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First total synthesis of chapecoderin A: absolute configuration of the natural product

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Abstract—A *seco*-labdane, chapecoderin A **1**, has been synthesized starting from (*S*)-(+)-Wieland–Miescher ketone analogue **9**. The absolute configuration has been determined to be 5*S*,10*S*.

In their efforts to develop new pharmaceutical agents, Kobayashi, Ohsaki and co-workers[1] isolated a new *seco*-labdane type diterpenoid, chapecoderin A **1** accompanied by two new rearranged labdane-type diterpenoids, chapecoderin B **2** and C **3**, from the leaves of the Brazilian medicinal plant *Echinodorus macrophyllus*, which has been used to treat hepatitis, rheumatism and difficulties in urination (Fig. 1). Chapecoderins B **2** and C **3** exhibited cytotoxicity against murine lymphoma L1210 cells with IC_{50} values of 7.2 and 6.0 μg/ml, respectively.

Their gross structures were determined based on modern NMR techniques and the relative stereochemistries were assigned by NOESY correlation. However, the absolute stereochemistries are yet to be clarified. In view of its interesting structure as a precursor of cytotoxic compounds **2** and **3** as well as our recent interest in the synthetic studies of *seco*-norsesquiterpenoids,[2] we delineate herein the first total synthesis and determination of the absolute stereochemistry of chapecoderin A **1**.

Our synthetic design is outlined in Scheme 1. The butenolide ring might be introduced by nucleophilic reaction of sulfur substituted γ-butyrolactone **4** or **5** with halide **6**, which would be obtained by cleavage of tetrasubstituted olefin **7**. The olefin **7**, in turn, would be synthesized from the known decalone **8**[2b,3] derived from (*S*)-(+)-Wieland–Miescher ketone analogue **9**.[4]

With no inkling of the absolute configuration of the natural product **1**, we selected (*S*)-(+)-enantiomer of Wieland–Miescher ketone analogue **9** as the starting material. According to our previously reported procedure,[2b] (*S*)-(+)-Wieland–Miescher ketone analogue **9**[4] was transformed into the known decalone **8**.

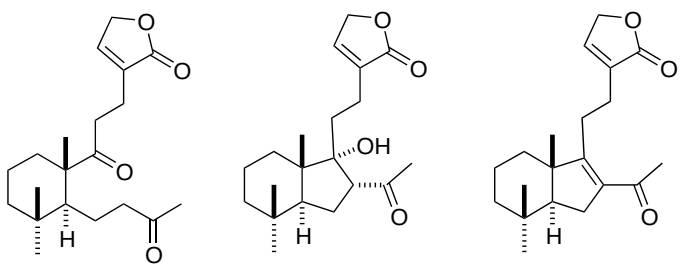

Figure 1.

Keywords: chapecoderin A; *seco*-labdane; Wieland–Miescher ketone analogue.
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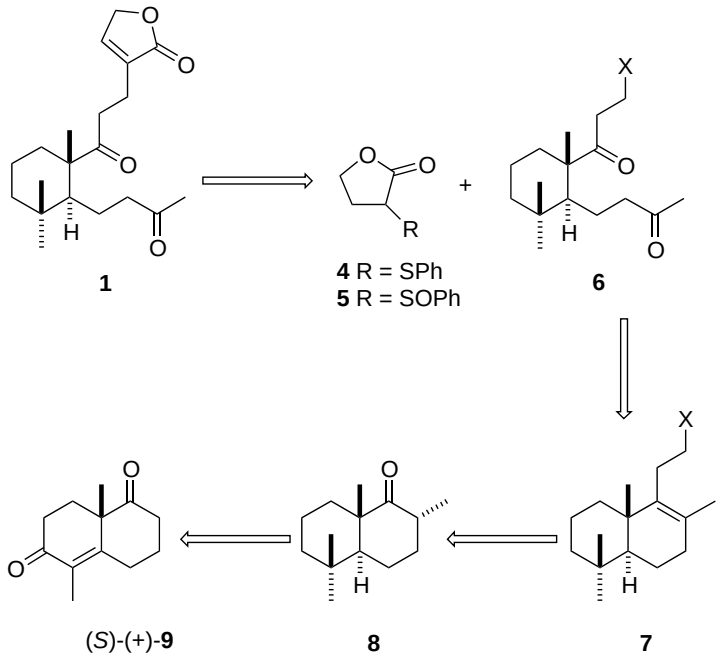


Scheme 1.

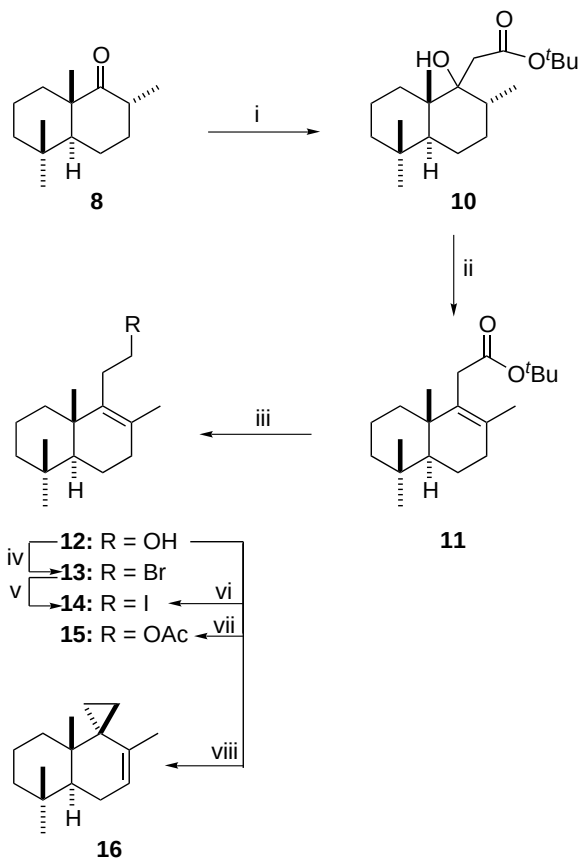
At first, introduction of a hydroxyethyl unit to the decalone **8** leading to primary alcohol **12** was examined by addition of vinylmagnesium bromide followed by dehydration and hydroxylation of the vinyl group. However, various efforts for the selective hydroboration of the terminal double bond were all unsuccessful.

As an alternative hydroxyethyl addend, the *tert*-butyl acetate anion was reacted with the ketone **8** to provide hydroxy-ester **10** as a mixture of diastereomers (Scheme 2). Dehydration of the alcohol **10** by $SOCl_2$ gave in 86% overall yield unsaturated ester **11** which was reduced with lithium aluminumhydride to afford the primary alcohol **12** quantitatively. Bromination of the alcohol **12** with carbon tetrabromide and triphenylphosphine gave bromide **13** in 94% yield.

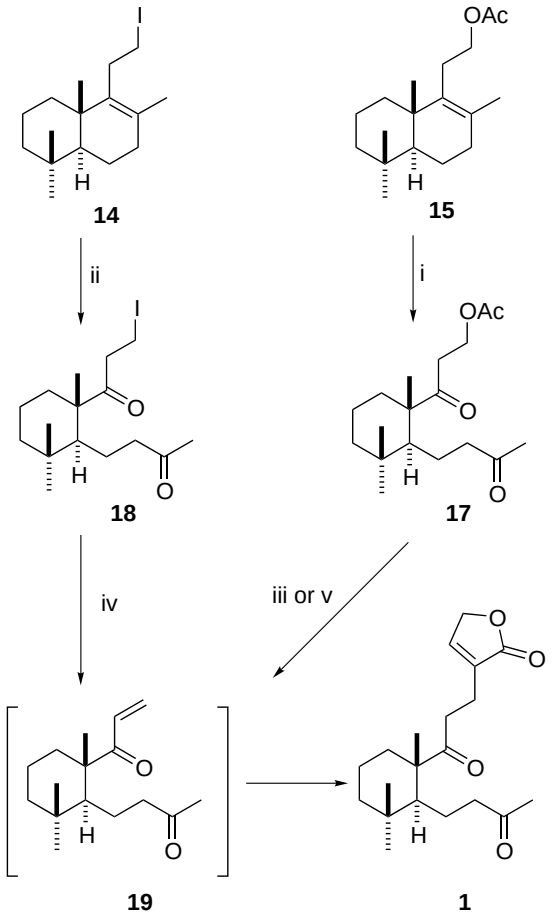
Substitution of the bromide **13** with sodium iodide was incomplete to give a mixture of the bromide **13** and iodide **14**, and three repeated reactions were required for complete conversion to the iodide **14** (98% yield). Direct iodination of the alcohol **12** with sodium iodide mediated by cerium chloride[5] also afforded the iodide **14** in 70% yield (Scheme 3).

In order to introduce a butenolide moiety, alkylation of the α-phenylthio **4** or the α-phenylsulfinyl-γ-butyrolactone **5**[6] with the halide **13** or **14** was investigated. However, the halide **13** or **14** was recovered completely. An attempt to prepare the more reactive trifluoromethanesulfonate of the alcohol **12** resulted in the formation of cyclopropane derivative **16** exclusively in 98% yield even at −78°C.

The order and method of introduction of the butenolide and diketo moieties were then changed. Exposure



Scheme 2. *Reagents*, *conditions and yields*: (i) LDA, HMPA, CH_3CO_2t-Bu, −78°C; (ii) $SOCl_2$, DMAP, pyridine, rt, 86% in two steps; (iii) $LiAlH_4$, Et_2O, rt, quant.; (iv) CBr_4, PPh_3, $CHCl_3$, rt, 94%; (v) NaI, acetone, reflux, repeated three times, 96%; (vi) NaI, $CeCl_3{\cdot}7H_2O$, CH_3CN, 70%; (vii) acetic anhydride, DMAP, pyridine, rt, 97%; (viii) Tf_2O, pyridine, CH_2Cl_2, −78°C, 98%.



Scheme 3. *Reagents, conditions and yields*: (i) O_3/O_2, CH_3OH, −20°C, Me_2S, 75%; (ii) O_3/O_2, CH_2Cl_2, Me_2S, −78°C, 41%; (iii) **17**+**5**, DBU, benzene, rt→90°C, 40%; (iv) **18**+**5**, K_2CO_3, *n*-Bu_4NI, DME, 0→98°C, 19%; (v) DBU, benzene, 80%.

of the iodide **14** to ozone provided diketo-iodide **18** in 41% yield. The acetate **15** derived by acetylation of the alcohol **12** in 97% yield was also cleaved by ozonolysis to give diketo-acetate **17** in 52% yield in dichloromethane. The yield was considerably improved to 75% by carrying out the reaction in methanol at −20°C in 0.01 M solution.[7]

Installation of the butenolide moiety and completion of total synthesis were finally achieved as follows. Treatment of the diketo-acetate **17** and the α-phenylsulfinyl-γ-lactone **5** with DBU in benzene at room temperature followed by gradual warming to 90°C furnished chapecoderin A **1** in 40% yield. The reaction proceeded via β-elimination of acetic acid from the acetate **17** followed by DBU-promoted conjugate addition of the γ-lactone **5** to the resulting vinylketone **19** and subsequent thermal elimination of sulfinic acid. The vinylketone **19** was actually isolated by the treatment of the acetate **17** with DBU in 80% yield. The diketo-iodide **18** also provided chapecoderin A **1** by the treatment with potassium carbonate and tetrabutylammonium iodide in DME in 19% yield. Spectral data (^1H and ^{13}C NMR and IR) of the synthetic **1** were completely identical with those of natural chapecoderin A **1**. Since the value and sign of optical rotation of the synthetic compound **1** {$[\alpha]_D$+6.0 (*c* 0.86, $CHCl_3$), lit. $[\alpha]_D$+5.5 (*c* 0.86, $CHCl_3$)[1]} were identical with those of natural chapecoderin A **1**, the absolute stereostructure was unambiguously determined to be 5*S*,10*S* as depicted in structure **1** (Fig. 1).

In summary, we have completed the first enantioselective total synthesis of chapecoderin A **1** in 25% overall yield in six steps from the known ketone **8**, which establishes the absolute stereostructure of the natural product **1**.

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