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Caryophyllene driven diversity in an one-pot rearrangement of oxidation and transanular reactions

Hao-Yu Tang [a], Lu-Lu Quan [a], Jie Yu [a], Qiang Zhang [a, b, *], Jin-Ming Gao [a, **]

[a] Shaanxi Key Laboratory of Natural Products & Chemical Biology, College of Chemistry & Pharmacy, Northwest A&F University, Yangling, 712100, PR China
[b] Stake Key Laboratory of Natural and Biomimetic Drugs, Peking University, Beijing, 100191, PR China

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ABSTRACT

Diversity oriented synthesis starting from natural products is a newly coming strategy to build diverse skeletons to meet the demands of high throughput screening in drug development. Caryophyllene was being considered as an ideal starting point to build divers natural-like sesquiterpenes due to its rich sources and build-in reactivity. In this paper, six new natural-like products (**2**–**7**) were synthesized form the natural cryophyllene oxide via cascade oxidation and transannular reactions in a one-pot procedure. Their structures were elucidated by exhaustive spectra method including 2D NMR and X-ray diffraction. Of the products, compounds **6** and **7** possess very similar skeleton to natural products. Our findings demonstrated that one-pot cascade reactions on macrocyclic natural products is a concise strategy to create diverse natural-like skeletons.

1. Introduction

The chemical space represented by natural products (NP) is now being recognized as an important source for drug discovery [1]. NPs and their intricate backbones offer a range of uncharted chemotypes for the discovery of chemical probes and drugs [2]. Especially they often feature biologically relevant molecular scaffolds and pharmacophore patterns which are evolved in preferred ligand–protein binding motifs. Therefore, NPs have been an invaluable sources of inspiration for drug design, with particular effectiveness in cancerous and infectious diseases [1,3]. However, their use over the past two decades has decreased in the pharmaceutical industry [4]. This decline is mainly attributed to the limitation of plant resources and the elaborate isolation procedures for active NPs from complex extracts [5]. Thus, it is crucial to develop new approaches to inspire NP-like libraries based on small molecules [6].

Recently, diversity-oriented synthesis (DOS) starting from NPs has emerged as an efficient methodology to access chemically diverse libraries with NP or NP-like scaffolds [7–10]. Furthermore, biosynthesis-type reactions may be a useful approach for building NP-like libraries. In biosynthetic pathways towards terpenoids, Wagner-Meerwein reaction (including transannular cyclization) has shaped a wide variety of natural skeletons from macrocycle precursors by thermal, photochemical or acid-catalyzed methods. They involve carbocation intermediates and typically hydride or alkyl shifts. In light of the naturally powerful diversity generation process, we have recently employed the cascade Wagner-Meerwein reaction on β-caryophyllene to yield NP-like library with high skeletal diversity [11]. Furthermore, those natural process sometimes incorporate oxidations to form fused O-containing heterocycles in natural products. Therefore in is paper, we developed a further procedure incorporating cascaded oxidation and transannular rearrangements in one-pot to construct a library covering novel sesquiterpene-like skeletons (Scheme 1).

2. Experimental

2.1. General procedure

IR were recorded on a Bruker Tensor 27 spectrophotometer with KBr disks (Bruker Corp., German). Optical rotations were measured on a Autopol III automatic polarimeter (Rudolph Research Analytical, USA). ESIMS was performed on a LTQ Fleet instrument (Thermo Fisher Scientific Inc., USA). HRESIMS was performed on a Thermo Scientific LTQ Orbitrap XL. 1D and 2D NMR spectra were

* Corresponding author. Shaanxi Key Laboratory of Natural Products & Chemical Biology, College of Chemistry & Pharmacy, Northwest A&F University, Yangling, 712100, PR China.
** Corresponding author.
E-mail addresses: zhangq@nwsuaf.edu.cn (Q. Zhang), jinminggao@nwsuaf.edu.cn (J.-M. Gao).

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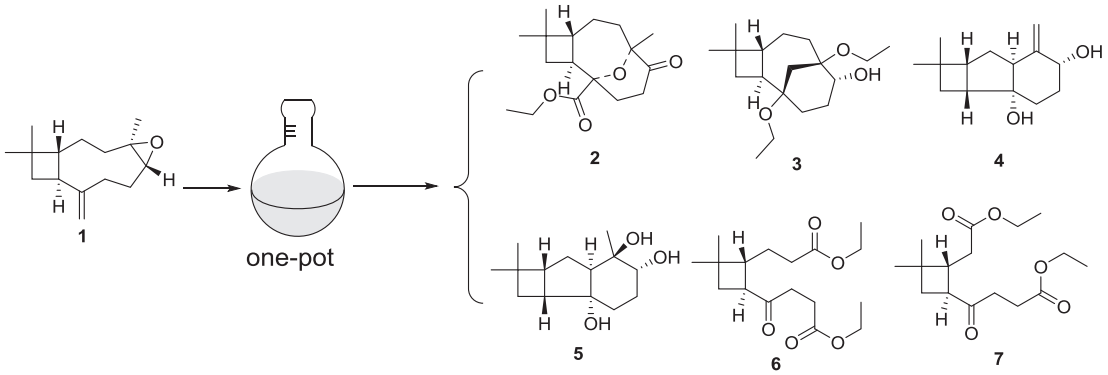

Scheme 1. One-pot reaction on 1. Reaction condition: (1) $NaIO_4/RuCl_3$; (2) H_2SO_4/EtOH.

recorded on an AVANCE III (500 MHz) instrument (Bruker Corp., German). Chemical shifts (in ppm) were reported using residual solvent as the internal standard. Coupling constants (J values) are reported in Hertz (Hz) and multiplicity of the signals in ^{1}H NMR is reported as doublet (d), triplet (t), quartet (q), doublet of doublet (dd) and multiplet (m).

GF_{254} plates (Qingdao Marine Chemical Inc., China) were used for thin-layer chromatography (TLC). High performance liquid chromatography (HPLC) analysis and semi-preparation were performed on a Waters 1525 instrument (Waters Corp. USA). Column chromatography was performed on silica gel (90–150 μm; Qingdao Marine Chemical Inc., China), Sephadex LH-20 (40–70 μm; Amersham Pharmacia Biotech AB, Sweden), and RP C_{18} silica gel (Chromatorex MB100-40/75, 40–75 μm; Fuji Silysia Chemical LTD, Japan).

2.2. One-pot reaction procedure

β-Caryophyllene oxide (**1**, 2.0 g) was treated with $NaIO_4$ (15.8 g) and $RuCl_3$ (35.0 mg) in solvent system $H_2O/CH_3CN/AcOEt$ (3:2:2). The mixture was stirred for 6 h at room temperature and monitored by TLC. When the caryophyllene oxide was exhausted, 50 mL H_2SO_4 (5% in EtOH) was added into the mixture. The reaction mixture was kept at 45 °C for a further 12 h. After intermediate products transformed absolutely, the reaction mixture was neutralized by saturated $NaHCO_3$. Then, the mixture was extracted with chloroform three times. The combined organic layer was dried by anhydrous Na_2SO_4 and concentrated to afford the crude products (1.9 g).

The crude products was chromatographed on a silica column and eluted with gradient EtOAc in petroleum ether to yield 4 fractions (Fr.1–4); Fr. 1 was subsequently chromatographed on Sephadex LH-20 column (MeOH) and silica column to yield **3** (62 mg); Fr. 2 was chromatographed by silica column and prep. HPLC to yield **2** (35 mg); Fr. 3 was separated by RP-18 column and purified by semi-prep. HPLC to yield **6** (24 mg) and **7** (5 mg). Fr. 4 was purified by semi-prep. HPLC to yield **5** (5 mg). Fr. 5 was subjected on Sephadex LH-20 (MeOH) and semi-prep. HPLC to yield **4** (7 mg).

Compound 2: colorless needles; m.p. 112.2–112.4 °C; $[\alpha]_D^{23}$ 131 (*c* 0.2, $CHCl_3$); IR (KBr) ν_{max} 2959, 2934, 2868, 1724, 1467, 1367, 1292, 1202, 1071 cm^{-1}; ESIMS *m/z* 611 ($[2\,M + Na]^+$); HR ESIMS *m/z* 295.1904 ($[M+H]^+$, calcd. for $C_{17}H_{27}O_4$ 295.1904); ^{1}H NMR (500 MHz, $CDCl_3$) δ in ppm (mult. *J* in Hz): 1.70 (td, 11.0, 7.9, H-1), 1.56 (m, H_a-2), 1.35 (m, H_b-2), 2.22 (ddd, 15.2, 8.0, 1.3, H_a-3), 1.84 (dt, 15.2, 9.3, H_b-3), 2.77 (m, H_a-6), 2.32 (m, H_b-6), 2.60 (dd, 13.1, 10.9, H_a-7), 2.35 (m, H_b-7), 2.38 (m, H-9), 1.50 (m, H_a-10), 1.40 (m, H_b-10), 1.34 (s, H_3-12), 0.98 (s, H_3-14), 0.96 (s, H_3-15), 4.17 (q, 7.2, H_2-16), 1.23 (t, 7.2, H_3-17); ^{13}C NMR see Fig. 1.

Compound 3: colorless oil; $[\alpha]_D^{23}$ 14.1 (*c* 0.2, $CHCl_3$); IR (KBr) ν_{max} 3447, 2944, 2860, 1460, 1387, 1308, 1284, 1071 cm^{-1}; EIMS *m/z* 296 ($[M]^+$), 278 ($[M - H_2O]^+$), 252, 237; HRESIMS *m/z* 319.2247 ($[M+Na]^+$, calcd. for $C_{18}H_{32}O_3Na$ 319.2249); ^{1}H NMR (500 MHz, $CDCl_3$) δ in ppm (mult. *J* in Hz): 1.96 (m, H-1), 1.62 (m, H_a-2), 1.45 (m, H_b-2), 1.85 (m, H_a-3), 1.53 (m, H_b-3), 3.60 (dd, 11.0,5.7, H-5), 1.93 (m, H_a-6), 1.57 (m, H_b-6), 1.79 (m, H_a-7), 1.56 (m, H_b-7), 2.06 (ddd, 12.3, 9.7, 7.6, H-9), 1.66 (dd, 9.7, 7.6, H_a-10), 1.48 (m, H_b-10), 2.22 (dd, 12.4, 3.3, H_a-12), 1.32 (d, 12.4, H_b-12), 1.00 (s, H_3-14), 0.97 (s, H_3-15), 3.51 (dq, 8.7, 7.0, H_a-16), 3.23 (dq, 8.7, 7.0, H_b-16), 1.11 (t, 7.0, H_3-17), 3.42 (dq, 8.7, 7.0, H_a-18), 3.22 (dq, 8.7, 7.0, H_b-18), 1.14 (t, 7.0, H_3-19); ^{13}C NMR see Fig. 1.

Compound 4: colorless needles; m.p. 140.0–140.4 °C; $[\alpha]_D^{23}$ − 76.8 (*c* 0.1, $CHCl_3$); IR (KBr) ν_{max} 3356, 2944, 2863, 1648, 1450, 1365, 1075 cm^{-1}; EIMS *m/z* 222 ($[M]^+$), 204 ($[M - H_2O]^+$), 189, 133; HRESIMS *m/z* 223.1692 ($[M+H]^+$, calcd. for $C_{14}H_{23}O_2^+$ 223.1693); ^{1}H NMR (500 MHz, pyridine-d_5) δ in ppm (mult. *J* in Hz): 2.16 (m, H-1), 2.43 (ddd, 13.5, 12.0, 3.9, H_a-2), 1.74 (m, H_b-2), 3.45 (dd, 12.0, 8.4, H-3), 4.74 (br. d, 10.4, H-5), 2.22 (m, H_a-6), 2.18 (m, H_b-6), 1.95 (dt, 13.4, 8.8, H_a-7), 1.82 (m, H_b-7), 2.54 (dt, 8.5, 7.3, H-9), 1.85 (m, H_a-10), 1.82 (m, H_b-10), 5.83 (br. s, H_a-12), 5.25 (br. s, H_b-12), 0.94 (s, H_3-14), 1.15 (s, H_3-15); ^{13}C NMR see Fig. 1.

Compound 5: white powder; $[\alpha]_D^{23}$ − 87.9 (*c* 0.1, $CHCl_3$); IR (KBr) ν_{max} 3385, 3314, 2945, 2863, 1451, 1187, 1120, 1079 cm^{-1}; EIMS *m/z* 222 ($[M - H_2O]^+$), 211 ($[M - C_2H_5]^+$), 153; HRESIMS *m/z* 241.1799 ($[M+H]^+$, calcd. for $C_{14}H_{25}O_3$ 241.1798); ^{1}H NMR (500 MHz, $CDCl_3$) δ in ppm (mult. *J* in Hz): 2.11 (br. t, 7.6, H-1), 1.64 (m, H_a-2), 1.58 (m, H_b-2), 2.47 (dd, 12.9, 8.5, H-3), 3.82 (dd, 11.8, 4.4, H-5), 1.83 (m, H_a-6), 1.19 (dt, 14.2, 4.4, H_b-6), 1.82 (m, H_a-7), 1.67 (m, H_b-7), 2.52 (dt, 8.2, 7.1, H-9), 1.74 (dd, 12.3, 7.1, H_a-10), 1.54 (m, H_b-10), 1.40 (s, H_3-12), 0.92 (s, H_3-14), 1.15 (s, H_3-15); ^{13}C NMR see Fig. 1.

Compound 6:colorless oil; $[\alpha]_D^{23}$ 71.2 (*c* 0.1, $CHCl_3$); IR (KBr) ν_{max} 2955, 2867, 1735, 1710, 1451, 1372, 1178 cm^{-1}; ESIMS *m/z* 335.29 ($[M+Na]^+$); HR ESIMS *m/z* 313.2010 ($[M+H]^+$, calcd. for $C_{17}H_{29}O_5$ 313.2009); ^{1}H NMR (500 MHz, $CDCl_3$) δ in ppm (mult. *J* in Hz): 2.18 (m, H-1), 1.71 (m, H_2-2), 2.21 (m, H_2-3), 2.57 (m, H_2-6), 2.67 (m, H_2-7), 2.82 (ddd, 10.3, 9.5, 9.2, H-9), 1.86 (dd, 10.5, 9.2, H_a-10), 1.78 (dd, 10.3, 10.3, H_b-10), 1.07 (s, H_3-14), 1.05 (s, H_3-15), 4.10 (q, 7.2, H_2-16), 1.27 (t, 7.2, H_3-17), 4.14 (q, 7.2, H_2-18), 1.24 (t, 7.2, H_3-19); ^{13}C NMR see Fig. 1.

Compound 7:colorless oil; $[\alpha]_D^{23}$ 51.6 (*c* 0.1, $CHCl_3$); IR (KBr) ν_{max} 2957, 2869, 1734, 1711, 1371, 1176, 1030 cm^{-1}; ESIMS *m/z* 321.23 ($[M+Na]^+$); HR ESIMS *m/z* 299.1853 ($[M+H]^+$, calcd. for $C_{16}H_{27}O_5$ 299.1853); ^{1}H NMR (500 MHz, $CDCl_3$) δ in ppm (mult. *J* in Hz): 2.61 (m, H-1), 2.36 (m, H_2-2), 2.55(m, H_2-6), 2.70 (m, H_2-7), 2.90 (ddd, 9.3, 9.2, 9.1, H-9), 1.85 (d, 9.2, H_2-10), 1.05 (s, H_3-14), 1.07 (s, H_3-15), 4.06 (q, 7.0, H_2-16), 1.22 (t, 7.0, H_3-17), 4.12 (q, 7.0, H_2-18), 1.24 (t, 7.0, H_3-19); ^{13}C NMR see Fig. 1.