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Formal total synthesis of (−)-balanol: a potent PKC inhibitor

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ABSTRACT

An efficient formal total synthesis of the PKC inhibitor balanol **1** is described, starting from the commercially available pentane1,5-diol. A Shi epoxidation and Pd(0)-mediated nitrogen substitution with double inversion established the correct configuration of the balanol precursor **3**.

Balanol **1** is a fungal metabolite, isolated at Sphynx Pharmaceuticals from *Verticillium balanolides*[1] and *Fusarium merismoides*.[2] Initially, Balanol was reported as a PKC inhibitor,[1,3] and later it was found to be a competitive inhibitor of ATP and to potently inhibit PKA and other kinases as well.[4] Some balanol analogues inhibit PKA more specifically than PKC (some 2000-fold more potent than the parent molecule).[5] The selectivity of balanol itself is different among different PKC isoenzymes; the nanomolar IC_{50} values for PKA made it a promising lead structure for drug development. This high selectivity and potency indicates the focused attention of synthetic and medicinal chemists for synthesizing novel analogues for the development of therapeutic drugs. The first total synthesis of balanol was published by Nicolaou et al.[6a] Later, various research groups throughout the world published additional total[6] and formal syntheses[7] of balanol and its analogues.

Generally, the formal syntheses are focused on making the two segments namely, hexahydroazepine segment with 4-hydroxy benzamide (**3**) and benzophenone moiety (**2**) with suitable protections on oxygen and nitrogen atoms (Scheme 1).[6f,7f,p,u]

As part of our ongoing program directed toward the development of therapeutic agents for the treatment of PKC- and PKA-mediated disorders, we planned a procedure amenable to the synthesis of **3**, a key intermediate frequently employed in total syntheses of balanol. This compound contains a hexahydroazepine core and a protected 4-hydroxy benzamide segment of balanol. This would enable the discovery of more analogues for enhanced enzyme selectivity and improved pharmacokinetic properties. Herein we report the synthesis of this common intermediate **3**.[7]

The structure of balanol **1** consists of four rings, linked by amide and ester bonds. A commonly used retrosynthesis of **1** is shown in Scheme 1.

As shown in Scheme 2, we envisaged a practical synthesis that the hexahydroazepine **3** could be synthesized from hydroxyl azide **5**, which in turn could be constructed from the Pd (0)-catalyzed azide substitution on epoxy ester **6.**

The synthesis of azepine compound **3** commenced with the commercially available 1,5-pentanediol (see Scheme 3). This was selectively silylated as its mono *tert*-butyldimethylsilyl ether under standard conditions (TBDMSCl, imidazole, DMF, rt, 6 h) in 90% yield. PDC oxidation of the resultant alcohol in dichloromethane at rt furnished aldehyde **7** in 88% yield. Aldehyde **7** was treated with lithiated ethyl propiolate at −78 °C to furnish the hydroxyl alkynoate **8** in 83% yield. Triphenylphosphine-mediated deoxygenative rearrangement (via allene formation)[8] of **8** in benzene at rt yielded the (*E,E*)-α,β,γ,δ-unsaturated ester **9** in 76% yield. Treatment of this diene ester **9** under Shi epoxidation[9] conditions with ketone **12** as **a** catalyst provided the desired epoxide **6** in moderate yield (46%, 60% conversion) along with ~5% of bis-epoxide. However, enantioselectivity of the epoxidation was excellent (96.2% ee).[10] The resultant α,β-unsaturated γ,δ-epoxy ester **6** was subjected to Pd(0)-catalyzed stereospecific azide substitution ($TMSN_3$, $Pd(PPh_3)_4$, THF, rt, 5 h) to furnish *syn*-azido alcohol **5** in 91% yield with double inversion of configuration.[11] The secondary hydroxyl of **5** was silylated quantitatively with *tert*-butyldimethylsilyl trifluoromethanesulfonate and 2,6-lutidine (CH_2Cl_2, rt, 12 h) to yield the corresponding disilyl compound. We initially tried the deprotection of the primary silyl ether with oxone in aqueous methanol (1:1).[12] Unfortunately after stirring for 24 h, we observed that both the silyl groups were deprotected (30%) along with the required

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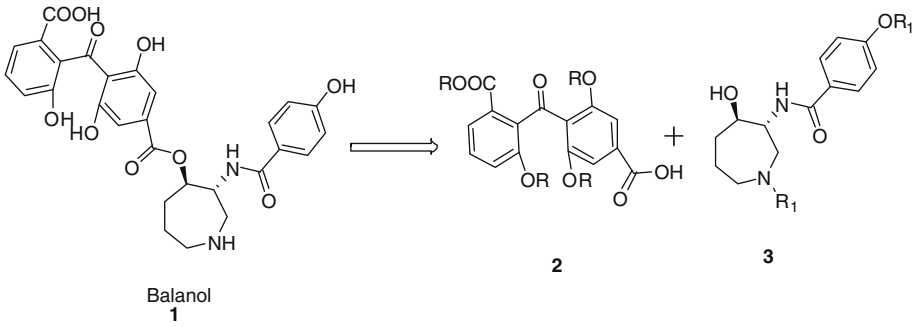
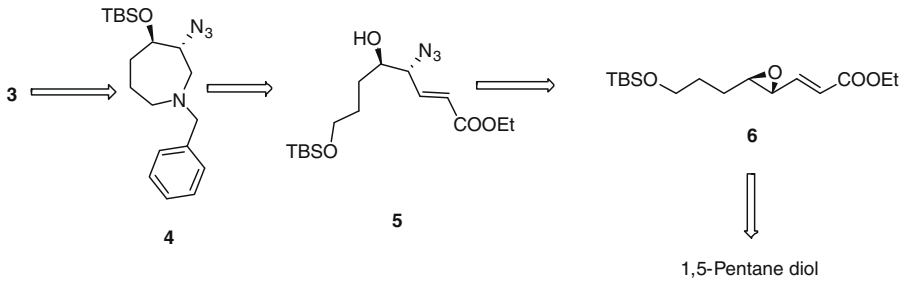
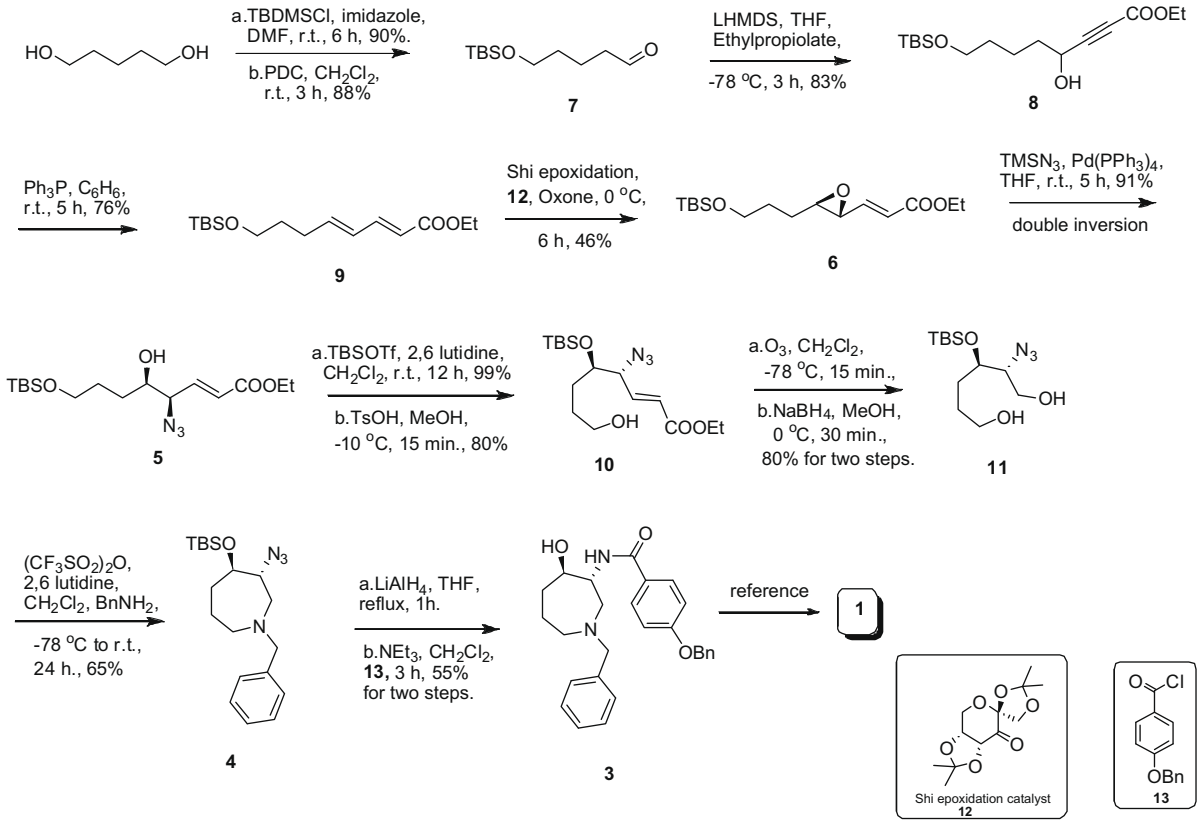


Scheme 1. Retrosynthetic analysis of balanol **1**; R, R_1 are some suitable protecting groups (R_1 = Bn).



Scheme 2.



Scheme 3. Synthesis of azepine **3** of (−)-balanol.

compound **10** (~80% conversion of the starting material). This deprotection was successfully achieved instead with a catalytic amount of *para*-toluenesulfonic acid in methanol at −10 °C, for 15 min,[13] which provided monoalcohol **10** in 80% yields. In one-pot, ozonolysis of compound **5** at −78 °C followed by the reduction ($NaBH_4$, MeOH, 0 °C, 30 min) of the resultant aldehyde to alcohol yielded diol **11** in 80% yield. Diol **11** was treated with trifluoromethanesulfonic anhydride in the presence of 2,6-lutidine (CH_2Cl_2,

−78 °C, 30 min) to form the ditriflate of **11**. This was treated in situ with excess benzylamine (−78 °C to rt) for 24 h to provide the azepine **4** in 65% yield. Lithium aluminum hydride reduction ($LiAlH_4$, THF, 0 °C to reflux, 1 h) of azepine **4** followed by treatment of the resultant hydroxy amine with 4-benzyloxy benzoyl chloride (NEt_3, CH_2Cl_2, 0 °C, 3 h) provided the key intermediate hexahydroazepine **3** (55% yield for two steps), the spectral data for which are in agreement with the literature data.[7v,u]

In conclusion, an efficient formal total synthesis of protein kinase inhibitor balanol is described, starting from the known aldehyde (**7**) in eight steps in high overall yields (6%). Triphenylphosphine-mediated deoxygenative rearrangement of hydroxy alkynoate to the corresponding (*E,E*)-α,β.γ,δ-unsaturated diene ester and its Shi epoxidation followed by Pd(0)-mediated nitrogen substitution with double inversion of configuration were key steps in the construction of the hexahydroazepine **3.**[14]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.120.

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14. *Experimental section and spectral data for some key intermediates*: (*E*)-Ethyl 3-((2*R*,3*R*)-3-(3-(*tert*-butyldimethylsilyloxy) propyl)oxiran-2-yl)acrylate (**6**): A mixture of 5 mL acetonitrile, 10 mL buffer (0.05 M, $Na_2B_2O_4{\cdot}10H_2O$ in EDTA 4×10^{-4} M), 10 mL dimethoxymethane, diene ester **9** (0.8 g, 2.8 mmol), tetrabutylammonium hydrogen sulfate (38 mg, 0.1 mmol), and Shi epoxidation catalyst[9b] **12** (218 mg, 0.9 mmol) was stirred at 0 °C. A solution of Oxone (1.5 g, 3.0 mmol) in 10 mL of 4×10^{-4} M EDTA and a solution of potassium carbonate (1.9 g, 14.0 mmol) in 10 mL of water were added separately and simultaneously, via a syringe pump over a 6h period. The reaction was then immediately quenched by the addition of hexanes (30 mL) and the aqueous layer was further extracted with hexanes (3×20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexanes/ethyl acetate = 25/1, buffered with 1% NEt_3) to afford the compound **6** as a light yellow oil (390 mg, 46% yield) with 96.2% ee (determined by HPLC: Chiralcel OD-H, 98/2 hexanes/*i*PrOH, 254 nm). $[\alpha]_D^{21}$ +20.8 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 6.62 (dd, *J* = 7.1, 15.7 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.65–3.54 (m, 2H), 3.15 (dd, *J* = 1.8, 7.08 Hz, 1H), 2.89–2.86 (m, 1H), 1.69–1.59 (m, 4H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.84 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.6, 144.7, 123.6, 62.3, 61.2, 60.5, 56.3, 28.9, 28.5, 25.9 (3C), 18.2, 14.2,−5.3 (2C); IR (film) ν_{max}: 3021, 2985, 1733, 1374, 1265, 1249, 1216, 1046 cm^{-1}; Mass (ESI, *m*/*z*): 315.4 $(M+H)^+$; HRMS (ESI, *m*/*z*): calcd for $C_{16}H_{30}O_4Si$: 315.1992. found: 315.1995.; *(4R,5R,E)-Ethyl 4-azido-8-(tert-butyldimethylsilyloxy)-5-hydroxyoct-2-enoate* (**5**): To a stirred solution of (*E*)-α,β-unsaturated -γ,δ -epoxy ester **6** (300 mg, 1.0 mmol) in THF (15 mL) were added $TMSN_3$ (0.25 mL, 2.0 mmol) and $Pd(PPh_3)_4$ (126 mg, 0.10 mmol) under nitrogen atmosphere at room temperature and the mixture was stirred for 5 h. Then 2 mL of 10% citric acid in methanol was added to the reaction mixture and stirred for 2 h at room temperature; the solvent was removed under reduced pressure and the crude solid was triturated with diethyl ether (3×10 mL). The combined organic layers were dried over Na_2SO_4, concentrated, and purified by column chromatography (hexanes/ethyl acetate = 1/5) to afford *syn* azido alcohol **5** as a colorless oil (318 mg, 91% yield). $[\alpha]_D^{21}$ −3.2 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 6.80 (dd, *J* = 7.1, 15.6 Hz, 1H), 6.02 (dd, *J* = 1.2, 15.6 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.95–3.91 (m, 1H), 3.67–3.51 (m, 2H), 3.40 (d, *J* = 4.0 Hz, 1H), 1.69–1.57 (m, 3H), 1.48–1.39 (m, 1H), 1.23 (t, *J* = 7.2 Hz, 3H), 0.82 (s, 9H), 0.00 (s, 6H); ^{13}C NMR $CDCl_3$, 100 MHz): δ 165.5, 141.5, 124.8, 73.1, 67.3, 63.2, 60.7, 30.9, 28.8, 25.9 (3C), 18.3, 14.2, −5.4 (2C); IR (neat) ν_{max}: 3430, 2980, 2932, 2108, 1733, 1685, 1450, 1250, 1180 cm^{-1}; Mass (ESI, *m*/*z*): 358.2 $(M+H)^+$; HRMS (ESI, *m*/*z*): calcd for $C_{16}H_{32}N_3O_4Si$: 358.2162. found: 358.2151.; *N*-((3*R*,4*R*)-1-Benzyl-4-hydroxyazepan-3-yl)-4-(benzyloxy) benzamide (**3**): To a stirred solution of $LiAlH_4$ (31 mg, 0.8 mmol) in 6 mL dry THF at 0 °C was slowly added azepine **4** (100 mg, 0.28 mmol, in 2 mL THF) and stirred at reflux for 1 h under nitrogen atmosphere. The reaction was cooled to 0 °C and Glaubler's salt (sodium sulfate decahydrate) was slowly added to precipitate the aluminum salts and then filtered on a Celite pad. Celite cake was washed with ethyl acetate (2×5 mL) and the filtrate was dried over anhyd Na_2SO_4, concentrated under reduced pressure to provide the crude azepine core with free hydroxyl and amine functionalities. This crude azepine was used for the amide bond formation without further purification. Azepine amine (50 mg, 0.02 mmol) was dissolved in CH_2Cl_2 (5 mL) and was added to triethylamine (0.12 mmol, 0.12 mL) and 4-benzyloxybenzoylchloride (56 mg, 0.02 mmol) at 0 °C under nitrogen atmosphere and stirred for 3 h. Water (5 mL) was added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted (2×10 mL) with dichloromethane and the combined organic layers were washed with brine (10 mL), dried over sodium sulfate, and concentrated under reduced pressure to give the crude product. This crude mixture was purified by silica gel column chromatography (hexanes/ethyl acetate = 1/2) to yield compound **3** as a yellow viscous liquid (67 mg, 55% for two steps). $[\alpha]_D^{23}$ −5.6 (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.47–7.38 (m, 4H), 7.37–7.23 (m, 8H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.61 (d, *J* = 6.8 Hz, 1H), 5.12 (s, 2H), 3.90–3084 (m, 1H), 3.77–3.74 (m, 1H), 3.71 (d, *J* = 12.8 Hz, 1H), 3.42 (d, *J* = 12.8 Hz, 1H), 3.04–2.98 (m, 1H), 2.95 (dd, *J* = 2.8, 14.4 Hz, 1H), 2.72 (dd, *J* = 2.9, 14.4 Hz, 1H), 2.53-2.44 (m, 1H), 1.94-1.85 (m, 2H), 1.71–1.69 (m, 1H), 1.68–1.57 (m, 1H); ^{13}C

NMR ($CDCl_3$, 100 MHz): δ 167.6, 161.3, 139.6, 136.3, 129.4 (2C), 128.9, 128.8 (2C), 128.7 (2C), 128.2 (2C), 127.5 (2C), 127.4 (2C), 126.5, 114.5 (2C), 77.4, 76.5, 64.1, 59.4, 57.5, 53.8, 31.2, 24.6. IR (film) ν_{max}: 3407, 3376, 2955, 1638, 1611, 1296, 1140 cm^{-1}; Mass (ESI, m/z): 431.2 $(M+H)^+$; HRMS (ESI, m/z): calcd for $C_{27}H_{31}N_2O_3$: 431.2335, found: 431.2328.