Tetrahedron Letters 53 (2012) 3274–3276

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

First total synthesis of (+)-heteroplexisolide E

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ARTICLE INFO

Article history:
Received 26 December 2011
Revised 29 March 2012
Accepted 13 April 2012
Available online 21 April 2012

Keywords:
Heteroplexisolide E
Total synthesis
One-pot regioselective methylation
Aldol condensation
Palladium-catalyzed hydrogenolysis

ABSTRACT

In this study, we achieved the first total synthesis of (+)-heteroplexisolide E. The synthetic highlights of our approach include a one-pot regioselective methylation method and the transformation of a β-methallyl alcohol moiety to a prenyl group using palladium-catalyzed hydrogenolysis.

In 2009, Shi and co-workers isolated a novel diterpene lactone, (+)-heteroplexisolide E (**1**), from an ethanolic extract of *Heteroplexis micocephala* (Compositae family), together with almost 50 other compounds.[1] The structural features of (+)-**1** include a γ-lactone core, a side chain of unsaturated ketone, and a branched prenyl group. *Heteroplexis micocephala*, which grows in the limestone terrains of Longzhou and Yangshuo, Guangxi Province, China, is traditionally used as a folk medicine for the treatment of indigestion and dropsy. Shi and co-workers investigated various biological activities of *Heteroplexis micocephala* such as selective cytotoxicity, inhibition of HIV-1 replication, and antioxidation *in vitro*. However, (+)-**1** was found to be inactive, and to date, the active components in traditional Chinese medicines using *Heteroplexis micocephala* have not been reported. In order not only to achieve the first total synthesis of (+)-**1** but also to synthetically provide enough amounts of (+)-**1** for the exact evaluation of its additional activities, we started a synthetic study of (+)-**1**. Thus we reveal herein the first total synthesis of (+)-**1** from the known chiral building block (+)-**2**.

As shown in Scheme 1, the retrosynthetic analysis indicated that the branched prenyl group of (+)-**1** can be transformed from the corresponding β-methallyl alcohol moiety at the final stage. Allyl alcohol (+)-**4** can be derived from compound (+)-**3** via aldol condensation of the side-chain aldehyde. The compound (+)-**3** can be synthesized from the known chiral building block (+)-**2** using one-pot chemoselective methylation.[2]

We began the total synthesis of (+)-**1** starting from the known chiral building block (+)-**2**, which can be easily prepared from commercially available 1,4-pentadien-3-ol in three steps.[3,4] The allyl alcohol derivative (+)-**2** was successfully converted into (+)-**3** in excellent yield in a single-pot operation (Scheme 2). This three-step key reaction was based on the one-pot methodology for tandem/sequential bromination of allyl alcohol derivatives, regioselective HBr-elimination, and C–C coupling, which was developed recently by our group.[2] After much effort, we achieved the methylation of (+)-**6** by Negishi coupling using excess amounts of dimethylzinc with addition of THF in the presence of the precatalyst PEPPSI™-IPr[5] in the same pot.[6]

Next, an aldol reaction between (+)-**3** and aldehyde **7** in the presence of LDA followed by dehydration gave only *E*-alkene (+)-**8** in good yield.[7,8] Consecutive removal of the *p*-methoxybenzyl (PMB) group with 1,2-dichloro-4,5-dicyanobenzoquinone (DDQ) and the acetal group using pyridinium *p*-toluenesulfonate (PPTS) from (+)-**8** provided the desired (+)-**4** in good yield in a single operation. Conversions of (+)-**4** into **9a–d** were then performed using the methods of (a)–(d): (a) acetic acid anhydride, pyridine, and DMAP for (+)-**9a**; (b) ethyl chloroformate, pyridine, and DMAP (+)-**9b**; (c) methanesulfonyl chloride, triethylamine, and tetramethylethylenediamine (TMEDA)[9] for (+)-**9c**; and (d) tetrabromomethane and triphenylphosphine for (+)-**9d**.

At the final stage, the conversions of the allylic compound **9** into (+)-**1** were examined (Table 1). Palladium-catalyzed hydrogenolysis[10] of **9** with 1.1 equiv of Bu_3SnH as a hydride source was initiated using the allylic acetate (+)-**9a** (Entries 1 and 2). The reaction succeeded in providing the desired (+)-**1**, albeit in a low yield. In addition, the ratio of (+)-**1** was increased with increasing

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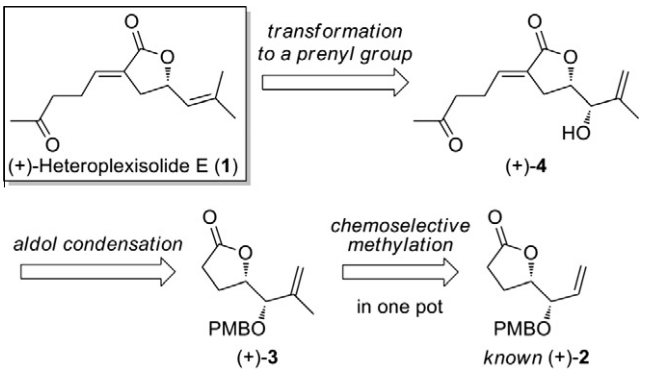
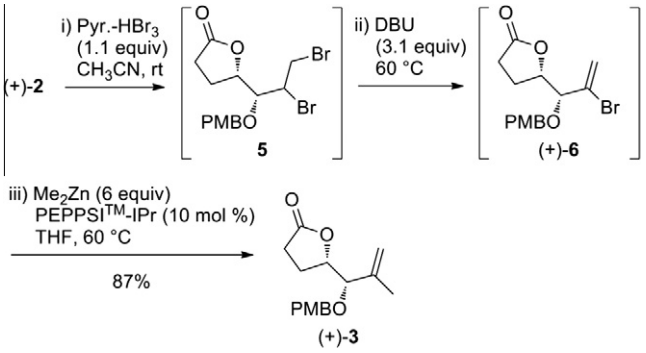
http://dx.doi.org/10.1016/j.tetlet.2012.04.065

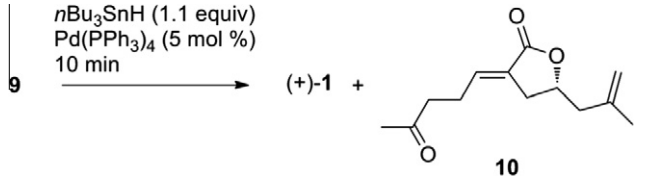


Scheme 1. Retrosynthesis of (+)-**1**.



Scheme 2. Bromine addition/regioselective elimination/Negishi coupling in one-pot operation.

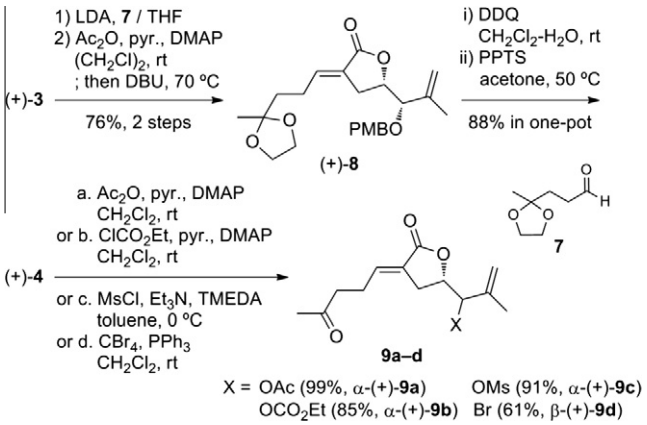
Table 1
Total synthesis of (+)-heteroplexisolide E (**1**)



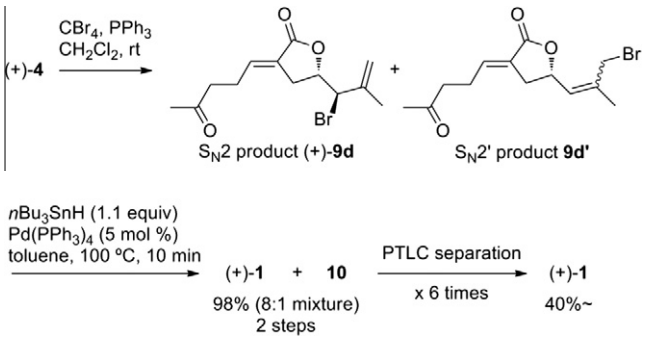
Entry	X	Conditions	Yield[a] /%	Ratio[b] (**1**:**10**)
1[c]	OAc	THF, 60 °C	13[d]	1:1
2[c]	OAc	toluene, 100 °C	15[e]	3:1
3	OCO_2Et	THF, 60 °C	64	1.7:1
4	OCO_2Et	toluene, 100 °C	32	1.6:1
5	OMs	THF, 60 °C	92	1:9
6	OMs	toluene, 100 °C	95	1:3
7	Br	THF, 60 °C	94	7:1
8	Br	toluene, 100 °C	96	8:1

[a] Isolated yield of the mixture (**1** + **10**).
[b] Ratio was determined by ^1H NMR.
[c] Reaction time was 1.5 h.
[d] The starting material (+)-**9a** was recovered (80%).
[e] The starting material (+)-**9a** was recovered (74%).

temperature (Entry 2). The transformation of the ethyl carbonate (+)-**9b** (Entries 3 and 4) or the mesylate (+)-**9c** (Entries 5 and 6) proceeded (+)-1, but was still accompanied by byproduct **10** in appreciable amounts. Finally, the reaction of allylic bromide (+)-**9d** in toluene at 100 °C gave excellent yields and sufficient selectivity (Entry 8).



Scheme 3. Synthesis of **9** from (+)-**3**.



Scheme 4. Improved process for the Appel reaction and the sequential palladium-catalyzed hydrogenolysis

Moreover, we also improved the synthesis at the last stage (Scheme 4). The Appel reaction[11] of the sterically hindered secondary alcohol (+)-**4** gave the bromide (+)-**9d** in moderate yield (61% yield, Scheme 3), together with S_N2' isomeric product **9d′**.[12] As the isomer **9d′** was assumed to be a precursor of (+)-**1**, the entire mixture of products was exposed to palladium-catalyzed hydrogenolysis. Gratifyingly, the final two-step yield was increased to 98% as a mixture of (+)-**1** and **10**,[13,14] which were finally separated by preparative TLC on silica gel.[15]

In summary, the first total synthesis of (+)-**1** was achieved from the known chiral building block (+)-**2**. Highlights include a one-pot regioselective methylation method and the transformation of a β-methallyl alcohol moiety to a prenyl group using palladium-catalyzed hydrogenolysis.

Acknowledgments

We thank Dr. Tadaaki Ohgiya (Manager, Organic Chemistry Department, Organic Chemistry Group 1, Tokyo New Drug Research Laboratories, Pharmaceutical Division, Kowa Co., Ltd.) for chemical discussions. This work was partly supported by the Sasakawa Scientific Research Grant from The Japan Science Society.

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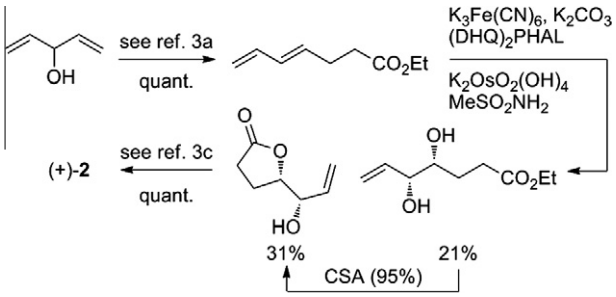
4. Compound (+)-**2** was prepared from commercially available 1,4-pentadien-3-ol.[3a,c]



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6. A mixture of (+)-**2** (1.09 g, 4.17 mmol) and pyridinium bromide perbromide (1.47 g, 4.58 mmol) in acetonitrile (41.7 mL) was stirred at room temperature for 15 h. DBU (1.96 mL, 12.9 mmol) was added to the reaction mixture at 0 °C and the system was then stirred at 60 °C for 2.5 h. After confirming consumption of (+)-**6** by a thin layer chromatography (TLC), THF (10.5 mL), PEPPSI™-IPr (283 mg, 0.427 mmol), and dimethyl zinc (24.0 mL, 25.0 mmol, 1.0 M sol. of hexane) were added to the reaction mixture at 0 °C without evaporation, and the system was then stirred at 60 °C for 1 h. The reaction was quenched with H_2O at 0 °C and the reaction mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4, concentrated in vacuo, and purified by silica gel column chromatography (hexane/EtOAc = 3/2) to afford (+)-**3** (1.00 g, 87%).
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8. To a solution containing diisopropylamine (0.20 mL, 1.42 mmol) in THF (4.0 mL) under argon at −78 °C was added n-butyllithium (0.53 mL, 1.42 mmol, 2.69 M sol. of hexane). Stirring at −78 °C was continued for 10 min, followed by the addition of (+)-**3** (223.2 mg, 0.808 mmol) in THF (2.0 mL). The mixture was stirred at −78 °C for 1 h, followed by the addition of **7** (234.1 mg, 1.62 mmol) in THF (2.0 mL). Stirring was continued at −78 °C for 30 min and then at room temperature for 30 min, followed by the addition of a saturated aqueous NH_4Cl solution. The mixture was extracted with EtOAc, washed with brine, and dried over $MgSO_4$. The residue obtained after the evaporation of the solvent was dissolved in 1,2-dichloroethane (8.1 mL), then pyridine (0.26 mL, 3.22 mmol), DMAP (10.2 mg, 0.0834 mmol), and acetic acid anhydride (0.30 mL, 3.17 mmol) were added at 0 °C, and solution was stirred at room temperature for 2 h. DBU (0.61 mL, 4.03 mmol) was added, and the mixture was stirred at 70 °C for 2 h. The reaction was quenched with a saturated aqueous NH_4Cl solution at 0 °C. The mixture was extracted with EtOAc, washed with brine, dried over $MgSO_4$, concentrated in vacuo, and purified by silica gel column chromatography (hexane/EtOAc = 2/1–3/2, then $CHCl_3$/acetonitrile = 20/1) to afford (+)-**8** (247.4 mg, 76% from (+)-**3**) as the sole product and (+)-**3** (30.4 mg, 14% recovered).
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13. A mixture of (+)-**4** (10.3 mg, 0.0429 mmol), tetrabromomethane (29.1 mg, 0.0877 mmol), and triphenylphosphine (23.0 mg, 0.0877 mmol) in dichloromethane (0.43 mL) was stirred at room temperature for 22 h. After evaporation, the residue was purified by silica gel column chromatography (hexane/EtOAc = 1/1) to afford a mixture of (+)-**9d** and the isomeric product. To the mixture in toluene (0.43 mL) was added tetrakis(triphenylphosphine) palladium (2.5 mg, 0.00216 mmol) and then heated to 100 °C. Tributyltin hydride (13 μL, 0.0483 mmol) was added and the system was stirred for 10 min. After being cooled to room temperature, the solvent was removed under reduced pressure, and the residue was purified by column chromatography (10% w/w anhydrous K_2CO_3-silica;[14] hexane/EtOAc = 2/1–1/1) to afford the mixture of (+)-**1** and **10** (9.3 mg, (+)-**1**/**10** = 8/1, 98% in 2 steps).[14]
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15. Spectral data of the synthetic (+)-heteroplexisolide E (**1**, 19.0 mg), which were partially separated (7.6 mg) by preparative TLC (Silica gel 60 F_{254}, 0.5 mm, Merck, dichloromethane/2-propanol = 2/1) × 6 times, were identical to those of the natural product in all respects. In addition, a 2:1 mixture of (+)-**1** and **10** was also separated (5.4 mg). $[\alpha]_D^{20}$ +74.0 (*c* 0.38, MeOH); lit.[1] $[\alpha]_D^{20}$ +15.6 (*c* 0.27, MeOH).