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

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Received May 28, 2008; accepted July 22, 2008; published online July 29, 2008

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-diols11,12) and 2-alkyl-2-propargylcyclohexane-1,3-diones13,14) catalyzed by palladium(II) with chiral bisoxazoline (box) ligands. In addition, we recently reported a parallel kinetic resolution of racemic propargyl ketols15) 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 ketols15),15) we report the total synthesis of (+)-bakkenolide-A using Mitsuhashi’s protocol16) 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 (Chart 2).15) 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 ketols15),15) we report the total synthesis of (+)-bakkenolide-A using Mitsuhashi’s protocol16) for construction of the spirolactone moiety.

Optically active hydrindanone 4 was obtained by the 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 diastereomeric purity 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 hydroxymethylactone 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 Reddy9) and Naya.4)

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.

Experimental

General Experimental Methods All melting points were measured on a Yanaco MP-3S micro melting point apparatus and are uncorrected.1H- and 13C-NMR spectra were recorded on JEOL AL 400 and JEOL Lambda 500
spectrometer in CDCl₃ with Me₄Si 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 spectrometers. IR spectra were recorded with a JASCO FT/IR-300 spectrometer. All reagents were purchased from commercial sources and used without purification. All evaporation were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

Preparation of Cyanodiaster 5 To a solution of 4 (70.8 mg, 0.43 mmol) in CH₂Cl₂ (3 ml) were added TiCl₄ (242 mg, 1.28 mmol) in CH₂Cl₂ (0.5 ml) and pyridine (202 mg, 2.56 mmol) in CH₂Cl₂ (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 CH₂Cl₂ (15 ml). The organic layer was separated, the aqueous layer was extracted with CH₂Cl₂ (30 ml), and the combined organic layers were dried with MgSO₄ and concentrated in vacuo. To a solution of the crude product in DME (3 ml) were added water (1 ml), NH₄Cl (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 MgSO₄ and concentrated in vacuo. The residue was purified by preparative TLC (hexane/EtOAc=4/1) to afford (+)-cyanodiaster (13.4 mg, 67% yield).

(+)-Bakkenolide-A: [α]₂⁰⁺ 16.3 (c = 0.54, MeOH); 1H-NMR (CDCl₃) δ: 0.85 (3H, d, J = 6.3 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); 13C-NMR (CDCl₃) 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-El m/z: [M⁺] Calcd for C₁₅H₂₄O₃ 234.1620; Found 234.1615.

References