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Asymmetric total synthesis of pleurospiroketals A and B†

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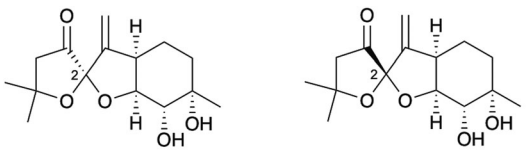
The first asymmetric total synthesis of pleurospiroketals A and B has been accomplished in 16 steps from 5-methyl-5-hexenoic acid. Key features of the synthesis are the highly *syn*-selective Evans aldol reaction, ring-closing metathesis, highly diastereoselective dihydroxylation and acid-mediated spiroketalization.

In 2013, Liu and co-workers reported the isolation of new sesquiterpenoids, pleurospiroketals A (**1**) and B (**2**), from the edible mushroom *Pleurotus cornucopiae*, along with pleurospiroketals C–E.[1] The structures of these terpenoids were established through analysis of 2D NMR spectra, single-crystal X-ray diffraction, and CD data analysis as depicted in Fig. 1. Pleurospiroketals A and B are epimers at the C2 position and possess a unique perhydrobenzannulated 5,5-spiroketal skeleton bearing four contiguous stereocenters. Compounds **1** and **2** possess inhibitory activities against nitric oxide production in lipopolysaccharide-activated macrophages and cytotoxicity against the HeLa cell line.[1] A structurally closed sesquiterpenoid, pleurospiroketal F (**3**), was also isolated from the solid-state fermentation of *Pleurotus citrinopile*.[2] Although no total syntheses or synthetic studies of these unique sesquiterpenoids have been reported, the total synthesis of pleurolactone (**4**),[3] which has a perhydrobenzofuran skeleton, as a racemate was achieved by our group[4] and the Mehta group.[5] The structural features and biological activities of these terpenoids attracted our interest, and a synthetic study of pleurospiroketals A (**1**) and B (**2**) in optically active form was initiated.

Herein, we describe the first asymmetric total synthesis of pleurospiroketals A (**1**) and B (**2**) in 16 steps using the highly *syn*-selective Evans aldol reaction, ring-closing metathesis, highly diastereoselective dihydroxylation and acid-mediated spiroketalization as key steps.



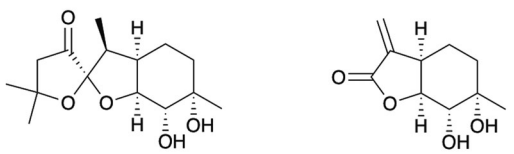


Fig. 1 Structures of pleurospiroketals A (**1**) and B (**2**) and related natural products **3** and **4**.

The synthetic strategy for pleurospiroketals A (**1**) and B (**2**) is outlined in Scheme 1. The target molecules **1** and **2** could be synthesized by deprotection of silyl ethers and acetonide groups and construction of the 5,5-spiroketal moiety from diketone **5**. Compound **5** would be obtained using nucleophilic addition of an acyl anion equivalent onto unsaturated aldehyde **6** and conversion of the resulting adduct in a few steps. Compound **6** could be obtained using an established procedure for pleurolactone synthesis,[4] which includes highly diastereoselective dihydroxylation of **7** to construct four contiguous stereocenters. Ketone **7** would be synthesized by the conversion of the chiral auxiliary of compound **8** to a methyl ketone and protection of the alcohol group. Compound **8** would be constructed using ring-closing metathesis of compound **9**, which could be obtained by the asymmetric *syn*-selective aldol reaction of compound **10** with acrolein.

Our investigation started with the synthesis of compound **10** with a chiral auxiliary for the subsequent *syn*-selective Evans

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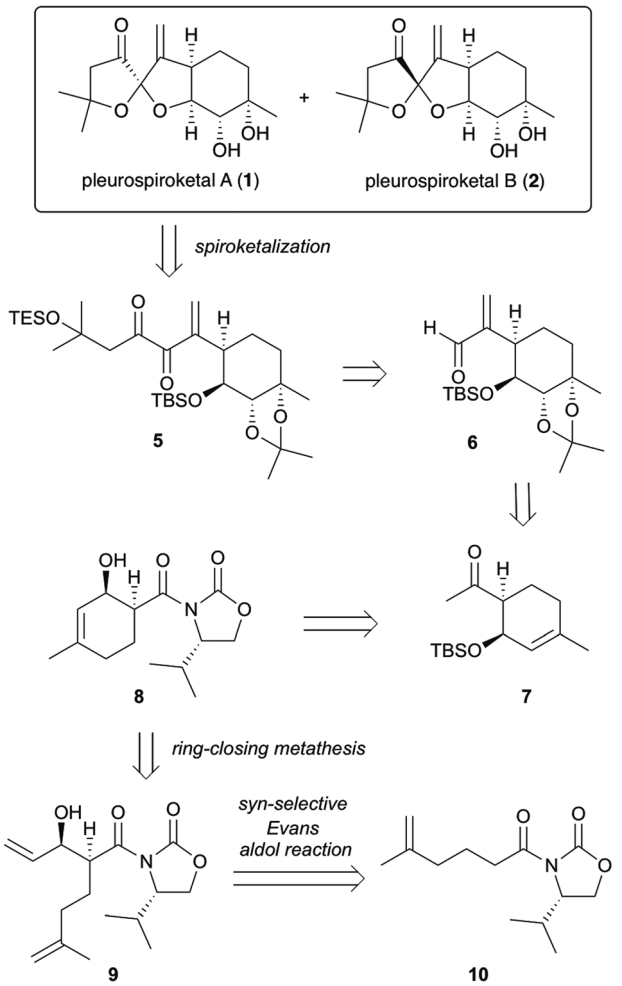
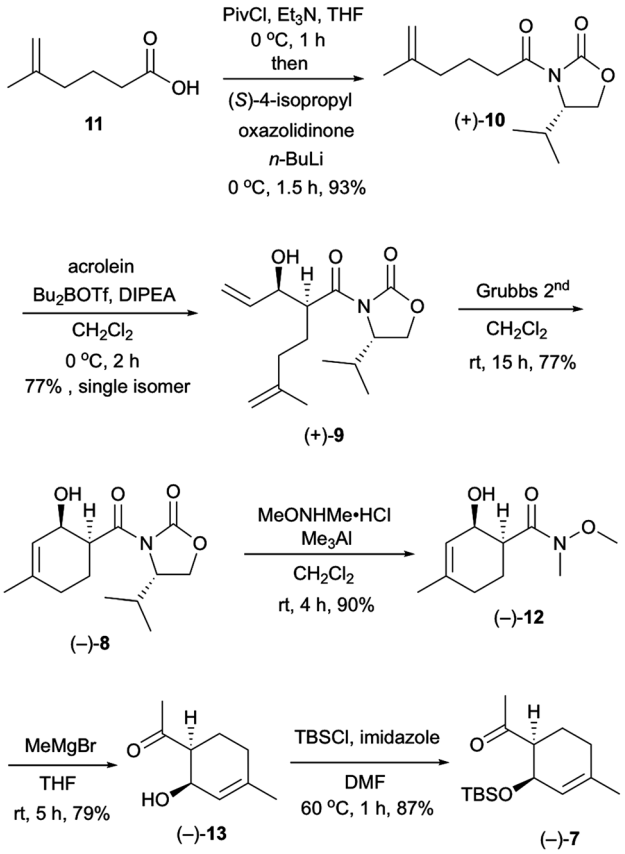
† Electronic supplementary information (ESI) available. CCDC 1858657 and 1858659. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8cc06185h



Scheme 1 Retrosynthesis of pleurospiroketals A (**1**) and B (**2**).

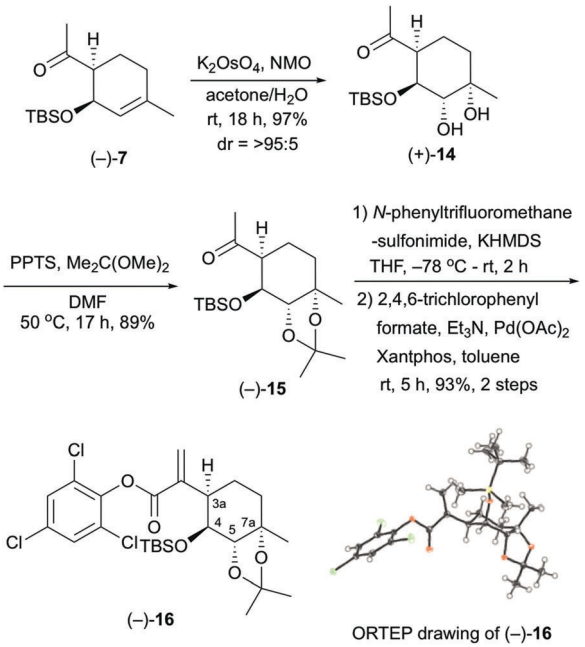


Scheme 2 Synthesis of compound (−)-**7** in an optically active form.

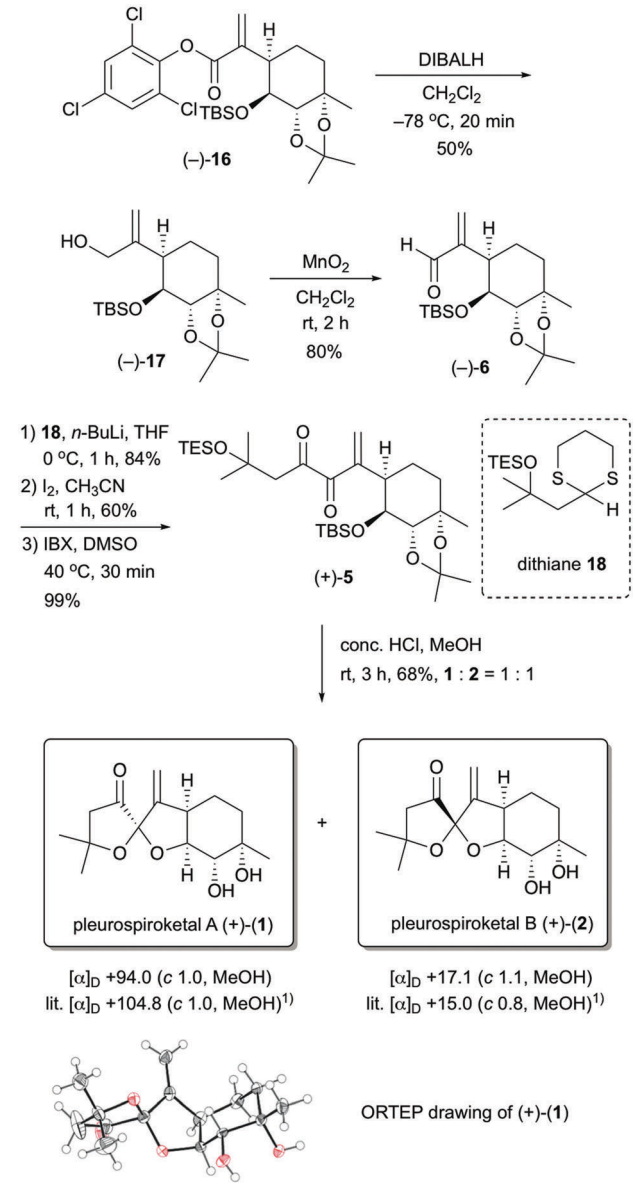
aldol reaction as shown in Scheme 2. Installation of (*S*)-4-isopropyloxazolidinone as the chiral auxiliary into the known carboxylic acid **11**[6] was achieved by a two-step operation: transformation of the carboxylic acid to the mixed anhydride, followed by addition of the lithiated oxazolidinone into the resulting mixed anhydride to afford **10** in 93% yield. The *syn*-selective Evans aldol reaction[7] of **10** and acrolein using di-*n*-butylboryl trifluoromethanesulfonate and diisopropyl(ethyl)-amine provided the desired Evans *syn* product (+)-**9** in 77% yield as a single isomer. The absolute stereochemistries of the two newly formed stereocenters of (+)-**9** were confirmed by X-ray crystallographic analysis of compound (−)-**16**. The RCM[8] of diene compound (+)-**9** with a Grubbs second-generation reagent afforded the desired cyclohexenol derivative (−)-**8** in 77% yield. Conversion of the chiral auxiliary to methyl ketone was achieved *via* a Weinreb amide derivative. Thus, treatment of compound (−)-**8** with *N*,*O*-dimethylhydroxylamine hydrochloride and trimethylaluminum provided the Weinreb amide (−)-**12** in 90% yield. Compound (−)-**13** was obtained by the addition of methylmagnesium bromide to the Weinreb amide (−)-**12** in 79% yield. Protection of the hydroxy group of compound (−)-**13** with a *tert*-butyldimethylsilyl group gave compound (−)-**7** in 87% yield.

The stereocontrolled synthesis of (−)-**16** from compound (−)-**7** was achieved using a procedure established by our group for pleurolactone synthesis[4] (Scheme 3). Thus, diastereoselective dihydroxylation of (−)-**7** with potassium osmate gave the desired diol (+)-**14** in 97% yield as the sole product. This dihydroxylation with potassium osmate occurred on the opposite side of the TBS-protected hydroxyl group. Protection of the dihydroxyl group using 2,2-dimethoxypropane in *N*,*N*-dimethylformamide afforded the acetonide (−)-**15** in 89% yield. Treatment of (−)-**15** with *N*-phenyltrifluoromethanesulfonimide and potassium hexamethyldisilazide provided the corresponding vinyl triflate. The unsaturated ester (−)-**16** was obtained in 93% yield (2 steps) using 2,4,6-trichlorophenyl formate as the carbon monoxide equivalent,[9] palladium catalyst [$Pd(OAc)_2$, Xantphos], and triethylamine in toluene. The determination of the absolute configuration of compound (−)-**16**, which included three chlorine atoms, was accomplished by single-crystal X-ray crystallographic analysis.[10] Therefore, the absolute configuration of (−)-**16** was established as 3a*R*, 4*S*, 5*S*, 7a*S* on the basis of the value of the Flack absolute structure parameter, –0.01(3).[11] Thus, the stereocontrolled synthesis of the cyclohexane core with four contiguous stereocenters in the chiral form was achieved successfully.

With the stereocontrolled synthesis of compound (−)-**16** in hand, we next focused on the construction of the 5,5-spiroketal moiety (Scheme 4). Unsaturated aldehyde (−)-**6** was obtained *via* a two-step operation. Reduction of ester (−)-**16** with diisobutylaluminum



Scheme 3 Synthesis of compound (–)-**16** and determination of absolute configuration.



Scheme 4 Asymmetric synthesis of pleurospiroketals A (**1**) and B (**2**).

hydride in dichloromethane provided the allyl alcohol (–)-**17** in 50% yield, and then oxidation of allyl alcohol (–)-**17** with manganese dioxide gave the unsaturated aldehyde (–)-**6** in 80% yield. After several attempts at the nucleophilic addition of the acyl anion equivalent to the unsaturated aldehyde (–)-**6**, we found that dithiane derivative **18**[12] was suitable as an acyl anion equivalent. Treatment of unsaturated aldehyde (–)-**6** with the lithiated dithiane derivative, which was derived from dithiane **18** and *n*-BuLi, in THF at 0 °C provided the desired adduct in 84% yield as a single diastereomer. Removal of the dithiane protecting group was achieved by treatment of the resulting adduct with iodine to give the corresponding ketone in 60% yield. Oxidation of the resulting compound with 2-iodoxybenzoic acid (IBX) provided the spiroketalization precursor (+)-**5** in 99% yield.[13] Finally, upon treatment of (+)-**5** with conc. HCl in MeOH for 3 h at room temperature, deprotection of the TBS, TES and acetonide groups and construction of the 5,5-spiroketal moiety proceeded simultaneously, and the target molecules **1** and **2** were obtained in 68% yield as a 1 : 1 mixture. These compounds could easily be separated by HPLC. Both ^{1}H and ^{13}C NMR spectra of the synthetic compounds **1** and **2** were identical to those of natural pleurospiroketals A and B. The optical rotations of synthetic **1** and **2** had the same rotations as those reported for the natural products [synthetic **1**: $[\alpha]_D$ +94.0 (*c* 1.0, MeOH); natural product **1**: $[\alpha]_D$ +104.8 (*c* 1.0, MeOH);[1] synthetic **2**: $[\alpha]_D$ +17.1 (*c* 1.1, MeOH); natural product **2**: $[\alpha]_D$ +15.0 (*c* 1.0, MeOH)[1]]. Additionally, the structure of compound **1** was unambiguously confirmed by X-ray crystallographic analysis.[14]

In conclusion, the first asymmetric total synthesis of pleurospiroketals A (**1**) and B (**2**) was accomplished in 16 steps from known carboxylic acid **11**. This synthesis featured the highly *syn*-selective Evans aldol reaction of compound (+)-**10** with acrolein, the synthesis of cyclohexenol derivative (–)-**8** by ring-closing metathesis of Evans aldol adduct (+)-**9**, the highly diastereoselective dihydroxylation of compound (–)-7 and the acid-mediated spiroketalization of diketone (+)-**5**. Our methodology can be extended to the synthesis of other pleurospiroketals and structurally related terpenoids. Further investigations are now in progress in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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10 CCDC 1858657 contains the supplemental crystallographic data of compound (−)-**16**†.
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12 The synthetic procedure of dithiane derivative **18** is described in the ESI†.
13 In the case of using manganese dioxide, compound (+)-**5** was obtained in 10–20% yield, and when Parikh−Doering oxidation was carried out, a complex mixture was obtained.
14 CCDC 1858659 contains the supplemental crystallographic data of compound (+)-**1**†.