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Asymmetric total synthesis of pleurospiroketals A and B†

Toyoharu Kobayashi, 🕩 a Konomi Tanaka, a Masako Ishida, a Natsumi Yamakita, a Hideki Abe 🕩 and Hisanaka Ito*

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. 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*.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

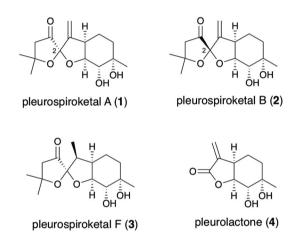


Fig. 1 Structures of pleurospiroketals A (1) and B (2) and related natural products $\bf 3$ and $\bf 4$.

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

^a School of Life Sciences, Tokyo University of Pharmacy and Life Sciences, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan

b Department of Chemical and Biological Sciences, Faculty of Science, Japan Women's University, 2-8-1 Mejirodai, Bunkyo-ku, Tokyo 112-8681, Japan

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

aldol reaction as shown in Scheme 2. Installation of (S)-4isopropyloxazolidinone as the chiral auxiliary into the known carboxylic acid 116 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 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 RCM⁸ 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 synthesis⁴ (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, 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 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

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TBSO

THF,
$$-78 \, ^{\circ}\text{C} - \text{rt}$$
, $2 \, \text{h}$

2) 2,4,6-trichlorophenyl formate, Et₃N, Pd(OAc)₂

Xantphos, toluene rt, $5 \, \text{h}$, 93%, $2 \, \text{steps}$

CI

TBSO

TBSO

TBSO

TBSO

TBSO

TBSO

THF, $-78 \, ^{\circ}\text{C} - \text{rt}$, $2 \, \text{h}$

TBSO

THF, $-78 \, ^{\circ}\text{C} - \text{rt}$, $2 \, \text{h}$

TBSO

THF, $-78 \, ^{\circ}\text{C} - \text{rt}$, $2 \, \text{h}$

TBSO

THF, $-78 \, ^{\circ}\text{C} - \text{rt}$, $2 \, \text{h}$

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TBSO

THF, $-78 \, ^{\circ}\text{C} - \text{rt}$, $2 \, \text{h}$

THF, $-78 \, ^{\circ}\text{C} - \text{rt}$, $2 \, \text{h}$

TBSO

THF, $-78 \, ^{\circ}\text{C} - \text{rt}$, $2 \, \text{h}$

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THF, $-78 \, ^{\circ}\text{C} - \text{rt}$, $2 \, \text{h}$

THF, $-78 \, ^{\circ}\text{C} - \text{rt}$

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 18¹² 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. 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: $[\alpha]_D$ +94.0 (c 1.0, MeOH); natural product 1: $[\alpha]_D$ +104.8 (c 1.0, MeOH); 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 pleuro-spiroketals 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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- 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†.