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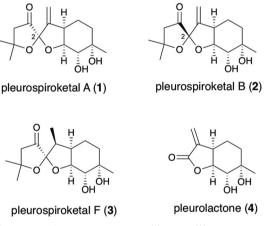
Asymmetric total synthesis of pleurospiroketals A and B<sup>+</sup>

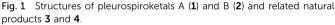
Toyoharu Kobayashi, 🕒 a Konomi Tanaka, a Masako Ishida, a Natsumi Yamakita, Hideki Abe 🖻 ab and Hisanaka Ito\*a

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.<sup>1</sup> The structures of these terpenoids were established through analysis of 2D NMR spectra, singlecrystal 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 solidstate fermentation of *Pleurotus citrinopile*.<sup>2</sup> 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<sup>4</sup> and the Mehta group.<sup>5</sup> 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.

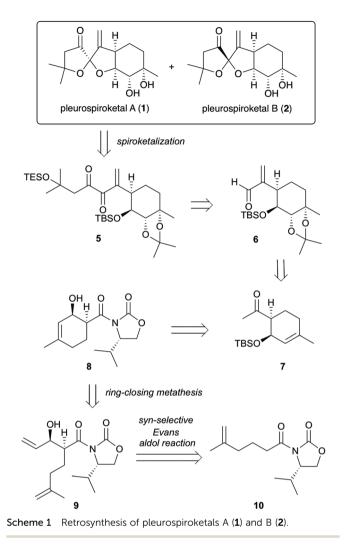
The synthetic strategy for pleurospiroketals A(1) and B(2) is outlined in Scheme 1. The target molecules 1 and 2 could be synthesized by deprotection of silvl ethers and acetonide groups and construction of the 5,5-spiroketal moiety from diketone 5. Compound 5 would be obtained using nucleophilic addition 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,<sup>4</sup> 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

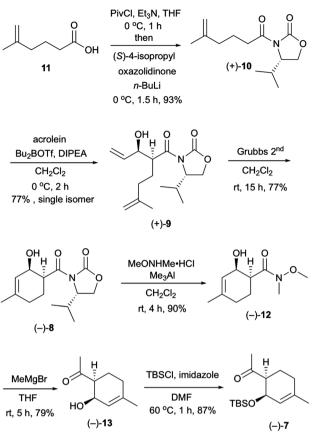
<sup>&</sup>lt;sup>a</sup> School of Life Sciences, Tokyo University of Pharmacy and Life Sciences, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan

<sup>&</sup>lt;sup>b</sup> Department of Chemical and Biological Sciences, Faculty of Science, Japan Women's University, 2-8-1 Mejirodai, Bunkyo-ku, Tokyo 112-8681, Japan

<sup>†</sup> 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



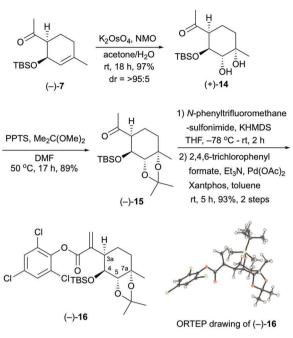
aldol reaction as shown in Scheme 2. Installation of (S)-4isopropyloxazolidinone as the chiral auxiliary into the known carboxylic acid 11<sup>6</sup> was achieved by a two-step operation: transformation of the carboxylic acid to the mixed anhydride, followed by addition of the lithiated oxazolidinone into the resulting mixed anhydride to afford 10 in 93% yield. The syn-selective Evans aldol reaction<sup>7</sup> 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<sup>8</sup> 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.



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

The stereocontrolled synthesis of (-)-16 from compound (-)-7 was achieved using a procedure established by our group for pleurolactone synthesis<sup>4</sup> (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,<sup>9</sup> palladium catalyst [Pd(OAc)<sub>2</sub>, 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.<sup>10</sup> Therefore, the absolute configuration of (-)-16 was established as 3aR, 4S, 5S, 7aS 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.

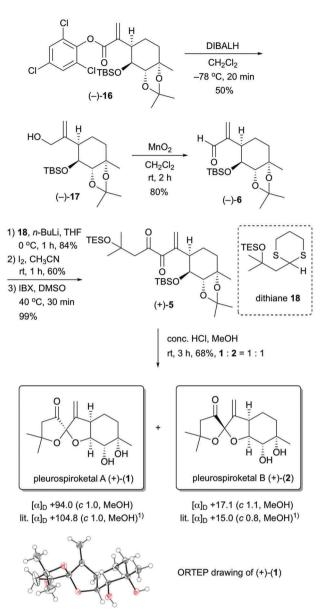
With the stereocontrolled synthesis of compound (-)-**16** in hand, we next focused on the construction of the 5,5-spiroketal moiety (Scheme 4). Unsaturated aldehyde (-)-**6** was obtained *via* a two-step operation. Reduction of ester (-)-**16** with diisobutylaluminum



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

hydride in dichloromethane provided the allyl alcohol (-)-17 in 50% vield, 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<sup>12</sup> 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.<sup>13</sup> 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 <sup>1</sup>H and <sup>13</sup>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);<sup>1</sup> synthetic 2:  $[\alpha]_D$  +17.1 (c 1.1, MeOH); natural product 2:  $[\alpha]_{D}$  +15.0 (*c* 1.0, MeOH)<sup>1</sup>]. Additionally, the structure of compound 1 was unambiguously confirmed by X-ray crystallographic analysis.<sup>14</sup>

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<sup>†</sup>.
- 11 H. D. Flack, Acta Crystallogr., 1983, A39, 876.
- 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†.