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Synthesis of constrained L-phenylalanine derivatives incorporating a benzazepinone or an azepinone ring as VCAM/VLA-4 antagonists

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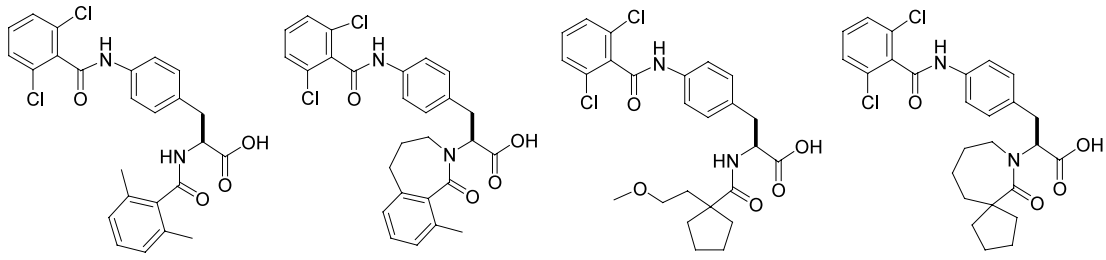
Abstract—Novel constrained L-phenylalanine derivatives incorporating a benzazepinone or an azepinone ring were synthesized in 13 and 8 steps, respectively, employing a key base-catalyzed intramolecular cyclization reaction. The product, **2**, was comparable in potency in a VCAM/VLA-4 ELISA assay to the corresponding unconstrained analog **1** suggesting that cyclization favored the bioactive conformation. However, compound **4** was 100-fold less potent than the unconstrained analog **3**.

We have been interested for some time in developing orally active VCAM/VLA-4 antagonists for the treatment of inflammatory diseases and have previously reported the identification of a series of potent *N*-acylphenylalanines.[1–3] The *N*-benzoyl and *N*-(methoxyethyl)cyclopentanoyl derivatives **1** and **3** are among the more interesting of these compounds based on their potency in our ELISA and cell based assays. We have previously proposed that members of this class reside in a compact, *gauche*(−) conformation and that key features of **1** and **3**, including the carboxylic acid, the *N*-benzoyl or *N*-(methoxyethyl)cyclopentanoyl moieties and the phenylalanine aromatic ring overlap very closely with the corresponding elements in our NMR model of a cyclic peptide lead VCAM/VLA-4 antagonist.[4]

In order to test this conformational hypothesis and simultaneously improve the potency and bioavailability of these lead compounds, we modeled various constrained analogues in which the amide NH was incorporated into a ring in an effort to mimic the putative bioactive conformation. This effort lead to our selection of the benzazepinone **2** and spirocyclic azapinone **4** as synthetic targets and their preparation as shown in Schemes 1–3. A comparison of the modeled conformation of **2** with the putative bioactive conformation of **1** is shown in Fig. 1.[5]

As shown in Schemes 1 and 2, the synthesis of **2** involved three crucial steps: synthesis of the sterically hindered benzoic acid **10**, coupling of **10** with methyl 4-nitro-L-phenylalanine **11**, and a base-promoted intramolecular cyclization reaction of the iodide **13** to form the azepinone ring. The required 2,6-disubstituted benzoic acid **10** was prepared in six steps starting from commercially available 2-allyl-6-methyl phenol **5**. The allylic double bond of **5** was functionalized through a hydroboration–oxidation protocol with 9-BBN in THF to obtain the dihydroxy compound **6** in 67% yield as a single regioisomer. The primary hydroxyl group of **6** was protected selectively by treatment with TBDMS-Cl and imidazole in DMF and the phenol was converted into the triflate **7** in 94% yield for the two steps.



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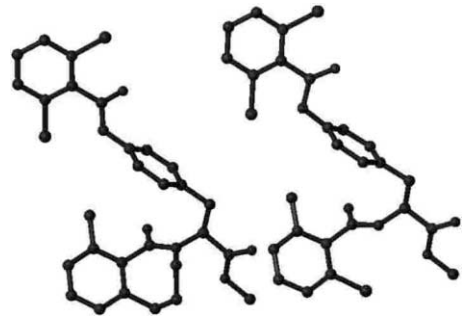
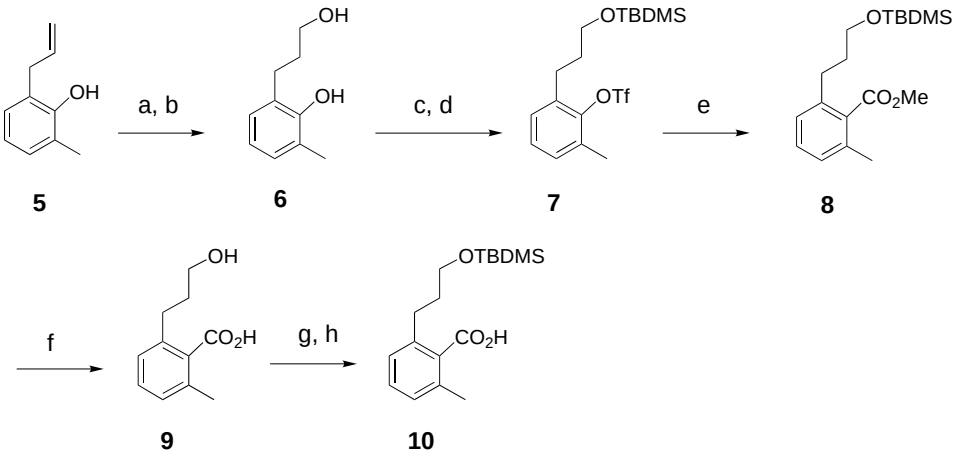
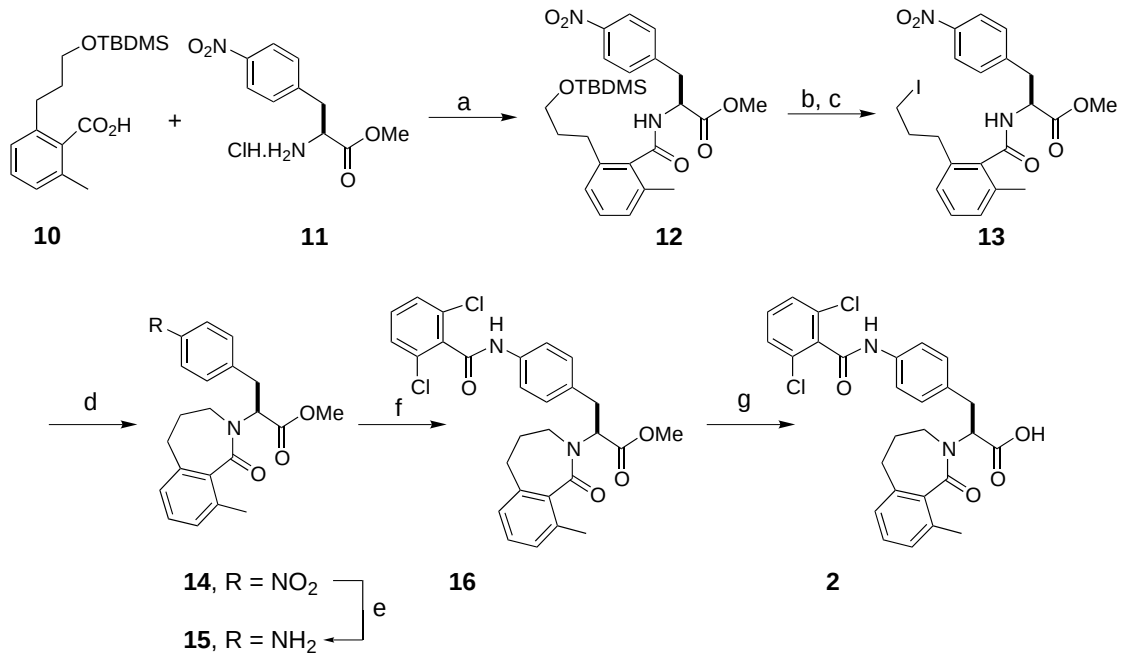


Figure 1.

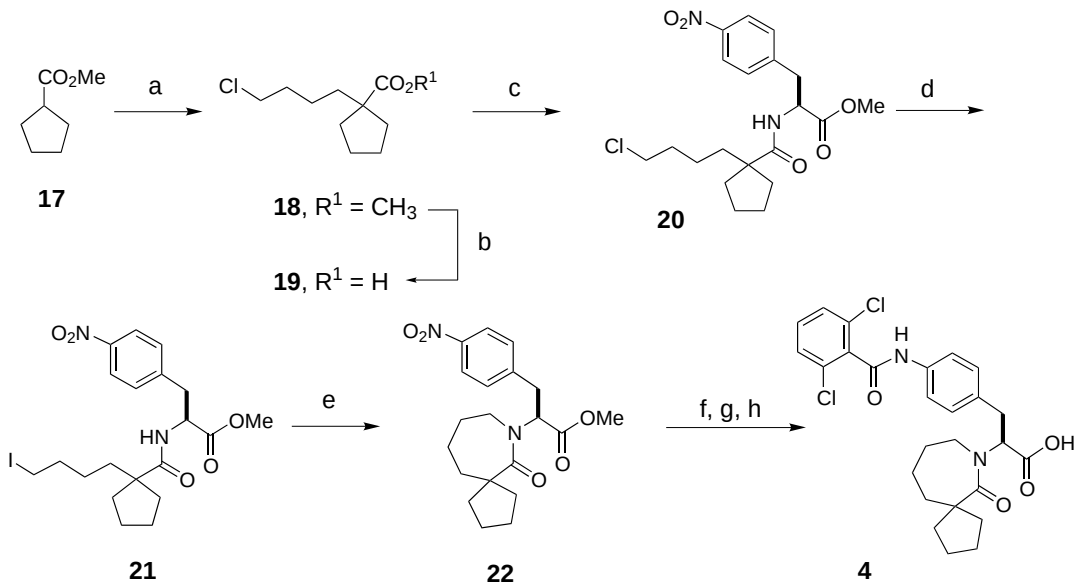
Although attempted direct formation of a carboxyl group under a variety of palladium-catalyzed conditions in aqueous DMSO was unsuccessful, carbomethoxylation was employed successfully. Thus, the triflate **7** was treated with palladium acetate in the presence of 10 mol% of dppp and triethylamine under 50 psi carbon monoxide in DMSO and methanol at 80°C to afford **8** in quantitative yield. Basic hydrolysis of the ester group of **8** resulted in the formation of 2-(3-hydroxypropyl)-6-methylbenzoic acid **9**. During the hydrolysis, the TBDMS hydroxyl-protecting group was lost and was then reintroduced using a two-step protocol. In the first step, **9** was reacted with excess



Scheme 1. *Reagents and conditions*: (a) 9-BBN, THF, reflux, 24 h; (b) NaOH, H_2O_2, 0–40°C, 4 h, 67%; (c) TBDMSCl, imidazole, DMF, rt, 5 h, 96%; (d) Tf_2O, DMAP, CH_2Cl_2, −70°C to rt, 3 h, 93%; (e) $Pd(OAc)_2$, dppp, CO, DMSO, MeOH, NEt_3, 80°C, 4 h, 99%; (f) LiOH, MeOH, H_2O, reflux, 15 h, 99%; (g) TBDMSCl, imidazole, DMF, rt, 15 h; (h) K_2CO_3, MeOH, rt, 20 h, 83%.



Scheme 2. *Reagents and conditions*: (a) HBTU, DIPEA, DMF, rt, 15 h, 28%; (b) TBAF, THF, 0°C to rt, 3 h, 62%; (c) PPh_3, imidazole, I_2, CH_2Cl_2, rt, 15 h, 70%; (d) $KOBu^t$, THF, −70°C to rt, 24 h, 68%; (e) Zn dust, NH_4Cl, MeOH, H_2O, reflux, 30 min, 90%; (f) 2,6-dichlorobenzoyl chloride, DIPEA, CH_2Cl_2, rt, 15 h, 67%; (g) NaOH, EtOH, 40–45°C, 4 h, 95%.



Scheme 3. *Reagents and conditions*: (a) LDA, THF, −70 to −50°C, 1 h, then 4-chloro-1-bromobutane, −70°C to rt, 15 h, 64%; (b) NaOH, THF, MeOH, 45–50°C, 4 h, 65%; (c) methyl 4-(nitro)-L-phenylalanine hydrochloride, HBTU, DIPEA, DMF, rt, 15 h, 55%; (d) NaI, acetone, reflux, 15 h, 96%; (e) KOBu^t, THF, −70°C to rt, 20 h, 49%; (f) Zn dust, NH_4Cl, MeOH, H_2O, rt, 2 h, 90%; (g) 2,6-dichlorobenzoyl chloride, DIPEA, CH_2Cl_2, rt, 15 h, 67%; (h) NaOH, EtOH, 45–50°C, 4 h, 95%.

TBDMSCl and imidazole in DMF to obtain the bis-protected intermediate which, upon exposure to potassium carbonate in methanol gave the protected acid **10** in 83% yield.

The coupling reaction between compound **10** and methyl 4-nitro-L-phenylalanine hydrochloride salt **11** was carried out in DMF using HBTU in the presence of DIPEA to give **12** in low yield (28%). The low yield is likely due to the steric hindrance caused by the presence of two *ortho* substituents in the acid and we did not attempt to optimize the reaction. To set a stage for an intramolecular cyclization, the TBDMS group of **12** was removed under normal conditions (TBAF, THF, rt, 24 h) and the resulting hydroxyl group was transformed to the corresponding iodide using triphenylphosphine, iodine and imidazole in dichloromethane to furnish compound **13** in 70% yield.

Attempts to carry out the crucial intramolecular cyclization of **13** were unsuccessful using sodium hydride as a base in THF under variety of conditions and generally lead to elimination products. However, when potassium *tert*-butoxide was added to a dilute THF solution of **13** at −78°C and the mixture was allowed to warm slowly to room temperature, the reaction proceeded cleanly to provide a 68% yield of the cyclized product **14**. To complete the synthesis, the nitro group of **14** was reduced using zinc dust and ammonium chloride in aqueous methanol at reflux for 30 min to produce the amine **15** in 90% yield. Treatment of **15** with 2,6-dichlorobenzoyl chloride in the presence of DIPEA in dichloromethane followed by ester hydrolysis under basic conditions afforded a 95% yield of the target compound **2**.[6]

The synthesis of **4** is outlined in Scheme 3; the main highlight of the synthesis is the base promoted intramolecular cyclization of iodide **21** to the spirocyclic azapinone **22**. The desired 1-(4-chlorobutyl)-cyclopentane carboxylic acid **19** was prepared in two steps starting from commercially available cyclopentanecarboxylic acid methyl ester **17**. In the first step, the anion generated from **17** in the presence of LDA in THF at −70°C was alkylated with 4-chloro-1-bromobutane. The alkylated product **18** was isolated in 64% yield after distillation under high vacuum. The methyl ester group of **18** was hydrolyzed by treatment with sodium hydroxide in THF and methanol at 40–45°C. The slow reaction and moderate yield of the acid **19** was attributable to the steric environment of the ester group.

The coupling reaction between the cyclopentyl acid **19** and methyl 4-nitro-L-phenylalanine was carried out in DMF using HBTU in the presence of DIPEA to give **20** in moderate yield (55%). To set a stage for intramolecular cyclization, the chloride **20** was converted to the corresponding iodide **21** by treatment with sodium iodide in acetone at reflux (96%). As expected, the intramolecular cyclization proceeded cleanly when a dilute THF solution of **21** was cooled to −78°C, treated with potassium *tert*-butoxide in THF and was allowed to warm slowly to room temperature to afford the cyclized product **22** in 49% yield. The synthesis was completed uneventfully under the conditions described above to afford the target compound **4** in 57% yield for the three steps.[6]

Compounds were assayed for VLA-4 antagonist activity using a solid-phase, dual antibody ELISA in which VLA-4 derived from Ramos cells was allowed to com-

pete for bound recombinant human VCAM in the presence of serial dilutions of test compound. VLA-4 bound to VCAM-1 was detected by a complex of anti-β1 antibody and HRP-conjugated anti-mouse IgG: chromogenic substrate (K-Blue).[3] In this assay system compounds **1**, **2**, **3** and **4** had IC_{50}s of 1.2, 8, 0.25, and 25 nM, respectively. Thus, introduction of the benzazepinone ring constraint lead to a highly potent VCAM/VLA-4 antagonist suggesting that compound **2** can access a bioactive conformation and that the compound–receptor interaction is not dependent on the presence of the phenylalanine NH. On other hand, the introduction of the azapinone ring in cyclopentane series lead to a moderately potent VCAM/VLA-4 antagonist, the constrained molecule was 100-fold less potent than its conformationally more mobile parent.

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5. Modeling experiments were carried out using the SYBYL ver. 6.0 modeling package employing the Sybyl force field including electrostatics. The model for **2** was derived from a X-ray crystal structure of a closely related compound which will be described in a forthcoming paper. The conformational model for **3** was build from **2** by appending the appropriate atoms and carrying out a minimization with an annealing step.
6. All new compounds reported herein were characterized by ^{1}H NMR and high resolution mass spectroscopy. Data for compound **2**: ^{1}H NMR (400 MHz, DMSO-d_6), spectrum run at room temperature, δ 12.84 (br s, 1H), 10.65 (s, 1H), 7.63–7.46 (m, 5H), 7.32–7.09 (m, 3H), 7.04–6.94 (m, 2H), 5.5 (m, 1H), 3.43–3.0 (m, 4H), 2.94–2.5 (m, 2H), 2.34 (s, 3H, $ArCH_3$, belongs to one rotamer), 2.09–1.94 (m, 2H, $ArCH_2$, belongs to the above rotamer), 1.76 (s, 3H, $ArCH_3$, belongs to another rotamer), 1.54–1.41 (m, 2H, $ArCH_2$, belongs to the later rotamer). Spectrum run at 100°C (400 MHz, DMSO-d_6), δ 10.33 (s, 1H), 7.56 (d, 2H, $J=8.2$ Hz), 7.5 (d, 1H, $J=6.8$ Hz), 7.5 (d, 1H, $J=8.8$ Hz), 7.45 (dd, 1H, $J=6.8$, 8.8 Hz), 7.24 (d, 2H, $J=8.2$ Hz), 7.17 (t, 1H, $J=7.3$ Hz), 7.05 (d, 1H, $J=7.3$ Hz), 6.94 (d, 1H, $J=7.3$ Hz), 5.3 (m, 1H), 3.32 (dd, 1H, $J_{gem}=14.5$, $J_{vic}=5.8$ Hz), 3.12 (dd, 1H, $J_{gem}=14.5$, $J_{vic}=10.7$ Hz), 3.21–2.83 (m, 2H, NCH_2), 2.55 (m, 2H, $ArCH_2$), 2.10 (m, 3H, $ArCH_3$), 1.76 (m, 2H); HRMS (FAB)$^+$ calcd for $C_{27}H_{24}N_2O_4Cl_2$ 511.1191, found 511.1195 (M+H). Data for compound **4**: ^{1}H NMR (400 MHz, DMSO-d_6), spectrum run at room temperature, δ 12.5 (br s, 1H), 10.64 (s, 1H), 7.6–7.54 (m, 4H), 7.5 (dd, 1H, $J=6.8$, 8.8 Hz), 7.15 (d, 2H, $J=8.2$ Hz), 5.0 (m, 1H), 3.25–2.95 (m, 4H), 2.0 (m, 1H), 1.65–1.25 (m, 13H); HRMS (FAB)$^+$ calcd for $C_{26}H_{28}N_2O_4Cl_2$ 503.1505, found 503.1523 (M+H).