ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2018, **54**, 10316

Received 30th July 2018,
Accepted 17th August 2018

DOI: 10.1039/c8cc06185h

rsc.li/chemcomm

Asymmetric total synthesis of pleurospiroketals A and B†

Toyoharu Kobayashi,[a] Konomi Tanaka,[a] Masako Ishida,[a] Natsumi Yamakita,[a] 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.[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.

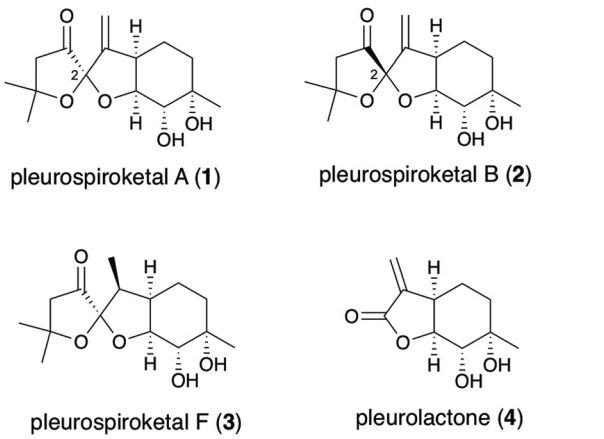


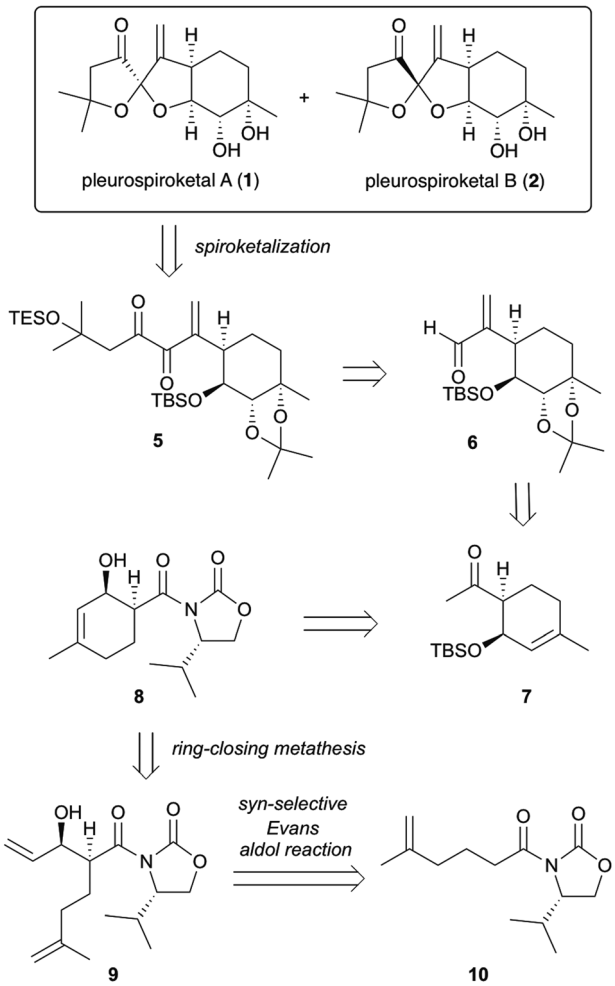
Fig. 1 Structures of pleurospiroketals A (**1**) and B (**2**) and related natural products **3** and **4**.

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.

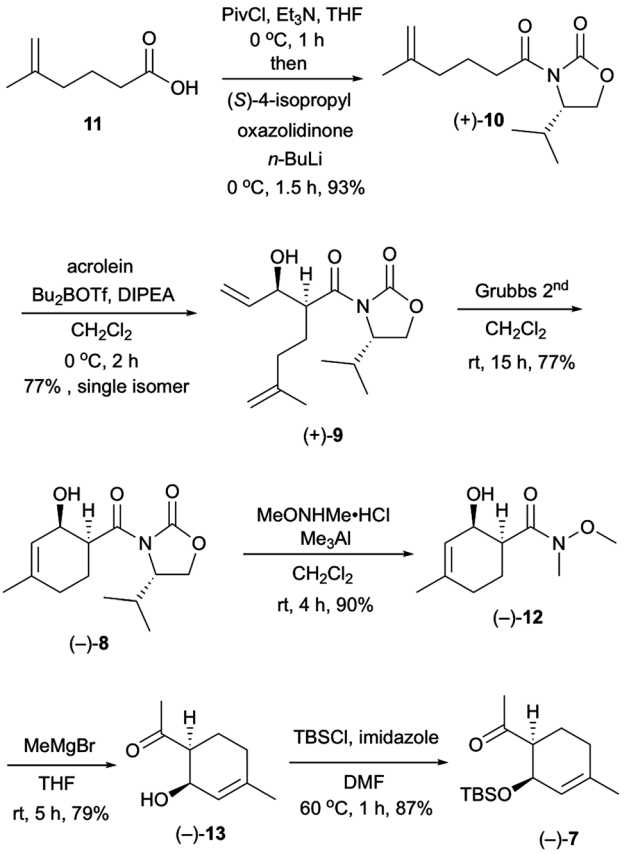
Our investigation started with the synthesis of compound **10** with a chiral auxiliary for the subsequent *syn*-selective Evans

[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*

† 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**).

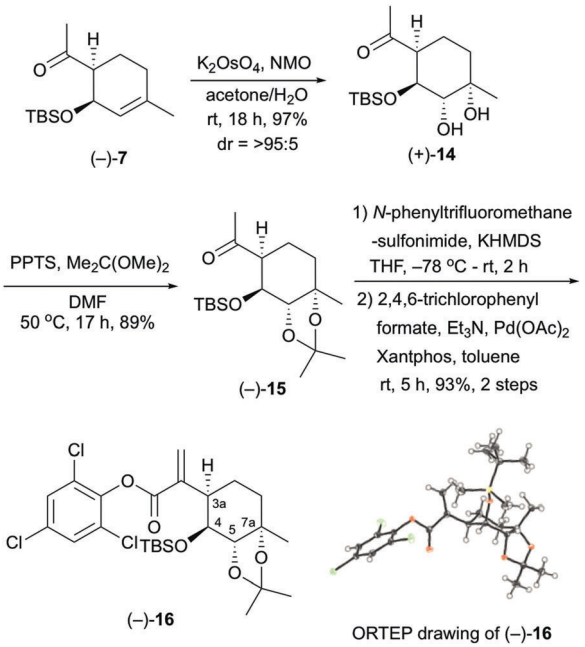


Scheme 2 Synthesis of compound (−)-**7** in an optically active form.

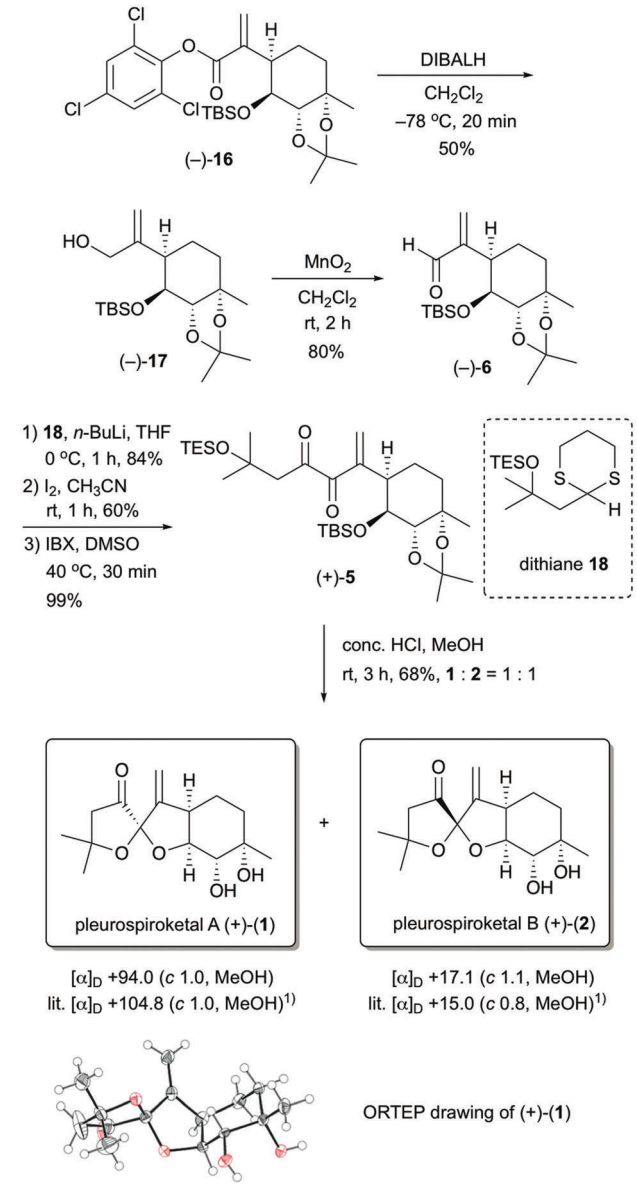
aldol reaction as shown in Scheme 2. Installation of (*S*)-4-isopropyloxazolidinone as the chiral auxiliary into the known carboxylic acid **11**[6] was achieved by a two-step operation: transformation of the carboxylic acid to the mixed anhydride, followed by addition of the lithiated oxazolidinone 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.

This work was supported by the Platform for Drug Discovery, Informatics, and Structural Life Science from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 S.-J. Wang, L. Bao, J.-J. Han, Q.-X. Wang, X.-L. Yang, H.-A. Wen, L.-D. Guo, S.-J. Li, F. Zhao and H.-W. Liu, *J. Nat. Prod.*, 2013, **76**, 45.

2 Q.-Q. Tao, K. Ma, L. Bao, K. Wang, J.-J. Han, W.-Z. Wang, J.-X. Zhang, C.-Y. Huang and H.-W. Liu, *Planta Med.*, 2016, **82**, 639.
3 (*a*) L. Y. Liu, Z. H. Li and J. K. Liu, *Chin. J. Nat. Med.*, 2013, **11**, 71; (*b*) S. J. Wang, L. Bao, F. Zhao, Q. X. Wang, S. J. Li, J. W. Ren, L. Li, H. Wen, L. D. Guo and H. W. Liu, *J. Agric. Food Chem.*, 2013, **61**, 5122.
4 T. Kobayashi, M. Ishida, K. Imaida, H. Abe and H. Ito, *Tetrahedron Lett.*, 2017, **58**, 3294.
5 S. Rashid, B. A. Bhat and G. Mehta, *Tetrahedron Lett.*, 2017, **58**, 3800.
6 E. E. Lee and T. Rovis, *Org. Lett.*, 2008, **10**, 1231.
7 (*a*) D. A. Evans, J. V. Nelson, E. Vogel and R. Taber, *J. Am. Chem. Soc.*, 1981, **103**, 3099; (*b*) S. Kriening, A. Evagelou, B. Claasen, A. Baro and S. Laschat, *Eur. J. Org. Chem.*, 2014, 6720.
8 For reviews, see: (*a*) A. Gradillas and J. Pérez-Castells, *Angew. Chem., Int. Ed.*, 2006, **45**, 6086; (*b*) K. C. Nicolaou, P. G. Bulger and D. Sarlah, *Angew. Chem., Int. Ed.*, 2005, **44**, 4490; (*c*) A. Deiters and S. F. Martin, *Chem. Rev.*, 2004, **104**, 2199; (*d*) R. H. Grubbs, *Tetrahedron*, 2004, **60**, 7117.
9 (*a*) T. Ueda, H. Konishi and K. Manabe, *Org. Lett.*, 2012, **14**, 5370; (*b*) H. Konishi, T. Ueda and K. Manabe, *Org. Synth.*, 2015, **90**, 39.
10 CCDC 1858657 contains the supplemental crystallographic data of compound (−)-**16**†.
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**†.