



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 group⁴ 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

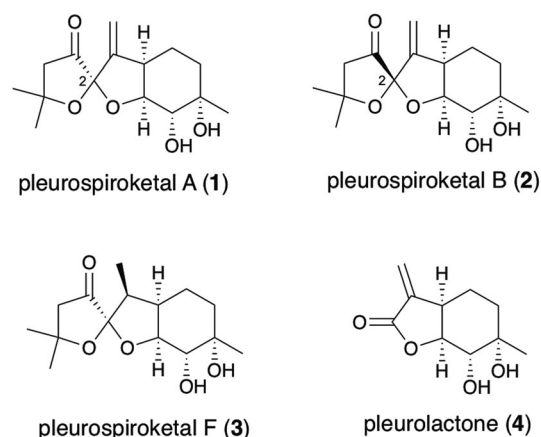


Fig. 1 Structures of pleurospiroketals A (1) and B (2) and related natural products 3 and 4.

diastereoselective dihydroxylation and acid-mediated spiroketalization as key steps.

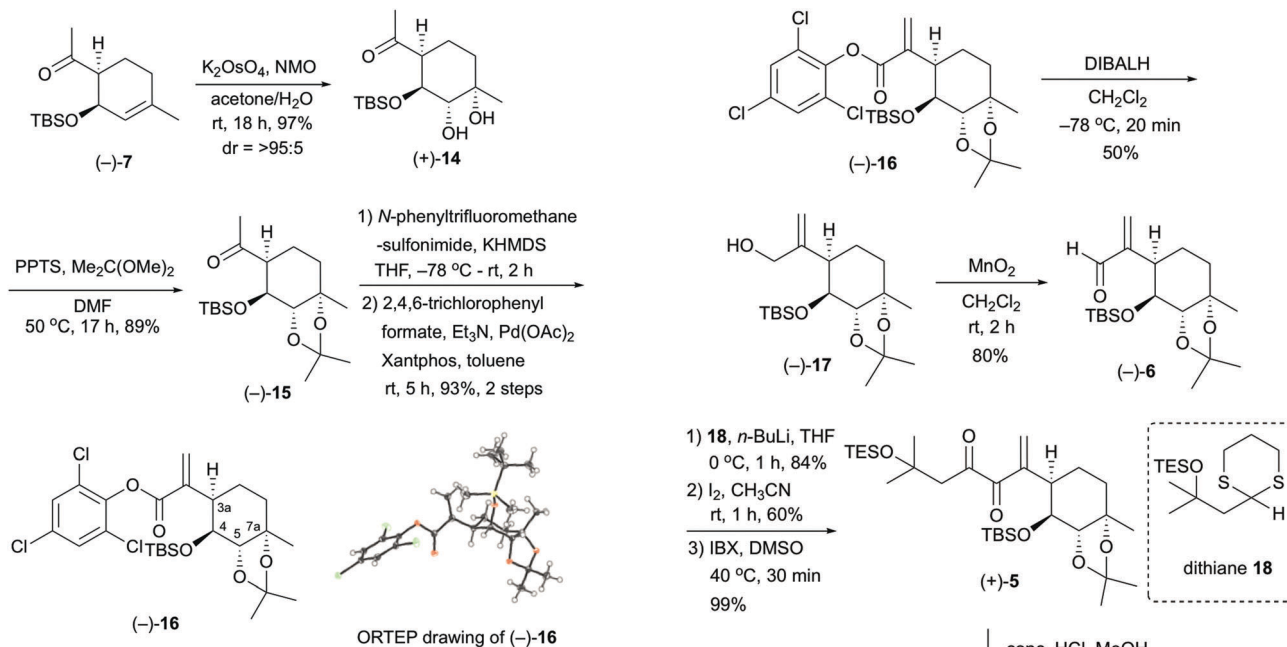
The synthetic strategy for pleurospiroketals A (1) and B (2) is outlined in Scheme 1. The target molecules 1 and 2 could be synthesized by deprotection of silyl ethers and acetonide groups and construction of the 5,5-spiroketal moiety from diketone 5. Compound 5 would be obtained using nucleophilic addition 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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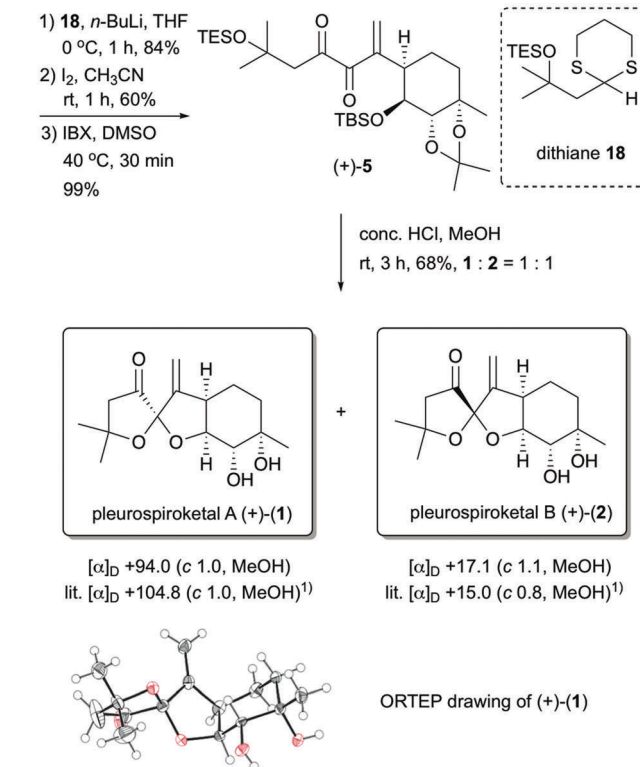
† Electronic supplementary information (ESI) available. CCDC 1858657 and 1858659. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8cc06185h



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

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 ¹H and ¹³C 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**: [α]_D +94.0 (c 1.0, MeOH); natural product **1**: [α]_D +104.8 (c 1.0, MeOH);¹ synthetic **2**: [α]_D +17.1 (c 1.1, MeOH); natural product **2**: [α]_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



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

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**[†].