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Ring expansion approach for the synthesis of the (3*S*,4*S*)-hexahydroazepine core of balanol and ophiocordin☆

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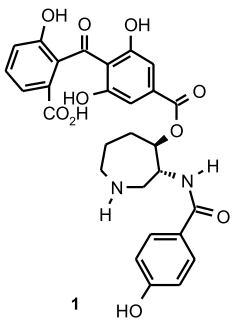
Abstract—A new and efficient formal total synthesis of (3*S*,4*S*)-balanol, a potent protein kinase C inhibitor, was accomplished from tri-*O*-acetyl-D-glucal. Balanol and ophiocordin consists of a chiral hexahydro azepine-containing fragment and a benzophenone fragment. The azepine core was prepared in chiral form through intramolecular aza Wittig reaction. A triphenylphosphine mediated ring expansion process was employed to form the seven-membered nitrogen heterocycle. The aldehyde equivalent key intermediate was treated with triphenylphosphine to give the azepine core. To demonstrate the applicability of the new route, a synthesis of the balanol is described.

1. Introduction

Protein kinase C (PKC) closely related to a family of core enzymes (serine/threonine specific protein kinases), is a key element in the wide range of cellular responses including oncogenesis and inflammation.[1,2] It can be activated by diacylglycerol[3] or tumor promoting phorbol ester,[4,5] and it has the ability to phosphorylate lipocortin.[6,7] Protein phosphorylation mediated by PKC is a critical step in the signal transduction cascades controlling processes such as cellular proliferation and gene expression,[8] and the enzyme has been implicated in the progression of a wide variety of diseases, such as cancer, cardiovascular disorders, asthma, diabetes, central nervous system dysfunction, inflammation, rheumatoid arthritis and HIV infection. Consequently, the identification of potent and selective PKC inhibitors may not only serve to further illuminate signal transduction pathways but also may result in the development of novel drug with a unique therapeutic approach to these diseases.[9] Although several inhibitors of PKC have been reported,[10] they are either highly toxic or not very potent.

Balanol **1**, a metabolite which is produced in trace amounts by the fungus *Verticillium balanoides*[11] and *Fusarium merismoides*,[12] selectively and potently inhibited human PKC enzymes α, β-I, β-II, γ, δ, ε, and η with an IC_{50} value of 4–9 nM. Such an endeavor may not only provide useful tools for illuminating signal transduction pathways involving PKC, but may also result in the introduction of novel drugs with considerable therapeutic value. Due to its high inhibitory activity in the nanomolar range, combined structural novelty and low availability of the compound has generated substantial interest in the development of synthetic approaches to the natural material and related structures. The synthetic community responded quickly to the challenge of preparing balanol and analogues. Systematic structural modifications of balanol were carried out for the development of promising analogues[13] with therapeutic applications. Modification of the azepine ring system resulted in several interesting lead compounds with potent enzyme and cellular activity during the continuing lead optimization study at Sphinx pharmaceuticals, now a part of Eli Lilly.[14]



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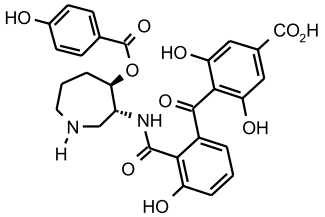

2

We have recently provided two efficient approaches including shortest route to the (3*R*,4*R*)-hexahydroazepine ring of balanol.[18m] Considerable modifications of the azepine ring of the balanol can be tolerated with certain cases resulting in an increase in biological activity. Hence,

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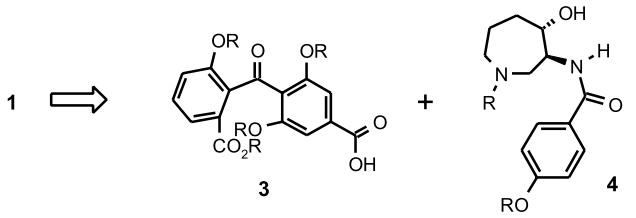
in continuation of our two formal total syntheses of (3*R*,4*R*)-balanol, we herein describe a novel and efficient approach for the synthesis of the (3*S*,4*S*)-azepine segment of balanol and its regio isomer, antibiotic ophiocordin[15] **2** from tri-*O*-acetyl-D-glucal. Balanol consists of two distinct structural domains, a chiral hexahydroazepine-containing fragment and a benzophenone fragment (Scheme 1).



Scheme 1.

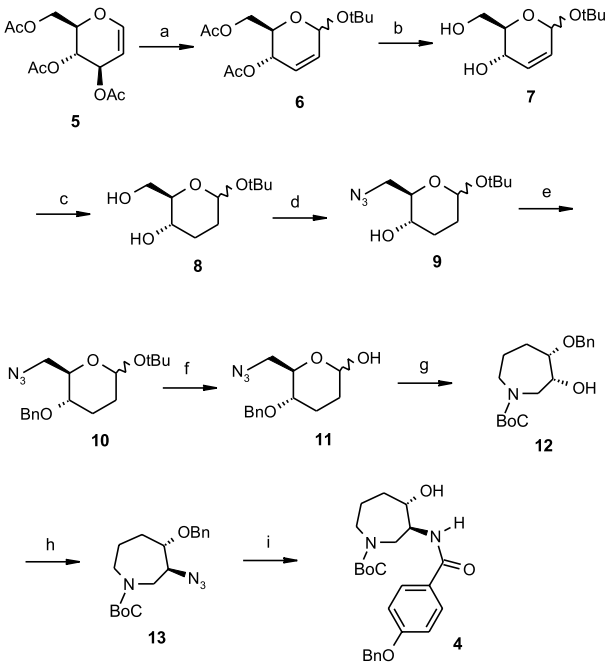
Total syntheses of balanol were achieved by Nicolaou's group and by researchers at Sphinx and at Rhone-Poulenc Rorer.[16] The hexahydroazepine has been targeted in several formal synthesis of balanol[17] Our synthetic approach includes the preparation of the (3*S*,4*S*)-hexahydroazepine segment **4** through ring expansion of six-membered ring into seven-membered ring using triphenylphosphine.

2. Results and discussion: ring expansion approach and chiral hexahydroazepine synthesis

Strategies involving aza Wittig reactions have become useful tools in organic synthesis. Particularly, the intramolecular aza Wittig approach could be applied for the construction of various type of cyclic nitrogen heterocycles. The synthesis of **4** began with tri-*O*-acetyl-D-glucal **5** as shown in Scheme 2. Accordingly tri-*O*-acetyl-D-glucal was obtained from D-glucose by a known literature procedure.[18]

Ferrier rearrangement of tri-*O*-acetyl-D-glucal **5** with *tert*-butyl alcohol in DCM provided the desired *tert*-butyl ether **6**. Removal of acetyl groups from **6** with K_2CO_3 in aq. methanol afforded the free diol **7** in quantitative yield. The double bond in the diol was hydrogenated with 5% Pd/C in ethyl acetate to afford the saturated diol **8** in good chemical yield (92%). The primary hydroxyl of the diol **8** was tosylated, followed by the displacement with NaN_3 in DMF to furnish the azido alcohol **9**. The free hydroxy functionality of the azidoalcohol was protected as its benzyl ether using BnBr, NaH to give compound **10**. The cleavage of the *tert*-butyl ether group from **10** with 60% AcOH, and cat. dil. H_2SO_4, afforded the key intermediate **11**. Aldehyde equivalent **11** was treated with TPP in toluene at reflux temperature. After completion of the reaction toluene was removed and the resulting crude imine was subjected to reduction with $NaBH_4$ in methanol.

The resultant amine was protected in situ with BOC_2O, TEA to afford the azepine segment **12**. Subsequent conversion of its secondary alcohol into an azido group to get **13** was achieved via treatment with Tf_2O and 2,6-lutidine followed by NaN_3 displacement. Alternatively the desired product **13** can be obtained with MsCl, TEA followed by NaN_3 treatment. The final elaboration of the targeted hexahydroazepine moiety **4** of balanol is very straightforward. Hydrogenation of **13** in ethyl acetate liberated the amino group from its azido surrogate, and simultaneously deprotected the benzyl ether function with PtO_2. Acylation of the resulting amino alcohol with *p*-benzyloxybenzoylchloride delivers the product **4**, which is directly amenable to the total synthesis of balanol.



Scheme 2. *Reagents and conditions*: (a) *t*-BuOH, CH_2Cl_2, $BF_3{\cdot}Et_2O$, 10°C (95%); (b) K_2CO_3, MeOH/H_2O, rt (quantitative); (c) H_2, Pd/C, EtOAc, rt (92%); (d) *p*-TsCl, TEA, CH_2Cl_2, 0°C then NaN_3, DMF, 80°C (90%); (e) BnBr, NaH, THF, Bu_4NI, rt (97%); (f) 60%AcOH, cat. dil. H_2SO_4, 70°C (95%); (g) TPP, Toluene, reflux, then toluene was removed, $NaBH_4$, MeOH, 0°C, then $(Boc)_2O$, TEA, rt (75%); (h) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0°C, then NaN_3, DMF (91%) (or) MsCl, TEA, CH_2Cl_2, 0°C, then NaN_3, DMF, 80°C (97%); (i) H_2, Pt_2O, EtOAc, rt, then *p*-benzyloxybenzoyl chloride, TEA, CH_2Cl_2, 0°C to rt (53%).

3. Conclusion

In summary we have described efficient synthesis of the balanol heterocycle from tri-*O*-acetyl-D-glucal which incorporated a novel ring expansion process to the seven-membered azepine core. It is noteworthy that the aforementioned synthetic strategy for the hexahydroazepine fragment is particularly suitable for the analogue generation. This approach offers readily available starting materials at low cost and simple experimental conditions. Further work is currently ongoing.

4. Experimental

4.1. General

Unless otherwise stated, all reactions were carried out under nitrogen and dry glassware. THF was dried and freshly distilled over sodium/benzophenone. Dichloromethane and DMF were freshly distilled over P_2O_5 and $CaSO_4$, respectively. Reactions were monitered by thin-layer

chromatography (TLC) analysis. IR spectra were recorded as neat thin film on Perkin–Elmer I spectrometer. ^1H and ^{13}C were recorded on Varian Gemini-200 MHz or Avance-300 MHz spectrophotometers in $CDCl_3$ using TMS as internal standard.

4.1.1. 6-(*tert*-Butoxy)-3-methylcarbonyloxy-(2*R*,3*S*)-3,6-dihydro-2*H*-2-pyranylmethyl acetate (6). Compound **5** (12.5 g, 45.9 mmol) and *t*-butyl alcohol (7 ml, 91.9 mmol) were dissolved in dry DCM (100 ml) cooled in an ice bath (10°C) and treated with catalytic $BF_3{\cdot}Et_2O$ (0.3 ml). After stirring the reaction mixture for 12 h at ambient temperature, reaction mixture was quenched with saturated sodium bicarbonate, and extracted with DCM. Organic layer was washed with water, brine and dried over Na_2SO_4. Volatiles were removed under reduced pressure. Crude compound was purified using column chromatography with 3% EtOAc, in hexane as eluent to furnish **6** (12.25 g, 95% yield) as a pale yellow liquid. $[\alpha]_D$=+100.69 (*c* 0.75, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz): δ 1.25 (s, 9H, OC(C*H*$_3$)$_3$), 2.05 (s, 6H, OCOC*H*$_3$, OCOC*H*$_3$), 4.10 (m, 3H, C*H*$_2$OAc, *H*CO), 5.20 (m, 2H, C*H*Ot-Bu, C*H*OAc), 5.75 (m, 2H, C*H*=C*H*). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.9, 170.5, 129.9, 128.4, 89.2, 75.5, 66.8, 65.5, 63.5, 29.0, 21.2, 21.0. IR (Neat) (cm^{-1}): 2976, 1746, 1436, 1370, 1236, 1195, 1099, 1044, 1025, 982, 891, 774. Mass: [M$^-$otBu]+($C_{10}H_{13}O_5$) theoretical mass 213.0763, found 213.0770. [M$^-$otBu–AcOH]+($C_8H_9O_3$) theoretical mass 153.0551, found 153.0543. Anal. calcd for $C_{14}H_{22}O_6$: C 58.73, H 7.74, found: C 58.64, H 7.83.

4.1.2. 6-(*tert*-Butoxy)-2-hydroxymethyl-(2*R*,3*S*)-3,6-dihydro-2*H*-3-pyranol (7). A well-stirred solution of **6** (5 g, 17.45 mmol) in MeOH/H_2O (50 ml) was added K_2CO_3 (7.25 g, 52.4 mmol) at room temperature. After stirring for 12 h, the reaction mixture was filtered off through a sintered funnel. Methanol was removed under reduced pressure and compound was extracted with EtOAc, to give **7** (3.5 g) as a colorless solid in quantitative yield. $[\alpha]_D$=+38.63 (*c* 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz): δ 1.25 (s, 9H, OC(C*H*$_3$)$_3$), 3.80 (m, 3H, C*H*$_2$OAc, *H*CO), 4.10 (m, 1H, C*H*OH), 5.25 (bs, 1H, OC*H*O), 5.60 (m, 1H, C*H*=), 5.90 (m, 1H, C*H*=). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 132.9, 127.6, 88.9, 75.2, 71.0, 63.8, 62.5, 28.8. IR (Neat) (cm^{-1}): 3418, 2975, 2927, 1645, 1368, 1193, 1042, 771. Mass: [M$^-$otBu]+($C_6H_9O_3$) theoretical mass 129.0551, found 129.0549. Anal. calcd for $C_{10}H_{18}O_4$: C 59.39, H 8.97, found: C 59.21, H 9.07.

4.1.3. 6-(*tert*-Butoxy)-2-hydroxymethyl-(2*R*,3*S*)-tetrahydro-2*H*-3-pyranol (8). Pd/C (5%, w/w) is added to a solution of compound **7** (1.5 g, 7.42 mmol) in dry ethyl acetate (7 ml), and the resulting suspension is stirred under H_2 for 12 h. The catalyst is filtered off through a pad of celite, which is carefully rinsed with ethyl acetate in several portions. Evaporation of the solvent under reduced pressure and column chromatographed with 25% EtOAc in hexane as eluent furnished **8** (1.4 g, 92% yield) as a colorless viscous liquid. $[\alpha]_D$=+116.22 (*c* 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz): δ 1.25 (s, 9H, OC(C*H*$_3$)$_3$), 1.70 (m, 2H, C*H*$_2$), 1.85 (m, 2H, C*H*$_2$), 3.50–3.70 (m, 4H, C*H*$_2$OH, *H*CO, C*H*OH), 5.05 (bs, 1H, OC*H*O). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 90.5, 74.2, 72.5, 69.9, 62.7, 30.9, 28.8, 26.8. IR (Neat) (cm^{-1}): 3428, 2927, 1726, 1176, 1044, 770. Mass: [M$^-$C$_4$H$_8$]+($C_6H_{12}O_4$) theoretical mass 148.0735, found 148.0726. Anal. calcd for $C_{10}H_{20}O_4$: C 58.80, H 9.87, found: C 58.58, H 9.92.

4.1.4. 2-Azidomethyl-6-(*tert*-butoxy)-(2*R*,3*S*)-tetrahydro-2*H*-3-pyranol (9). To a well-stirred solution of **8** (2 g, 9.8 mmol) in dry DCM (25 ml) was added triethylamine (1.36 ml, 9.8 mmol) followed by *p*-toluene sulphonyl chloride (1.86 g, 9.8 mmol) at 0°C. The reaction mixture was stirred for 6 h at the same temperature. The CH_2Cl_2 was removed under reduced pressure and crude sulphonate was dissolved in dry DMF (7 ml) and treated with sodium azide (3.18 g, 49 mmol). The reaction mixture was stirred further for 12 h at 80°C. After completion of the reaction, it was extracted with ether (3×50 ml). Combined organic layer was washed with water, brine and dried over Na_2SO_4. After removing the volatiles under reduced pressure, crude azide was purified by column chromatography with 7% EtOAc in hexane as eluent to furnish **9** (2 g, 90% yield) as a colorless liquid. $[\alpha]_D$=+69.91 (*c* 0.75, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz): δ 1.20 (s, 9H, OC(C*H*$_3$)$_3$), 1.70 (m, 2H, C*H*$_2$), 1.80 (m, 2H, C*H*$_2$), 3.40 (m, 3H, C*H*$_2$N$_3$, C*H*OH), 3.75 (m, 1H, *H*CO), 5.05 (bs, 1H, OC*H*O). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 90.4, 74.4, 72.3, 67.6, 52.2, 30.8, 28.6, 27.3. IR (Neat) (cm^{-1}): 3415, 2972, 2100, 1590, 1440, 1348, 1288, 1196, 1121, 1042, 989, 922, 590. Mass: [M–C$_4$H$_8$]+($C_6H_{11}N_3O_3$) theoretical mass 173.0800, found 173.0808. Anal. calcd for $C_{10}H_{19}N_3O_3$: C 52.39, H 8.35, N 18.33, found: C 52.02, H 8.13, N 18.02.

4.1.5. 2-Azidomethyl-3-benzyloxy-6-(*tert*-butoxy)-(2*R*,3*S*)-tetrahydro-2*H*-pyran (10). To a well-stirred suspension of freshly activated NaH (0.225 g, 9.375 mmol) in dry THF (5 ml), a solution of **9** (1.75 g, 7.6 mmol) in dry THF was added dropwise at 0°C. After 30 min, BnBr (1.15 ml, 9.9 mmol) and catalytic Bu_4NI (0.28 g, 0.75 mmol) were added and the reaction mixture was stirred for 3 h. Then aq. NH_4Cl solution was added to quench the reaction, THF layer was separated and the aqueous layer was extracted with ether (3×30 ml). The combined organic layer was washed with water, brine and dried over Na_2SO_4. After removing the volatiles under reduced pressure, crude benzyl ether was purified by column chromatography with 3% EtOAc in hexane as eluent to furnish **10** (2.3 g, 95% yield) as a colorless liquid. $[\alpha]_D$=+106.01 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 1.25 (s, 9H, OC(C*H*$_3$)$_3$), 1.65–2.05 (m, 4H, C*H*$_2$–C*H*$_2$), 3.25–3.45 (m, 3H, C*H*$_2$N$_3$, C*H*OBn), 3.95 (m, 1H, *H*CO), 4.40 (d, 1H, *J*=12 Hz, C*H*$_2$Ph), 4.60 (d, 1H, *J*=12 Hz, C*H*$_2$Ph), 5.05 (bs, 1H, OC*H*O), 7.25 (m, 5H, C$_6$*H*$_5$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.5, 128.5, 128.4, 127.6, 127.5, 90.2, 70.4, 70.2, 70.1, 50.2, 30.1, 28.2, 20.3. IR (Neat) (cm^{-1}): 2974, 2100, 1456, 1364, 1270, 1195, 1097, 1005, 914, 739, 698. Mass: [M–C$_4$H$_9$ON$_2$]+($C_{13}H_{16}NO_2$) theoretical mass 218.1181, found 218.1175. Anal. calcd for $C_{17}H_{25}N_3O_3$: C 63.93, H 7.89, N 13.16, found: C 63.91, H 7.75, N 12.84.

4.1.6. 6-Azidomethyl-5-benzyloxy-(5*S*,6*R*)-tetrahydro-2*H*-2-pyranol (11). Compound **10** (1.5 g, 4.7 mmol) was treated with 60% acetic acid (15 ml) and catalytic 50% sulphuric acid (0.2 ml). The reaction mixture was warmed at

70°C using water bath for 30 min. After completion of reaction it was quenched with saturated sodium bicarbonate solution and extracted with EtOAc. Organic layer was washed with water, brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure and was column chromatographed with 15% EtOAc in hexane as eluent furnished **11** (1.15 g, 95% yield) as a colorless liquid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.80 (m, 4H, C*H*$_2$–C*H*$_2$), 3.40 (m, 3H, C*H*$_2$N$_3$, C*H*OBn), 4.00 (m, 1H, *H*CO), 4.40 (d, 1H, J=10.4 Hz, C*H*$_2$Ph), 4.60 (d, 1H, J=10.4 Hz, C*H*$_2$Ph), 5.25 (bs, 1H, OC*H*O), 7.30 (m, 5H, C$_6$*H*$_5$). IR (Neat) (cm^{-1}): 3416, 2938, 2121, 1725, 1632, 1496, 1455, 1351, 1289, 1219, 1106, 989, 903, 817, 749, 703.

4.1.7. *tert*-Butyl 4-benzyloxy-3-hydroxy-(3*R*,4*S*)-azipane-1-carboxylate (12). To a stirred solution of **11** (1 g, 3.8 mmol) in dry toluene (15 ml) was added triphenyl phosphene (1.49 g, 5.7 mmol). The reaction mixture was stirred under reflux for 12 h. Evaporation of the solvent provide the crude imine, which was used in the subsequent step without further purification. The crude imine was dissolved in anhydrous methanol (10 ml) cooled to 0°C and treated with sodium borohydride (0.15 g, 3.95 mmol). The reaction mixture was stirred for 5 h at room temperature. The resulting secondary amine was protected in situ with $(Boc)_2O$ (1 g, 4.55 mmol) and triethyl amine (0.79 ml, 5.7 mmol) at room temperature. After stirring for 6 h at ambient temperature volatiles were removed under reduced pressure. The crude azepine compound **12** was extracted with ethyl acetate and washed with water, brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure and column chromatographed with 7% EtOAc in hexane as eluent furnished **12** (0.9 g, 75% yield from 10) as a colorless liquid. $[\alpha]_D$=+35.2 (*c* 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.45 (s, 9H, OC(C*H*$_3$)$_3$), 1.50–2.10 (m, 4H, C*H*$_2$–C*H*$_2$), 2.90–3.85 (series of multiplets, 6H, C*H*$_2$NBOC, C*H*$_2$NBOC, C*H*OH, C*H*OBn), 4.55 (m, 2H, C*H*$_2$Ph), 7.25 (m, 5H, C$_6$*H*$_5$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.9, 138.2, 128.4, 127.7, 127.6, 85.8, 80.1, 76.0, 73.1, 70.5, 46.2, 28.4, 26.3, 20.8. IR (Neat) (cm^{-1}): 3448, 2974, 2932, 2870, 1691, 1523, 1476, 1454, 1414, 1366, 1248, 1168, 1105, 1066, 890, 738, 699. FABMS: *m*/*z* 322 (M+1). Anal. calcd for $C_{18}H_{27}NO_4$: C 67.26, H 8.47, N 4.36, found: C 67.02, H 8.25, N 4.02.

4.1.8. *tert*-Butyl 3-azido-4-benzyloxy-(3*S*,4*S*)-azepene-1-carboxylate (13). Compound **12** (0.375 g, 1.16 mmol) and 2,6-lutidine (0.16 ml, 1.4 mmol) were dissolved in dry DCM (5 ml) cooled in an ice bath and treated with Tf_2O (0.21 ml, 1.28 mmol). After stirring for 16 h, the mixture was recooled and treated with 2,6-lutidine (0.16 ml, 1.4 mmol) followed by triflic anhydride (0.21 ml, 1.28 mmol). After completion of the reaction solvent was removed and crude triflate was dissolved in dry DMF (3 ml) and treated with NaN_3 (0.38 g, 5.8 mmol) and stirred for 3 days at ambient temperature. The reaction mixture was extracted with ether (3×25 ml), combined organic layer was washed with water, brine and dried over Na_2SO_4. Concentrated and column chromatographed to get **13** (0.36 g, 91% yield) as a colorless liquid. The compound **13** could also be synthesized using MsCl, TEA followed by NaN_3 displacement. $[\alpha]_D$=−12.5 (*c* 0.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.45 (s, 9H, OC(C*H*$_3$)$_3$), 1.60 (m, 2H, C*H*$_2$), 1.95 (m, 2H, C*H*$_2$), 2.95–3.82 (series of multiplets, 6H, C*H*$_2$NBOC, C*H*$_2$NBOC, C*H*N$_3$, C*H*OBn), 4.60 (m, 2H, C*H*$_2$Ph), 7.30 (m, 5H, C$_6$*H*$_5$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.5, 137.8, 128.3, 127.8, 127.7, 82.7, 80.1, 71.5, 65.2, 64.2, 45.4, 28.3, 27.2, 21.7. IR (Neat) (cm^{-1}): 2932, 2104, 1693, 1410, 1257, 1164. FABMS: *m*/*z* 347 (M+1). Anal. calcd for $C_{18}H_{26}N_4O_3$: C 62.41, H 7.56, N 16.17, found: C 62.24, H 7.32, N 16.02.

4.1.9. *tert*-Butyl 3-(4-benzyloxy phenyl carboxamido)-4-hydroxy-(3*S*,4*S*)-azepane-1-carboxylate (4). PtO_2 (5%, w/w) is added to a solution of compound **13** (110 mg, 0.317 mmol) in ethyl acetate (5 ml), and the resulting suspension is stirred under H_2 atmosphere for 14 h. The catalyst was filtered off through a pad of celite. Evaporation of the solvent provides amine, which is used in the subsequent step without further purification. The benzyloxy benzoyl chloride (77 mg, 0.317 mmol) is added to a solution of crude amine prepared as described above. After stirring for 2 h at room temperature the reaction mixture was extracted with ethyl acetate. After usual workup, solvent was evaporated under reduced pressure. Purification of the crude product by 50% ethylacetate in hexane provided the title compound **4** (73 mg, 53% over both steps). $[\alpha]_D$=+2.3 (*c* 0.9, CH_3OH). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.30 (s, 9H, OC(C*H*$_3$)$_3$), 1.57–1.95 (m, 4H, C*H*$_2$–C*H*$_2$), 2.60 (m, 1H, C*H*NHCO), 3.45 (m, 1H, C*H*$_2$NCO), 3.70 (m, 1H, C*H*$_2$NCO), 4.30–4.45 (m, 3H, C*H*OH, C*H*$_2$NCO), 5.10 (s, 2H, C*H*$_2$Ph), 6.98 (d, 2H, J=8.8 Hz, COC$_6$*H*$_4$–), 7.20–7.47 (m, 5H, C$_6$*H*$_5$), 7.95 (d, 2H, J=8.8 Hz, COC$_6$*H*$_4$–), 8.09 (s, 1H, N*H*CO). FABMS: *m*/*z* 441 (M+1). Anal. calcd for $C_{25}H_{32}N_2O_5$: C 68.16, H 7.32, N 6.36, found: C 68.04, H 7.18, N 6.04.

Acknowledgements

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