Synthesis of the Hexahydroazepine Core of (–)-Balanol

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Protein kinase C (PKC) is involved in a variety of cellular responses. As the activation of PKC is critically related to the progression of a wide range of diseases, chemotherapeutic agents that inhibit PKC have attracted a great deal of attention.

(–)-Balanol (1), a metabolite isolated from the fungus Verticillium balanoides1 and Fusarium merismoides,2 exhibits potent activity as a PKC inhibitor (Fig. 1)3 and hence been an attractive target in numerous synthetic studies.4 (–)-Balanol is structurally divided into two parts: a hexahydroazepine segment (with 4-hydroxybenzamide) and a benzophenone moiety. The hexahydroazepine core of (–)-balanol has also drawn the attention of the synthetic community, because it can be utilized not only for the synthesis of (–)-balanol but for an example testing a new synthetic route to introduce an amino alcohol moiety.5

Because of our interest in natural product synthesis, we attempted to employ cis-2,3-bis(hydroxymethyl)aziridine (3) as a useful synthetic intermediate for introducing an amino alcohol moiety.6 Compound 3 can be easily converted into an optically active form by enzymatic desymmetrization.7 We thought that 3 could be efficiently used for the synthesis of the hexahydroazepine core of (–)-balanol.

To demonstrate the potential of 3 as a versatile starting material, we decided to investigate the efficient synthetic route to (3R,4R)-hexahydroazepine core of (–)-balanol. Compound 3 could be readily obtained from cis-2-butene-1,4-diol via a well-known synthetic sequence.6 Retrosynthetic analysis of the (3R,4R)-hexahydroazepine core of (–)-balanol is summarized in Figure 2. We envisioned that hexahydroazepine core 2 can be derived from intermediate 4, which can be synthesized from the diene 5 by ring-closing metathesis.8 Diene 5, which shows the required stereocchemical relationships for the synthesis of 2, could be prepared by the selective ring opening of aziridine 6,9,10 which in turn, could be derived from 3 by the enzymatic desymmetrization.

Our synthetic pathway to the (3R,4R)-hexahydroazepine core (2) is summarized in Scheme 1. The entire synthetic sequence is based on the availability of enantiomerically pure chiral cis-aziridine derivative 6. In addition, the stereo and regioselective ring opening of 6, and cyclization by ring-closing metathesis to construct the azepine ring, are the two most critical reactions for the success of the synthesis.

The chiral derivative 6 was prepared from meso-aziridine-diol 7 by Amano PS lipase desymmetrization according to the reported procedure.7,11 Oxidation of 6 with Dess-Martin periodinane (DMP) afforded aldehyde 8, which was subsequently subjected to the Wittig reaction. The resulting olefin product 9 underwent regioselective aziridine ring opening.9,10 Nucleophilic ring opening in the presence of a Lewis acid is useful for the introduction of 1,2-amino alcohol functionality.8 With benzyl alcohol as the nucleophile, the aziridine ring was success-
fully opened to provide a fully protected amino alcohol 10. Deprotection and subsequent tosylation set the stage for the introduction of another amino group. After substitution with allylamine followed by protection with a Cbz group, the desired diene product 13 was successfully obtained. Next, ring-closing metathesis with Grubbs catalyst (first generation) was performed to give cyclic product 14 in reasonable yield. Both of 13 and 14 were obtained as 1:1 mixtures of rotamers due to the presence of Cbz groups for protecting amino groups. Hydrogenation of the C=C group and deprotection of the benzyl group were achieved simultaneously. Finally, deprotection of the Boc group under acidic conditions completed the synthesis of the hexahydroazepine core of (−)-balanol.

In conclusion, we have shown that an enantiopure chiral vinyl aziridine, which is easily accessible by enzymatic de-symmetrization, can be efficiently used for introducing 1,2-amino alcohol functionality. Regio- and stereoselective ring opening of the chiral aziridine in combination with ring-closing metathesis could be an efficient strategy for constructing cyclic compounds bearing vicinal amino alcohol in an asymmetric manner. This strategy was successfully applied to the synthesis of the hexahydroazepine core of (−)-balanol.

Experimental Section

General Methods. 1H NMR spectra were recorded on either 400 or 500 MHz spectrometer at ambient temperature with CDCl3 as the solvent unless otherwise stated. 13C NMR spectra were recorded on either 100 or 125 MHz spectrometer (with complete proton decoupling) at ambient temperature. High-resolution mass spectrometry (HRMS) was performed using ESI-TOF technique. Flash chromatography was performed using 230-400 mesh silica gel.

(2S,3R)-tert-Butyl 2-(acetoxymethyl)-3-formylaziridine-1-carboxylate (8). (2S,3R)-tert-Butyl 2-(acetoxymethyl)-3-(hydroxymethyl)aziridine-1-carboxylate (6) (480 mg, 1.96 mmol) prepared according to the reported procedure7,11 was dissolved in CH2Cl2 (15 mL). To this solution was added Dess-Martin periodinane (DMC) (1.66 g, 3.92 mmol). The resulting solution was stirred for 2 h at room temperature. After the reaction was completed, aqueous saturated NaHCO3 (15 mL) and aqueous saturated Na2SO3 (10 mL) were added. The mixture was extracted with CH2Cl2 (3 × 15 mL). The organic layer was separated, dried (MgSO4), and concentrated. Purification by flash chromatography (hexane:EtOAc = 4:1) offered the desired aldehyde 8 (330 mg, 69%) as a colorless oil: 1H NMR (300 MHz, CDCl3) δ 5.24 (m, 1H), 5.39 (td, 1H), 2.99 (s, 3H), 3.04 (dd, 1H); 13C NMR (100 MHz, CDCl3) δ 156.0, 159.7, 82.5, 60.8, 44.4, 41.1, 27.4, 20.2; HRMS-ESI (m/z): [M+Na]+ calcd for C11H15NNaO4, 266.0999; found, 266.1001.

(2S,3R)-tert-Butyl 2-(acetoxymethyl)-3-vinylaziridine-1-carboxylate (9). To a solution of methyltriphenylphosphonium bromide (971 mg, 2.72 mmol) in THF (10 mL) was added potassium bis(trimethylsilyl)amide (KHMDS) (0.23 mL, 2.72 mmol). The resulting mixture was stirred for 30 min at -20 °C. After dropwise addition of aldehyde 8 (330 mg, 1.36 mmol) dissolved in THF (2 mL) to the above solution via cannula, the reaction mixture was stirred for 3 h at -20 °C. After the reaction was completed, aqueous saturated NH4Cl (15 mL) was added. The mixture was extracted with ether (3 × 10 mL). The organic layer was separated, dried (MgSO4), and concentrated. Purification by flash chromatography (hexane:EtOAc = 7:1) offered the desired vinylaziridinol 9 (249 mg, 76%) as a colorless oil: 1H NMR (300 MHz, CDCl3) δ 5.24 (m, 1H), 5.39 (td, 1H), 2.99 (s, 3H), 3.04 (dd, 1H); 13C NMR (100 MHz, CDCl3) δ 156.0, 159.7, 82.5, 60.8, 44.4, 41.1, 27.4, 20.2; HRMS-ESI (m/z): [M+Na]+ calcd for C11H15NNaO4, 266.0999; found, 266.1001.
found, 264.1205.

(2R,3R)-3-(Benzylx)-2-((tert-butoxycarbonyl)amino)pent-4-en-1-yl acetate (10). Vinylaziridine 9 (249 mg, 1.03 mmol) was dissolved in CH₂Cl₂ (10 mL) at −20 °C. To this solution were added benzyl alcohol (1.13 mL, 10.30 mmol) and catalytic amount of BF₃·OEt₂ (3 drops). The reaction mixture was stirred for 1 h at −20 °C. After the reaction was completed, aqueous saturated NaHCO₃ (15 mL) was added. The mixture was extracted with CH₂Cl₂ (3 × 15 mL). The organic layer was separated, dried (MgSO₄), and concentrated. Purification by flash chromatography (hexane:EtOAc = 4:1) offered the desired benzyl ether 10 (292 mg, 81%) as a colorless oil: [α]D²⁹ = −7.6 (c 1.56, CHCl₃); IR (film) 3401, 3030, 1695, 1496, 1544, 1366, 1244, 1167, 1022, 739 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.42 (s, 9H), 1.95 (s, 3H), 3.93 (m, 1H), 4.02 (m, 2H), 4.11 (m, 1H), 4.24 (d, J = 11.7 Hz, 1H), 4.53 (d, J = 11.3 Hz, 1H), 4.83 (bd, J = 8.6 Hz, 1H), 5.33 (m, 2H), 5.77 (dd, J = 7.6, 9.5, 17.5 Hz, 1H), 7.24 (d, J = 7.0 Hz, 2H), 7.31 (m, 5H), 7.78 (d, J = 8.3 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 155.2, 149.4, 137.6, 134.1, 132.6, 129.8, 128.3, 127.9, 127.8, 119.6, 79.7, 77.4, 70.8, 67.8, 52.4, 28.2, 21.5; HRMS-ESI (m/z): [M+Na]⁺ calcd for C₁₇H₁₈NNaO₂S, 484.1764; found, 484.1765.

Benzyl N-allyl-N-((2R,3R)-3-(benzylx)-2-((tert-butoxycarbonyl)amino)pent-4-en-1-yl)carbamate (11). To a stirred solution of the tosylated product 12 (200 mg, 0.43 mmol) in methanol (5 mL) was added allylamine (5 mL) at room temperature. The reaction solution was stirred for 18 h at 65 °C in a sealed tube. The reaction mixture was concentrated, and the residue was dissolved in CH₂Cl₂ (5 mL) at 0 °C. To this solution were added triethylamine (1 mL, 6.77 mmol) and benzyl chloroformate (CbzCl) (121 µL, 0.86 mmol). The solution was stirred for 4 h at 0 °C. After reaction was completed, and mixture was diluted with EtOAc (20 mL) and washed with water (20 mL) and brine (20 mL). The organic layer was dried (MgSO₄), and concentrated. Purification by flash chromatography (hexane:EtOAc = 4:1) offered the product 11 (114 mg, 55%) as a colorless oil: [α]D²⁹ = +5.0 (c 0.79, CHCl₃); IR (film) 3444, 3066, 3032, 2977, 2929, 1711, 1499, 1417, 1368, 1240, 1168, 1067 cm⁻¹; ¹H NMR (500 MHz, CDCl₃), (mixture of rotamers) δ 1.41 (s, 9H), 3.44 (m, 2H), 3.97 (m, 4H), 4.30 (m, 1H), 4.56 (dd, J = 11.4, 23.6 Hz, 1H), 4.93 (m, 1H), 5.13 (m, 4H), 5.29 (m, 2H), 5.80 (m, 2H), 7.29 (m, 10H); ¹³C NMR (100 MHz, CDCl₃), (mixture of rotamers) δ 156.8, 156.1, 155.9, 155.7, 138.2, 136.7, 134.9, 133.5, 133.4, 128.3, 127.9, 127.6, 119.0, 118.8, 117.2, 116.7, 79.2, 79.1, 70.7, 70.4, 67.3, 67.2, 52.6, 50.0, 49.6, 47.7, 47.3, 28.3; HRMS-ESI (m/z): [M+Na]⁺ calcd for C₂₃H₂₃NNaO₃S, 503.2516; found, 503.2516.

(3R,4R)-Benzyl 4-(benzylx)-3-((tert-butoxycarbonyl)amino)-2,3,4,7-tetrahydro-1H-azepine-1-carboxylate (14). To a stirred solution of product 13 (78 mg, 0.16 mmol) in dry CH₂Cl₂ (15 mL) at room temperature was added Grubbs catalyst (first generation) (13 mg, 0.016 mmol). The resulting light brown solution was stirred for 18 h at 40 °C. After the solution was then concentrated, purification by flash chromatography (hexane:EtOAc = 4:1) offered the desired tetrahydroazepine core 14 (48 mg, 67%) as a brown oil: [α]D²⁹ = −41.3 (c 1.65, CHCl₃); IR (film) 3365, 3031, 2928, 1698, 1500, 1459, 1367, 1243, 1168, 1108, 866 cm⁻¹; ¹H NMR (400 MHz, CDCl₃), (mixture of rotamers) δ 1.43 (s, 9H), 3.65 (m, 2H), 3.92 (m, 1H), 4.11 (m, 2H), 4.52 (m, 3H), 5.12 (s, 2H), 5.83 (m, 2H), 7.32 (m, 10H); ¹³C NMR (100 MHz, CDCl₃), (mixture of rotamers) δ 156.4, 155.8, 155.2, 138.1, 138.0, 136.4, 131.6, 130.0, 128.8, 128.5, 128.3, 128.2, 128.1, 128.0, 127.7, 127.6, 127.5, 79.4, 79.2, 70.5, 70.4, 67.3, 67.2, 52.6, 50.0, 49.6, 47.7, 47.3, 28.3; HRMS-ESI (m/z): [M+Na]⁺ calcd for C₂₃H₂₃NNaO₂S, 503.2516; found, 503.2516.

(3R,4R)-4-hydroxyazepan-3-yl)carbamate (15). To a solution of tetrahydroazepine core 14 (31 mg,
The product treated added 3 N HCl (2 mL) at room temperature. The resulting solution was concentrated. Purification by flash chromatography (EtOAc:methanol = 10:1) offered the desired product (EtOAc:methanol = 10:1) offered the desired product. 9.5 Hz, 1H); 1.76 (m, 1H), 1.87 (m, 1H), 2.05 (m, 1H), 2.25 (m, 1H), 3.33 (3. Boros, C.; Hamilton, S. M.; Katz, B.; Kulanthaivel, P. J. Antibiot. 1994, 47, 639.


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