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First Total Synthesis of an Analogue of (±)-Hypargenin B

An Pai LI, Hui WANG, Cheng Lu ZHANG, Tong Xing WU, Xin Fu PAN*

Department of Chemistry, National Laboratory of Applied Organic Chemistry,
Lanzhou University, Lanzhou 730000

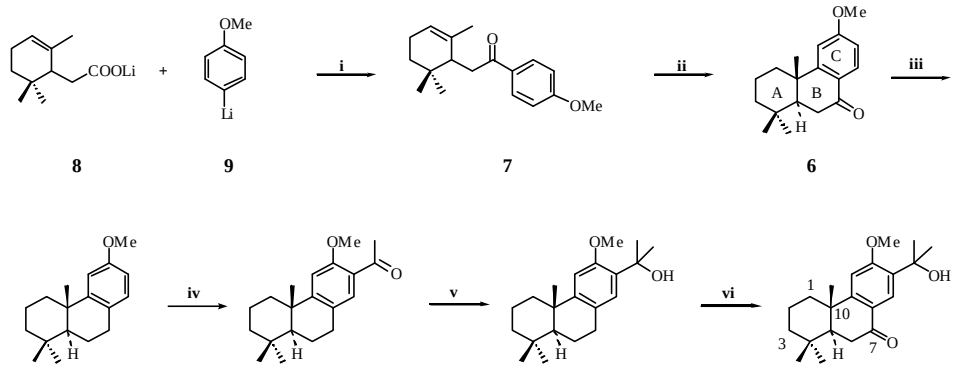
Abstract: First total synthesis of (±)-hypargenin B methyl ether **2** was accomplished *via* a strategy of AC→ABC, in which CrO_3/H_2O/NaOAc/HOAc system was utilized for introducing 7-keto group in order to avoid dehydration of benzyl tertiary alcohol.

Keyword: Hypargenin B, diterpene, intramolecular, steroselective.

Hypargenin B, a diterpene with the abietane skeleton, was isolated by Ayhan from the root of an endemic species *salvia hypargenia* and showed antibacterial activity[1]. In this diterpene, the junction of A/B ring is *trans*. In order to provide for studying further the relationship between the structure and bioactivities, we develop a novel route whereby the hypargenin B methyl ether **2**[2] could be obtained in good yield. To our knowledge no total synthetic work has been reported on the title compound yet.

As shown in **Scheme 1**, our synthetic strategy is AC→ABC, we utilized α-cyclocitral as the A ring starting material and **8** was prepared according to reference[3]. Lithium reagent of **9** was obtained from *p*-bromoanisole as the C ring synthon.

Scheme 1



Reagents and conditions: (i) THF, 0°C, 2 h (70%); (ii) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 12 h (95%); (iii) 5% Pd/C, HCl, THF, r. t., 8 h (95%); (iv) CH_3COCl, CH_2Cl_2, -5°C, 5 h (90%); (v) CH_3Li, Et_2O, r. t., 6 h (95%); (vi) CrO_3/H_2O/NaOAc/HOAc, r. t., 1 h (90%).

* E-mail: panxf@lzu.edu.cn

Condensation of compound **8** with **9** at 0°C afforded the desired acetophenone derivative **7** in 70% yield. $BF_3{\cdot}Et_2O$ was used in the intramolecular cyclization step (B ring) at room temperature. The product **6** was afforded only in *trans* form in 95% yield. According to the literature[4], when the A/B ring is in *cis* junction, the C_4-α-methyl group remains within the sphere of magnetic influence of aromatic ring C, the δ value of C_4-α-methyl group will appear at about 0.4 ppm. If the A/B ring is in *trans* junction, the C_4-α-methyl group is slightly deshielded by the aromatic ring C, the δ value of C_4-α-methyl group will appear at about 1.0 ppm. From the ^{1}H-NMR of compound **6**, we did not find any signal at 0.4 ppm and GC-MS also showed only one isomer. Hydrogenation of compound **6** over 5% Pd/C in THF and a drop of HCl afforded compound **5**. Compound **5** was acetylated by acetyl chloride and anhydrous $AlCl_3$ in CH_2Cl_2 at -5°C to afford compound **4** in 90% yield. Compound **4** was then reacted with CH_3Li to give the alcohol **3** in high yield. In order to obtain 7-keto compound **2**, according to reference[5], we tried PCC/Cetile and HOAc/CrO_3 system, but the yield of target product was low owing to the dehydration of C-15 benzyl tertiary alcohol. Considering the higher acidity in this system to lead to the dehydration, we substituted PDC for PCC, but the reaction with **3** could not proceed. Then we utilized a system of CrO_3/H_2O/NaOAc/HOAc (12 mmol : 2 mL : 1 g : 6 mL). Compound **3** (10 mmol) in HOAc (1 mL) was added into above solution, after stirring at room temperature for 1 h, compound **2** was obtained in 90% yield, almost no dehydration product was found, the result owes mainly to that the buffer (NaOAc/HOAc, pH = 5.1) solution which decreased the acidity of the system.

Acknowledgments

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References and Notes

1. U. Ayhan, *J. Nat. Prod*., **1988**, *51*, 1187.
2. Compound **2**: White needle crystals, mp 169-170°C; ^{1}H-NMR (d_6-acetone, 400MHz, δ ppm): 0.92 and 0.99 (s, each 3H), 1.25 (s, 3H), 1.50 and 1.51 (s, each 3H), 1.29-2.56 (m, 9H), 3.97 (s, 3H), 6.97 (s, 1H), 8.17 (s, 1H). ^{13}C-NMR (d_6-acetone, 100MHz, δppm): 19.58, 21.68, 23.37, 29.85, 32.96, 33.69, 36.50, 38.54, 39.13, 42.10, 50.59, 56.03, 71.79, 106.89, 124.60, 126.41, 136.33, 158.12, 162.08, 197.93. FAB-MS: 331(M+1). anal. Calcd. For $C_{21}H_{30}O_3$: requires C, 76.32; H, 9.16. Found: C, 76.38; H, 9.08. IR (KBr/cm^{-1}): 3599, 3479, 2950, 2855, 1668, 1598, 1557, 1484.
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5. S. Ghosh, B. K. Banik, U. R. Ghatak, *J Chem. Soc., Perkin Trans. 1*, **1991**, 3195.

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