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Total Synthesis of (+)-Przewalskin B

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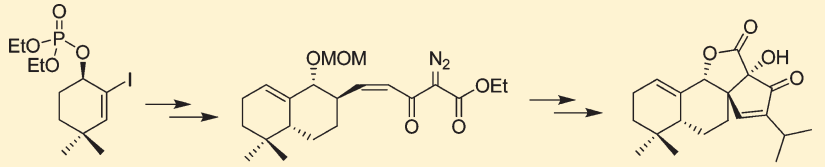
Supporting Information

ABSTRACT:



(+)-Przewalskin B

An efficient strategy for the total synthesis of (+)-przewalskin B is reported. The key steps feature an intermolecular S_N2' substitution of iodoallylic phosphate with organocupper reagent, a diastereoselective organocatalytic aldol cyclization, as well as a $Rh_2(OAc)_4$-mediated intramolecular carbene insertion to the tertiary C−H bond.

Przewalskin B, which was isolated in 2007 by Zhao and co-workers from a chinese medicinal plant *Salvia przewalskii*, is a novel diterpenoid and exhibits modest *anti*-HIV-1 activity (EC_{50} = 30 μg/mL).[1] It possesses an unprecedented tetracyclic framework with two spiro rings, an α-hydroxy-γ-lactone moiety, and an all-carbon quaternary center. Since it has a typical structure and biologically important properties, przewalskin B as a challenging synthetic target has attracted the interest of synthetic chemists. Recently, She and co-workers determined the absolute configuration of the natural product by the asymmetric synthesis of (−)-przewalskin B via an intramolecular nucleophilic acyl substitution (INAS) reaction.[2] Herein we report the total synthesis of (+)-enantiomer of this natural product, with the purpose of examining its biological activity and generating a new synthetic route to the enantiomeric structure.

Among the methodologies for constructing the fused polycyclic system, the Rhodium-catalyzed intramolecular carbene insertion reactions have played a particularly important role. This reaction usually tends to take a carbene insertion of tertiary C−H bond and forms a five-membered ring containing a quaternary center.[3] By use of this procedure many challenging syntheses of polycyclic natural products have been accomplished perfectly,[4] which greatly inspires us. In considering of our total synthesis of **1**, we recognized that the most challenging steps would be the formation of the fused tricyclic system (B, C and D rings), which contains an all-carbon quaternary stereogenic center. So, as described in our retrosynthetic analysis (Scheme 1), we postulated that C- and D-rings of this tricyclic core could be constructed through a $Rh_2(OAc)_4$−mediated intramolecular C−H insertion reaction[5] of 4-(Z)-β-vinyl-α-diazo-β-ketoester **2**, followed by a lactonization. The aldehyde **3** would be used to give **2** via carbon chain elongation, and its B-ring would be formed via a diastereoselective aldol cyclization from dialdehyde **4**. We planned to assemble the requisite dialdehyde **4** through an *anti*-S_N2' reaction[6] followed by a formylation from iodoallylic phosphate **5** and the Grignard reagent **6**.[7]

As depicted in Scheme 2, iodoallylic phosphate **5**[8] was treated with an organocuprate generated in situ from Grignard reagent **6** in the presence of CuCN to give the desired S_N2' substitution product **7** in 90% yield. Iodide **7** was lithiated using *t*-BuLi at −78 °C and then reacted with DMF to install a formyl group on the A-ring system, giving dioxolane **8**.[9] Treating **8** with formic acid in THF at 50 °C for 10 h afforded dialdehyde **4** as the precursor of intramolecular aldol reaction.[10] Exposure of the resulting dialdehyde **4** to aldol condensation conditions produced the B-ring closure product, which was quickly converted to its MOM ether without purification, to avoid dehydration of the β-hydroxyaldehyde. Initially, however, the expected diastereoselective aldol condensation of **4** under the promotion of $(n\text{-BuO})_4$Ti/*t*-BuOK failed to give the sole product **10a** but a mixture of compound **10a** and its diastereoisomer **10b** in the ratio of 1:2.[11] The generation of **10b** could be attributed to the stabilization of the cyclic chelated intermediate **9b** (Figure 1). Therefore, a series of condition optimizations of this aldol reaction were undertaken for avoiding the formation of **10b**. To our delight, using 0.1 equivalent of L-prolinamide in NMP resulted in the formation of **10a** as a sole product.[12] Based on the mechanism of the Corey−Bakshi−Shibata reduction for preparation of compound **5**[13] and the relative configuration of the tetracyclic compound **15**, we propose the intermediacy of transition state **A**, which also represents the lower energy conformation than state **B** (Figure 1). In transition state **A**, the *Re* face of the carbonyl of α,β-unsaturated aldehyde is much more accessible to *Re* face of enamine and thus the *anti* product **10a** was formed absolutely. While in state **B** the repulsion

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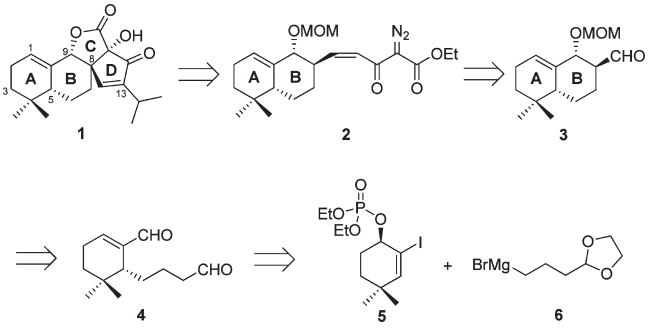
Scheme 1. Retrosynthetic Analysis for (+)-Przewalskin B



between pyrrolidine and cyclohexene moiety of the substrate **4** would led it unfavorable to form the *syn* product **10b**.

Having demonstrated that highly diastereoselective construction of bicyclic intermediate **3** was indeed feasible, we turned our attention to formation of **C**/**D** rings of the core skeleton. Transformation of aldehyde **3** to alkyne **11** was best realized by the Shioiri protocol using $TMSCHN_2$ in combination with *n*-BuLi.[14] Terminal alkyne **11** was lithiated and then reacted with DMF to give α,β-acetylenic aldehyde **12** in excellent yield as long as a reverse quench into an aqueous KH_2PO_4 solution was employed.[15] The aldol-type condensation of alkynyl aldehyde **12** with ethyl diazoacetate was carried out using NaH as the base. The newly formed β-alkynyl-β-hydroxy-α-diazo ester **13** was subjected to MnO_2 oxidation and then efficiently hydrogenated in the presence of Lindlar catalyst to afford 4-(*Z*)-β-vinyl-α-diazo-β-ketoester **2**. The slow addition of **2** in CH_2Cl_2 to a suspension of rhodium(II) acetate in CH_2Cl_2 resulted in the formation of spiro-enone **14**. Upon exposure of **14** to *p*-toluenesulfonic acid, the tetracyclic ketolactone **15** was obtained as a single stereoisomer.[16] At this point, the **A**−**D** rings of **1** had been successfully constructed. Single-crystal X-ray analysis of **15**[17] confirmed the relative stereochemistry as 5*R*,8*S*,9*S* (Scheme 3).

With the key tetracyclic intermediate **15** in hand, we next tackled the installation of the isopropyl and hydroxy groups in the cyclopentone ring to complete the total synthesis. Direct alkylation of α-iodinated **15** with isopropylzinc in the presence of a Pd−phosphine complex unfortunately gave an undesired isomerized *n*-propyl product.[18] An indirect approach was therefore adopted. As depicted in Scheme 4, iodination at the α-position of the cyclopentenone moiety, followed by Negishi coupling with isopropenylmagnesium bromide yielded the terminal alkene **16**.[19] Subsequently, **16** was carefully hydrogenated at atmospheric pressure with PtO_2 catalysis to give tetracyclic β-ketone **17**.[20] Finally, the treatment of **17** with LDA and Davis′ oxaziridine[21] gave (+)-przewalskin B (**1**) in 59% yield, which was identical in all respects (^1H, ^{13}C NMR, and HRMS) with the natural product, except for the opposite sign of its optical rotation ($[\alpha]^{20}_D$ = +16.7 (*c* = 0.48, $CHCl_3$) [lit. $[\alpha]^{20}_D$ = −26 (*c* = 0.49, $CHCl_3$)]). Based on the X-ray determined configuration of compound **15** (Scheme 3), Davis′ reagent preferred to attack the convex face of the **C**/**D**-rings system and α-OH was introduced. In fact, we were not able to isolate and detect the C-11 epimer with β-OH. The total synthesis of the unnatural enantiomer was thus achieved.

In summary, we have developed an asymmetric synthesis of (+)-przewalskin B via a Cu(I)-mediated S_N2' substitution, a diastereoselective organocatalytic aldol condensation and an intramolecular C−H insertion reaction. In particular, the key Rh(II)-mediated intramolecular insertion of keto-carbene to C−H allowed the highly efficient construction of **C**/**D**-rings, the all-carbon quaternary center as well as three of the oxygenic functional groups in the target molecule, which has corroborated the use of carbenoid insertion as a convenient strategy in the synthesis of natural products. Investigation of the biological activities of (+)-przewalskin B is currently underway and will be reported in due course.

EXPERIMENTAL SECTION

(*R*)-2-(3-(2-Iodo-6,6-dimethylcyclohex-2-en-1-yl)propyl)-1,3-dioxolane (7). Magnesium turnings (510 mg, 21.3 mmol) were placed into an argon-filled flask. A solution of 2-(3-bromopropyl)-1,3-dioxolane (1.50 g, 7.7 mmol) in 1.5 mL of THF was added, and the mixture was warmed in a 70 °C bath at which temperature the reaction began with no need for further measure to initiate Grignard reagent formation. The mixture was stirred at 25 °C for 20 min and then diluted with additional THF (5 mL) and stirred for further 30 min. To a suspension of CuCN (700 mg, 7.8 mmol) in THF (5 mL) at −40 °C was added dropwise the freshly prepared Grignard reagent. The reaction mixture was allowed to warm to 0 °C over 1 h. The solution was recooled to −40 °C, and a solution of **5** (1.70 g, 4.4 mmol) in THF (5 mL) was added dropwise. The resulting mixture stirred overnight and quenched with saturated aqueous NH_4Cl solution (10 mL). The mixture was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with water (3 × 20 mL) and brine (30 mL) and dried over Na_2SO_4. After solvent removal, the crude oil was purified by flash chromatography (petroleum ether/ethyl acetate = 10/1) to give **7** (1.47 g) as a colorless liquid in 96% yield: R_f 0.6 (petroleum ether/ethyl acetate = 4/1); $[\alpha]^{20}_D$ = +67 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.27 (t, *J* = 4.0 Hz, 1H), 4.87 (t, *J* = 4.8 Hz, 1H), 4.02−3.94 (m, 2H), 3.90−3.82 (m, 2H), 2.10−2.06 (m, 2H), 1.98 (brs, 1H), 1.72−1.62 (m, 2H), 1.60−1.42 (m, 5H), 1.26−1.20 (m, 1H), 0.99 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2 (CH), 105.1 (C), 104.5 (CH), 64.8 (CH_2), 56.3 (CH), 35.0 (C), 34.4 (CH_2), 31.8 (CH_2), 30.3 (CH_2), 28.1 (CH_3), 27.5 (CH_3), 27.0 (CH_2), 24.0 (CH_2); IR ν (cm^{-1}) 2950, 2872, 1632, 1467, 1409, 1364, 1138, 1042; HRMS (ESI) calcd for $C_{14}H_{27}INO_2$ $[M + NH_4]^+$ 368.1081, found 368.1077.

(*R*)-6-(3-(1,3-Dioxolan-2-yl)propyl)-5,5-dimethylcyclohex-1-enecarbaldehyde (8). To a solution of vinyl iodide **7** (900 mg, 2.57 mmol) in 6 mL of dry THF was added 3.2 mL of *t*-BuLi (5.12 mmol, 1.6 M in pentane) at −78 °C under argon, and the mixture was stirred at −78 °C for 10 min. Then 1.5 mL (8 equiv) of dry DMF was added in one portion. The mixture was allowed to warm to room temperature and stirred for 10 min, and then the THF solution was poured into a vigorously stirred biphasic solution prepared from a 10% aqueous solution of KH_2PO_4 (20 mL, 15 mmol) and methyl *tert*-butyl ether (20 mL) cooled over ice. Organic layers were separated, and the combine organic layers were washed with water (3 × 10 mL) and brine (20 mL) and dried over Na_2SO_4. After solvent removal, the crude oil was purified by flash chromatography (petroleum ether/ethyl acetate = 4/1) to give aldehyde **8** (533 mg) as a pale yellow oil in 82% yield: R_f 0.3 (petroleum ether/ethyl acetate =4/1); $[\alpha]^{20}_D$ = +164 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, 1H), 6.70 (t, *J* = 3.6 Hz, 1H), 4.80 (t, *J* = 4.8 Hz, 1H), 3.95−3.89 (m, 2H), 3.86−3.80 (m, 2H), 2.41−2.23 (m, 3H), 1.70−1.52 (m, 5H), 1.42−1.31 (m, 2H), 1.20−1.10 (m, 1H), 1.00 (s, 3H), 0.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.4 (CH), 150.2 (CH), 145.7 (C), 104.5 (CH), 64.8 (CH_2), 40.7 (CH), 34.5 (CH_2), 32.4 (CH_2), 31.7 (C), 30.4 (CH_2), 28.0 (CH_3), 26.7 (CH_3), 24.6 (CH_2), 23.6 (CH_2); IR ν (cm^{-1}) 2952,

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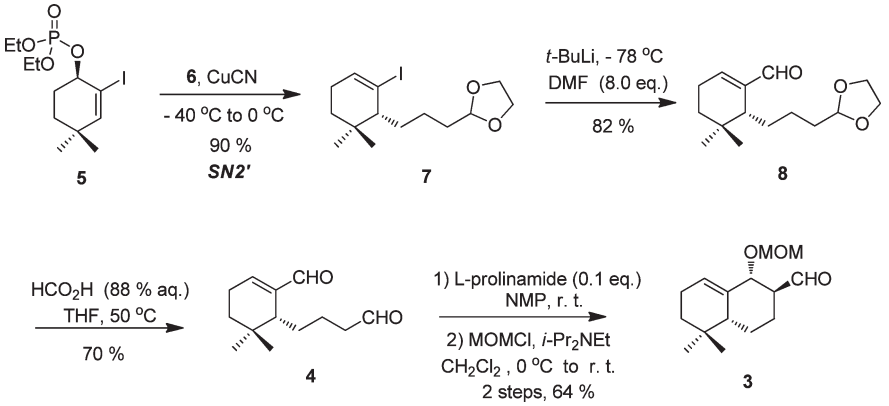
Scheme 2. Synthesis of Bicyclic Compound 3



2873, 1684, 1638, 1460, 1415, 1201, 1138, 1042; HRMS (ESI) calcd for $C_{15}H_{28}NO_3$ $[M + NH_4]^+$ 270.2064, found 270.2059.

(*R*)-5,5-Dimethyl-6-(4-oxobutyl)cyclohex-1-enecarbaldehyde (4). To a solution of dioxolane **8** (2.317 g, 9.19 mmol) in THF (50 mL) was added at 50 °C a solution of formic acid in water (88%, 27 mL). After 10 h of stirring at 50 °C, the THF solution was cooled to 0 °C, and a saturated aqueous solution of Na_2CO_3 was added until a basic pH was reached. The aqueous layers were extracted with EtOAc (2 × 150 mL), and the combined organic layers were washed with water (3 × 20 mL) and brine (30 mL) and dried over Na_2SO_4. After solvent removal, the crude oil was purified by flash chromatography (petroleum ether/ethyl acetate = 5/1) to give dialdehyde **4** (1.347 g) as a pale yellow oil in 70% yield: R_f 0.4 (petroleum ether/ethyl acetate = 4/1); $[\alpha]^{20}_D$ = +147 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 9.43 (s, 1H), 6.72 (t, *J* = 3.6 Hz, 1H), 2.43−2.30 (m, 4H), 2.23−2.22 (m, 1H), 1.66−1.51 (m, 4H), 1.29−1.24 (m, 1H), 1.14−1.08 (m, 1H), 0.99 (s, 3H), 0.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7 (CH), 194.5 (CH), 150.7 (CH), 145.4 (C), 44.2 (CH_2), 40.4 (CH), 31.9 (CH_2), 31.7 (C), 30.3 (CH_2), 28.0 (CH_3), 26.6 (CH_3), 24.6 (CH_2), 21.7 (CH_2); IR ν (cm^{-1}) 2954, 2872, 1724, 1682, 1638, 1458, 1387, 1201, 1138; HRMS (ESI) calcd for $C_{13}H_{21}O_2$ $[M + H]^+$ 209.1536, found 209.1540.

(1*R*,2*S*,4a*R*)-1-(Methoxymethoxy)-5,5-dimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalene-2-carbaldehyde (3). To a solution of dialdehyde **4** (769 mg, 3.70 mmol) in NMP (16 mL) was added L-prolinamide (40 mg, 0.35 mmol) at room temperature. After 12 h of stirring, the reaction was quenched with H_2O (2 mL) and extracted with Et_2O (2 × 60 mL). The combined organic layers were washed with water (3 × 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated. Residue (878 mg, 4.22 mmol) was dissolved in CH_2Cl_2 (30 mL) and cooled to 0 °C, *N*,*N*-diisopropylethylamine (3.9 mL, 22.4 mmol) and MOMCl (1.3 mL, 17.0 mmol) were added, and the reaction solution was warmed to room temperature and stirred for an additional 15 h. After that, saturated aqueous NH_4Cl solution (5 mL) was added to quench the reaction. Aqueous layers were back-extracted with Et_2O (2 × 50 mL), and the combined organic layers were washed with water (3 × 10 mL) and brine (20 mL) and dried over Na_2SO_4. After solvent removal, the crude oil was purified by flash chromatography (petroleum ether/ethyl acetate = 25/1) to give MOM ether **3** (593 mg) as a colorless oil in 64% yield (two steps): R_f 0.5 (petroleum ether/ethyl acetate = 4/1); $[\alpha]^{20}_D$ = +365 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (d, *J* = 4.0 Hz, 1H), 5.63 (brs, 1H), 4.71 (d, *J* = 6.8 Hz, 1H), 4.58 (d, *J* = 7.2 Hz, 1H), 4.20 (dd, J_1 = 10.4 Hz, J_2 = 1.6 Hz, 1H), 3.35 (s, 3H), 2.38−2.30 (m, 1H), 2.04−2.03 (m, 2H), 1.92−1.85 (m, 2H), 1.57−1.46 (m, 2H), 1.41−1.37 (m, 1H), 1.22−1.10 (m, 2H), 0.91 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9 (CH), 137.4 (C), 117.0 (CH), 95.5 (CH_2), 77.4 (CH), 58.0 (CH), 56.1 (CH_3), 46.8 (CH), 32.6 (CH_2), 31.1 (C), 28.0 (CH_2), 27.6 (CH_3), 26.9 (CH_3), 25.0 (CH_2), 22.3 (CH_2); IR ν (cm^{-1}) 2946, 2862, 1728, 1449, 1362, 1149, 1096, 1036; HRMS (ESI) calcd for $C_{15}H_{25}O_3$ $[M + NH_4]^+$ 270.2064, found 270.2057.

(1*R*,2*R*,4a*R*)-2-Ethynyl-1-(methoxymethoxy)-5,5-dimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalene (11). To a −78 °C solution of trimethylsilyldiazomethane (2 M in hexane, 4.6 mL, 9.2 mmol) in THF (20 mL) was added *n*-BuLi (1.6 M in hexane, 4.5 mL, 7.2 mmol). After 30 min, a solution of aldehyde **3** (1186 mg, 4.7 mmol) in THF (5 mL) was added, and the mixture was allowed to stir for 30 min at −78 °C then for 15 min between −10 and 0 °C. Saturated aqueous NH_4Cl solution (2 mL) was added. The organic layers were separated, and the aqueous layers were extracted with Et_2O (2 × 60 mL). The combined organic layers were washed, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification of residue by flash chromatography (petroleum ether/ethyl acetate = 200/1) gave terminal alkyne **11** (938 mg) as a brown yellow oil in 80% yield: R_f 0.6 (petroleum ether/ethyl acetate =8/1); $[\alpha]^{20}_D$ = +292 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65 (brs, 1H), 4.77 (d, *J* = 6.8 Hz, 1H), 4.75 (d, *J* = 6.8 Hz, 1H), 3.87 (d, *J* = 10.4 Hz, 1H), 3.50 (s, 3H), 2.34−2.26 (m, 1H), 2.15−2.06 (m, 2H), 2.02−2.00 (m, 2H), 1.80−1.74 (m, 1H), 1.65−1.54 (m, 1H), 1.50−1.47 (m, 1H), 1.42−1.34 (m, 1H), 1.19−1.14 (m, 1H), 1.10−1.00 (m, 1H), 0.89 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2 (C), 116.5 (CH), 95.5 (CH_2), 86.6 (C), 80.0 (CH), 69.2 (CH), 56.0 (CH_3), 47.0 (CH), 38.8 (CH), 32.4 (CH_2), 31.8 (CH_2), 31.0 (C), 28.5 (CH_2), 27.5 (CH_3), 27.1 (CH_3), 22.3 (CH_2); IR ν (cm^{-1}) 3308, 2943, 2865, 1448, 1363, 1149, 1100, 1034; HRMS (ESI) calcd for $C_{16}H_{25}O_2$ $[M + Na]^+$ 271.1669, found 271.1675.

3-((1R,2R,4aR)-1-(Methoxymethoxy)-5,5-dimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-yl)propiolaldehyde (12). The alkyne **11** (938 mg, 3.78 mmol) was dissolved in THF (20 mL), and the solution was cooled to −40 °C under argon. *n*-BuLi (1.6 M in hexane, 2.7 mL, 4.32 mmol) was added dropwise. After completion of the addition, anhydrous DMF (2.0 mL, 25.8 mmol) was added in one portion. The reaction mixture was allowed to warm to room temperature and stirred for 15 min. The THF solution was poured into a vigorously stirred biphasic solution prepared from a 10% aqueous solution of KH_2PO_4 (20 mL, 15 mmol) and methyl *tert*-butyl ether (20 mL) cooled over ice. Organic layers were separated, and the aqueous layers were extracted with Et_2O (2 × 30 mL). The combined organic layers were washed with water (3 × 10 mL) and brine (10 mL) and dried over Na_2SO_4. After solvent removal, the crude oil was purified by flash

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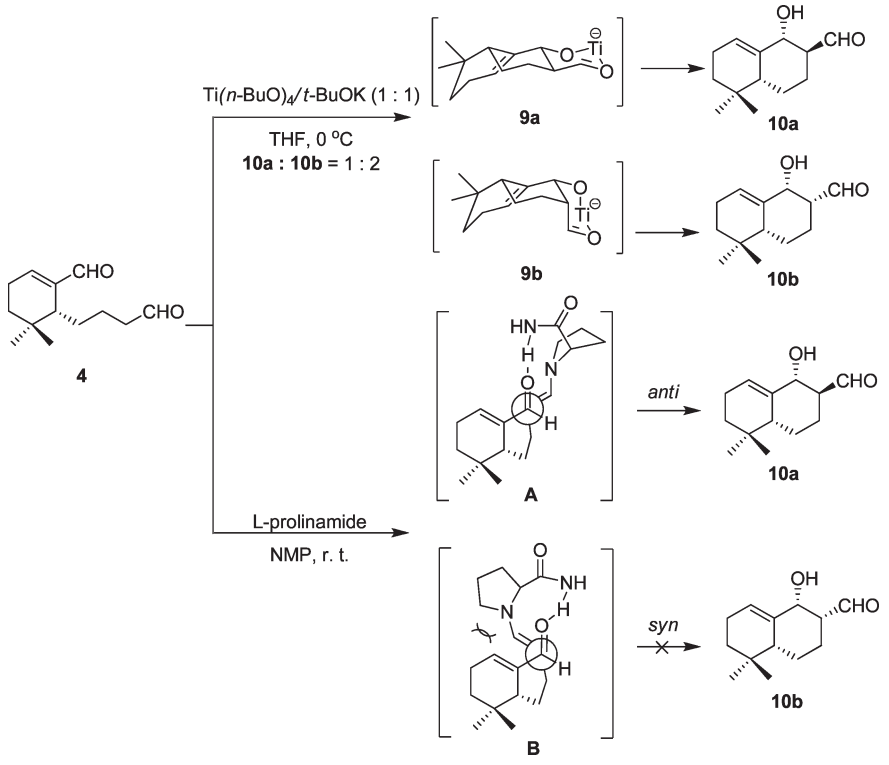
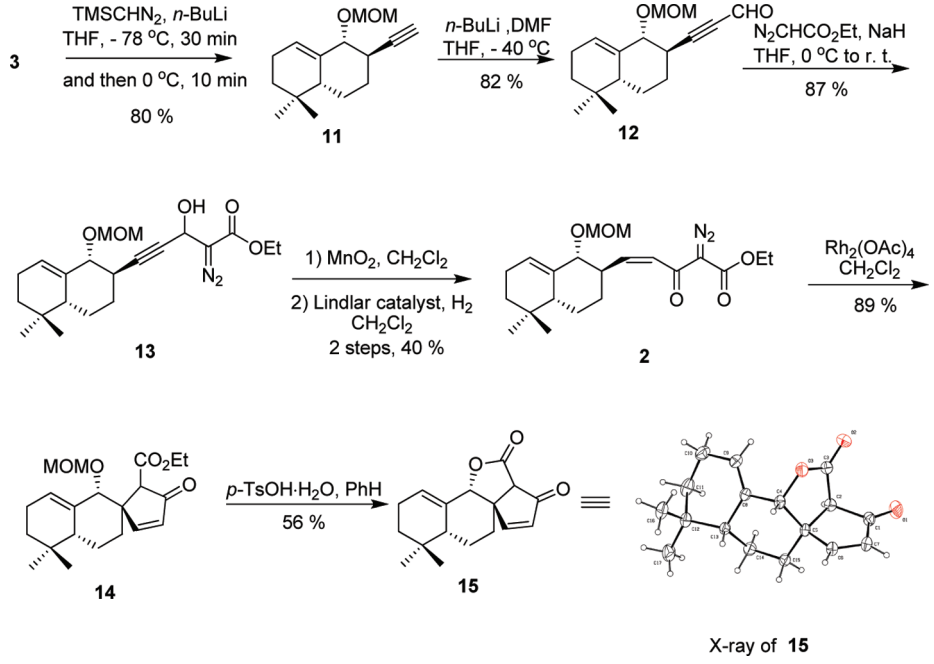


Figure 1. Proposed process of aldol reaction.

Scheme 3. Synthesis of Tetracyclic Compound 15



chromatography (petroleum ether/ethyl acetate = 50/1) to give acetylenic aldehyde **12** (860 mg) as a brown yellow oil in 82% yield: R_f 0.3 (petroleum ether/ethyl acetate =8/1); $[\alpha]^{20}_D$ = +353 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 5.66 (brs, 1H), 4.73 (d, J = 6.8 Hz, 1H), 4.69 (d, J = 6.8 Hz, 1H), 3.93 (d, J = 10.0 Hz, 1H), 3.49 (s, 3H), 2.55−2.48 (m, 1H), 2.18−2.14 (m, 1H), 2.05−2.03 (m, 2H), 1.84−1.80 (m, 1H), 1.70−1.59 (m, 1H), 1.50−1.47 (m, 1H), 1.42−1.34 (m, 1H), 1.19−1.13 (m, 1H), 1.10−1.03 (m, 1H), 0.89 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0 (CH), 137.5 (C), 117.3 (CH), 100.4 (C), 95.3 (CH_2), 82.1 (C), 79.1 (CH), 56.1 (CH_3), 46.8 (CH), 39.3 (CH), 32.3 (CH_2), 31.0 (C), 30.7 (CH_2), 28.4 (CH_2), 27.4 (CH_3), 27.0 (CH_3), 22.2 (CH_2); IR ν (cm^{-1}) 2949, 2865,

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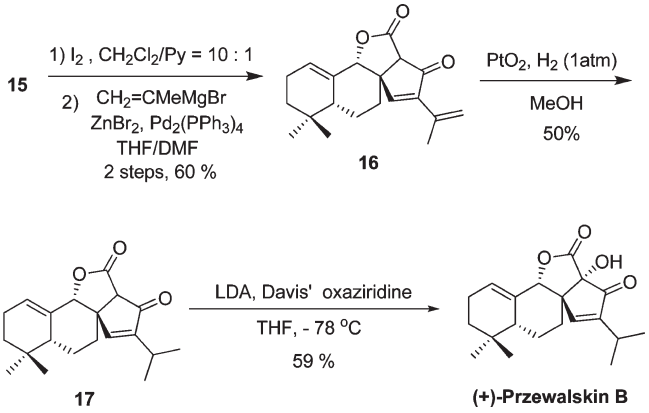
Scheme 4. Total Synthesis of (+)-Przewalskin B



2201, 1667, 1449, 1386, 1148, 1038; HRMS (ESI) calcd for $C_{17}H_{25}O_3$ $[M + NH_4]^+$ 294.2064, found 294.2066.

Ethyl 2-Diazo-3-hydroxy-5-((1*R*,2*R*,4a*R*)-1-(methoxymethoxy)-5,5-dimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-yl)-pent-4-ynoate (13). To a suspension of NaH (190 mg, 80%, 6.33 mmol) in THF (10 mL) at 0 °C was added dropwise ethyl diazoacetate (0.51 mL, 4.92 mmol) in THF (2 mL). The reaction mixture was stirred for 15 min at 0 °C and then warmed to room temperature. Stirring was continued for another 1 h. Acetylenic aldehyde **12** (860 mg, 3.12 mmol) in THF (3 mL) was then added dropwise to this mixture. The reaction mixture was stirred for another 1 h at room temperature. After that, the solution was cooled to 0 °C. H_2O (2 mL) was added slowly to quench the reaction. Organic layers were separated, and the aqueous layers were back-extracted with EtOAc (2 × 80 mL). The combined organic layers were washed, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/ethyl acetate = 4/1) gave **13** (1061 mg) (inseparable isomers) as a brown yellow oil in 87% yield: R_f 0.2 (petroleum ether/ethyl acetate =4/1); $[\alpha]^{20}_D$ = +162 (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65 (brs, 1H), 5.53 (d, J = 4.4 Hz, 1H), 4.75−4.71 (m, 2H), 4.26 (q, J = 7.2 Hz, 2H), 3.85−3.81 (m, 1H), 3.48 (s, 1.3H), 3.47 (s, 1.4H), 2.84 (brs, 1H), 2.39−2.31 (m, 1H), 2.12−2.01 (m, 3H), 1.80−1.75 (m, 1H), 1.62−1.53 (m, 1H), 1.49−1.41 (m, 1H), 1.38−1.34 (m, 1H), 1.30 (t, J_2 = 7.2 Hz, 3H), 1.20−1.14 (m, 1H), 1.10−1.00 (m, 1H), 0.89 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3 (C), 138.1 (C), 116.8 (CH), 95.7 (CH_2), 90.6 (C), 90.5 (C), 80.31 (CH), 80.28 (CH), 77.2 (C), 61.2 (CH_2), 58.5 (CH), 56.0 (CH_3), 47.0 (CH), 38.9 (CH), 32.5 (CH_2), 31.9 (CH_2), 31.8 (CH_2), 31.1 (C), 28.4 (CH_2), 27.5 (CH_3), 27.0 (CH_3), 22.3 (CH_2), 14.5 (CH_3); IR ν (cm^{-1}) 3416, 2943, 2866, 2101, 1696, 1372, 1290, 1106, 1035; HRMS (ESI) calcd for $C_{21}H_{34}N_3O_5$ $[M + NH_4]^+$ 408.2493, found 408.2486.

(*Z*)-Ethyl 2-Diazo-5-((1*R*,2*R*,4a*R*)-1-(methoxymethoxy)-5,5-dimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-yl)-3-oxopent-4-enoate (2). Activated MnO_2 (1500 mg, 17.2 mmol) was added in two portions over 5 h to a solution of **13** (664 mg, 1.70 mmol) in CH_2Cl_2 (15 mL). After the mixture was stirred for 12 h at room temperature, the manganese dioxide was removed by filtration. The filtrate was concentrated in vacuo, and the residue (477 mg, 1.23 mmol) was dissolved in CH_2Cl_2 (10 mL). Lindlar catalyst (390 mg, 5 wt %, 0.18 mmol) was added, and the reaction mixture was stirred vigorously for 1 h at room temperature under hydrogen gas balloon. The precipitate was filtrated, and then the solvent was removed in vacuo. The residue was purified by chromatography (petroleum ether/ethyl acetate = 50/1) to give **2** (262 mg) as a yellow oil in 40% yield (2 steps): R_f 0.5 (petroleum ether/ethyl acetate = 4/1); $[\alpha]^{20}_D$ = +160 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (dd, J_1 = 11.6 Hz, J_2 = 0.8 Hz, 1H), 6.20 (dd, J_1 = 11.6 Hz, J_2 = 9.6 Hz, 1H), 5.56 (brs, 1H), 4.66 (d, J = 6.8 Hz, 1H), 4.54 (d, J = 6.8 Hz, 1H), 4.28 (q, J = 7.2 Hz, 2H), 3.78 (d, J = 10.0 Hz, 1H), 3.38 (s, 3H), 2.05−1.93 (m, 3H), 1.81−1.77 (m, 1H), 1.51−1.38 (m, 2H), 1.32 (t, J = 6.8 Hz, 3H), 1.30−1.27 (m, 3H), 1.18−1.11 (m, 1H), 0.89 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.3 (C), 161.2 (C), 152.7 (CH), 138.2 (C), 123.4 (CH), 116.0 (CH), 95.2 (CH_2), 82.1 (CH), 77.2 (C), 61.3 (CH_2), 55.9 (CH_3), 47.3 (CH), 46.7 (CH), 32.7 (CH_2), 31.1 (C), 30.4 (CH_2), 28.6 (CH_2), 27.6 (CH_3), 27.0 (CH_3), 22.3 (CH_2), 14.3 (CH_3); IR ν (cm^{-1}) 2928, 2851, 2132, 1717, 1646, 1305, 1227, 1097, 1035; HRMS (ESI) calcd for $C_{21}H_{31}N_2O_5$ $[M + H]^+$ 391.2227, found 391.2232.

(1*R*,1′*S*,4a′*R*)-Ethyl 1′-(Methoxymethoxy)-5′,5′-dimethyl-4-oxo-3′,4′,4a′,5′,6′,7′-hexahydro-1′*H*-spiro[cyclopent[2]ene-1,2′-naphthalene]-5-carboxylate (14). To a suspension of $Rh_2(OAc)_4$ (8 mg, 0.018 mmol) in CH_2Cl_2 (40 mL) at room temperature was added dropwise **2** (414 mg, 1.06 mmol) in CH_2Cl_2 (10 mL) over 15 min. After being stirred for another 3 h, the reaction mixture was concentrated in vacuo. The residue was purified by chromatography (petroleum ether/ethyl acetate = 20/1) to give the tricyclic material **14** (343 mg) as a colorless oil in 89% yield: R_f 0.2 (petroleum ether/ethyl acetate =4/1); $[\alpha]^{20}_D$ = +97 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 5.6 Hz, 1H), 6.17 (d, J = 5.6 Hz, 1H), 5.71 (brs, 1H), 4.59 (d, J = 6.8 Hz, 1H), 4.41 (d, J = 6.8 Hz, 1H), 4.22−4.04 (m, 2H), 3.97 (brs, 1H), 3.47 (s, 1H), 3.26 (s, 3H), 2.26−2.21 (m, 1H), 2.08−2.05 (m, 2H), 1.68−1.61 (m, 2H), 1.56−1.53 (m, 1H), 1.39−1.31 (m, 1H), 1.25(t, J = 7.2 Hz, 3H), 1.20−1.15 (m, 1H), 1.00−0.93 (m, 1H), 0.90 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.6 (C), 169.7 (C), 169.5 (CH), 135.8 (C), 132.1 (CH), 118.9 (CH), 94.9 (CH_2), 79.9 (CH), 61.1 (CH_2), 57.1 (C), 56.0 (CH_3), 54.9 (CH), 47.0 (CH), 32.1 (CH_2), 31.10 (CH_2), 31.05 (C), 27.3 (CH_3), 27.0 (CH_3), 26.2 (CH_2), 22.4 (CH_2), 14.0 (CH_3); IR ν (cm^{-1}) 2952, 1737, 1707, 1449, 1315, 1224, 1142, 1036; HRMS (ESI) calcd for $C_{21}H_{34}NO_5$ $[M + NH_4]^+$ 380.2431, found 380.2429.

(5a*R*,7a*R*,11b*S*)-8,8-Dimethyl-6,7,7a,8,9,10-hexahydrocyclopenta[*c*]naphtho[1,2-*b*]furan-2,3(2a*H*,11b*H*)-dione (15). Compound **14** (134 mg, 0.37 mmol) was dissolved in dry benzene (40 mL), and the solution was warmed to 40 °C. *p*-TsOH·H_2O (30 mg, 0.16 mmol) was added every 12 h, two times daily for 3 days. After that, the reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ (3 mL). The solvent was removed in vacuo. The resulting mixture was extracted with EtOAc (2 × 50 mL), and the combined organic layers were washed, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification of residue by flash chromatography (petroleum ether/ethyl acetate = 10/1) provided **15** (57 mg) as a white solid in 56% yield: R_f 0.3 (petroleum ether/ethyl acetate = 2/1); $[\alpha]^{20}_D$ = −10 (c = 1.0, $CHCl_3$); mp 189−192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 5.6 Hz, 1H), 6.18 (d, J = 5.6 Hz, 1H), 5.87 (brs, 1H), 4.83 (d, J = 1.6 Hz, 1H), 3.13 (s, 1H), 2.07−2.06 (m, 2H), 1.94−1.89 (m, 1H), 1.86−1.75 (m, 2H), 1.66−1.62 (m, 1H), 1.42−1.35 (m, 1H), 1.32−1.22 (m, 2H), 0.96 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.0 (C), 169.9 (C), 167.5 (CH), 135.1 (C), 132.0 (CH), 122.5 (CH), 80.9 (CH), 56.2 (CH), 55.5 (C), 44.7 (CH), 32.9 (CH_2), 31.4 (CH_2), 31.3 (C), 27.8 (CH_3), 25.3 (CH_3), 25.0 (CH_2), 22.4 (CH_2); IR ν (cm^{-1}) 3406, 2919, 2858, 1770, 1709, 1451, 1156, 1110, 1014; HRMS (ESI) calcd for $C_{17}H_{24}NO_3$ $[M + NH_4]^+$ 290.1762, found 290.1758.

(5a*R*,7a*R*,11b*S*)-8,8-Dimethyl-4-(prop-1-en-2-yl)-6,7,7a,8,9,10-hexahydrocyclopenta[*c*]naphtho[1,2-*b*]furan-2,3(2a*H*,11b*H*)-dione (16). The tetracyclic material **15** (33 mg, 0.12 mmol) was dissolved in a mixed solution of pyridine−CH_2Cl_2 (1: 10, 4 mL). To this was added dropwise I_2 (60 mg, 0.24 mmol) in a solution of pyridine−CH_2Cl_2 (1: 10, 1 mL). The mixture was stirred for 12 h at room

temperature, quenched with 1 N HCl (1 mL), and extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with a saturated aqueous solution of $Na_2S_2O_3$ (5 mL), $NaHCO_3$ (5 mL), and brine (5 mL), dried, and concentrated. The resulting crude material was used in the next step without further purification. A solution of flame-dried $ZnBr_2$ (66 mg, 0.29 mmol) in dry, degassed THF (0.5 mL) was cooled to −78 °C. Isopropenylmagnesium bromide (0.5 M in THF, 0.44 mL, 0.22 mmol) was then added, and the reaction temperature was raised to room temperature over 2 h. In a separate flask, a mixture of α-iodoenone (46 mg, 0.12 mmol) freshly prepared and (tetrakis)triphenylphosphine palladium (6.6 mg, 0.006 mmol) was dissolved in a 1:1 mixture of dry, degassed DMF/THF (1 mL) and then added to the flask containing the Grignard solution and $ZnBr_2$ mixture. Upon completion, saturated aqueous NH_4Cl (2 mL) solution was added. The aqueous layers were extracted with EtOAc (3 × 30 mL), and the combined organic layers were washed, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/ethyl acetate = 30/1) gave the desired **16** (23 mg) as a white solid in 60% yield (two steps): R_f 0.4 (petroleum ether/ethyl acetate =4/1); $[\alpha]^{20}_D$ = +15 (*c* = 1.0, $CHCl_3$); mp 209 − 212 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (s, 1H), 6.14 (s, 1H), 5.86 (t, *J* = 2.0 Hz, 1H), 5.28 (s, 1H), 4.82 (d, *J* = 2.0 Hz, 1H), 3.21 (d, *J* = 0.4 Hz, 1H), 2.07−2.06 (m, 2H), 1.94 (s, 3H), 1.85−1.77 (m, 2H), 1.64−1.60 (m, 1H), 1.42−1.35 (m, 1H), 1.30−1.23 (m, 3H), 0.96 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3 (C), 170.3 (C), 159.7 (CH), 140.8 (C), 135.3 (C), 133.0 (C), 122.2 (CH), 119.7 (CH_2), 81.4 (CH), 57.6 (CH), 52.0 (C), 44.9 (CH), 32.7 (CH_2), 31.7 (CH_2), 31.3 (C), 27.7 (CH_3), 25.6 (CH_3), 25.2 (CH_2), 22.4 (CH_2), 21.7 (CH_3); IR ν (cm^{-1}) 3427, 2919, 2855, 1773, 1708, 1634, 1449, 1154, 1106, 1011; HRMS (ESI) calcd for $C_{20}H_{28}NO_3$ $[M + NH_4]^+$ 330.2064, found 330.2060.

(5a*R*,7a*R*,11b*S*)-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 (17). Compound **16** (12 mg, 0.038 mmol) was dissolved in methanol (4 mL), PtO_2 (8 mg, 0.035 mmol) was added, and the mixture was hydrogenated at atmospheric pressure at room temperature. Hydrogenation was interrupted after uptake of 1 equiv of H_2, and the catalyst was filtered off. After solvent removal, the residue was chromatographed on silica gel (petroleum ether/ethyl acetate = 50/1) to give **17** (6.0 mg) as a white solid in 50% yield: R_f 0.3 (CH_2Cl_2/hexane = 10/1); $[\alpha]^{20}_D$ = +10 (*c* = 1.0, $CHCl_3$); mp 172−175 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.12 (s, 1H), 5.86 (brs, 1H), 4.77 (s, 1H), 3.15 (s, 1H), 2.62 (dq, J_1 = 19.8 Hz, J_2 = 6.6 Hz, 1H), 2.07 (brs, 2H), 1.92−1.88 (m, 1H), 1.82−1.70 (m, 2H), 1.64−1.62 (m, 1H), 1.41−1.36 (m, 1H), 1.30−1.24 (m, 2H), 1.12 (d, *J* = 6.6 Hz, 3H), 1.10 (d, *J* = 6.6 Hz, 3H), 0.96 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.8 (C), 170.4 (C), 158.2 (CH), 150.9 (C), 135.4 (C), 122.2 (CH), 81.4 (CH), 57.0 (CH), 52.7 (C), 44.8 (CH), 32.9 (CH_2), 31.9 (CH_2), 31.3 (C), 27.8 (CH_3), 25.5 (CH_3), 25.1 (CH_2), 24.9 (CH), 22.4 (CH_2), 21.0 (CH_3), 20.8 (CH_3); IR ν (cm^{-1}) 2920, 2853, 1770, 1708, 1453, 1383, 1155, 1107, 1014; HRMS (ESI) calcd for $C_{20}H_{30}NO_3$ $[M + NH_4]^+$ 332.2220, found 332.2216.

Przewalskin B (1). To a solution of **17** (5 mg, 0.016 mmol) in THF (0.6 mL) was added LDA (2.0 M in THF, 15 μL, 0.03 mmol) at −78 °C under argon. This solution was stirred for 30 min at −78 °C, and then Davis' oxaziridine (8 mg, 0.03 mmol) in THF (0.5 mL) was added via syringe. The mixture was stirred at −78 °C for 1 h and saturated aqueous solution of NH_4Cl (0.5 mL) was added. The organic layers were separated, and the aqueous layers were extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (CH_2Cl_2/hexane = 1/1) provided **1** (3.1 mg) as a white solid in 59% yield: R_f 0.3 (CH_2Cl_2/hexane = 40/1); $[\alpha]^{20}_D$ = +16.7 (*c* = 0.48, $CHCl_3$); mp 168−170 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.11 (s, 1H), 5.81 (brs, 1H), 4.80 (s, 1H), 3.63 (s, 1H), 2.64 (dq, J_1 = 19.8 Hz, J_2 = 6.6 Hz, 1H), 2.12−2.06 (m, 2H), 1.85−1.71 (m, 3H), 1.60−1.56 (m, 2H), 1.45−1.41 (m, 1H), 1.27−1.23 (m, 1H), 1.15 (d, *J* = 6.6 Hz, 3H), 1.10 (d, *J* = 6.6 Hz, 3H), 0.96 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.3 (C), 173.0 (C), 158.3 (CH), 149.0 (C), 135.8 (C), 121.2 (CH), 82.1 (CH,C), 54.2 (C), 45.0 (CH), 32.3 (CH_2), 31.2 (C), 29.4 (CH_2), 27.6 (CH_3), 26.4 (CH_3), 25.3 (CH), 25.2 (CH_2), 22.4 (CH_2), 20.6 (CH_3), 20.5 (CH_3); IR ν (cm^{-1}) 3474, 2922, 2853, 1765, 1704, 1652, 1616, 1458, 1373, 1269, 1211, 1114; HRMS (ESI) calcd for $C_{20}H_{30}NO_4$ $[M + NH_4]^+$ 348.2169, found 348.2164.

■ ASSOCIATED CONTENT

Supporting Information. Copies of ^{1}H and ^{13}C NMR spectra for all new compounds and X-ray crystallographic data of compound **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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