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Total Synthesis of (±)-Przewalskin B

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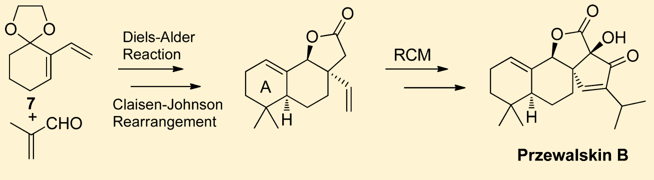
S Supporting Information

ABSTRACT: A concise total synthesis of przewalskin B was accomplished from readily available diene 7. Key features of the synthesis involved a Diels−Alder reaction to install the A ring, a Claisen−Johnson rearrangement to establish the spiro-quaternary center, and a ring-closing metathesis (RCM) of a sterically crowded system to construct the cyclic enone moiety.



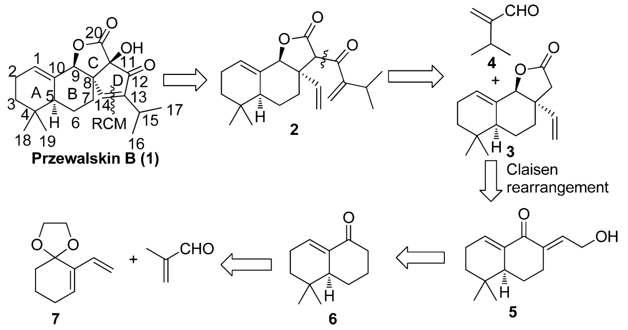
Salvia is the largest genus in the economically and medicinally important Labiatae family. Many species of this widely distributed genus have been used for centuries as folk medicine to treat a variety of illnesses. One such species is *Salvia przewalskii* Maxim, a traditional medicinal plant used as a surrogate of *S. miltiorrhhiza* (Danshen) for treating various cardiovascular diseases.[1,2]

In 2007, Zhao et al. isolated przewalskin B (**1**) from the acetone extract of *S. przewalskii* Maxim.[2] **1** has attracted the attention of synthetic chemists because it possesses a unique tetracyclic skeleton that contains a spirocyclic enone system and an α-hydroxy-β-ketone lactone moiety. Moreover, it shows modest anti-HIV activity with EC_{50} = 30.32 μg/mL. In 2011, She and Tu achieved the total synthesis of (−)- and (+)-przewalskin B, respectively.[3] She used an intramolecular nucleophilic acyl substitution (INAS) reaction to close the B ring and determined the absolute configuration of the natural product. Tu, on the other hand, adopted diastereoselective organocatalytic aldol cyclization to form the B ring and initiated $Rh_2(OAc)_4$-mediated intramolecular carbene insertion to construct the five-member spiro ring. In this paper, a concise method for the total synthesis of (±)-przewalskin B is described from another perspective.

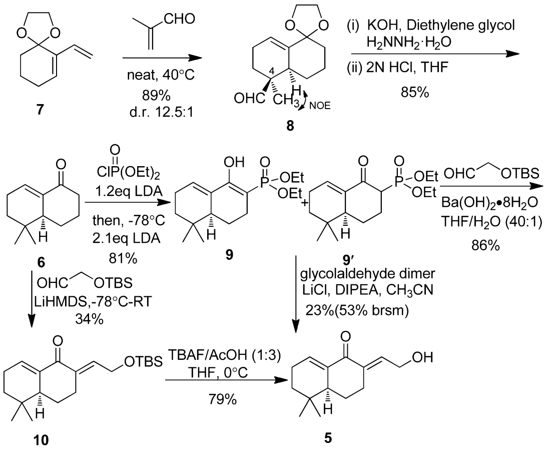
Scheme 1 outlines our retrosynthetic analysis of przewalskin B (**1**). We believe the cyclic enone could be constructed from diene **2** via ring-closing metathesis (RCM) to form the C13−C14 bond. Diene **2** could be formed from lactone **3** by an aldol reaction with aldehyde **4** and subsequent oxidation. The spiro-quaternary center could be constructed by Claisen rearrangement of allyl alcohol **5** obtained by aldol condensation between bicyclic enone **6** and the corresponding glycolaldehyde derivative. Further, bicyclic enone **6** could be accessed via the Diels−Alder reaction of methylacrolein and diene **7**.

The synthesis began with diene **7**, which was prepared in three steps from 2-cyclohexenone on a multigram scale according to a modified protocol.[4] A Diels−Alder reaction between diene **7** and methylacrolein proceeded smoothly at 40 °C and afforded aldehyde **8** in 89% yield with excellent regio- and diastereoselectivity (d.r. 12.5:1) (Scheme 2).[5] ^{1}H NOE spectroscopy determined the configuration of aldehyde **8**, which was reduced under the Huang−Minlon conditions[6] and subsequently treated with 2 N HCl to deliver enone **6** in 85% overall yield.[7] Aldol condensation between enone **6** and TBS-protected glycolaldehyde resulted in a 34% yield. Hence, enone **6** was first converted to phosphonate **9** and **9′**[8] and then

Scheme 1. Retrosynthetic Analysis of Przewalskin B



Scheme 2. Synthesis of Allylic Alcohol 5



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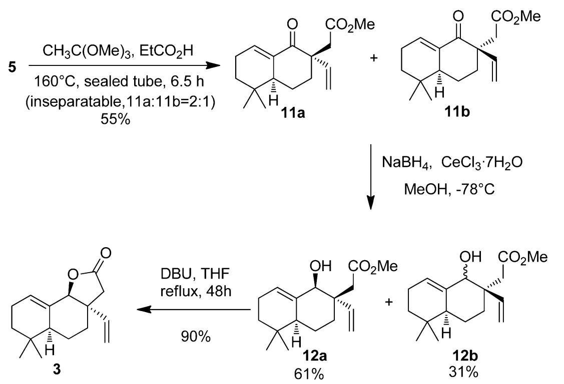
subjected to Horner−Wadsworth−Emmons olefination[9] with TBS-protected glycolaldehyde to afford *E*-olefin **10** in 68% overall yield. Careful treatment of **10** with TBAF/AcOH (1:3) in THF at 0 °C gave allylic alcohol **5** in 79% yield. By contrast, direct olefination reaction between phosphonate and a glycolaldehyde dimer[10] afforded allylic alcohol **5** in low yield (23%, 53% based on recovered starting materials).

Although a large variety of substrates have been applied in Claisen−Johnson rearrangement, very little attention has been given to the utilization of allylic alcohols with a double bond conjugated with an electron-withdrawing group.[11] A solution of allylic alcohol **5** in trimethyl orthoacetate was heated in the presence of a catalytic amount of propanoic acid at 160 °C to produce esters **11a** and **11b** (2:1, inseparable) in reasonable yield. The diastereoselectivity could not be improved despite several trials because of a slight steric difference between the α and β faces of **5**. Subsequent reduction of **11a** and **11b** was carried out under Luche conditions to afford the desired γ-hydroxy ester **12a** in 61% yield and stereoisomer **12b** in 31% yield. After treatment of **12a** and **12b** with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in refluxing THF, only **12a** was converted to lactone **3** (Scheme 3).

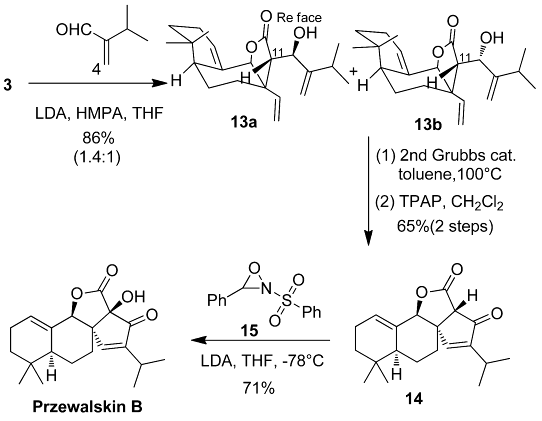
Scheme 3. Synthesis of Lactone 3



With lactone **3** in hand, construction of the cyclic enone moiety followed. Although it has been generally used to establish five-membered rings,[12] RCM between a 1,1-disubsituted olefin and a sterically hindered terminal alkene remains a challenge. An aldol reaction of lactone **3** with unsaturated aldehyde **4** afforded two stereoisomers **13a** and **13b** (Scheme 4). It was notable that the reaction was quenched by 1 N HCl at −78 °C to inhibit a retro-aldol reaction. We envisioned that the configuration of C11 was desired due to the steric hindrance on the *Si* face of the lactone enolate. To avoid complicated NMR spectra, **13a** and **13b** were first oxidized with Dess-Martin periodinane to afford β-ketoester **2**; however, treatment of **2** with the second-generation Grubbs catalyst[13] or the second-generation Hoveyda−Grubbs catalyst[14] afforded β-ketoester **14** in low yield (<20%). To our delight, RCM of allylic alcohol **13a** and **13b** using the second-generation Grubbs catalyst (30 mol %) in toluene at 100 °C, followed by oxidation with TPAP, produced β-ketoester **14** in 65% overall yield. According to the model, cyclization cannot occur if the stereochemistry of two alkene chains in **13a** or **13b** is in the *trans* configuration. The success of RCM confirmed the stereochemistry at C11.

The enol is generally the actual reactant in the α-hydroxylation of β-dicarbonyl compounds under conditions such as $FeCl_3/H_2O_2$[15] and IBX.[16] However, considering steric constraints in the present system, keto−enol tautomerization cannot occur in β-ketoester **14**. Cerium-catalyzed α-hydroxylation[17] under oxygen (1 atm) was studied to yield only unconverted **14**. Finally, the hydroxy was introduced using Davis oxaziridine[18] **15** to provide przewalskin B in 71% yield.[19] The spectral data of synthetically obtained przewalskin B (^{1}H NMR, ^{13}C NMR, and HRMS) were in full agreement with those of the natural product.[2]

Scheme 4. Completion of the Total Synthesis of (±)-Przewalskin B



In conclusion, the total synthesis of przewalskin B was accomplished using commercially available 2-cyclohexenone. The key steps in the synthesis procedure included Diels−Alder and Wolf−Kishner reactions to install the A ring, Claisen−Johnson rearrangement to establish the spiro-quaternary center, and RCM of a sterically crowded system to construct the cyclic enone moiety. The asymmetric synthesis of przewalskin B, which could be approached via an enantioselective Diels−Alder reaction[20] of diene **7** and methylacrolein, is in progress and will be reported in due course.

■ EXPERIMENTAL SECTION

6-Vinyl-1,4-dioxaspiro[4.5]dec-6-ene(7). Trimethylsilyl triflate (0.58 mL, 3.2 mmol) was added dropwise to a solution of 2-iodocyclohex-2-enone[21] (14.2 g, 64 mmol) and bis(trimethylsilyl ethers)[22] (19.8 g, 96 mmol) in CH_2Cl_2 (150 mL) at −40 °C. The reaction was allowed to warm to 0 °C over 1 h and was stirred for 26 h at this temperature. Water was added, and the mixture was extracted with CH_2Cl_2. The organic layers were washed with saturated aqueous $Na_2S_2O_3$ and brine and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed under vacuum and the resulting mixture was purified by silica gel chromatography (petroleum ether/ethyl acetate = 16:1 to 12:1) to afford 6-iodo-1,4-dioxaspiro[4.5]dec-6-ene (14.1 g, 83%) as a white solid.

A solution of flame-dried $ZnCl_2$ (5.4 g, 39.5 mmol) in anhydrous THF (100 mL) was cooled to −78 °C. Vinylmagnesium bromide (1 M in THF, 34.2 mL) was then added, and the reaction temperature was raised to room temperature over 1 h. In a separate flask, a mixture of 6-iodo-1,4-dioxaspiro[4.5]dec-6-ene (7.0 g, 26.3 mmol) and $Pd(PPh_3)_4$ (912 mg, 0.79 mmol) was dissolved in a 1:1 mixture of anhydrous DMF/THF (5 mL/5 mL) and then added, via canula, to the flask containing the Grignard solution and $ZnCl_2$ mixture at room temperature. The mixture was stirred overnight. Saturated aqueous NH_4Cl was added, and the mixture was extracted with EtOAc. The organic layers were washed with brine and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed under vacuum and the resulting mixture was purified by silica gel chromatography (petroleum ether/ethyl acetate = 12:1) to afford **7** (3.9 g, 89%) as a colorless oil.

(±)-(4a′*S*,5′*S*)-5′-Methyl-3′,4′,4a′,5′,6′,7′-hexahydro-2′*H*-spiro[[1,3]dioxolane-2,1′-naphthalene]-5′-carbaldehyde (8). Methylacrolein (2.3 mL, 80%, 27.6 mmol) and **7** (2.29 g, 13.8 mmol) were stirred at 40 °C for 24 h, and then the volatile liquid was removed under reduced pressure. The resulting mixture was purified by silica gel chromatography (petroleum ether/ethyl acetate = 16:1) to afford **8** (2.9 g, 89%) as a white solid. Mp = 26−29 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ9.59 (s, 1H), 5.80 (s, 1H), 3.88−3.93 (m, 3H), 3.70−3,75 (m, 1H), 2.24 (d, *J* = 12.2 Hz, 1H), 2.09−2.18 (m, 1H), 1.95−2.04 (m, 1H), 1.81 (d, *J* = 11.6 Hz, 1H), 1.51−1.77 (m, 5H), 1.38−1.44 (m,1H), 1.08−1.12 (m, 1H), 1.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.4, 137.5, 118.8, 108.1, 64.7, 63.1, 46.7, 41.8, 37.3, 29.5, 24.7, 23.0, 20.8, 19.4; HRMS (ESIMS) calcd for $C_{14}H_{21}O_3^+$ $[M + H]^+$ 237.1485, found 237.1490.

(±)-5,5-Dimethyl-3,4,4a,5,6,7-hexahydronaphthalen-1(2*H*)-one (6). A mixture of **8** (3.4 g, 14.4 mmol), hydrazine monohydrate (17.5 mL, 80%, 288 mmol), and KOH (3.23 g, 57.6 mmol) in diethylene glycol (15 mL) was heated at 160 °C for 4 h and then cooled to room temperature. The excess hydrazine, the water, and most of the reduction product were distilled off under reduced pressure (40 Torr, the mixture was first heated at 120 °C for 0.5 h and heated further 1 h at 180 °C for 1 h). The pump was dismantled, and the resulting mixture in the flask was heated at 190 °C for 1.5 h. THF and concentrated HCl (5 mL) were added at 0 °C, adjusting the pH to 3. The reaction mixture was stirred for 0.5 h, then extracted with EtOAc followed by washing with H_2O and brine, and dried over anhydrous Na_2SO_4. Meanwhile, the distillation was extracted with EtOAc and washed with H_2O, and then the organic solvent was evaporated. The residue was dissolved in THF (10 mL) and 2 N HCl (2 mL). After stirring for 0.5 h, followed by addition of H_2O and EtOAc, the EtOAc layer was washed with H_2O and brine and then dried over anhydrous Na_2SO_4. The two dried organics were combined, evaporated, and purified with silica gel chromatography (petroleum ether/ethyl acetate = 8:1) to afford **6** (2.2 g, 85%) as a white solid. Mp = 26−29 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ6.81 (d, *J* = 2.8 Hz, 1H), 2.49 (m, 1H), 2.11−2.25 (m, 4H), 1.94−2.02 (m, 2H), 1.58−1.69 (m, 1H), 1.35−1.39 (m, 2H), 1.18−1.29 (m, 1H), 0.99 (s, 3H), 0.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.8, 137.9, 135.9, 47.3, 39.7 36.4, 31.2, 29.0, 24.1, 23.3, 22.2, 19.6; HRMS (ESIMS) calcd for $C_{12}H_{19}O^+$ $[M + H]^+$ 179.1430, found 179.1428.

(±)-Diethyl-(1-hydroxy-5,5-dimethyl-3,4,4a,5,6,7-hexahydronaphthalen-2-yl)phosphonate (9) and (±)-Diethyl (5,5-Dimethyl-1-oxo-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-yl)phosphonate (9′). A solution of **6** (0.5 g, 2.81 mmol) in anhydrous THF (10 mL) was added dropwise via syringe to a stirred solution of lithium diisopropylamide [LDA, 1.2 equiv, prepared in situ from diisopropylamine (0.54 mL, 3.87 mmol) and *n*-BuLi (1.35 mL, 2.5 M in hexane, 3.37 mmol)] in THF (4.8 mL) at −78 °C. After 1 h, the resulting enolate was treated with diethyl chlorophosphate (0.44 mL, 3.09 mmol, freshly distilled under vacuum) and the mixture was allowed to warm to 0 °C over the course of 1.5 h. After this mixture was cooled to −78 °C, a solution of LDA (2.1 equiv in 8.5 mL of THF) was added. The resulting solution was allowed to warm to 0 °C over 2 h. The reaction was quenched by the addition of acetic acid (4 equiv), and the resulting mixture was filtered through a 1-cm layer of Florisil. Purification of the crude product by silica gel chromatography (petroleum ether/ethyl acetate = 10:1 to 6:1) gave corresponding phosphate **9** and **9′** (715 mg, ∼5:1, inseparable, 81%) as a white solid. The ratio was determined from ^{1}H NMR (see Supporting Information). Mp = 43−44 °C; ^{31}P NMR (400 MHz, $CDCl_3$) δ 27.85, 24.55, 24.25; HRMS (ESIMS) calcd for $C_{16}H_{28}O_4P^+$ $[M + H]^+$ 315.1720, found 315.1717.

(±)-(*E*)-2-(2-((*tert*-Butyldimethylsilyl)oxy)ethylidene)-5,5-dimethyl-3,4,4a,5,6,7-hexahydronaphthalen-1(2*H*)-one (10). Phosphate **9** and **9′** (1.2 g, 3.82 mmol) in 15 mL of THF was added to $Ba(OH)_2 \cdot 8H_2O$, which had been heated in a 130 °C oil bath under vacuum for 1.5 h. The aldehyde (1.0 g, 5.73 mmol) in 5 mL of THF and 0.5 mL of H_2O was then added. After stirring for 8 h, the reaction was diluted with dichloromethane and added to a separatory funnel. The reaction was washed with saturated $NaHCO_3$. The aqueous layers were extracted with dichloromethane, and the organics were washed with brine and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed under vacuum and the resulting mixture was purified by silica gel chromatography (petroleum ether/ethyl acetate = 16:1) to give **10** (1.1g, 86%) as a white solid. Mp = 47−54 °C; ^{1}H NMR (400 MHz, $CDCl_3$)δ7.11 (d, *J* = 3.6 Hz, 1H), 6.80 (s, 1H), 4.25−4.39 (m, 2H), 2.67 (d, *J* = 16.0 Hz, 1H), 2.12−2.27 (m, 3H), 1.94−1.98 (m, 2H), 1.36−1.43 (m, 2H), 1.17−1.27 (m, 1H), 1.02 (s, 3H), 0.89 (s, 9H), 0.73 (s, 3H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.1, 139.4, 137.6, 136.7, 134.5, 60.4, 46.1, 36.3, 31.3, 29.0, 25.9, 25.8, 23.7, 22.5, 19.4, 18.2, −5.2; HRMS (ESIMS) calcd for $C_{20}H_{34}O_2Si^+$ $[M + H]^+$ 335.2401, found 335.2398.

(±)-(*E*)-2-(2-Hydroxyethylidene)-5,5-dimethyl-3,4,4a,5,6,7-hexahydronaphthalen-1(2*H*)-one (5). To a solution of **10** (209 mg, 0.62 mmol) in THF (1 mL) was added a solution of TBAF and AcOH in THF (7.5 mL, 0.75 mmol TBAF, 2.25 mmol AcOH, freshly prepared) at 0 °C, and the reaction was stirred for 4 h at this temperature. The mixture was extracted with EtOAc, and the organic layer was washed with saturated $NaHCO_3$ and brine and then dried over anhydrous Na_2SO_4. After filtration, the solvent was removed under vacuum. The resulting mixture was purified by silica gel chromatography (petroleum ether/ethyl acetate = 4:1 to 1:1) to give the allylic alcohol **5** as a colorless oil (108 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (t, *J* = 3.6 Hz, 1H), 6.80 (s, 1H), 4.21−4.35 (ddq, *J* = 2.0 Hz, 6.4 Hz, 16.0 Hz, 2H), 3.27 (s, 1H), 2.66 (d, *J* = 16.4 Hz, 1H), 2.17−2.70 (m, 3H), 2.08−2.13 (m, 1H), 1.91−1.95 (m, 1H), 1.36−1.40 (m, 2H), 1.12−1.22 (dq, J = 3.6 Hz, 13.2 Hz, 1H), 0.99 (s, 3H), 0.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.5, 139.0, 138.1, 136.5, 135.1, 59.4, 45.9, 36.1, 31.2, 28.9, 25.7, 23.7, 22.4, 19.3; HRMS (ESIMS) calcd for $C_{14}H_{21}O_2^+$ $[M + H]^+$ 221.1536, found 221.1537.

(±)-Methyl-2-((2*R*,4a*S*)-5,5-dimethyl-1-oxo-2-vinyl-1,2,3,4,-4a,5,6,7-octahydronaphthalen-2-yl) Acetate (11a and 11b). To a solution of **5** (205 mg, 0.93 mmol) in trimethyl orthoacetate (9 mL, freshly distilled) was added a catalytic amount of propionic acid (7 μL, 0.093 mmol), and the mixture was heated in a sealed tube under argon for 6.5 h at 160 °C. After evaporation of the organics under vacuum, the crude product was purified by silica gel chromatography to afford a 2:1 inseparable mixture of **11a** and **11b** (141 mg, 55%) as a colorless liquid. The ratio was determined by ^{1}H NMR (see Supporting Information). HRMS (ESIMS) calcd for $C_{17}H_{25}O_3^+$ $[M + H]^+$ 277.1798, found 277.1802.

(±)-Methyl-2-((1*S*,2*R*,4a*S*)-1-hydroxy-5,5-dimethyl-2-vinyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-yl) Acetate (12a). $NaBH_4$ (17 mg,0.44 mmol) was added to a stirred solution of **11a** and **11b** (101 mg, 0.37 mmol) and $CeCl_3 \cdot 7H_2O$ (272 mg, 0.73 mmol) in methanol (5 mL) at −78 °C. The reaction mixture was stirred at this temperature for 1 h, diluted with Et_2O (10 mL), and washed with 5% aqueous HCl (10 mL). The mixture was extracted with Et_2O, and the organic layer was washed with brine and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed under vacuum, and the resulting mixture was purified by silica gel chromatography (petroleum ether/ethyl acetate = 8:1) to afford **12a** (61.8 mg, 61%, white solid) and **12b** (31.5 mg, 31%). Spectral data of **12a**: Mp = 85−88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.05 (dd, *J* = 11.2 Hz, 18.0 Hz, 1H), 5.75 (s, 1H), 5.17 (d, *J* = 4.8 Hz, 1H), 5.14 (s, 1H), 3.87 (s, 1H), 3.62 (s, 3H), 3.11 (d, *J* = 5.2 Hz, 1H), 2.64 (d, *J* = 15.2 Hz, 1H), 2.31 (d, *J* = 15.2 Hz, 1H), 2.05 (d, *J* = 2.0 Hz, 2H), 1.91−1.95 (m, 1H), 1.57−1.67 (m, 2H), 1.45−1.53 (m, 1H), 1.35−1.42 (m, 1H), 1.18−1.28 (m, 2H), 0.91 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 143.7, 138.0, 118.4, 113.8, 51.5, 46.9, 46.2, 34.5, 34.3, 33.8, 31.1, 28.0, 25.7, 23.7, 22.2; HRMS (ESIMS) calcd for $C_{17}H_{26}O_3Na^+$ $[M + Na]^+$ 301.1774, found 301.1777.

(±)-(3a*R*,5a*S*,9b*S*)-6,6-Dimethyl-3a-vinyl-3,3a,4,5,5a,6,7,8-octahydronaphtho[1,2-*b*]furan-2(9b*H*)-one (3). To a solution of **12a** (75 mg, 0.27 mmol) in THF (8 mL) was added DBU (120 μL, 0.81 mmol), and the reaction was refluxed for 48 h. Evaporation of organics and purification by silica gel chromatography (petroleum ether/ethyl acetate = 8:1) gave lactone **3** (60 mg, 90%) as a white solid. Mp = 78−80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (dd, *J* =

10.8 Hz, 17.6 Hz, 1H), 5.74 (s, 1H), 5.14 (d, *J* = 8.0 Hz, 1H), 5.11 (s, 1H), 4.61 (s, 1H), 2.51 (d, *J* = 16.8 Hz, 1H), 2.14 (d, *J* = 16.8 Hz, 1H), 2.00 (d, *J* = 2.0 Hz, 1H), 1.74−1.86 (m, 2H), 1.60−1.68 (m, 1H), 1.45 (d, *J* = 12.0 Hz, 1H), 1.32−1.48 (m, 1H), 1.17−1.27 (m, 2H), 0.90 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 176.2, 143.0, 135.4, 120.1, 113.5, 83.9, 46.6, 45.1, 34.9, 32.4, 31.5, 30.9, 27.4, 26.4, 24.0, 22.2; HRMS (ESIMS) calcd for $C_{16}H_{23}O_2^+$ [M + H]$^+$ 247.1693, found 247.1696.

(±)-(3*S*,3a*S*,5a*S*,9b*R*)-3-((*R*)-1-Hydroxy-3-methyl-2-methylenebutyl)-6,6-dimethyl-3a-vinyl-3,3a,4,5,5a,6,7,8-octahydronaphtho[1,2-*b*]furan-2(9b*H*)-one (13a) and (±)-(3*S*,3a*S*,5a*S*,9b*R*)-3-((*S*)-1-Hydroxy-3-methyl-2-methylenebutyl)-6,6-dimethyl-3a-vinyl-3,3a,4,5,5a,6,7,8-octahydronaphtho[1,2-*b*]furan-2(9b*H*)-one (13b). LDA (1.1 mL, 0.5 M in THF, freshly prepared) was added dropwise to a solution of **3** (52 mg, 0.21 mmol) and HMPA (180 μL, 1.1 mmol) in anhydrous THF (5 mL) at −78 °C. After the mixture stirred for 1 h at this temperature, aldehyde was added, and the reaction was stirred for 15 min at −78 °C. HCl (1 N, 1 mL) was added to the flask at −78 °C, and the mixture was stirred for 10 min at room temperature. The reaction was extracted with EtOAc, and the organic layer was washed with brine and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was removed under vacuum and the resulting mixture was purified by silica gel chromatography (petroleum ether/ethyl acetate = 8:1) to afford two stereoisomers **13a** and **13b** (62.7 mg, 86%) as white solids. Spectral data of one isomer (25.7 mg): Mp = 97−99 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.90 (dd, *J* = 11.2 Hz, 17.6 Hz, 1H), 5.77 (s, 1H), 5.22 (d, *J* = 10.8 Hz, 1H), 5.04−5.25 (m, 4H), 4.56 (m, 2H), 4.27 (dd, *J* = 2.4 Hz, 9.2 Hz, 1H), 2.80 (d, *J* = 9.2 Hz, 1H), 2.19−2.25 (m, 1H), 1.97−2.05 (m, 3H), 1.72−1.76 (m, 1H), 1.53−1.61 (m, 1H), 1.46 (d, *J* = 4.0 Hz, 1H), 1.34−1.42 (m, 1H), 1.14−1.27 (m, 2H), 1.11 (d, *J* = 6.4 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 179.6, 154.6, 139.3, 134.6, 120.6, 115.2, 111.3, 83.5, 72.3, 48.8, 46.3, 45.3, 32.8, 31.0, 30.4, 29.0, 27.6, 26.0, 23.5, 23.4, 22.2, 22.1; HRMS (ESIMS) calcd for $C_{22}H_{33}O_3^+$ [M + H]$^+$ 345.2424, found 345.2428. Spectral data of the other isomer (37 mg): Mp = 36−39 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.13 (dd, *J* = 17.6 Hz, 11.2 Hz, 1H), 5.77 (d, *J* = 2.0 Hz, 1H), 5.16−5.23 (m, 3H), 5.06 (s, 1H), 4.59 (d, *J* = 2.0 Hz, 1H), 4.47 (t, *J* = 6.0 Hz, 1H), 2.92 (d, *J* = 6.8 Hz, 1H), 2.31−2.36 (m, 1H), 2.20−2.23 (m, 1H), 2.03 (s, 2H), 1.76−1.80 (m, 1H), 1.58−1.66 (m, 1H), 1.49 (d, *J* = 11.6 Hz, 1H), 1.35−1.40 (m, 1H), 1.22−1.28 (m, 2H), 1.11 (d, *J* = 6.8 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.92 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 175.9, 156.6, 140.6, 135.2, 120.3, 113.9, 109.0, 82.2, 71.3, 49.6, 46.9, 45.3, 33.2, 31.1, 31.0, 30.5, 27.8, 25.7, 23.7, 23.2, 22.2, 21.3.

(±)-(5a*S*,7a*S*,11b*R*)-4-Isopropyl-8,8-dimethyl-6,7,7a,8,9,10-hexahydrocyclopenta[*c*]naphtho[1,2-*b*]furan-2,3(2a*H*,11b*H*)-dione (14). To a solution of the second generation of Grubbs catalyst (12.6 mg, 0.015 mmol) in freshly distilled toluene (2 mL) was added a solution of **13a** and **13b** (17 mg, 0.049 mmol), which was azeotroped with anhydrous toluene under vacuum three times. The reaction was heated for 6 h at 100 °C, and the organics were evaporated under reduced pressure. Purification of the residue by silica gel chromatography (petroleum ether/ethyl acetate = 8:1 to 4:1) gave the desired ring-closing product (15.3 mg, 86%).

To a solution of the ring-closing product (15.3 mg, 0.048 mmol) in CH$_2$Cl$_2$ (2 mL) was added tetrapropylammonium perruthenate (20 mg, 0.058 mmol), and the reaction was stirred for 1 h at room temperature. CH$_2$Cl$_2$ was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (petroleum ether/ethyl acetate = 8:1) to give the desired product **14** (11.3 mg, 75%) as a white solid. Mp = 180−183 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.12 (s, 1H), 5.84 (s, 1H), 4.77 (s, 1H), 3.14 (s, 1H), 2.58−2.64 (m, 1H), 2.05 (s, 2H), 1.72−1.91 (m, 3H), 1.69 (d, *J* = 4.4 Hz, 1H), 1.34−1.41 (m, 1H), 1.21−1.29 (m, 2H), 1.10 (dd, *J* = 10.4 Hz, 7.2 Hz, 6 Hz), 0.95 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 197.8, 170.4, 158.2, 150.7, 135.3, 122.0, 81.3, 56.9, 52.7, 44.7, 32.8, 31.8, 31.2, 27.7, 25.4, 25.1, 24.8, 22.3, 20.9, 20.7; HRMS (ESIMS) calcd for $C_{20}H_{26}O_3K^+$ [M + K]$^+$ 353.1514, found 353.1512.

(±)-Przewalskin B. To a solution of **14** (6 mg, 0.019 mmol) in THF was added LDA (57 μL, 0.5 M in THF, 0.029 mmol, freshly prepared) at −78 °C, and the mixture was stirred for 30 min at this temperature. A solution of Davis' oxaziridine **15** (6.4 mg, 0.025 mmol, freshly prepared[18a]) in THF was added, and the reaction was stirred for 1 h at −78 °C. The reaction was quenched by addition of 1 N HCl (0.5 mL) and stirred at room temperature for 1 h. The mixture was extracted with EtOAc, and the organic layer was washed with brine and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was removed under vacuum and the resulting mixture was purified by silica gel chromatography (petroleum ether/ethyl acetate = 6:1) to afford przewalskin B (**1**) (4.5 mg, 71%) as a white solid. Mp = 194−196 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.11 (s, 1H), 5.80 (s, 1H), 4.79 (s, 1H), 3.65 (s, 1H), 2.60−2.67 (m, 1H), 2.05−2.08 (m, 2H), 1.69−1.85 (m, 3H), 1.55−1.59 (m, 2H), 1.39−1.46 (m, 1H), 1.20−1.28 (m, 1H), 1.13 (d, *J* = 6.8 Hz, 3H), 1.08 (d, *J* = 7.2 Hz, 3H), 0.95 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 200.3, 173.0, 158.3, 149.0, 135.8, 121.1, 82.0, 54.2, 45.0, 32.3, 31.2, 29.4, 27.5, 26.3, 25.2, 25.1, 22.3, 20.5, 20.4; HRMS (ESIMS) calcd for $C_{20}H_{26}O_4Na^+$ [M + Na]$^+$ 353.1723, found 353.1725.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR (Dept 135) spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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