Total Synthesis of (±)-Chinensiolide B from α-Santonin

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A short and efficient total synthesis of (±)-chinensiolide B is reported, starting from commercially available α-santonin. This strategy could be used for rapid preparation of chinensiolides and their derivative for further structure activity relationship studies.

Keywords total synthesis, (±)-chinensiolide B, santonin, guaianolide

Introduction

Sesquiterpene lactones are often found in nature and attracted considerable interest for their biological activities, such as antibiotic, insecticide, antitumor activities. As one of the largest type of sesquiterpene lactones, guaianolides have more significant activities.[1] The chinensiolides (Figure 1), containing cis-fused 5,7,5-tricyclic ring, were recently isolated from the whole plant of Siyekucai (Ikeris chinensis Naka), which has been used in China for haemostatic and anti-inflammatory effects.[2] Among them, chinensiolide B has efficient in vitro cytotoxic activities against human lung fibroblast (WI-38, VA-13) and especially one human primary liver cancer (HepG2) cell line.[3] The outstanding activities and complex structure with six continuous stereocenters and a double bond in lactone ring make their synthesis very challenging. To the best of our knowledge, only one group, Hall’ group for the first time, has reported an impressive synthesis of (±)-chinensiolide B. It was achieved in 15 steps with an overall yield of 6.7% for the longest linear sequence starting from (R)-carvone.[4] The key step was stereoselective and E/Z-selective tandem allylboration/lactonization reaction to build γ-butyrolactone moiety. Then a ring-closing metathesis formed the requisite seven-membered ring in a chemoselective fashion. Due to studies on structure-activity relationship of 5,7,5-tricyclic lactones and natural product synthesis still being intensive, the development of a fast and efficient approach is necessary.[5] Herein, we reported our method for total synthesis of (±)-chinensiolide B from α-santonin.

Results and Discussion

Our retrosynthetic strategy is shown in Scheme 1. To establish the double bond in lactone ring, a ketone ring and lactone are key to synthesis. Compound 1 was envisioned to be formed by oxidative-elimination of ester 2. The trans-hydrogen of C-4, C-5 was afforded by olefin reduction of enone 3. Intermediate 3, which is a well-known compound, can be fast prepared from available α-santonin according to previous reports.[6] The synthetic sequence starting from α-santonin is shown in Scheme 2. The key reaction to construct core structure of guaianolide went through photochemical rearrangement, which provided a perfect starting point for various 5,7,5-tricyclic lactone to synthesize several natural products. Normally, the guaianolide 3 could be transformed by high-pressure Hg Lamp in acetic acid or mixture with water under yield about 40%, even the...
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**Scheme 1** Retrosynthesis of (+)-chinensiolide B

Addition of the palladium-catalyzed hydrogenation product.\(^9\)

Hydrolysis of ester 4 with 5% aq. KOH in ethanol at room temperature generated alcohol 2. In order to get the additional double bond in lactone, the strong base should be used. So the alcohol and ketone group of compound 2 should be protected. Firstly, treatment of 2 with NaBH\(_4\) gave the dihydrolactone 5. The stereochemistry of C-3 hydroxyl group of 5 could be confirmed in the next steps. In order to improve the yield in protecting step, two different protecting groups were used to form 6 in 86% yield, with TBSCI protecting C-3 hydroxyl group and TMSCl protecting C-10 hydroxyl group. Selenylation of compound 7 with (PhSe)\(_2\) in the presence of HMPA followed by oxidative elimination with H\(_2\)O\(_2\) at AcOH gave the double bond in the lactone ring. The Silyl-ethers were removed by treatment with 1 mol/L TBAF in THF solution giving the dialcohols 8 in 74% in 3 steps. The configuration of C-3 hydroxyl group was confirmed by comparing with the reduced product of (+)-chinensiolide B by Dai.\(^3\) Finally, oxidation of alcohol by Dess-Martin periodinane, provided the guainane sesquiterpene (+)-chinensiolide B in 93% yield. \(^1\)H NMR and \(^13\)C NMR spectral data of compound 1 in CDCl\(_3\) and D\(_5\)-pyridine and optical rotation were identical to those of the natural and synthetic product. The single-crystal X-ray data of 1 confirmed configuration of (+)-chinensiolide B.\(^{10}\)

**Scheme 2** Total synthesis of (+)-chinensiolide B

addition of the palladium-catalyzed hydrogenation product.\(^9\)

Hydrolysis of ester 4 with 5% aq. KOH in ethanol at room temperature generated alcohol 2. In order to get the additional double bond in lactone, the strong base should be used. So the alcohol and ketone group of compound 2 should be protected. Firstly, treatment of 2 with NaBH\(_4\) gave the dihydrolactone 5. The stereochemistry of C-3 hydroxyl group of 5 could be confirmed in the next steps. In order to improve the yield in protecting step, two different protecting groups were used to form 6 in 86% yield, with TBSCI protecting C-3 hydroxyl group and TMSCl protecting C-10 hydroxyl group. Selenylation of compound 7 with (PhSe)\(_2\) in the presence of HMPA followed by oxidative elimination with H\(_2\)O\(_2\) at AcOH gave the double bond in the lactone ring. The Silyl-ethers were removed by treatment with 1 mol/L TBAF in THF solution giving the dialcohols 8 in 74% in 3 steps. The configuration of C-3 hydroxyl group was confirmed by comparing with the reduced product of (+)-chinensiolide B by Dai.\(^3\) Finally, oxidation of alcohol by Dess-Martin periodinane, provided the guainane sesquiterpene (+)-chinensiolide B in 93% yield. \(^1\)H NMR and \(^13\)C NMR spectral data of compound 1 in CDCl\(_3\) and D\(_5\)-pyridine and optical rotation were identical to those of the natural and synthetic product. The single-crystal X-ray data of 1 confirmed configuration of (+)-chinensiolide B.\(^{10}\)
Conclusions

In conclusion, we have developed an efficient method for total synthesis of (+)-chinensiolide B from α-santonin in 10 steps with 18.6% overall yield. Using this fast and efficient method, other chinensiolides could be synthesized as well as the preparation of their derivatives for further structure-activity relationship studies.

Experimental

General methods

All reactions under standard conditions were monitored by thin-layer chromatography (TLC) on silica gel GF254 plates. Column chromatography was performed on silica gel (200–300 mesh), and the eluting petroleum ether’s distillation range was 60–90 °C. All solvents were purified under standard method. Unless otherwise noted, 1H NMR and 13C NMR spectra were recorded in CDCl3 solution on Bruker AX-500 MHz instruments. HRMS (ESI-MS) was recorded using Agilent 6520 accurate-Mass Q-TOF LC/MS system (1200–6520/Agilent). Column chromatography was carried out on silica gel (200–300 mesh). Chemical shifts are reported relative to chloroform (δH, δ 7.27; 13C, δ 77.0). Data for 1H NMR are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet) and coupling constants.

Preparation of 3

A solution of α-santonin (15 g, 60.8 mmol) in distilled glacial AcOH (230 mL) was irradiated under Ar at 20 °C for 18 h using a 350 W high-pressure mercury lamp. After the AcOH was evaporated in vacuo, diethyl ether (30 mL) was added to the resulting residue then cooled to 0 °C. Filtration of the precipitate afforded compound 3 (7.6 g, 38%) as a white solid. 1H NMR (500 MHz, CDCl3) δ: 4.80 (d, J = 11.0 Hz, 1H), 4.15–4.16 (m, 1H), 2.62 (dd, J = 4.5, 13.5 Hz, 1H), 2.17–2.53 (m, 5H), 2.06–2.10 (m, 1H), 2.01 (s, 3H), 1.91 (s, 3H), 1.42–1.50 (m, 1H), 1.29 (d, J = 7.0 Hz, 3H), 1.09 (s, 3H); 13C NMR (125 MHz, CDCl3) δ: 206.9, 177.0, 170.3, 160.8, 143.2, 85.5, 81.2, 48.2, 47.2, 41.3, 37.9, 36.8, 25.3, 22.2, 20.0, 12.4, 9.4. HRMS (EI-MS) calculated for C17H22O5Na 331.1521, found 329.1356. Spectroscopic data are in accordance with reported literature values.

Preparation of 4

Anhydrous EtOH (degassed) (40 mL) was added to the mixture of Te powder (1.7 g, 13.4 mmol) and NaBH4 (1.2 g, 31.6 mmol) under Ar. The solution was then heated to reflux for 1 h. After the solution was cooled to −20 °C, AcOH (1 mL) in anhydrous EtOH (2 mL) was injected to the mixture followed by compound 3 (500 mg, 1.63 mmol) in toluene (5 mL) and EtOH (5 mL). The reaction mixture was warmed to room temperature and stirred for 3 d. Then the reaction was quenched by water. The resulting mixture was filtered, extracted with EtOAc, concentrated in vacuo to afford the crude compound 4, which was purified by column chromatography using EA/PE (1 : 1) giving compound 4 (488 mg, 97%) as a white solid. [α]D = −25 (c 0.25, CHCl3) (lit.[9] [α]D = −24.5 (c 1.22, CHCl3)); 1H NMR (500 MHz, CDCl3) δ: 4.09 (t, J = 10.0 Hz, 1H), 3.30 (dd, J = 8.0, 16.0 Hz, 1H), 2.50–2.56 (m, 1H), 2.45–2.47 (m, 1H), 2.39–2.44 (m, 2H), 2.23–2.28 (m, 2H), 2.01–2.11 (m, 6H), 1.38–1.61 (m, 5H), 1.27 (d, J = 7.0 Hz, 3H), 1.22 (d, J = 7.5 Hz, 3H); 13C NMR (125 MHz, CDCl3) δ: 218.3, 177.8, 170.0, 85.7, 84.0, 50.3, 48.2, 48.1, 43.2, 42.8, 39.2, 33.5, 25.8, 24.4, 22.3, 15.8, 13.0. HRMS (ESI-MS) calculated for C17H24O5Na 331.1521, found 329.11524. Spectroscopic data are in accordance with reported literature values.

Preparation of 2

A solution of compound 4 (308 mg, 1 mmol) in ethanol (20 mL) was treated with 5% aqueous KOH (50 mL). After stirring at room temperature for 3 h, the reaction was acidified with 18% HCl to pH = 4 and stirred for an additional 20 min. The resulting mixture was extracted with EA. The organic layer was washed with sat. NaHCO3 brine, dried over anhydrous Na2SO4, and concentrated in vacuo to give compound 2 (250 mg, 92%) as a white solid. [α]D = +62 (c 0.5, CHCl3) (lit.[9] [α]D = +36 (c 1.2, CHCl3)); 1H NMR (500 MHz, CDCl3) δ: 4.11 (t, J = 10 Hz, 1H), 2.73 (ddd, J = 2.0, 5.5, 19.5 Hz, 1H), 2.61 (ddd, J = 5.5, 9.0, 14.5 Hz, 1H), 2.39 (dd, J = 9.5, 19.5 Hz, 1H), 2.23–2.30 (m, 3H), 2.04–2.10 (m, 2H), 1.96–2.01 (m, 1H), 1.67–1.73 (m, 1H), 1.38–1.46 (m, 1H), 1.25 (d, J = 6.5 Hz, 3H), 1.21 (d, J = 7.0 Hz, 3H), 1.18 (s, 3H); 13C NMR (125 MHz, CDCl3) δ: 219.5, 178.2, 86.3, 73.9, 50.1, 48.4, 48.3, 45.6, 42.1, 42.0, 39.8, 26.6, 25.8, 15.3, 13.0. HRMS (EI-MS) calculated for C17H24O5Na 289.1416, found 289.1413. Spectroscopic data are in accordance with reported literature values.

Preparation of 5

To a solution of compound 2 (200 mg, 0.75 mmol) in methanol (10 mL), NaBH4 (32 mg, 0.83 mmol) was slowly added in three portions. The reaction mixture was stirred at 0 °C for 0.5 h and then quenched by sat. NH4Cl. The resulting solution was concentrated in vacuo, then extracted with EA. The extract was washed with brine, dried over anhydrous Na2SO4, and concentrated in vacuo to give crude product, purified by column chromatography using EA/PE (1 : 1) giving compound 5 (194 mg, 93%) as a colorless oil. [α]D = +7.3 (c 0.5, CHCl3) (lit.[9] [α]D = +3 (c 1.4, CHCl3)); 1H NMR (500 MHz, CDCl3) δ: 4.18 (t, J = 9.5 Hz, 1H), 3.66 (dd, J = 8.0, 16.0 Hz, 1H), 2.18–2.30 (m, 3H), 1.93–2.00 (m, 3H), 1.60–1.87 (m, 4H), 1.33–1.36 (m, 1H), 1.23 (s, 3H), 1.20 (d, J = 7.0 Hz, 3H), 1.13 (d, J = 6.0 Hz, 3H);
Preparation of 6

A solution of compound 5 (150 mg, 0.56 mmol) and imidazole (57 mg, 0.84 mmol) in dichloromethane (5 mL) was added TBSCl (168.5 mg, 1.1 mmol) at room temperature. After being stirred at r.t. for 10 h, the reaction was quenched by water, extracted with EA, and concentrated in vacuo, purified by column chromatography using EA/PE (5:1) to afford TBS protected 5 as a white solid.

The TBS protected 5 was dissolved in dichloromethane (5 mL) with TEA (117 μL, 0.84 mmol) and treated with TMSCl (121.5 mg, 0.84 mmol). The reaction was stirred at r.t. for 24 h, then quenched by water, extracted with EA, washed with brine, dried over anhydrous Na₂SO₄, and concentrated in vacuo, purified by column chromatography using EA/PE (20:1) to afford compound 6 as a white solid.

Preparation of 8

A solution of compound 6 (200 mg, 0.44 mmol) in anhydrous THF (5 mL) was slowly added to a cooled (−78 °C) solution of LDA freshly prepared from diisopropylamine and n-BuLi in anhydrous THF (2 mL). After 1.5 h a solution of (PhSe)₂ (415 mg, 1.3 mmol) containing HMPA (225 μL, 1.3 mmol) in anhydrous THF (5 mL) was slowly added over 30 min. The mixture was stirred at −78 °C for 1 h and then warmed to −40 °C while stirring was continued for an additional 1.5 h. The mixture was poured into 0.2 mol/L aqueous HCl (20 mL), extracted with EA, washed with brine, dried over anhydrous Na₂SO₄, and concentrated in vacuo to give crude product. The crude product dissolved in THF (2 mL) was treated with 1 mol/L Bu₄NF in THF (660 μL, 0.66 mmol). The mixture was stirred for 30 min and then quenched by water, extracted with EA and concentrated in vacuo to give crude product, purified by column chromatography using EA/PE (2:1) to afford compound 8 (86 mg, 74%, three steps) as a colorless oil.

Preparation of (+)-chinenisolide B (1)

A solution of compound 8 (80 mg, 0.3 mmol) in DCM (2 mL) was added to a solution of DMP (165 mg, 3.9 mmol) in DCM (1 mL) with stirring. After 1 h, the reaction was quenched by sat. NaHCO₃, extracted with EA, washed with brine, dried over anhydrous Na₂SO₄, and concentrated in vacuo to give crude product, purified by column chromatography using EA/PE (20:1) to afford chinenisolide B as a white solid (74 mg, 93%).

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[10] CCDC 1415239 contains the crystallographic data of which could be obtained from the Cambridge Crystallographic Data Center.


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