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Communication

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Asymmetric Total Synthesis of (-)-Spirochensilide A

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Supporting Information Placeholder

ABSTRACT: An asymmetric total synthesis of (-)-spirochensilide A has been achieved for the first time. The synthesis features a semi-pinacol rearrangement reaction to stereoselectively construct the two-vicinal quaternary chiral centers at C8 and C10, a tungsten-mediated cyclopropene-based Pauson–Khand reaction to install the C13 quaternary chiral center, and a furan-based oxidative cyclization to stereoselectively form the spiroketal motif.

Spirochensilide A (**1**, Figure 1)[1] is a member of an emerging and biologically important class of natural products with a unique spirocyclic core,[2] and has been isolated by Gao and co-workers from *Abies chensiensis*, which is an endemic Chinese plant.[3] The crude extracts and metabolites of the *Abies* species have been found to possess various bioactivities, including anti-tumor, anti-microbial, anti-ulcerogenic, anti-inflammatory, anti-hypertensive, anti-tussive, and central nervous system activities.[4] Biologically, **1** showed a moderate inhibitory effect on the NO production with 30% inhibition at the concentration of 12.5 μg/mL, indicating **1** could be a useful probe for study of inflammatory diseases.[5]

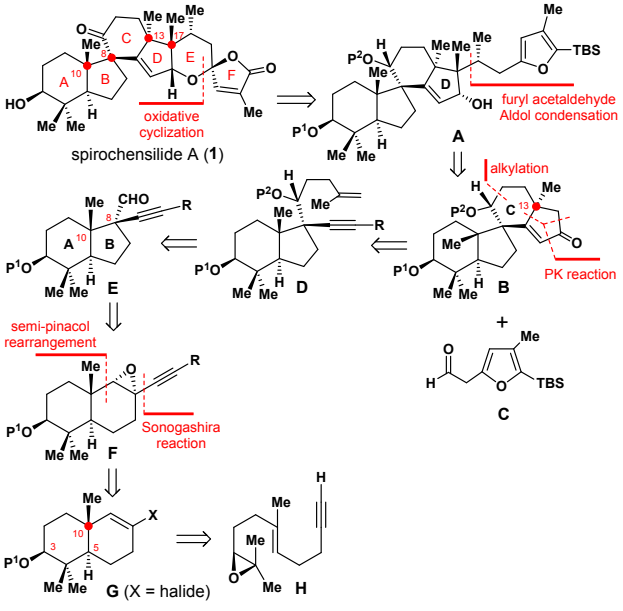


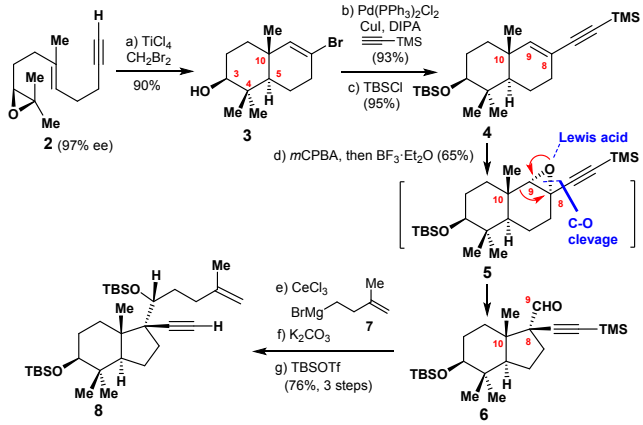
Figure 1. Retrosynthetic analysis of spirochensilide A (**1**).

The structure of **1** was determined on the basis of NMR spectroscopic data and single-crystal X-ray diffraction analysis. The structure contains two pairs of vicinal all-carbon quaternary chiral centers[6] (C8/C10 and C13/17), an unusual spiro[4.5]ring system (BC ring), and an anomeric spiroketal (EF ring).[7] Natural products bearing both quaternary chiral centers and spirocycles can impose conformational constraints to reduce the conformational entropy penalty upon binding to a protein target in a favorable geometry.[8]

Herein, we report our effort on the development of an approach for the asymmetric total synthesis of spirochensilide A (**1**). The synthesis features a semi-pinacol rearrangement and a tungsten-mediated cyclopropene-based Pauson–Khand (PK) reaction as key steps.

Figure 1 illustrates our retrosynthetic analysis. We envisioned that the anomeric spiroketal of **1** could be derived from furyl alcohol **A** via an intramolecular oxidative cyclization.[9] **A** was expected to be constructed from ketones **B** and **C** via a furyl acetaldehyde Aldol condensation[10] as a key step. To construct the cyclopentenone bearing an all-carbon quaternary chiral center in intermediate **B**, we intended to employ the PK reaction[11] of enyne **D** because this reaction has been successfully applied in our total synthesis of the nontriterpenoid propindilactone G.[12] Enyne **D** was expected to be derived from aldehyde **E** with a pair of vicinal quaternary chiral centers at C8 and C10, which was envisioned to be derived from epoxide **F** through a semi-pinacol rearrangement.[13] **F** could be prepared via a sequential Pd-catalyzed Sonogashira reaction and epoxidation from vinyl halide **G**, which in turn could be prepared via a biomimetic cyclization of the functionalized isoprenoid polyene **H**.[14]

Scheme 1. Diastereoselective synthesis of enyne 8[a]



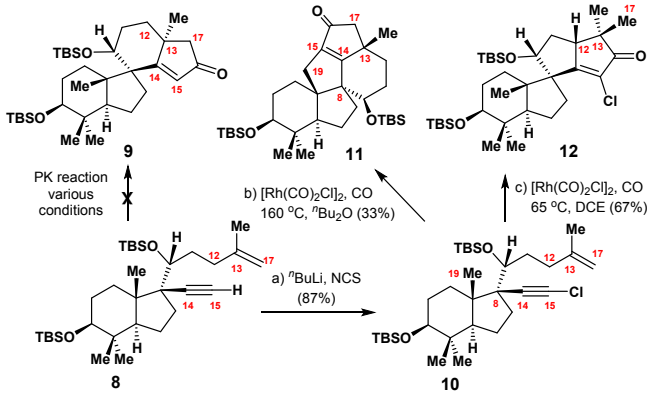
[a]Reagents and conditions: (a) $TiCl_4$ (0.4 equiv.), CH_2Br_2 (epoxide **2** was 0.2 M in CH_2Br_2), -35 °C, 1 h, 90%; (b) $Pd(PPh_3)_2Cl_2$ (0.05 equiv.), CuI (0.03 equiv.), DIPA (5.0 equiv.), HC≡CTMS (3.0 equiv.), THF, 50 °C, 16 h, 93%; (c) TBSCl (1.3 equiv.), imidazole (2.5 equiv.), DMF, rt, 15 h, 95%; (d) *m*CPBA (2.0 equiv.), DCM, -30 °C to 0 °C; then $BF_3{\cdot}Et_2O$ (0.05 equiv.), DCM, 0 °C, 1 h, 65%, 2 steps; (e) $CeCl_3$ (1.5 equiv.), Grignard reagent **7** (1.5 equiv.), THF, 0 °C, 30 min; (f) K_2CO_3 (5.0 equiv.), MeOH, rt, 16 h; (g) TBSOTf (1.5 equiv.), Et_3N (3.0 equiv.), DCM, -78 °C to rt, 3 h, 76%, 3 steps.

Our synthesis began by exploring the chemistry for an enantioselective preparation of enyne **8** (Scheme 1). We rationed that a Lewis acid-induced cyclization[15] of polyenoid **2** could enantioselectively afford halogenated decalin[16] **3** bearing three stereogenic centers at C3, C5, and C10 via a concerted cyclization process.[17] The selectivity results from the chair-like transition state achieved via a sequence of biomimetic epoxide-initiated cationic cyclization and nucleophilic bromination reaction.

Experimentally, we found that vinyl bromide **3** could be obtained in 90% yield when acetylenic epoxide **2**[18] of 97% ee was treated with $TiCl_4$ (0.4 equiv.) in CH_2Br_2 at -35 °C for 1 h (Scheme 1),[19] and unlike the previously reported protocols,[20] the current reaction could be carried out on 50 g scale.

We next turned our attention to map out an effective stereoselective synthesis of aldehyde **6**, which bears two vicinal quaternary chiral centers at C8 and C10. To this end, **3** was converted into alkyne **4** in an 88% overall yield by a sequence of conventional Sonogashira and silylation reactions. After epoxidation of **4** with *m*CPBA, the resultant epoxide, formed as a single diastereoisomer, could undergo the proposed semi-pinacol rearrangement via treatment with $BF_3{\cdot}Et_2O$ (0.05 equiv.)[21] to afford **6** in 65% yield. The reaction of **6** with Grignard reagent **7** in the presence of $CeCl_3$[22] followed by a silylation afforded **8** in 76% overall yield.

Scheme 2. Pauson–Khand reaction of enyne 8[a]

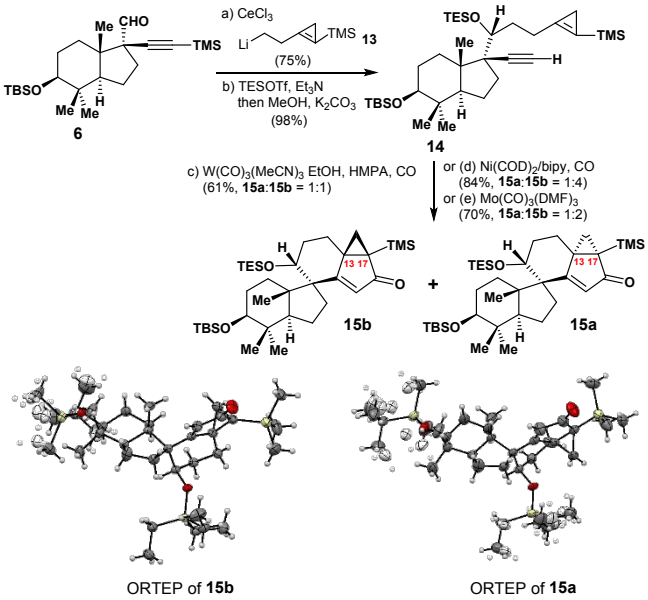


[a]Reagents and conditions: (a) ^{n}BuLi (1.2 equiv.), NCS (1.2 equiv.), THF, -78 °C to rt, 87%; (b) $[Rh(CO)_2Cl]_2$ (0.5 equiv.), CO (1.0 atm), $^n Bu_2O$, 160 °C, 48 h, 33%; (c) $[Rh(CO)_2Cl]_2$ (0.5 equiv.), CO (1.0 atm), DCE, 65 °C, 48 h, 67%.

We then turned our attention to the synthesis of the cyclopentenone motif in **9** by the proposed PK reaction (Scheme 2). Initially, we attempted various Co-mediated PK reactions of **8**; however, desired product **9** was not observed (see SI for details). We attributed this failure to the low reactivity of enyne **8**, and its steric rigidity. Since enynes bearing a chloride as a σ-electron-withdrawing group could promote polarization and thereby reduce the activation barrier of the Rh-catalyzed PK reaction,[23] we prepared chloroenyne **10**. However, under different optimized conditions, **11** or **12** was obtained in 33% or 67% yield, respectively. The formation of **11** indicated the expected carbonylative annulation reaction had indeed proceeded and provided the desired C13 quaternary center, but the resultant product underwent a further Rh-catalyzed carbonylative C–H insertion[24] to afford **11**. While the formation of **12** could be a result of a double bond isomerization followed by a PK reaction. The structures of **11** and **12** were confirmed by X-ray crystallographic analysis (see SI for details).

In 2005, Fox and co-workers reported a cyclopropene-based, Co-mediated PK reaction[25] for the stereoselective synthesis of structurally diverse cyclopropane-based cyclopentenones. We also considered the fact that the inherent strain of cyclopropene[26] can increase its reactivity in PK reactions, and their defined chiral environment can influence the diastereoselective outcome of the PK reaction.[27] Since the three-membered ring can be cleaved under mild conditions, we identified an alternative pathway to install the CD ring system into the target molecule **1**.

Scheme 3. Synthesis of cyclopentenones 15a and 15b[a]



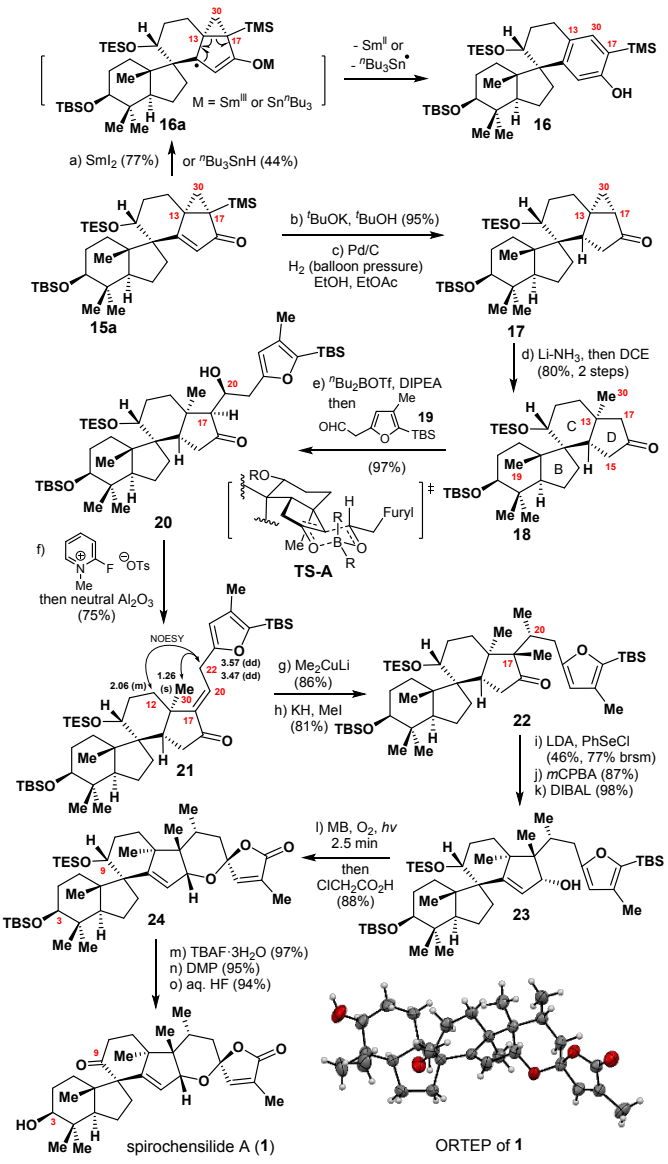
[a]Reagents and conditions: (a) $CeCl_3$ (1.3 equiv.), lithium reagent **13** (1.3 equiv.), pentane:Et_2O = 3:2, -98 °C to -60 °C, 2.5 h, 75%; (b) TESOTf (1.2 equiv.), Et_3N (3.0 equiv.), DCM, -78 °C to 0 °C, 2 h; then MeOH, K_2CO_3 (10.0 equiv.), rt, 24 h, 98%; (c) $W(CO)_3(MeCN)_3$ (1.5 equiv.), EtOH:HMPA = 20:1, CO (1.0 atm), rt to 80 °C, 61% (**15a**:**15b** = 1:1); (d) $Ni(COD)_2$ (1.1 equiv.), 2,2'-bipyridine (1.2 equiv.), toluene, CO (1.0 atm), rt, 84%, **15a**:**15b** =1:4; (e) $Mo(CO)_3(DMF)_3$ (1.5 equiv.), toluene, 60 °C, 30 min, 70%, **15a**:**15b** = 1:2.

With these chemistries in mind, we then applied this strategy for the synthesis of **15a**. To this end, we have developed a diastereoselective approach for the synthesis enyne **14** via the reaction of aldehyde **6** with lithium reagent **13**[28] (see SI for details) in the presence of $CeCl_3$ at -98 °C. The resultant secondary alcohol was protected as its TES ether followed by removal of TMS to afford **14** in 73% overall yield in two steps (Scheme 3). However, the annulation of enyne **14**, under both the conventional PK reaction ($Co_2(CO)_8$) and PK-type reactions (with other metal complexes derived from Rh, Pd, Ir, or Ru), failed to afford **15a**. To further explore the PK reactions with other types of metal catalysts, such as $W(CO)_3(MeCN)_3$,[29] $Ni(COD)_2$/bipy,[30] and $Mo(CO)_3(DMF)_3$,[31] we fortunately found out that when $W(CO)_3(MeCN)_3$ was used as the catalyst, **15a** was isolated in ca. 30% yield, together with its diastereoisomer **15b** in 30% yield. Other catalysts, such as $Ni(COD)_2$/bipy or $Mo(CO)_3(DMF)_3$, could also provide **15a** and **15b**, but in favor of **15b**, although the overall yields were higher (Scheme 3). We also attempted to improve the yield by systematic investigation of the $W(CO)_3(MeCN)_3$-catalyzed PK reaction for the formation of **15a**; no better results were obtained (see SI for details).

To complete the total synthesis of **1** (Scheme 4). Initially, we attempted to carry out the reductive cyclopropane ring-opening reaction by treatment of **15a** with SmI_2 or $^n Bu_3SnH$. However, under such reaction conditions, **15a** was converted to **16** through **16a**, presumably because the orbitals of the double bond in **15a** overlapped better with its carbonyl group than orbitals of its cyclopropane motif. To achieve the regioselective cyclopropane opening, **15a** underwent a selective desilylation to remove its TMS via treatment with ^{t}BuOK,[32] and the resultant cyclopropane then participated in a Pd/C-catalyzed regioselective hydrogenation to

afford ketone **17**. **17** was then subjected to a Li/NH_3-mediated regioselective reductive ring-opening reaction followed by aprotic-quenching[33] with dichloroethane (DCE) to afford **18** bearing the *trans*-fused bicyclic CD ring with the desired C13 stereogenic center in 76% yield over three steps.

Scheme 4. Synthesis of spirochensilide A 1[a]



[a]Reagents and conditions: (a) SmI_2 (2.0 equiv.), THF:HMPA = 10:1, rt, 30 min, 77%; or $^nBu_3SnH$ (5.0 equiv.), AIBN (0.5 equiv.), PhH, 80 °C, 6 h, 44%; (b) ^{t}BuOK (7.5 equiv.), ^{t}BuOH, 85 °C, 4 d, 95%; (c) 5% Pd/C (0.2 wt., type 87L), H_2 (balloon), EtOH:EA = 1:1, rt, 12 h; (d) Li-NH_3, THF, -78 °C, 15 min; then quenched with DCE, 80%, 2 steps; (e) $^nBu_2BOTf$ (2.0 equiv.), DIPEA (2.5 equiv.), DCM, -78 °C, then furyl acetaldehyde **19** (4.0 equiv.), -78 °C to -50 °C, 1.5 h, 97%; (f) 2-fluoro-1-methylpyridin-1-ium tosylate (3.0 equiv.), Et_3N (10 equiv.), DCM, rt, 12 h; then neutral Al_2O_3, rt, 1 h, 75%; (g) Me_2CuLi (2.0 equiv.), Et_2O, -78 °C to -30 °C, 5 h, 86%; (h) KH (1.5 equiv.), MeI (4.0 equiv.), THF, rt to -78 °C, 81%; (i) LDA (1.2 equiv.), THF, -78 °C to 0 °C; then PhSeCl (1.3 equiv.), -98 °C, 15 min, 46% (77% brsm); (j) *m*-CPBA (1.05 equiv.), Et_3N (3.5 equiv.), DCM, -78 °C to rt, 87%; (k) DIBAL (2.0 equiv.), DCM, -78 °C to -10 °C, 3 h, 98%; (l) methylene blue (MB) (10^{-4} M), O_2 (bubble), DCM, *hv* (tungsten lamp), 0 °C, 2.5 min; then $ClCH_2CO_2H$, H_2O, MeCN, rt, 1 h, 88%; (m) TBAF·$3H_2O$ (3.0 equiv.), THF, rt, 15 min, 97%; (n) DMP (2.0 equiv.), $NaHCO_3$ (20 equiv.), pyridine (15 equiv.), DCM, rt, 20 min, 95%; (o) aq. 48%~51% HF, DCM:MeCN = 1:4, rt, 4 h, 94%.

To regioselectively install the *trans*-double bond between C17-C20, **18** was reacted with ^{n}Bu$_2$BOTf/DIPEA, and the resultant enolate participated in an enol-borane-mediated aldol reaction[34] with TBS-stabilized furyl acetaldehyde **19** to afford **20** as a sole isomer in 97% yield. The observed excellent diastereoselectivity should be attributed to the formation of the chair-like transition state **TS-A**[35] in the presence of bulky DIPEA,[36] and the structure of **20** was confirmed by X-ray crystallographic analysis of its ester derivative (see SI for details). Thus, further reaction of **20** with 2-fluoro-1-methylpyridin-1-ium tosylate[37] followed by a neutral Al_2O_3-mediated *syn*-elimination afforded enone **21** in 75% yield. The *trans*-configurated C17-C20 double bond in **21** was confirmed by 2D-NMR analysis.

To diastereoselectively generate the allylic alcohol in **23**, enone **21** underwent a cuprate-mediated 1,4-addition via treatment with Me_2CuLi, and the resultant ketone was methylated (MeI/KH) to give ketone **22** bearing the desired C17 and C20 stereogenic centers (see SI for a DFT experiment to account for the diastereoselectivity). Thus, further treatment of **22** with LDA followed by reaction with PhSeCl gave a selenide, which was then selectively oxidized with *m*-CPBA and reduced with DIBAL to afford **23** in 66% yield over three steps.

To complete the total synthesis, **23** bearing a TBS group[38] was first oxidized by singlet oxygen (generated by irradiation of oxygen with tungsten lamp in the presence of methylene blue), and the resultant 4-oxo-2-alkenoic acid intermediate[39] was then treated with $ClCH_2CO_2H$ in MeCN to afford **24** in 88% yield. Selective desilylation of **24** with TBAF·$3H_2O$ followed by DMP-oxidation of the newly generated secondary alcohol afford a C9-ketone, which was further subjected to a desilylation with HF to afford **1** in 87% yield over three steps. The structure of synthetic spirochensilide A was confirmed by single-crystal X-ray diffraction, and its NMR and optical rotation data were in agreement with those reported in the literature. More than 150 mg of **1** was made in our first round of synthesis.

In summary, the total synthesis of (-)-spirochensilide A (**1**) has been accomplished for the first time in 22 steps from epoxide **2**, with a total yield up to 2.2%. The keys to the success of the synthesis were the use of 1) a semi-pinacol rearrangement of epoxide **2** to stereoselectively generate the chiral aldehyde **6**; 2) a rarely-investigated tungsten-mediated cyclopropene-based PK reaction to form **15a**, bearing the spiro-bicyclic core of **1**; and 3) singlet oxygen-mediated oxidative cyclization of furyl alcohol **23** to form the anomeric spiroketal motif of **1**. The developed chemistry paves the way to the stereoselective construction of this unprecedented triterpenoid scaffold, which bears two spirocyclic systems and up to four all-carbon quaternary chiral centers.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and compound characterizations (PDF); X-ray diffraction of compound **11** (CIF), **12** (CIF), **15a** (CIF), **15b** (CIF), **20** ester derivative (CIF), spirochensilide A (CIF).

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Notes

The authors declare no competing financial interest.

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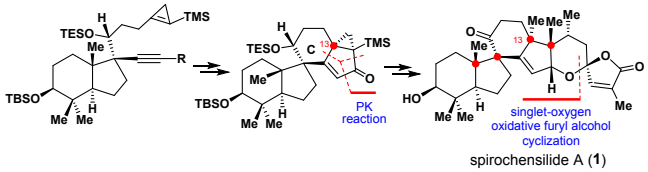
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