlett* **2004**, 140.
(5) (a) Corey, E. J.; Arnett, J. F.; Widiger, G. N. *J. Am. Chem. Soc.* **1975**, *97*, 430. (b) Aratani, M.; Dunkerton, L. V.; Fukuyama, T.; Kishi, Y. *J. Org. Chem.* **1975**, *40*, 2009. (c) Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron Lett.* **1978**, *19*, 4841. (d) Takahashi, K.; Witkop, B.; Brossi, A. *Helv. Chim. Acta* **1982**, *65*, 252. (e) Ibuka, T.; Minakata, H.; Mitsui, Y.; Hayashi, K.; Taga, T.; Inubushi, Y. *Chem. Pharm. Bull.* **1982**, *30*, 2840. (f) Fukuyama, T. Dunkerton, L. V.; Aratani, M.; Kishi, Y. *J. Org. Chem.* **1975**, *40*, 2011. (g) Ibuka, T.; Mitsui, Y.; Hayashi, K.; Minakata, H.; Inubushi, Y. *Tetrahedron Lett.* **1981**, *22*, 4425. (h) Keck, G. E.; Yates, J. B. *J. Org. Chem.* **1982**, *47*, 3590. (i) Evans, D. A.; Thomas, E. W. *Tetrahedron Lett.* **1979**, *20*, 411.
(6) (a) Takeda, Y.; Matsumoto, T.; Sato, F. *J. Org. Chem.* **1986**, *51*, 4731. (b) Gung, B. W.; Wolf, M. B. *J. Org. Chem.* **1993**, *58*, 7038. (c) Stampfer, W.; Kosjek, B. Moitzi, C.; Kroutil, W.; Faber, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 1014.

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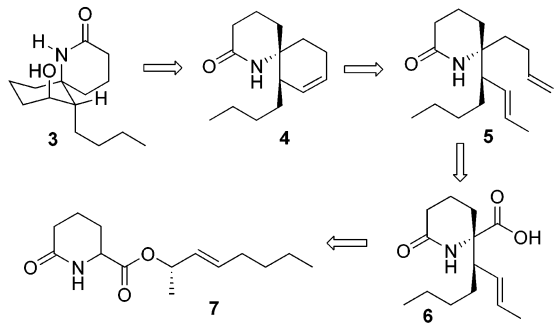
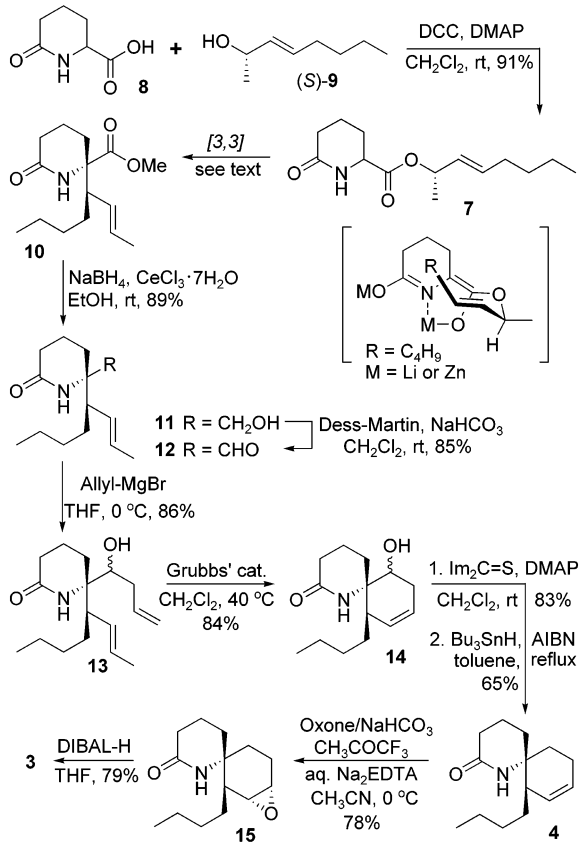
SCHEME 1. Retrosynthetic Analysis of Perhydrohistrionicotoxin



Our approach commenced with the preparation of ester **7** by DCC coupling of allylic alcohol (*S*)-**9** (98.5% ee) with racemic 6-oxopipecolic acid **8** (91%). With multigram quantities of diastereomeric mixture **7** in hand, we explored the cyclic amino acid ester-enolate Claisen rearrangement, focusing on both yield and diastereoselectivity. First, allylic ester **7** was exposed to LDA and TBSCl in THF at −78 °C (Bartlett's amino acid ester-enolate Claisen rearrangement standard conditions),[7] with gradual warming to room temperature to promote the rearrangement. After an acidic workup followed by treatment with diazomethane, these conditions predominantly afforded the desired ester **10**, along with a minor amount of the stereoisomer in 80% combined yield and 8:1 selectivity. Under the Kazmaier's zinc chelated enolate Claisen rearrangement conditions[8] (LDA, $ZnCl_2$, THF), the reaction took place with a higher stereoselectivity (30:1) in favor of the desired isomer **10** (98.2% ee by chiral HPLC analysis) with 75% combined yield. Chirality was conserved during the reaction, and as a result, the stereochemistry originating from the chiral allylic alcohol (*S*)-**9** was transferred to the functionalized cyclic amino ester **10**. The relative stereochemistry of the newly generated two stereocenters of **10** was tentatively assigned as shown on the basis of the literature precedent of Bartlett[7] and Kazmaier[8,9] and established by its conversion to **3**. This stereochemical outcome can be rationalized by considering the chelation control over enolate geometry and π-facial preferences dictated by the chairlike transition state, as shown in the bracket (Scheme 2).

We then turned our attention to the conversion of the methyl ester into the homoallyl group for the preparation of the metathesis precursor **5**. Thus, the ester of **10** was reduced to the primary alcohol under Luche conditions[10] to give **11** in 89% yield. Initial attempts at addition of allylmetal reagents to the corresponding primary iodide were unsuccessful, presumably due to the high degree of steric hindrance. Therefore, we oxidized the hydroxyl group of **11** to form aldehyde **12** with Dess−Martin periodinane[11] (85%) and then attempted the addition of allylmetal reagents. Grignard reaction between allylmagnesium bromide and aldehyde **12** successfully gave

SCHEME 2. Formal Synthesis of (−)-Perhydrohistrionicotoxin.



homoallylic alcohol **13** as an inseparable mixture (ca. 7:3 ratio) in 86% yield. Our attempts at accomplishing the removal of the sterically hindered hydroxy group in **13**, using various methods including the Barton's protocol,[12] were not successful. Thus, we decided to perform the ring-closing metathesis before the deoxygenation step.

The crucial ring-closing metathesis of **13** was successfully performed with Grubbs' phosphorylidine catalyst[13] [$RuCl_2$(=CHPh)(PCy_3)$_2$] in CH_2Cl_2 at 40 °C to produce the desired azaspiro-cyclohexene derivative **14** in high yield (84%). At this stage, the deoxygenation of the secondary neopentyl-like alcohol was readily accomplished by reaction of **14** with thiocarbonyldiimidazole and radical reduction[12b] to give **4** in 54% overall yield.

Efforts were next directed toward the functional group transformation of the $\Delta^{8,9}$-olefin of **4** to the C-8α hydroxy group of **3** for the completion of the formal synthesis of perhydrohistrionicotoxin. Treatment of the olefin **4** with *m*-CPBA provided the epoxide **15** and its stereoisomer in 77% combined yield and 1.6:1 selectivity. However, the reaction of **4** with the dioxirane, generated in situ from Oxone with 1,1,1-trifluoroacetone,[14] afforded the epoxide **15** with a high stereoselectivity (30:1 in crude ^{1}H NMR spectra) in 78% yield. The epoxide stereochemistry was

(7) Bartlett, P. A.; Barstow, J. F. *J. Org. Chem.* **1982**, *47*, 3933.
(8) (a) Kazmaier, U. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 998. (b) Kazmaier, U. *Liebigs Ann./Recueil* **1997**, 285.
(9) Kazmaier, U.; Mues, H.; Krebs, A. *Chem. Eur. J.* **2002**, *8*, 1850.
(10) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.
(11) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
(12) (a) Barton, D. H. R.; Jaszberencyi, J. Cs. *Tetrahedron Lett.* **1989**, *30*, 2619. (b) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.
(13) (a) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100. (b) Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887.
(14) Yang, D.; Wong, M.-K.; Yip, Y.-C. *J. Org. Chem.* **1995**, *60*, 3887.

tentatively assigned as α, on the basis of steric considerations. Finally, the regioselective cleavage of the epoxy ring with DIBAL-H in THF led to the formation of the desired alcohol **3** (79%) as a single regioisomer, which is an advanced intermediate in previous total syntheses of perhydrohistrionicotoxin. The structure of **3** was confirmed by comprehensive 2D NMR studies (COSY, HSQC, and HMBC), and the ^{1}H and ^{13}C NMR spectral data were virtually identical to those reported.[5b−e] Moreover, the structure and stereochemistry of **3** thus obtained was confirmed by converting **3** to other known advanced intermediates and comparing the spectral data (see the Supporting Information).

In conclusion, we have accomplished the stereoselective formal synthesis of (−)-perhydrohistrionicotoxin with a high overall yield from readily available starting materials. An important feature of this synthesis is the creation of stereogenic centers by using the cyclic amino acid ester−enolate Claisen rearrangement followed by a ring-closing metathesis for azaspirocyclic skeleton construction.

Experimental Section

(2*RS*,1′*S*)-6-Oxopiperidine-2-carboxylic Acid 1′-Methylhept-2′-enyl Ester (7). To a mixture of 6-oxopipecolic acid **8** (4.0 g, 25 mmol) and (*S*)-**9** (3.6 g, 28 mmol) in CH_2Cl_2 (50 mL) were added DMAP (310 mg, 2.5 mmol) and DCC (6.0 g, 29 mmol) at 0 °C. After the reaction mixture was stirred for 20 min at 0 °C, it was warmed to room temperature over 1 h. The reaction mixture was concentrated, dissolved in hexane, and filtered through a Celite pad. The filtrate was evaporated under reduced pressure and purified by column chromatography on silica gel (hexane/EtOAc = 1:1) to give a diastereomeric mixture **7** (5.8 g, 91%) as yellow oil: IR (film) ν_{max} 3225.3, 3107.6, 2932.1, 2872.3, 1743.8, 1680.2 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J = 7.8 Hz, 3H), 0.25−1.38 (m, 7H), 1.72−1.94 (m, 3H), 2.02 (dd, J = 12.9, 6.9 Hz, 2H), 2.14−2.24 (m, 1H), 2.34−2.40 (m, 2H), 4.04 (t, J = 11.7 Hz, 1H), 5.37 (dd, J = 13.5, 6.6 Hz, 1H), 5.46 (m, 1H), 5.71 (dt, J = 14.4, 6.9 Hz, 1H), 6.27 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7, 19.1, 19.3, 20.1, 21.9, 22.0, 25.2, 25.2, 30.79, 30.81, 30.83, 31.6, 54.65, 54.68, 72.7, 72.8, 128.4, 128.5, 134.3, 134.4, 170.3, 171.36, 171.39; MS-CI *m/z* (rel int) 254 ([M + 1]$^+$, 50), 144 (100), 98 (37), 172 (28); HRMS-CI (calcd for $C_{14}H_{24}NO_3$ ([M + H]$^+$)) 254.1756, found 254.1757.

(2*S*,1′*S*)-2-(1′-Butylbut-2′-enyl)-6-oxopiperidine-2-carboxylic Acid Methyl Ester (10). To a solution of **7** (120 mg, 0.47 mmol) in THF (10 mL) was added LDA (0.7 mL, 2.0 M in THF) at −78 °C. After the mixture was stirred for 5 min, $ZnCl_2$ (2.4 mL, 0.5 M in THF) was added. This reaction mixture was allowed to warm to room temperature and continued to stir for 15 h. The mixture was treated with 1 N $NaHSO_4$ and extracted with CH_2Cl_2 twice. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. This residue (**6**) was dissolved in Et_2O and treated with diazomethane. The mixture was evaporated under reduced pressure and purified by column chromatography on silica gel (hexane/EtOAc = 1:1) to give an inseparable mixture of **10** and its minor isomer (90 mg, 75%) as yellow oil. The ratio of two stereoisomers is 30:1 in the crude ^{1}H NMR spectrum.

Compound **10** was isolated from its minor isomer for analytical purposes by column chromatography on silica gel (hexane/EtOAc = 5:1, taking a small quantity on the top of the mixture). The enantiopurity was determined by chiral HPLC analysis (CHIRALCEL OD-H, 2% isopropyl alcohol in hexane, flow rate 0.2 mL/min, retention time: 71.82 min (−)-isomer, detected at 215 nm, 98.2% ee): IR (film) ν_{max} 3221.4, 3094.1, 2955.2, 2874.2, 1738.0, 1688.6 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80 (t, J = 6.9 Hz, 3H), 1.01−1.27 (m, 6H), 1.43−1.56 (m, 1H), 1.58 (dd, J = 13.2, 2.7 Hz, 1H) 1.65 (dd, J = 6.6, 1.8 Hz, 3H), 1.70−1.80 (m, 1H), 2.12−2.30 (m, 3H), 2.28−2.36 (m, 1H), 3.67 (s, 3H), 4.99 (dddd, J = 9.9, 5.3, 3.0, 1.8 Hz, 1H), 5.47 (dddd, J = 15.3, 6.6, 6.6, 6.6 Hz, 1H), 6.15 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7, 17.9, 18.0, 22.2, 28.3, 28.8, 29.5, 30.9, 51.4, 52.3, 66.0, 128.3, 130.8, 172.7, 173.5; MS-CI *m/z* (rel int) 268 ([M + 1]$^+$, 100), 156 (22), 296 (19); HRMS-CI (Calcd for $C_{15}H_{26}NO_3$ ([M + H]$^+$)) 268.1913, found 268.1911.

(6*R*,1′*S*)-6-(1′-Butylbut-2′-enyl)-6-hydroxymethylpiperidin-2-one (11). To a suspension of $NaBH_4$ (6.0 g, 159 mmol) and cerium chloride heptahydrate (8.0 g, 22 mmol) in EtOH (100 mL) was added dropwise the solution of **10** and its minor isomer (4.0 g, 15 mmol, 25:1 mixture) in EtOH (10 mL) for 1 h. The reaction mixture was stirred for 2 days at room temperature. The mixture was poured into saturated aqueous NH_4Cl solution and extracted with EtOAc three times. The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. This residue was purified by column chromatography on silica gel (hexane/EtOAc = 1:1) to give an inseparable mixture of **11** and its minor isomer (3.2 g, 89%) as colorless sticky foam. The ratio of two stereoisomers is 25:1 in crude ^{1}H NMR spectrum: IR (film) ν_{max} 3298.6, 3049.7, 2953.3, 1714.9, 1651.2, 1456.4, 1412.0 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.82 (t, J = 6.9 Hz, 3H), 0.97−1.30 (m, 5H), 1.38−1.44 (m, 1H), 1.50−1.60 (m, 2H), 1.64 (dd, J = 6.3, 1.5 Hz, 3H) 1.68−1.81 (m, 2H), 2.03−2.11 (m, 1H), 2.14−2.28 (m, 2H), 3.45 (dd, J = 21.0, 11.1 Hz, 2H), 4.18 (br s, 1H), 5.10 (ddd, J = 15.0, 9.6, 3.9 Hz, 1H), 5.47 (dddd, J = 15.0, 6.3, 6.3, 6.3 Hz, 1H), 6.70 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 17.9, 18.0, 22.6, 25.2, 28.1, 30.1, 31.2, 49.6, 60.2, 67.6, 129.2, 130.0, 173.8; MS-CI *m/z* (rel int) 240 ([M + 1]$^+$, 100), 128 (56); HRMS-CI (calcd for $C_{14}H_{26}NO_2$ ([M + H]$^+$)) 240.1963, found 240.1964.

(2*S*,1′*S*)-2-(1′-Butylbut-2′-enyl)-6-oxopiperidine-2-carbaldehyde (12). To a solution of **11** and its minor isomer (2.2 g, 9.2 mmol) in CH_2Cl_2 (10 mL) were added powered $NaHCO_3$ (2.3 g, 27 mmol) and Dess−Martin periodinane (7.8 g, 18 mmol). After the mixture was stirred for 24 h, $NaHCO_3$ (1.0 g, 12 mmol) and Dess−Martin periodinane (4.0 g, 9.4 mmol) were added once more. The reaction mixture was stirred for an additional 24 h, and isopropyl alcohol (5 mL) was added. The mixture was poured into saturated aqueous $NaHCO_3$ solution and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. This residue was purified by column chromatography on silica gel (hexane/EtOAc = 1:1) to give an inseparable mixture of **12** and its minor isomer (1.9 g, 85%) as yellow oil. The ratio of two stereoisomers is 25:1 in the crude ^{1}H NMR spectrum: IR (film) ν_{max} 3211.8, 3088.3, 2955.2, 2860.7, 1732.2, 1668.6, 1466.0, 1396.6 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.86 (t, J = 6.9 Hz, 3H), 1.04−1.27 (m, 4H), 1.29−1.36 (m, 2H), 1.38−1.53 (m, 2H), 1.64 (dd, J = 13.5, 3.3 Hz, 1H), 1.72 (dd, J = 6.3, 1.8 Hz, 3H) 1.75−1.85 (m, 1H), 2.10−2.22 (m, 1H), 2.23−2.31 (m, 1H), 2.33−2.42 (m, 1H), 5.05 (dddd, J = 15.3, 10.2, 3.3, 1.5 Hz, 1H), 5.59 (dddd, J = 15.0, 6.3, 6.3, 6.3 Hz, 1H), 6.09 (br s, 1H), 9.51 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.9, 17.5, 17.9, 22.3, 25.9, 28.1, 29.7, 31.0, 50.3, 67.8, 127.6, 131.8, 172.8, 201.6; MS-CI *m/z* (rel int) 238 ([M + 1]$^+$, 100), 208 (70), 114 (49), 128 (22); HRMS-CI (calcd for $C_{14}H_{24}NO_2$ ([M + H]$^+$)) 238.1807, found 238.1806.

(6*S*,1′*S*,1″*RS*)-6-(1′-Butylbut-2′-enyl)-6-(1″-hydroxybut-3″-enyl)piperidin-2-one (13). To a solution of **12** (700 mg, 3.0 mmol) in THF (7 mL) was added allylmagnesium bromide (6.0 mL, 1.0 M in EtO_2) at 0 °C. After the reaction mixture was stirred for 40 min at 0 C, the reaction was quenched with saturated aqueous NH_4Cl. The aqueous layer was then extracted with EtOAc and dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 1:2 to hexane/EtOAc = 1:4) to give yellowish oil **13** (712 mg, 86%) as a diastereomeric mixture: IR (film) ν_{max} 3377.7, 3074.8, 2955.2, 1653.1, 1454.5, 1412.0 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) (diastereomer ratio 7:3) major δ 0.84 (t, J = 6.9 Hz, 3H), 0.98−1.38 (m, 6H), 1.53−1.62 (m, 1H), 1.67 (dd, J = 6.3, 1.5 Hz, 3H), 1.71−1.86 (m, 2H), 1.98−2.44 (m, 6H), 2.65 (br s, 1H), 3.52 (dd, J = 10.2, 2.4 Hz, 1H), 5.08−5.20 (m, 3H), 5.39−5.54 (m, 1H), 5.74−5.87 (m, 1H), 6.10 (br s, 1H); minor δ 0.84 (t, J = 6.9 Hz, 3H), 0.98−1.38 (m, 6H),

1.53−1.62 (m, 1H), 1.67 (dd, J = 6.3, 1.5 Hz, 3H), 1.71−1.86 (m, 2H), 1.98−2.44 (m, 6H), 2.65 (br s, 1H), 3.58 (dd, J = 10.5, 2.4 Hz, 1H), 5.08−5.20 (m, 3H), 5.39−5.54 (m, 1H), 5.74−5.87 (m, 1H), 6.20 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.87, 13.90, 17.8, 17.9, 18.5, 18.8, 22.4, 22.5, 23.9, 25.4, 27.7, 28.2, 29.75, 29.82, 31.2, 31.3, 35.4, 35.8, 50.1, 50.5, 61.6, 61.9, 74.1, 76.2, 117.2, 117.4, 128.5, 129.9, 130.3, 135.3, 135.7, 173.9, 174.5; MS-CI *m/z* (rel int) 280 ([M + 1]$^+$, 100), 168 (55), 208 (35); HRMS-CI (calcd for $C_{17}H_{30}NO_2$ ([M + H]$^+$)) 280.2276, found 280.2271.

(6*S*,7*S*,11*RS*)-7-Butyl-11-hydroxy-1-azaspiro[5.5]undec-8-en-2-one (14). To a solution of **13** (700 mg, 2.5 mmol) in degassed CH_2Cl_2 (40 mL) was added Grubbs' phosphorylidine catalyst [$RuCl_2$(=CHPh)(PCy_3)$_2$] (103 mg, 0.13 mmol). The reaction mixture was heated (40 °C) for 20 h. The mixture was evaporated under reduced pressure and directly purified by column chromatography on silica gel in EtOAc to give colorless oil **14** (500 mg, 84%) as a diastereomeric mixture: IR (film) ν_{max} 3277.4, 2928.2, 1645.4, 1458.3, 1406.2 cm^{-1}; ^{1}H NMR ($CDCl_3$, D_2O, 300 MHz) (diastereomer ratio 7:3) major δ 0.84 (t, J = 6.6 Hz, 3H), 1.09−1.43 (m, 4H), 1.43−1.55 (m, 2H), 1.58−1.81 (m, 3H), 1.84−1.92 (m, 1H), 2.05−2.36 (m, 4H), 2.40−2.52 (m, 1H), 3.65 (dd, J = 9.9, 6.6 Hz, 1H), 5.45−5.65 (m, 2H); minor δ 0.84 (t, J = 6.6 Hz, 3H), 1.09−1.43 (m, 4H), 1.43−1.55 (m, 2H), 1.58−1.81 (m, 3H), 1.84−1.92 (m, 1H), 2.05−2.36 (m, 4H), 2.40−2.52 (m, 1H), 3.76 (dd, J = 3.6, 3.6 Hz, 1H), 5.45−5.65 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.9, 14.0, 17.5, 18.5, 19.6, 22.7, 22.8, 24.7, 28.4, 28.5, 29.9, 30.1, 31.0, 31.8, 32.0, 40.7, 46.9, 59.0, 60.6, 71.5, 73.2, 122.6, 124.7, 127.6, 127.9, 173.5, 175.7; MS-CI *m/z* (rel int) 238 ([M + 1]$^+$, 100), 236 (31), 127 (16); HRMS-CI (Calcd for $C_{14}H_{24}NO_2$ ([M + H]$^+$)) 238.1807, found 238.1815.

(6*S*,7*S*)-7-Butyl-1-azaspiro[5.5]undec-8-en-2-one (4). To a mixture of **14** (330 mg, 1.4 mmol) and DMAP (17 mg, 0.14 mmol) in CH_2Cl_2 (4 mL) was added thiocarbonyldiimidazole (1.5 g, 7.6 mmol). After being stirred for 20 h at room temperature, the reaction mixture was evaporated under reduced pressure and directly loaded on silica gel column chromatography (hexane/EtOAc = 1:1 to hexane/EtOAc = 1:3) to give imidazole derivatives (401 mg, 83%) as a diastereomeric mixture. To a mixture of imidazole derivatives (300 mg, 0.86 mmol) and AIBN (14 mg, 0.09 mmol) in degassed toluene (12 mL) was added tributyltin hydride (0.58 mL, 2.2 mmol). After the mixture was heated to reflux for 2 h, it was cooled to room temperature. The crude mixture was evaporated under reduced pressure and loaded on silica gel column chromatography (hexane/EtOAc = 1:1 to hexane/EtOAc = 1:3) to give a single isomer **4** (125 mg, 65%) as colorless oil: $[\alpha]^{21}_D$ −157.6 (*c* 1.0, $CHCl_3$); IR (film) ν_{max} 3188.6, 3022.7, 2930.1, 1660.9, 1456.4, 1402.4 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J = 6.9 Hz, 3H), 1.01−1.16 (m, 1H), 1.20−1.46 (m, 5H), 1.49−1.73 (m, 5H), 1.74−1.91 (m, 3H), 2.08−2.12 (m, 1H), 2.19−2.41 (m, 2H), 5.60−5.70 (m, 2H), 5.98 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 17.0, 22.7, 22.9, 28.8, 29.5, 30.8, 30.9, 31.3, 46.3, 55.6, 126.1, 128.4, 172.2; MS-CI *m/z* (rel int) 222 ([M + 1]$^+$, 100), 111 (17), 112 (13); HRMS-CI (Calcd for $C_{14}H_{24}NO$ ([M + H]$^+$)) 222.1858, found 222.1858.

(6*S*,7*S*,8*R*,9*S*)-7-Butyl-8,9-epoxy-1-azaspiro[5.5]undecan-2-one (15). To a solution of **4** (30 mg, 0.14 mmol) in CH_3CN (1.5 mL) and Na_2EDTA aqueous solution (1 mL, 4×10^{-4} M in H_2O) was added 1,1,1-trifluoroacetone (0.14 mL, 1.56 mmol) by using a precooled syringe at 0 °C, followed by treatment with a mixture of Oxone (420 mg, 0.68 mmol) and $NaHCO_3$ (86 mg, 1.02 mmol) in several portions at 0 °C. After this reaction mixture was stirred for 2 h at 0 °C, it was diluted with EtOAc and washed with H_2O. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. This residue was purified by column chromatography on silica gel (hexane/EtOAc = 1:3) to give compound **15** and its minor isomer (30:1 in crude ^{1}H NMR, 25 mg, 78%) as a yellow oil: IR (film) ν_{max} 2955.2, 2932.1, 2870.3, 1676.3, 1462.2 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, J = 7.2 Hz, 3H), 1.20−2.00 (m, 12H), 2.09−2.22 (m, 2H), 2.27 (dd, J = 10.2, 6.9 Hz, 1H), 2.31−2.40 (m, 2H), 3.00 (d, J = 3.9 Hz, 1H), 3.17 (t, J = 3.9 Hz, 1H), 6.12 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 16.3, 22.1, 22.7, 26.7, 27.2, 27.4, 29.6, 34.3, 43.3, 51.2, 55.2, 67.8, 168.7; MS-EI *m/z* (rel int) 237 (M$^+$, 3), 236 (17), 218 (14), 148 (37), 124 (54), 96 (52), 82 (74), 55 (100); HRMS-CI (calcd for $C_{14}H_{22}NO_2$ ([M − H]$^+$)) 236.1650, found 236.1649.

(6*S*,7*S*,8*S*)-7-Butyl-8-hydroxy-1-azaspiro[5.5]undecan-2-one (3). To a solution of **15** (15 mg, 0.06 mmol) in THF (2 mL) was added DIBAL-H (0.12 mL, 1.0 M in CH_2Cl_2) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, warmed to room temperature for 30 min, and quenched with saturated aqueous NH_4Cl. It was diluted with EtOAc and washed with 1 N HCl. The aqueous layer was extracted with EtOAc twice. The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel column chromatography in EtOAc only to give **3** (12 mg, 79%) as a colorless form: mp 98−99 C; $[\alpha]^{17}_D$ −59.2 (*c* 0.8, $CHCl_3$) [lit.[5d] $[\alpha]^{25}_D$ −65.3 (*c* 1.01, $CHCl_3$)]; IR (film) ν_{max} 3273.5, 2935.9, 2870.3, 1645.4, 1466.0, 1406.2 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.88 (t, J = 4.2 Hz, 3H); 1.11−1.15 (m, 1H), 1.24−1.50 (m, 8H), 1.52−1.60 (m, 1H), 1.62−1.84 (m, 6H), 1.85−1.89 (m, 1H), 2.22−2.26 (m, 1H), 2.31−2.36 (m, 1H), 4.01 (br s, 1H; dd, W1/2 = 7.8 Hz at 300 MHz), 4.68 (br s, 1H), 8.28 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.2, 16.5, 16.8, 23.2, 27.6, 29.3, 30.9, 31.6, 32.0, 33.8, 50.3, 57.9, 70.5, 172.0; MS-EI *m/z* (rel int) 239 (M$^+$, 29), 196 (26), 124 (41), 112 (100), 55 (89); HRMS-EI (calcd for $C_{14}H_{25}NO_2$) 239.1885, found 239.1884.

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Supporting Information Available: Experimental procedures for the synthesis of **9** and other known advanced intermediates; copies of ^{1}H NMR and ^{13}C NMR spectra of compounds **3**, **4**, **7**, **10**, and **13**−**15**, ^{1}H NMR spectrum of mixture of **15** and *epi*-**15**, and COSY, HSQC, and HMBC spectra of compound **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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