Chiron approach for the total synthesis of (+)-synargentolide B

Jun Liu a, *, Yangguang Gao b, Linlin Wang a, Yuguo Du a, b

a State Key Laboratory of Environmental Chemistry and Eco-toxicology, Research Center for Eco-Environmental Sciences, Chinese Academy of Sciences, Beijing, 100085, China
b School of Chemistry and Chemical Engineering, University of Chinese Academy of Sciences, Beijing, 100049, China

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A concise and efficient chiron approach for the total synthesis of natural product synargentolide B was achieved in 10 steps with overall yields of 11.3% from D-mannitol and L-ethyl lactate. The key reactions included anti-Barbier allylation, cross-metathesis, and an intramolecular Yamaguchi esterification.

1. Introduction

5,6-Dihydro-α-pyrene moiety is an ubiquitous heterocyclic unit found in a number of biologically active natural products, such as synargentolide B (1), synargentolide A (2), anamarine (3), syrrotolide (4), which have displayed a variety of biological properties, including cytotoxic, antifungal and antibacterial activity. Until now, four total syntheses were reported for (+)-synargentolide B and one synthesis for its analogue in the literature. Prasad et al. has accomplished the total syntheses of compound 1 and its diastereomers starting from (S)-lactic acid and the two enantiomers of tartaric acid using Wittig-Horner reaction and ring-closing metathesis as their key steps. Meanwhile, Sabitha’s work commenced with D-ribose, D-mannitol, and (+)/(-)-DET to synthesize synargentolide B and its diastereomers through a tandem ring-closing/cross-metathesis reaction.

Herein, we report the synthesis of natural (+)-synargentolide B beginning with D-mannitol and L-ethyl lactate as chiral templates.

2. Results and discussion

Our approach for the synthesis of (+)-synargentolide B (1) is depicted in Scheme 1. As shown in Scheme 1, the disconnection process began with two double bonds at C1-C2 and C3-C4, each of which could be realized by a cross-metathesis reaction and an intramolecular Yamaguchi esterification, respectively. The building block 6 was readily derived from L-ethyl lactate over 4 steps as shown in Scheme 2. Protection of L-ethyl lactate as its silyl ether with TBSCl, imidazole in DCM afforded compound 10 in a high yield (96%). Reduction of compound 10 by DIBAL-H in DCM at -78 °C furnished the corresponding aldehyde. Subsequent treatment of the aldehyde generated in situ with vinlylmagnesium chloride furnished the desired anti product 8 as a 5.8:1 mixture of diastereoisomers. Unfortunately, the attempted separation of the two diastereomers of 8 via flash chromatography proved problematic. Deprotection of compound 8 by TBAF in THF followed by peracylation with acetic anhydride in pyridine provided the building block 6 in 72% yield as a 7:1 separable mixture of C5'-diastereomers.

Reagents and conditions: (a) TBSCI, imidazole, DCM, rt, 96%; (b)
DIBAL-H, DCM, –78 °C-rt, then vinylmagnesium chloride, Et₂O, –98 °C-rt; (c) TBAF, THF, then Ac₂O, pyridine, 72% for 4 steps.

As depicted in Scheme 3, our synthesis of compound 7 commenced with D-mannitol, which was converted to 12 in 3 steps in excellent yield according to a modified reported procedure.[12]

Selective hydrolysis of primary acetonide and oxidative cleavage of resulting diol occurred simultaneously with H₂IO₆ resulted in 11 in almost quantitative yield. Allylation of the aldehyde 11 under the zinc-mediated Barbier reaction gave homoallyl alcohol 13 as an inseparable anomic mixture (81%, anti:syn = 4:1, determined by ¹H NMR). When aldehyde 11 was subjected to the Grignard reaction with allylmagnesium bromide in dry ether, homoallyl alcohol 13 was obtained only in 55% yield as diastereomeric mixture (65:35).

Reagents and conditions: (d) ref 12, 69% for 3 steps; (e) H₂IO₆, MeOH, RT; (f) Allyl bromide, excess Zn dust, saturated NH₄Cl, THF, 0–5 °C, 72% for 2 steps; (g) methyl acrylate (10 eq), Grubbs’ 2nd generation catalyst (0.03eq), DCM, RT, 18 h, 56%; (h) LiOH, THF, H₂O, RT; (i) 2,4,6-trichlorobenzoyl chloride, pyridine, DCM, 0 °C to RT, 83% for 2 steps;

In the next step, we planned to subject diene 13 to mono-cross-metathesis with methyl methacrylate. To ensure selective mono-cross-metathesis of diene, the sterically protecting group acetonide is necessary to be present (Scheme 3). In the case of acetonide protected diene 13, best results were obtained with 3 mol % of Grubbs’ 2nd generation catalyst in DCM at ambient temperature, 5 equiv of methyl acrylate present from the outset, and slow addition of further 5 equiv over 12 h, and the trans-α,β-unsaturated ester 9 was obtained in 56% yield with 9% bis-cross-metathesis byproduct 14.[13] Treatment of ester 9 with LiOH in THF/H₂O afforded the corresponding acid in almost quantitative yield.[10] Intramolecular esterification of acid 15 under modified Yamaguchi conditions[10] afforded cis-α,β-unsaturated lactone 7 in 83% yield as an 8:1 mixture of readily separable diastereomers. The δ-lactonization of 7 could be explained through activation of carboxylic acid with 2,4,6-trichlorobenzoyl and subsequent pyridine assisted assisted elimination.[10]

With these two key fragments in hand, we set out to prepare natural (+)-synargentolide B (1) through the planned cross-metathesis (Scheme 4). We are pleased to find that cross-metathesis between side chain 6 and core 7 was successfully carried out by treatment with Grubbs II catalyst in reflux DCM to provide compound 16 in 63% yield with 11% dimer 17. Finally, removal of the acetonide group in compound 16 by PPTS in MeOH proceeded smoothly to afford (+)-synargentolide B (1) in 78% yield.[8] The physical and spectroscopic data (¹H and ¹³C NMR) of our synthetic sample 1 were in good agreement with natural product synargentolide B.[1]
Scheme 2. Synthesis of compound 6.

Scheme 3. Synthesis of compound 7.

Scheme 4. Synthesis of (+)-synargentolide B (1). Reagents and conditions: (j) Grubbs’ 2nd generation catalyst (0.05eq), DCM, reflux, 4 h, 63%; (k) PPTS, MeOH, reflux, 6 h, 78%.
3. Conclusions

In summary, natural (+)-synargentolide B was successfully accomplished by using D-mannitol and L-ethyl lactate as chiral template. Key features of our strategy toward practical total synthesis of (+)-synargentolide B are the efficient combination of an anti-Barbier allylation, cross-metathesis, and an intramolecular Yamaguchi esterification. Our convergent and effective strategy provides a candidate for the synthesis of other related synargentolide analogs taking advantage of the inherent chiral centers from natural carbohydrates.

4. Experimental section

4.1. General experimental

Unless noted otherwise, commercially available materials were used without further purification. Yields refer to chromatographically and spectroscopically (1H NMR) homogeneous materials. All solvents were dried according to the established procedures ahead of use. Flash chromatography (FC) was performed using silica gel (200–300 meshes) according to the standard protocol. All reactions under standard conditions were monitored by thin-layer chromatography (TLC) on gel E254 plates. Optical rotations were measured using a polarimeter with a thermally jacketed 5 cm cell at approximately 25 °C. High-resolution mass spectrometry data (HRMS) were acquired using a Q-TOF analyzer in acetone or methanol as solvent. 1H NMR, 13C NMR were measured on 400 MHz (HRMS) were acquired using a Q-TOF analyzer in acetone or CHCl3; 1H NMR (400 MHz, CDCl3): δ = 5.82–5.71 (s, 1H), 5.33–5.27 (m, 3H), 5.08–5.01 (m, 1H), 2.07 (s, 3H), 2.02 (s, 3H), 1.18 (d, J = 6.4 Hz, 3H) ppm. 13C NMR (100 MHz, CDCl3): δ = 170.4, 170.1, 132.0, 119.4, 75.6, 70.4, 21.1, 21.0, 14.9 ppm. HRMS (ESI-TOF) m/z: [M+Na]+ Calcd for C8H14O4Na [M+ Na]+, 209.0790; found 209.0773.

4.2. Synthesis of compound 13

To a solution of the diacetonide 12 (150 mg, 0.66 mmol) in EtOAc (10 mL) was added orthoperiodic acid (300 mg, 1.3 mmol) at room temperature and stirred for 30 min. The reaction was quenched by aqueous saturated NaHCO3 (20 mL) and filtered through Celite. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic solution was concentrated to give the crude aldehyde 11 as colorless oil. (Caution: The aldehyde 11 was highly unstable and decomposed rapidly on flash column or in CDCl3 at room temperature.) The crude aldehyde obtained could be used in the next step without further purification. To a mixture of crude 11 (ca. 0.66 mmol), Zn dust (86 mg, 1.32 mmol) and allyl bromide (0.114 mL, 13.2 mmol) in THF (8 mL) was added a saturated solution of orthoephosphoric acid (1 mL) by two portions at 0 °C. After 15 min, the solution was warmed to rt and stirred for further 15 min. The mixture was filtered and washed with brine (20 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic phase was washed with brine, dried over Na2SO4 and concentrated under vacuum. The crude aldehyde obtained could be used in the next step without further purification. To a mixture of crude 11 (ca. 0.66 mmol), Zn dust (86 mg, 1.32 mmol) and allyl bromide (0.114 mL, 13.2 mmol) in THF (8 mL) was added a saturated solution of orthoephosphoric acid (1 mL) by two portions at 0 °C. After 15 min, the solution was warmed to rt and stirred for further 15 min. The mixture was filtered and washed with brine (20 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic phase was washed with brine, dried over Na2SO4 and concentrated under vacuum. The crude aldehyde obtained could be used in the next step without further purification. To a vigorously stirred solution of the crude diol in pyridine (8 mL) was added acetic anhydride (1 mL). The resulting mixture was stirred at room temperature for 2 h. The reaction was quenched by the addition of MeOH (10 mL) and concentrated with toluene. The residue was poured into saturated aqueous CuSO4 (10 mL) and extracted with DCM (3 × 20 mL). The combined organic phase was washed with brine, dried over Na2SO4 and concentrated under vacuum. The crude was purified by flash column chromatography (Hexanes/EtOAc 6:1) to give compound 6 as a colorless oil. [α]25D = −37 (c 0.42, CHCl3); 1H NMR (400 MHz, CDCl3): δ = 5.82–5.71 (1H, 1H), 5.33–5.27 (m, 3H), 5.08–5.01 (m, 1H), 2.07 (s, 3H), 2.02 (s, 3H), 1.18 (d, J = 6.4 Hz, 3H) ppm. 13C NMR (100 MHz, CDCl3): δ = 170.4, 170.1, 132.0, 119.4, 75.6, 70.4, 21.1, 21.0, 14.9 ppm. HRMS (ESI-TOF) m/z: [M+Na]+ Calcd for C8H14O4Na [M+ Na]+, 209.0790; found 209.0773.

4.2.3. Synthesis of compound 8

To a solution of the diacetone 10 (1.78 g, 7.6 mmol) in DCM (30 mL) was added DIBAL-H (1.2 M in toluene, 11.4 mmol) via syringe at −98 °C under N2 protection. After 10 min, vinyl magnesium chloride (215 mL, 15 mmol) was added into the mixture. The solution was then warmed to room temperature and stirred at room temperature overnight. The reaction was quenched by the addition of saturated K/Na tartrate. The aqueous layer was extracted with DCM. The combined organic phase was washed with brine, dried over Na2SO4 and concentrated under vacuum. The crude allylic alcohol could be used for next step without any purification. A small sample was purified by flash column chromatography (Hexanes/EtOAc 15:1) to get the physical data of 8 as a 5:8:1 mixture of diastereoisomers: [α]25D = +27.6 (c 0.45, CHCl3); 1H NMR (400 MHz, CDCl3): δ = 5.81 (d, J = 16.8, 10.8, 6.4 Hz, 1H), 5.28 (dt, J = 17.2, 16.7 Hz, 1H), 5.20 (dd, J = 10.4, 16.1 Hz, 1H), 4.02 (q, J = 2.0 Hz, 1H), 3.86–3.82 (m, 1H), 2.29 (dd, J = 4.0 Hz, 1H), 1.07 (d, J = 6.4 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 6H) ppm. 13C NMR (100 MHz, CDCl3): δ = 136.6, 116.5, 71.3, 25.8, 18.1, 17.8, −4.4, −4.99 ppm. HRMS (ESI-TOF) m/z: [M+Na]+ Calcd for C12H25O2SiNa [M+ Na]+, 239.1443; found 239.1461.

4.2.2. Synthesis of compound 6

To a stirred solution of crude 8 (0.85 g, 0.39 mmol) in dry THF (15 mL) was added TBAF (1.31 g, 5 mmol) at room temperature. After completion of the reaction (monitored by TLC), the solution was concentrated under vacuum. The crude diol was used in the next step without further purification. To a vigorously stirred solution of the crude diol in pyridine (8 mL) was added acetic anhydride (1 mL). The resulting mixture was stirred at room temperature for 2 h. The reaction was quenched by the addition of MeOH (10 mL) and concentrated with toluene. The residue was poured into saturated aqueous CuSO4 (10 mL) and extracted with DCM (3 × 20 mL). The combined organic phase was washed with brine, dried over Na2SO4 and concentrated under vacuum. The crude was purified by flash column chromatography (Hexanes/EtOAc 6:1) to give compound 6 as a colorless oil. [α]25D = −37 (c 0.42, CHCl3); 1H NMR (400 MHz, CDCl3): δ = 5.82–5.71 (1H, 1H), 5.33–5.27 (m, 3H), 5.08–5.01 (m, 1H), 2.07 (s, 3H), 2.02 (s, 3H), 1.18 (d, J = 6.4 Hz, 3H) ppm. 13C NMR (100 MHz, CDCl3): δ = 170.4, 170.1, 132.0, 119.4, 75.6, 70.4, 21.1, 21.0, 14.9 ppm. HRMS (ESI-TOF) m/z: [M+Na]+ Calcd for C8H14O4Na [M+ Na]+, 209.0790; found 209.0773.
4.2.5. Synthesis of compound 7

To a solution of 9 (44 mg, 0.17 mmol) in THF (5 mL) was added 2 M aqueous LiOH (3 mL) dropwise and the reaction was stirred for 2 h at room temperature. Amberlite IR-120 (H+) was then added to neutralize the solution and the mixture was poured into water (10 mL) and extracted with DCM (3 × 10 mL). The combined organic solution was concentrated to give 15 as colorless oil. The crude acid was used in the next step without further purification. To a solution of crude 15 in pyridine (3 mL) was added a solution of 2,4,6-trichlorobenzoyl chloride (53 mg, 0.20 mmol) in dry DCM (1 mL) at 0 °C and the reaction mixture was warmed to room temperature. After completion of the reaction (monitored by TLC), the solution was concentrated under vacuum. The residue was poured into saturated aqueous CuSO4 (10 mL) and extracted with DCM (2 × 10 mL). The combined organic phase was washed with brine, dried over Na2SO4 and concentrated under vacuum. The crude was purified by flash column chromatography (Hexanes/EtOAc 2:1) to give compound 7 as a colorless oil (32 mg, 83% for two steps). 1H NMR (400 MHz, CDCl3): δ 6.93 (dt, J = 9.6, 4.0 Hz, 1 H), 6.05 (dt, J = 9.8, 2.0 Hz, 1 H), 5.88–5.60 (m, 2 H), 5.42 (dd, J = 5.2, 4.0 Hz, 1 H), 5.08 (dq, J = 6.8, 3.6 Hz, 1 H), 4.43–4.53 (m, 2 H), 3.90 (t, J = 7.2 Hz, 1 H), 2.54–2.57 (m, 2 H), 2.10 (s, 3 H), 2.06 (s, 3 H), 1.45 (s, 6 H), 1.23 (d, J = 6.8 Hz, 3 H), 1.13 (m, 1 H), 1.05 (s, 3 H), 0.95 (t, J = 7.2 Hz, 3 H), 0.87 (s, 3 H). 

4.2.7. Synthesis of (+)-synargentolide B (1)

To a solution of 16 (22 mg, 0.058 mmol) in MeOH (5 mL) was added PTA. H2O2 (4 mg, 0.02 mmol) at room temperature. The mixture was stirred under reflux for 6 h and concentrated under vacuum. The crude was purified by flash column chromatography (Hexanes/EtOAc 1:2) to give synargentolide B (1) (15.4 mg, 78%). (+)-Synargentolide B: [α]D20 = +39 (c 0.45, CHCl3); [α]D20 = +25.8 (c 1.2, MeOH); [α]D20 = +23.3 (c 1.2, MeOH) [56]; 1H NMR (400 MHz, CDCl3): δ = 6.95 (dd, J = 9.2, 4.8, 3.6 Hz, 1H), 6.04 (d, J = 9.2 Hz, 1H), 5.89 (dd, J = 15.6, 4.8 Hz, 1H), 5.81 (dd, J = 15.6, 6.0 Hz, 1H), 5.31–5.34 (m, 1H), 5.06 (dq, J = 6.8, 3.6, 1H), 4.48–4.54 (m, 2H), 3.71–3.73 (m, 1H), 2.75 (br s, 2H), 2.55–2.57 (m, 2H), 2.09 (s, 3H), 2.05 (s, 3H), 1.21 (d, J = 6.4 Hz, 3H); 13C NMR (100 MHz, CDCl3): δ = 162.9, 144.6, 131.2, 121.3, 110.1, 80.5, 79.1, 77.9, 27.5, 26.9, 25.9 ppm. HRMS (ESI-TOF) m/z: [M+Na]+ Calc for C16H24O7Na [M+Na]+: 365.1212; found 365.1248.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2017.09.041.

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