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ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 2661–2665

Enantioselective synthesis of aminobenzazepinones

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Received 22 January 2007; revised 7 February 2007; accepted 15 February 2007
Available online 20 February 2007

Abstract—Enantioselective synthesis of constrained *trans*-aminobenzazepinone utilizing palladium-mediated Jeffery–Heck reaction and rhodium(II) catalyzed asymmetric hydrogenation as key steps are described. Diverse functional groups such as alkyl, aryl, basic or amino acid moieties were introduced with minimal racemization.

Design approaches involving structural and conformational changes in the ligand of ligand-receptor/acceptor interaction can provide important insights that can lead to critical tests of pharmacophore hypotheses.[1] Constraining the ligand to prefer a particular backbone conformation is an established strategy in the design of more selective and/or more potent peptides with improved pharmacokinetic profile as GPCR modulators or enzyme inhibitors. Compounds containing side chain constrained amino acids such as Freidinger's γ-lactam,[2] tetrahydroisoquinoline-3-carboxylic acid (Tic)[3] or an aminobenzazepinone[4] are particularly valuable in probing the active site of a biological target where crystal structure data are not available. As illustrated in Figure 1, each side chain χ^1 torsional angle can assume three low energy, staggered conformations: gauche (−) ($\chi^1 = -60°$); gauche (+) ($\chi^1 = +60°$); and trans ($\chi^1 = 180°$). Synthesis of conformationally constrained tyrosine- glycine-, phenylalanine–glycine dipeptide mimetics had been described in the literature.[5] In these approaches the presence of neighboring oxazolidinone moiety is critical, as it serves as a source of *N*-acyliminium ion (Fig. 2) which then undergoes intermolecular Pictet–Spengler cyclization in the presence of tin tetrachloride[6] or trifluoromethanesulfonic acid (TFMSA).[7]

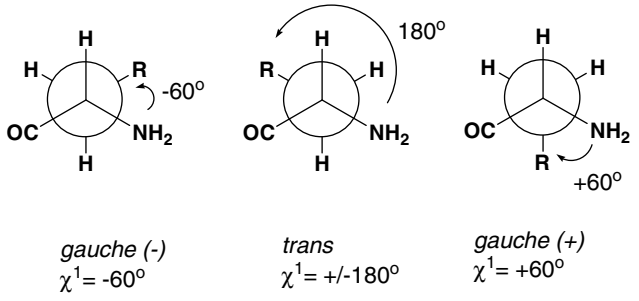

Figure 1. Newman projections of three staggered χ^1 rotamers in L-amino acids.

Figure 2. Cyclization through *N*-acyliminium ion.

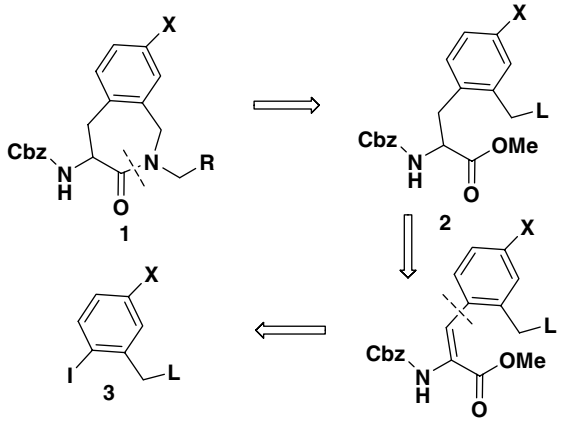

Figure 3. Retrosynthesis of benzazepinone.

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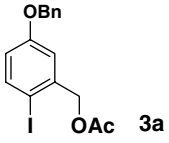
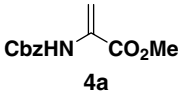
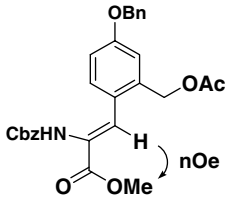
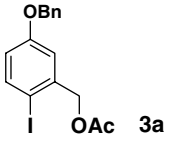
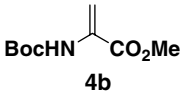
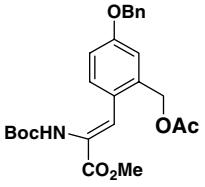
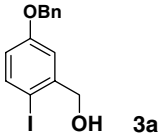
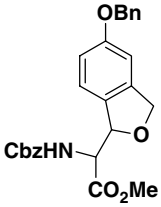
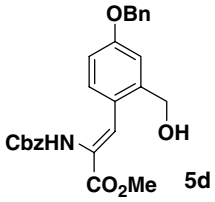
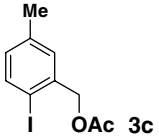
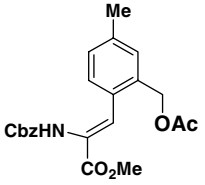
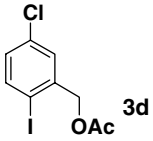
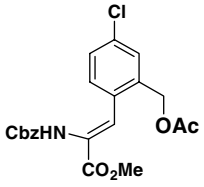
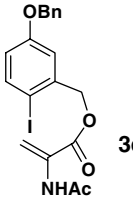
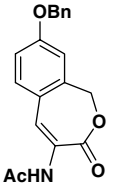
doi:10.1016/j.tetlet.2007.02.078

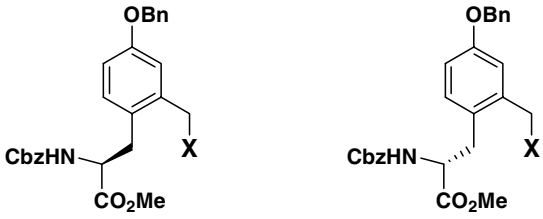
In connection with a medicinal chemistry program, we were interested in the synthesis of *trans*-benzazepinone represented by **1** with a diverse array of substituents (R = alkyl, aryl, amino acids or basic moieties) in enantiomerically pure form. Our retro synthetic bond disconnection is shown in Figure 3. A leaving group at the benzylic position could easily be displaced with a number of amines. The synthesis of key intermediate **2** with a leaving group would follow through a tandem palladium mediated Jeffery–Heck coupling[8,9] of aryl iodide **3** with dehydroamino acid **4** followed by asymmetric hydrogenation mediated by rhodium(II)-based chiral catalysts.[10] Iodide functionality needed for Jeffery–Heck coupling could be introduced regioselectively under the directing influence of functional group X. Successful implementation of this strategy is described below.

Aryl iodides **3a**–**c** were synthesized regioselectively with iodine monochloride in 62–85% yield.[11] The aryl iodide was coupled to dehydroamino acid **4a**–**b** in the presence of tetrabutylammonium chloride and a base ($NaHCO_3$, K_2CO_3 or Et_3N) mediated by 5–10 mol % of palladium(II) acetate in refluxing THF or DMF (Table 1). The coupled products **5a**–**f** were obtained as a single iso-

Table 1. Jeffery–Heck coupling of aryl iodide with dehydroamino acids

Entry	Aryl iodide	Dehydroamino acid	Enamide	Yield[b] (%)
1	 **3a**	 **4a**	 **5a**	74[a,c]
2	 **3a**	 **4b**	 **5b**	79[a,c]
3	 **3a**	**4a**	 **5c**  **5d**	57 (**5c**)[a] 16 (**5d**)[a]
4	 **3c**	**4a**	 **5e**	67[a]
5	 **3d**	**4a**	 **5f**	42[a]
6	 **3e**		 **5g**	59[d]

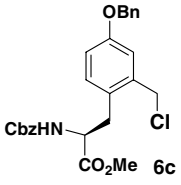
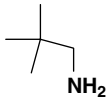
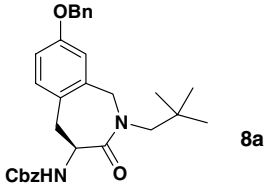
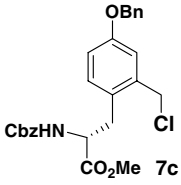
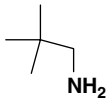
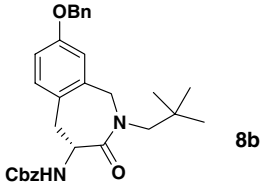
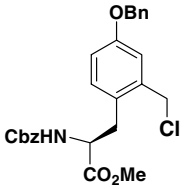
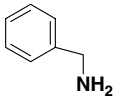
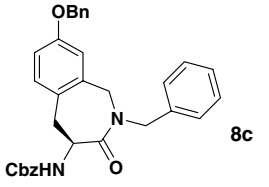
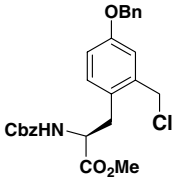
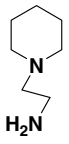
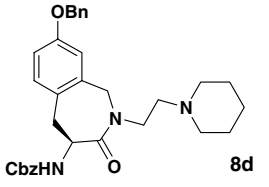
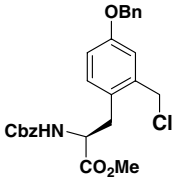
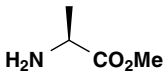
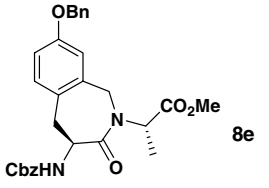
[a] Reaction conditions: 70 °C for 2.5 h, 1.1 equiv Bu_4NCl, 0.05 mol % $Pd(OAc)_2$, 1.3 equiv dehydroamino acid, 3.0 equiv Et_3N, in THF.
[b] Yields refer to weight of product obtained after flash chromatography. All of the examples in the Table were >95% pure as determined by ^1H NMR.
[c] ^3J (H_{vinyl}, $C_{carbonyl}$) = 6.7 Hz.
[d] Purified by Prep HPLC.



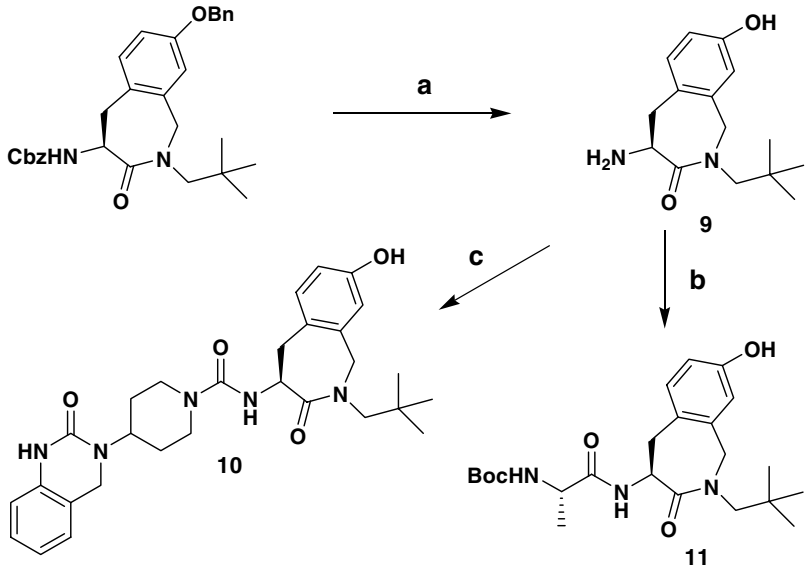
Scheme 1. Reagents and conditions: (a) $Mg(OMe)_2$, $CHCl_3$–MeOH (2:1), 99% and (b) $SOCl_2$, CH_2Cl_2, 86%.

mer with (*Z*)-stereochemistry in 42–79% yield. The geometry of the double bond for Heck coupled products was determined by the proton coupled ^{13}C NMR experiments using a gated decoupled pulse sequence. The observed H–C three-bond coupling constant (^3J H_{vinyl},$C_{methyl\ acetate\ carbonyl} = 6.9$ Hz) is consistent with the *cis*-$^3J_{COOR,\ H}$ coupling.[12] The (*Z*)-configuration was further supported by the observed NOE between the vinyl proton and the methyl protons on the acetate group. As shown in Table 1, alkoxy, alkyl groups and chloride functionality on the aryl iodide are compatible with the reaction conditions. Both Cbz- and Boc-protected dehydroamino acids provided enamides in 60–79% yield. Not surprisingly, in the absence of an *O*-acetate protecting group (entry 3), dihydroisobenzofuran **5c** was obtained as a major product. The stereochemistry of (*Z*)-alcohol was confirmed by treating the minor alcohol **5d** with acetic anhydride and comparing with the spectral properties of **5a**. Aryl iodide **3f** also coupled efficiently when an acrylate moiety was delivered in an intramolecular fashion (entry 6).[13] Asymmetric hydrogenation of (*Z*)-alkyl substituted enamides were carried out either with (+)-1,2-bis((2*S*,5*S*)-2,5-diethylphospholano)benzene(cyclooctadiene)rhodium(II) tetrafluoroborate[10] or its (*R*,*R*)-enantiomer in dichloromethane or in

Table 2. Alkylation and cyclization of benzylic chlorides

Entry	Benzylic chloride	Amine	Azepinone	Yield[c] (%)
1				91[a]
2				93[a]
3				91[a]
4				97[b]
5				42[b]

[a] Reaction conditions: alkylation with 3.0 equiv of amine in CH_2Cl_2 at rt for 24 h and then reflux in 10% acetic acid in toluene.
[b] Reaction conditions: alkylation with 1.5 equiv of amine, 1.0 equiv K_2CO_3 in CH_3CN at rt for 24 h and then reflux in 10% acetic acid in toluene.
[c] Refers to combined yield of alkylation and cyclization. All of the examples in the Table were >95% pure as determined by ^1H NMR.



Scheme 2. Reagents and conditions: (a) 10% Pd on carbon, MeOH, 97%; (b) Boc alanine–OH, CH_2Cl_2, 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate, triethylamine, 76%; (c) *N*,*N*′-disuccinimidylcarbonate, 3-(piperidin-4-yl)-3,4-dihydroquinazolin-2-(1*H*)-one, CH_2Cl_2, 87%.

1:1 dichloromethane–methanol to give the reduced chiral product in >95% yield. Chiral HPLC analysis of amino acid esters **6a** and **7a** suggested that reduction proceeded in >99% ee.[14] The absolute configuration of hydrogenation products **6**–**7** were tentatively assigned based on reported chiral preference of cationic rhodium catalysts.[10] Recently, Danishefsky and co-workers have also described a Jeffery–Heck reaction of aryl iodides with in situ generated dehydroalanine derivatives followed by asymmetric hydrogenation.[15]

The cleavage of acetate proceeded with cat K_2CO_3 in MeOH or NaOMe in $CHCl_3$–MeOH in good yield, but the obtained alcohol had only moderate chiral purity (60–95% ee). Magnesium methoxide[16] in a mixture (2:1) of chloroform and methanol provided alcohols **6b** and **7b** with 98.5% ee and in quantitative yield (Scheme 1). Treatment of alcohol with excess thionyl chloride in dichloromethane provided chlorides **6c** and **7c** in 86% yield.

Nucleophilic displacement of benzylic chloride **6c** by neopentyl amine proceeded smoothly either in the presence of excess amine in dichloromethane or potassium carbonate in acetonitrile (Table 2). The crude benzylic amines in turn were treated with acetic acid in refluxing toluene to give the desired benzazepinones **8a**–**b** in excellent yield. Both benzazepinones **8a** and **8b** retained their chiral integrity as evidenced by chiral HPLC analysis.[17–19]

Alkylation of chloride **6c** with benzyl amine or 2-(piperidin-1-yl)ethanamine followed by treatment with acetic acid in toluene gave the cyclized benzazepinones **8c**–**d** in good yield (Table 2). Amino acid esters also could be used to displace benzylic chloride cleanly. Thus, treatment of chloride **6c** with (*S*)-methyl-2-aminopropanoate in the presence of K_2CO_3 in acetonitrile followed by cyclization in the presence of acetic acid in refluxing toluene led to *trans(anti)*-TyrAla dipeptide mimetic **8e** in 42% yield.[20] No detectable racemization had occurred at either of chiral centers during these transformations as measured by ^{1}H NMR. Functionalization of the amino terminus of the benzazepinone was accomplished by hydrogenolysis of **8a** with 10% Pd on carbon (Scheme 2). The resultant amine **9** was converted either to urea **10** mediated by *N*,*N*′-succinimidylcarbonate or coupled with Boc-Ala–OH under standard peptide coupling agents (TBTU) to give **11** in good yield.[21]

In summary, a flexible and enantioselective approach to diverse *anti*-phenylalanine substituted dipeptide mimetics (**8a**–**e**) has been developed using a palladium-mediated Jeffery–Heck reaction, followed by asymmetric reduction with cationic rhodium catalysts. Alkylation conditions are mild and cyclization proceeds with a minimal amount of racemization. Functionalization of aminoazepinone is efficient and the deprotection and amide bond formation conditions are compatible with standard peptide coupling methods. Application of this methodology in our drug discovery program and relevant biological data will be reported in due course.

Acknowledgments

We would like to thank Dr. Stella Huang and Daniel Schroeder of the Discovery Analytical Services (DAS) for their skillful NMR assistance and to Edward Kozlowski of DAS for determining the enantiomeric excess.

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12. (a) Marshall, J. L. *Carbon–Carbon and Carbon–Proton NMR Couplings: Application to Organic Stereochemistry and Conformational Analysis*; Veriag Chemie International, 1983; (b) NMR experiments were performed on a Bruker 500 MHz spectrometer equipped with a TXI cryo probe.
13. Compound **3f** was prepared from (5-(benzyloxy)-2-iodophenyl)methanol and 2-acetamidoacrylic acid under Mitsunobu reaction conditions (1.3 equiv PPh_3, 1.3 equiv diethylazodicarboxylate in CH_2Cl_2) in 56% yield.
14. Chiral HPLC analysis was performed to determine the enantiomeric excess of **6a** and **7a.** The analysis was performed on a Chiralcel OD–H analytical column (4.6×250 mm, 5 mm) using 15% isopropanol in CO_2 @ 150 Bar and @ 35 °C as mobile phase at a flow rate of 2.0 mL/min. Absorbance was measured @ 220 nm and 5 μL of 1 mg/mL of **6a** or **7a** in ethanol was injected. Compound **6a** had a retention time of 11.91 min and an enantiomeric excess of **6a** was determined to be 99.4%. Compound **7a** had a retention time of 14.2 min and an enantiomeric excess of **7b** was determined to be 99.9%.
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17. Chiral HPLC analysis was performed to determine the enantiomeric excess of **6b** and **7b**. The analysis was performed on a Chiralcel OD–H analytical column (4.6×250 mm, 5 mm) using 15% isopropanol in CO_2 @ 150 Bar and @ 35 °C as mobile phase at a flow rate of 2.0 mL/min. Absorbance was measured @ 220 nm and 5 μL of 1 mg/mL of **6b** or **7b** in ethanol was injected. Compound **6b** had a retention time of 14.2 min and an enantiomeric excess of **6b** was determined to be 97.7%. Compound **7b** had a retention time of 15.8 min and an enantiomeric excess of **7b** was determined to be 99.5%.
18. Chiral HPLC analysis was performed to determine the enantiomeric excess of **8a**. The analysis was performed on a Chiralcel OD–H analytical column (4.6×250 mm, 5 mm) using 20% isopropanol in CO_2 @ 150 Bar and @ 35 °C as mobile phase at a flow rate of 2.0 mL/min. Absorbance was measured @ 220 nm and 5 μL of 1 mg/mL of **8a** in ethanol was injected. Compound **8a** had a retention time of 10.0 min and an enantiomeric excess of **8a** was determined to be 96.2%. Compound **8b** had a retention time of 12.6 min and an enantiomeric excess of **8b** was determined to be 99.0%.
19. Yields were not optimized. All compounds gave satisfactory spectroscopic data consistent with the proposed structures. Data for **3a**: IR (KBr): 3432, 3272, 2949, 1733, 1691, 1604, 1510, 1255, 1238, 1062, 753, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.48–7.26 (m, 11H), 7.14 (d, $J = 2.5$ Hz, 1H), 6.92 (m, 1H), 6.85 (dd, $J = 2.5$ Hz and $J = 8.5$ Hz, 1H), 6.37 (s, 1H), 5.06–5.04 (m, 6H), 3.81 (s, 3H), 2.07 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.8, 165.7, 159.3, 156,5, 153.7, 138.6, 136.6, 136.3, 136.0, 130.12, 130.02, 127.64, 127.45, 127.28, 125.6, 125.3, 123.4, 120.8, 115.8, 114.6, 112.8, 71.1, 70.2, 67.5, 65.0, 64.0, 52.8, 41.0, 21.1, 21.0; Compound **8a**: IR (KBr): 3403, 3063, 2954, 2867, 1720, 1659, 1503, 1476, 1363, 1254, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43–7.33 (m, 10H), 7.03 (d, $J = 8.5$ Hz, 1H), 6.86 (dd, $J = 2.5$ Hz, 8.5 Hz, 1H), 6.66 (d, $J = 2.5$ Hz, 1H), 6.32 (d, $J = 6.5$ Hz, 1H), 5.23–5.17 (m, 2H), 5.15 (s, 2H), 5.04 (s, 2H), 3.82 (d, $J = 16.5$ Hz, 1H), 3.43–3.40 (m, 1H), 3.37 (d, $J = 14$ Hz, 1H), 3.21 (d, $J = 1$H), 2.92–2.87 (m, 1H), 0.90 (s, 9H); MS (ES), 487 $(M+H)^+$; HRMS Calcd for $C_{30}H_{34}N_2O_4$: 487.2597. Obtained: 487.2577.
20. Data for **8e**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.24–7.44 (m, 10H) 6.99 (d, $J = 8.42$ Hz, 1H) 6.79 (dd, $J = 8.42$, 2.93 Hz, 1H) 6.56 (d, $J = 2.56$ Hz, 1H) 6.11 (d, $J = 6.59$ Hz, 1H) 5.12–5.22 (m, 2H) 5.10 (d, $J = 1.83$ Hz, 2H) 5.00 (s, 2H) 4.90–5.06 (m, 1H) 3.87 (d, $J = 17.20$ Hz, 1H) 3.37 (dd, $J = 16.47$, 4.03 Hz, 1H) 3.16 (s, 3H) 2.91 (dd, $J = 16.47$, 13.17 Hz, 1H) 1.38 (d, $J = 7.32$ Hz, 3H); MS (ES), 503 $(M+H)^+$.
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