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Total Synthesis of (−)-Przewalskin B

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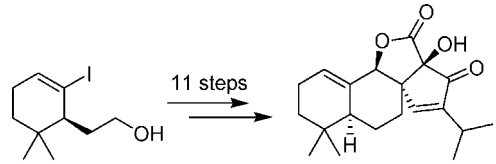
ABSTRACT



The first total synthesis of (−)-Przewalskin B has been accomplished with an intramolecular nucleophilic acyl substitution (INAS) reaction and an intramolecular aldol condensation as key steps.

Przewalskin B (**1**, Figure 1), a novel diterpenoid isolated from a Chinese medicinal plant *Salvia przewalskii* by Zhao et al. in 2007, was found to exhibit modest anti-HIV-1 activity with $EC_{50} = 30\ \mu g/mL$.[1] The structure of **1** was revealed by means of comprehensive NMR spectroscopic analysis and a single-crystal X-ray study to have a fused tetracyclic skeleton containing a five-membered spiro ring and α-hydroxy-β-ketone lactone moieties. Due to its biological profile and intriguing structure, Przewalskin B (**1**) represents an attractive target for the synthetic community. In this communication, we report the first total synthesis of (−)-Przewalskin B (**1**).

Our retrosynthetic analysis for Przewalskin B (**1**) is outlined in Scheme 1. It was our view that the γ-lactone ring (D) of **1** and its tertiary OH could be established from the spirocyclic enone **2** at the last stage. For enone **2**, its five-membered spiro ring (C) could be constructed from ester **3** via an intramolecular aldol condensation. Bicyclic ester **3** could be realized via an intramolecular nucleophilic acyl substitution (INAS) reaction[2] on the diastereotopic groups[3] of diester **4** which could easily be prepared from diiodide **5** and malonate derivative **6** by an alkylation reaction.

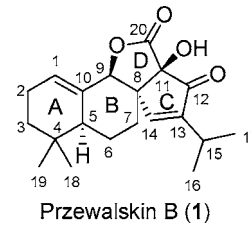


Figure 1. Structure of Przewalskin B (**1**).

Our synthesis started with the known chiral alcohol **7**[4] which was readily prepared from the commercially available 4,4-dimethyl-2-cyclohexenone in four steps (Scheme 2). Following iodination of alcohol **7**, diiodide **5** was obtained in 96% yield. For the required diester **6**, it was prepared from 1-bromo-4-methylpentan-2-one **8**[5] and diethyl malonate by an alkylation coupling followed by acetal protection in 90% yield for two steps. With **5** and **6** in hand, their coupling reaction was performed to afford the INAS reaction precursor **4** in 85% yield.

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(1) Xu, G.; Hou, A.; Zheng, Y.; Zhao, Y.; Li, X.; Peng, L.; Zhao, Q. *Org. Lett.* **2007**, *9*, 291–293.

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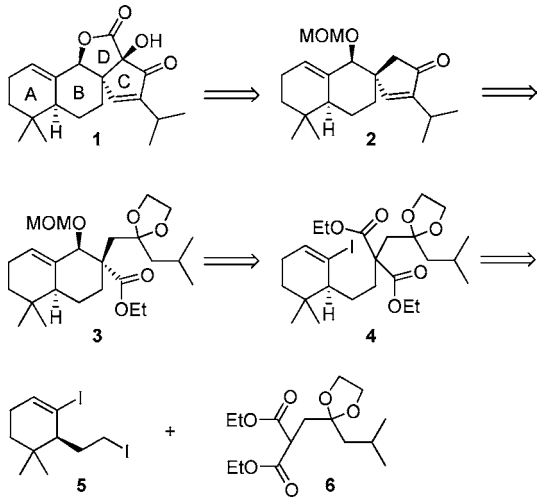
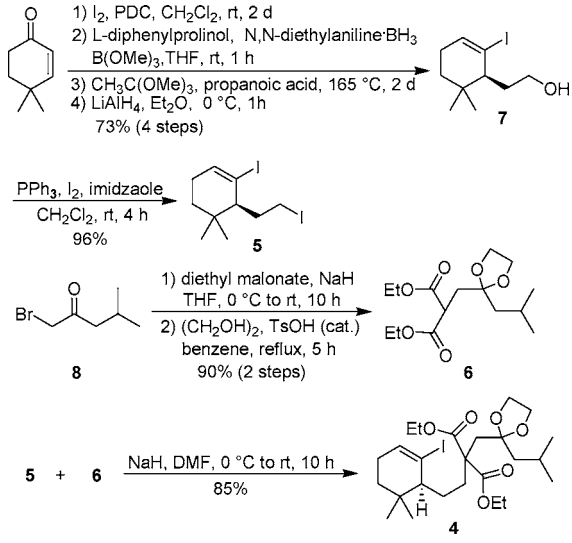
Scheme 1. Retrosynthetic Analysis

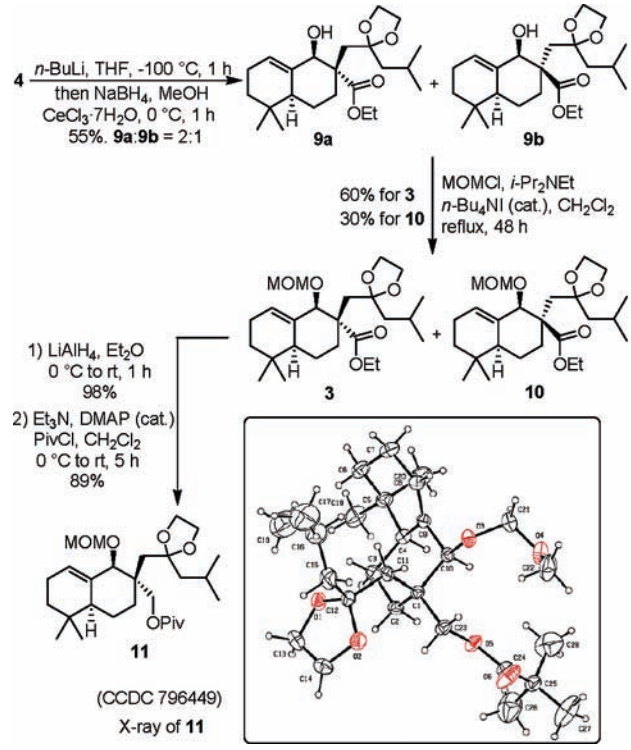


Scheme 2. Synthesis of the Key INAS Reaction Precursor **4**



The key INAS reaction was then performed. Treatment of vinyl iodide **4** with 1.0 equiv of *n*-BuLi in THF at −100 °C for 1 h, followed by Luche reduction[6] ($CeCl_3$, $NaBH_4$) at 0 °C for 40 min, gave a 2:1 inseparable mixture of **9a**/**9b** in a 55% combined yield (Scheme 3). Fortunately,

Scheme 3. Synthesis of **11**



protection of **9a** and **9b** as MOM ethers gave a separable mixture of **3** and **10** in 60% and 30% yield, respectively. The relative stereochemistry of the major isomer **3** was confirmed by single-crystal X-ray study of its derivative **11**, which could be obtained in 88% yield for the two steps.

With the key bicyclic intermediate **3** in hand, we continued to construct the CD ring system of **1** to finish the total synthesis. As depicted in Scheme 4, partial reduction of ester **3** with DIBAL-H followed by removal of the acetal protecting group gave 1,4-diketone **13** which underwent an intramolecular aldol condensation to afford tricyclic enone **2** in 71% overall yield for three steps. Subsquently, treatment of ketone **2** with LDA and ethyl cyanoformate[7] afforded the acylation product **14** as a single diastereoisomer in 96% yield. Deprotection of **14** followed by a DBU-promoted lactonization generated the tetracyclic β-ketone lactone **16** in 76% yield. Finally, treatment of **16** with LDA and Davis'oxaziridine **17**[8] at −78 °C for 0.5 h gave compound **1**, (−)-Przewalskin B,

(2) For related INAS reaction, see: (a) Wang, B.; Zhong, Z.; Lin, G. *Org. Lett.* **2009**, *11*, 2011–2014. (b) Chau, C. M.; Liu, K. M. *Org. Biomol. Chem.* **2008**, *6*, 3127–3134. (c) Lage, S.; Villaluenga, I.; Sotomayor, N.; Lete, E. *Synlett* **2008**, *20*, 3188–3192. (d) Faltz, H.; Bender, C.; Liebscher, J. *Synthesis* **2006**, *17*, 2907–2922. (e) Faltz, H.; Bender, C.; Wöhrl, B. M.; Vogel-Bechmayr, K.; Hübscher, U.; Ramadan, K.; Liebscher, J. *Eur. J. Org. Chem.* **2004**, 3484–3496. (f) Calaza, M. I.; Hupe, E.; Knochel, P. *Org. Lett.* **2003**, *5*, 1059–1061. (g) Otto, A.; Liebscher, J. *Synthesis* **2003**, *8*, 1209–1214. (h) Swaleh, S.; Liebscher, J. *J. Org. Chem.* **2002**, *67*, 3184–3193. (i) Ollero, L.; Castedo, L.; Domínguez, D. *Tetrahedron* **1999**, *55*, 4445–4456. (j) Kratzel, M.; Mabhoti, R. *J. Heterocyclic Chem.* **1998**, *35*, 871–874. (k) Mochizuki, T.; Itoh, E.; Shibata, N.; Nakatani, S.; Katoh, T.; Terashima, S. *Tetrahedron Lett.* **1998**, *39*, 6911–6914. (l) Paleo, M. R.; Castedo, L.; Domínguez, D. *J. Org. Chem.* **1993**, *58*, 2763–2767. (m) Flann, C. J.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6115–6118.

(3) For an excellent review of stereoselective synthesis using diastereotopic groups, see: Hoffmann, R. W. *Synthesis* **2004**, 2075.

(4) Jan, N.; Liu, H. *Org. Lett.* **2006**, *8*, 151–153.

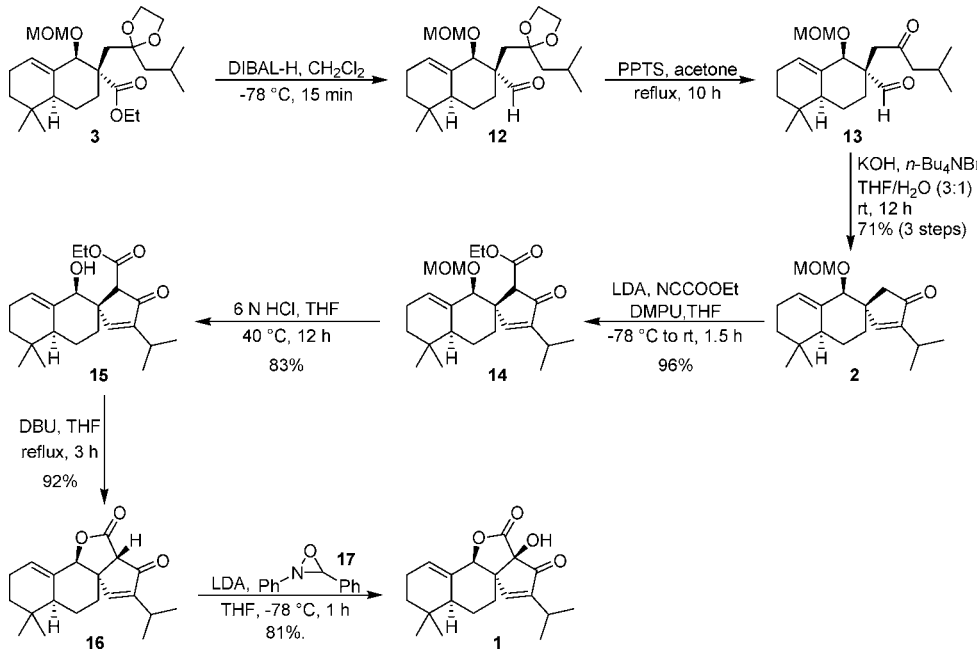
(5) Dickschat, J. S.; Reichenbach, H.; Wagner-Dobler, I.; Schulz, S. *Eur. J. Org. Chem.* **2005**, 4141–4153.

(6) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.

(7) Crabtree, S. R.; Mander, L. N.; Sethi, S. P. *Org. Synth.* **1990**, *70*, 256.

(8) Davis, F. A.; Chaltophadhyay, S.; Towson, T. C.; Lol, S.; Reddy, T. *J. Org. Chem.* **1988**, *53*, 2087–2089.

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



in 81% yield. ^{1}H and ^{13}C NMR spectra and other physical data of our synthetic compound **1** were all in good agreement with those of the natural (−)-Przewalskin B.

In summary, the first total synthesis of (−)-Przewalskin B has been achieved in 15 steps with 8.1% overall yield starting from the commercially available 4,4-dimethyl-2-cyclohexenone, involving an INAS reaction, intramolecular aldol condensation, and lactonization as key steps to furnish the unique fused tetracyclic skeleton of the natural product.

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Supporting Information Available: Experimental procedures and compound characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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