Conversion of Optically Active Hydrindanone to (+)-Bakkenolide-A

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A total synthesis of (+)-bakkenolide-A was carried out *via* the key intermediate 4, which was prepared based on an asymmetric cyclization-carbonylation reaction established in our laboratory. Diastereoselective construction of the spirolactone moiety was achieved using Mitsuhashi's protocol as a key step.

Key words (+)-bakkenolide-A; hydrindanone; asymmetric cyclization-carbonylation

The bakkanes are an interesting class of sesquiterpenes containing a *cis*-hydrindane skeleton decorated with two quaternary centers and a spiro-β-methylene-γ-lactone moiety.[1)] Bakkenolide-A, which was first reported from the buds of the *Petasites japonicus*,[2—4)] shows cytotoxicity toward several carcinoma cell lines, and is an effective insect antifeedant.[1)] Since the first synthesis of bakkenolide-A by Evans,[5,6)] a number of alternative syntheses have been described.[1,7—10)] We previously reported the first examples of an asymmetric cyclization-carbonylation of *meso*-2-alkyl-2-propargylcyclohexane-1,3-diols[11,12)] and 2-alkyl-2-propargylcyclohexane-1,3-diones[13,14)] catalyzed by palladium(II) with chiral bisoxazoline (box) ligands. In addition, we recently reported a parallel kinetic resolution of racemic propargyl ketols **1** for a formal synthesis of (+)-bakkenolide-A (Chart 1).[15)] These three reactions are possible routes to the synthesis of the same optically active hydrindanes. As an application of the parallel kinetic resolution of racemic propargyl ketols **1**,[15)] we report the total synthesis of (+)-bakkenolide-A using Mitsuhashi's protocol[16)] for construction of the spirolactone moiety.

We envisaged the chiral hydrindanone **4**, which was obtained by asymmetric cyclization-carbonylation reactions established in our laboratory,[15)] as a potential precursor to (+)-bakkenolide-A.[17,18)] Mitsuhashi and co-workers have synthesized spirolactones from steroids.[16)] We applied the Mitsuhashi's method for the synthesis of (+)-bakkenolide-A. (+)-Bakkenolide-A may be obtained from cyano diester **5** (Chart 2). In this case, the cyano group was to be introduced from the convex face of diester **6**,[5,6)] which may be prepared by Knoevenagel reaction of the chiral hydrindanone **4**.

Optically active hydrindanone **4** was obtained by the our previously reported procedure based on asymmetric cyclization-carbonylation reaction (37% yield; 6 steps from **2**), and Knoevenagel reaction of **4** with diisopropyl malonate gave diester **6** (Charts 2, 3). For construction of the spirolactone moiety of (+)-bakkenolide-A, a quaternary cyano group was introduced stereoselectively on the five-membered ring. The shape of the molecule allowed control of the cyanide approach from the convex face, giving cyano diester **5** in 84% yield (two steps). The use of diethyl malonate resulted in a decreased yield of **7** due to partial decarboxylation.[16)] The stereochemistry of **5** was determined by conversion to (+)-bakkenolide-A in a four-step sequence. Reduction of the ester groups of **5** followed by lactonization furnished hydroxymethyllactone **8** as a *ca.* 1 : 1 mixture of diastereomers. Treatment of **8** with *o*-nitrophenyl selenocyanate and tri-*n*-butylphosphine afforded the selenide,[19)] which was oxidized with hydrogen peroxide gave (+)-bakkenolide-A in 58% yield over four steps. The spectral data were found to be identical to those reported by Reddy[9)] and Naya.[4)]

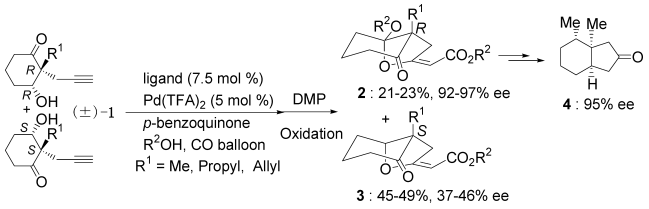

Chart 1

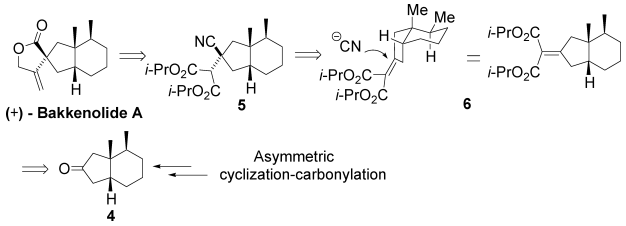

Chart 2

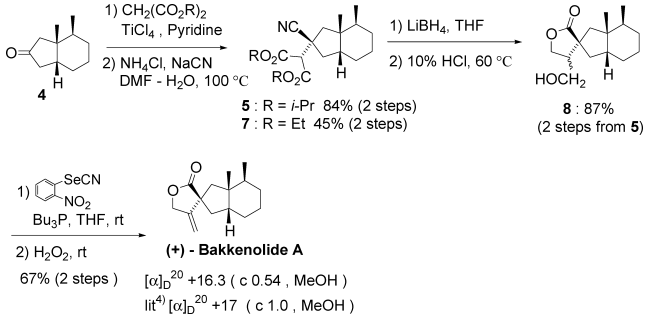

Chart 3

Experimental

General Experimental Methods All melting points were measured on a Yanaco MP-3S micro melting point apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on JEOL AL 400 and JEOL Lambda 500

In conclusion, we carried out a total synthesis of (+)-bakkenolide-A as an application of the asymmetric cyclization-carbonylation reactions established in our laboratory, using Mitsuhashi's protocol for construction of spirolactone moiety.

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spectrometer in $CDCl_3$ with Me_4Si as an internal reference. High-resolution mass spectra (HR-MS) and the fast atom bombardment mass spectra (FAB-MS) were obtained with a JEOL GC mate II, a JMS-SX102 and a JEOL JMS 600 H spectrometers. IR spectra were recorded with a JASCO FT/IR-300 spectrometer. All reagents were purchased from commercial sources and used without purification. All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

Preparation of Cyano Diester 5 To a solution of **4** (70.8 mg, 0.43 mmol) in CH_2Cl_2 (3 ml) were added $TiCl_4$ (242 mg, 1.28 mmol) in CH_2Cl_2 (0.5 ml) and pyridine (202 mg, 2.56 mmol) in CH_2Cl_2 (0.5 ml) at 0 °C, and the mixture stirred for 12 h at room temperature. The reaction mixture was then diluted with water (15 ml) and CH_2Cl_2 (15 ml). The organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (30 ml), and the combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*. To a solution of the crude product in DMF (3 ml) were added water (1 ml), NH_4Cl (46 mg, 0.86 mmol) and NaCN (63 mg, 1.29 mmol), and the mixture stirred at 100 °C for 8 h. The reaction mixture was diluted with water (15 ml) and AcOEt (15 ml). The organic layer was separated, the aqueous layer was extracted with AcOEt (15 ml), and the combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*. The crude product was chromatographed on silica gel (14 g, *n*-hexane/AcOEt=30 : 1 to 20 : 1) afforded (+)-**5** (130 mg, 84% yield) as a white solid.

(+)-**5**: White solid, mp 90—92 °C (hexane), $[\alpha]_D^{22}$ +15.7 (c=0.37, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 0.77 (3H, d, J=6.7 Hz), 1.00 (3H, s), 1.05—1.16 (1H, m), 1.29 (12H, d, J=6.3 Hz), 1.28—1.64 (6H, m), 2.01—2.18 (5H, m), 3.35 (1H, s), 5.10—5.14 (2H, m); ^{13}C-NMR ($CDCl_3$) δ: 16.2, 20.2, 21.3, 21.5, 21.5, 21.6, 21.6, 23.5, 30.7, 36.2, 40.3, 40.6, 42.9, 45.6, 50.5, 60.5, 69.9, 69.9, 124.1, 165.8, 165.9; IR (KBr) 2236, 1722 cm^{-1}; HR-MS-EI *m*/*z*: [M+] Calcd for $C_{21}H_{33}NO_4$ 363.2410; Found 363.2406.

(±)-**7** was obtained from preliminary experiments using racemic substrate.

(±)-**7**: Colorless oil, ^{1}H-NMR ($CDCl_3$) δ: 0.78 (3H, d, J=6.7 Hz), 1.01 (3H, s), 1.26—1.33 (3H, m), 1.31 (3H, t, J=7.2 Hz), 1.31 (3H, t, J=7.2 Hz), 1.39—1.52 (2H, m), 1.61—1.62 (2H, m), 2.02—2.19 (5H, m), 3.43 (1H, s), 4.25—4.29 (4H, m) ; ^{13}C-NMR ($CDCl_3$) δ: 14.0, 16.2, 20.2, 21.3, 23.5, 30.7, 36.3, 40.4, 40.6, 43.0, 45.7, 50.4, 60.1, 62.1, 124.1, 166.3, 166.4; IR (neat) 2929, 2239, 1731 cm^{-1}; HR-MS-EI *m*/*z*: [M+] Calcd for $C_{19}H_{29}NO_4$ 335.2097; Found 335.2097.

Synthesis of Hydroxymethyllactone 8 To a solution of (+)-**5** (20.9 mg, 0.06 mmol) in THF (2 ml) was added $LiBH_4$ (13.1 mg, 0.60 mmol), and the mixture was stirred at 50 °C for 5 h. The mixture was cooled to room temperature, quenched with 10% HCl (1.5 ml) and then stirred at 60 °C for 4 h. The reaction mixture was then diluted with water (10 ml) and extracted with $CHCl_3$ (15 ml). The organic layer was separated, the aqueous layer was extracted with $CHCl_3$ (15 ml), and the combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (3.5 g). The fraction eluted with hexane/acetone (8/1) afforded **8** (12.6 mg, 87% yield) as a 1 : 1 mixture of diastereomers.

8: White solid; mp 102—104 °C (Et_2O), ^{1}H-NMR ($CDCl_3$) (mixture of diastereomers, ratio=1 : 1) δ: 0.82 (1.5H, d, J=6.7 Hz), 0.83 (1.5H, d, J=6.7 Hz), 0.94 (1.5H, s), 0.97 (1.5H, s), 1.13—2.37 (13H, m), 2.33—2.37 (1H, m), 3.57—3.65 (1H, m), 3.80—3.85 (1H, m), 4.29—4.34 (2H, m); ^{13}C-NMR ($CDCl_3$) (mixture of diastereomers, ratio=1 : 1) δ: 16.3, 16.6, 19.0, 19.2, 20.9, 20.9, 23.2, 23.5, 30.7, 30.7, 32.1, 33.7, 34.1, 40.7, 41.4, 43.6, 43.9, 44.9, 45.7, 47.9, 48.1, 48.6, 49.3, 49.8, 61.1, 62.0, 68.4, 68.7, 183.2, 183.6 (15C×2); IR (KBr) 3432, 1732 cm^{-1}; HR-MS-EI *m*/*z*: [M+] Calcd for $C_{15}H_{24}O_3$ 252.1726; Found 252.1720.

Synthesis of (+)-Bakkenolide-A To a solution of **8** (21.6 mg, 0.086 mmol) in THF (4 ml) were added 2-nitrophenyl seleno cyanate (97 mg, 0.43 mmol) and tributyl phosphine (86.6 mg, 0.43 mmol), and the mixture was stirred at room temperature for 2 h. H_2O_2 (1.0 ml) was then added to the reaction mixture and stirring was continued at room temperature for 18 h. The reaction mixture was quenched with sat. Na_2SO_3 aq. (10 ml) at 0 °C and extracted with $CHCl_3$ (15 ml). The organic layer was separated, the aqueous layer was extracted with $CHCl_3$ (15 ml), and the combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by preparative TLC (hexane/EtOAc=4/1) to afford (+)-bakkenolide-A (13.4 mg, 67% yield).

(+)-Bakkenolide-A: $[\alpha]_D^{20}$ +16.3 (c=0.54, MeOH); ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, d, J=6.8 Hz), 0.99 (3H, s), 1.13—1.26 (1H, m), 1.45—1.61 (6H, m), 1.94—1.99 (3H, m), 2.09 (1H, t, J=13.0 Hz), 2.25—2.29 (1H, m), 4.70—4.82 (2H, m), 5.03 (1H, m), 5.10 (1H, m); ^{13}C-NMR ($CDCl_3$) δ: 16.3, 19.1, 21.0, 23.3, 30.9, 33.9, 42.3, 44.0, 46.2, 48.5, 49.8, 70.3, 105.8, 150.4, 182.5; IR (KBr) 1772, 1669 cm^{-1}; HR-MS-EI *m*/*z*: [M+] Calcd for $C_{15}H_{22}O_2$ 234.1620; Found 234.1615.

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