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Synthesis of Benzo-Fused, 7,5- and 7,6-Fused Azepinones as Conformationally Restricted Dipeptide Mimetics

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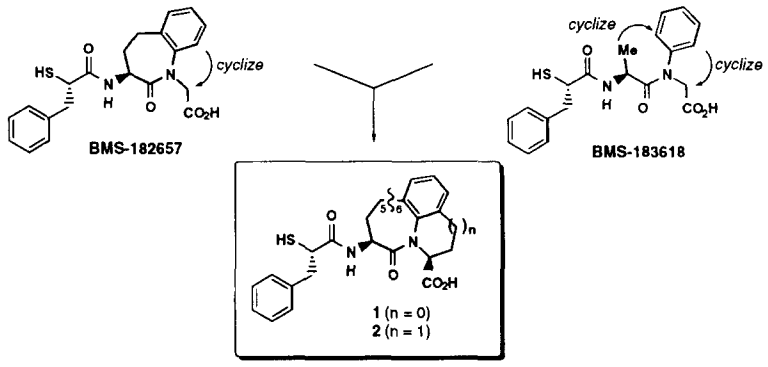
Abstract: Methodology for the generation of novel conformationally restricted dipeptide mimetics **9** and **16** has been developed. The key step involved intramolecular addition of an oxonium ion to the proximal indoline/tetrahydroquinoline aromatic ring. A dramatic difference in reactivity was observed in the formation of the 7,5- versus the 7,6-fused azepinone nuclei. Application of these mimetics in the synthesis of dual-acting ACE/NEP inhibitors **1** and **2** is described.

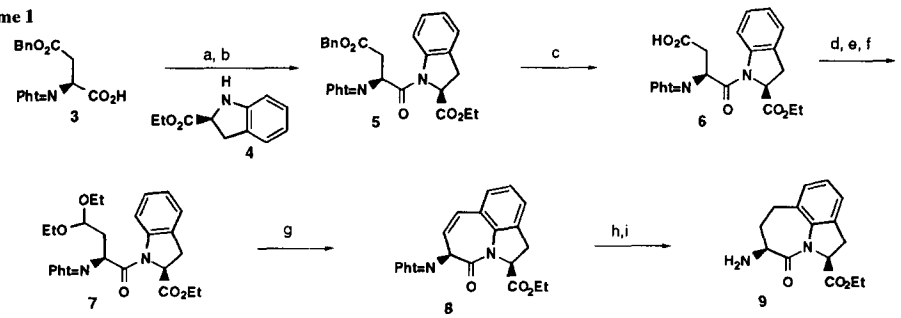
In a recent series of communications, we have described the application of conformationally restricted dipeptide mimetics to the generation of dual inhibitors of the zinc metalloproteases angiotensin converting enzyme (ACE) and neutral endopeptidase (NEP).[1] These compounds are typically represented by a dipeptide surrogate to which a mercaptoacetyl pharmacophore is appended. Inhibitors such as **BMS-182657** and **BMS-183618** (Figure 1) were demonstrated to exhibit superior *in vitro* activity against both ACE and NEP compared to the corresponding mercaptoacetyl Ala-Pro analog from which they were derived.[1a,b] Consequently we have devoted much of our efforts into the development of novel dipeptide surrogates which would satisfy the necessary structural requirements for enzyme binding within this class of compounds. Benzo-fused bicyclic dipeptide surrogates such as those depicted in structures **1** and **2** were viewed as novel conformationally restricted versions of **BMS-182657**, **BMS-183618**, and related bicyclic analogs[1a,c,e] and we speculated that they should possess excellent *in vitro* activity versus both metalloproteases.[2] At the initiation of this study, methods to generate the requisite azepinones in **1** and **2** had not been described and therefore a general methodology for the synthesis of both the 7,5- and 7,6-fused analogs was developed.[3]

Figure 1



We envisioned construction of the desired azepinone nucleus could be rapidly effected by carbon-carbon bond formation at the C5-C6 position of **1** (arbitrary numbering) via intramolecular electrophilic substitution to the proximal indoline (tetrahydroquinoline) ring. The route utilized for the generation of the 7,5-fused azepinone **9** by this methodology is depicted in Scheme 1. Mixed anhydride activation of N-phthalimido-γ-benzyl-L-aspartic acid (**3**)[4] (i-BuCOCl, NMM) followed by addition of ethyl (S)-indoline-2-carboxylate (**4**) gave dipeptide **5** in poor yield and modest diastereomeric purity. In contrast, amine **4** reacted readily with the acyl fluoride[5] of **3** to give **5** and its corresponding racemization product in 91% and 6% yield respectively. The diastereomers were readily separable by flash chromatography. Subsequent hydrogenolysis of **5** cleanly afforded acid **6**. Attempts to effect intramolecular acylation of acid **6** to its corresponding cyclic azepinone via either the acid or the acid chloride were unsuccessful. This is in contrast to a recent report where the N-trifluoroacetyl protected acid chloride of **6** was demonstrated to undergo intramolecular acylation to the proximal indoline aromatic ring in the presence of $AlCl_3$.[3] We suspect the difference in reactivity is likely due to the presence of the bulky phthalimido protecting group in **6** which may conformationally inhibit the desired cyclization. In order to enhance the reactivity of the carbon electrophile towards addition to the aromatic ring, the acid functionality was converted to an acetal group. Thus, conversion of **6** to the corresponding thioester followed by Fukuyama reduction[6] and acetalization gave **7**. In the key cyclization step, treatment of the acetal with polyphosphoric acid (PPA) at 100 °C for 30 minutes cleanly afforded unsaturated azepinone **8** in 84% yield and excellent diastereomeric purity. Formation of **8** is believed to occur via electrophilic addition of the oxonium ion to the aromatic ring followed by acid catalyzed elimination of methanol. Hydrogenation and subsequent removal of the phthalimido group under standard conditions thus provided the requisite 7,5-fused azepinone **9**.

Scheme 1

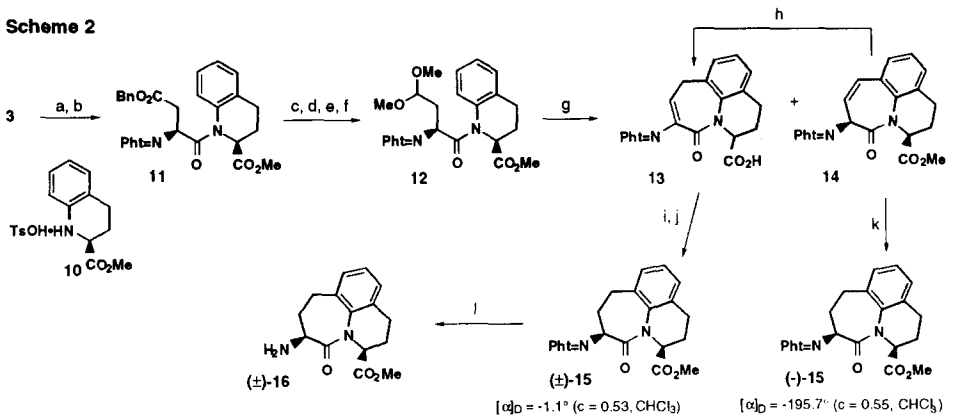


a) cyanuric fluoride, pyridine, CH_2Cl_2, b) amine **4**, 2,6-(di-tert-butyl-pyridine), CH_2Cl_2, -25 °C, (91%). c) H_2, $Pd(OH)_2/C$, EtOAc, rt, (93%). d) EtSH, EDAC, DMAP, CH_2Cl_2, (84%). e) Et_3SiH, Pd/C, CH_3CN, (73%). f) $CH(OEt)_3$, TsOH, EtOH, CH_2Cl_2, (97%). g) PPA, 100 °C, 30 min., (84%). h) H_2, Pd/C, EtOH, THF, (97%). i) H_2N-NH_2•H_2O, EtOH, rt, (84%)

Application of this methodology to the synthesis of the corresponding 7,6-fused derivative is depicted in Scheme 2. Unlike amine **4**, methyl (S)-1,2,3,4-tetrahydroquinoline-2-carboxylate (**10**)[7] failed to react with the acid fluoride of **3**. Subsequently it was found that conversion of acid **3** to the corresponding acid chloride followed by reaction with **10** under Schotten-Baumann type conditions afforded the desired coupling adduct **11** in good yield and 99.4% diastereomeric purity as determined by HPLC.[8] Four step conversion of **11** to acetal **12** proceeded in 61% overall yield. PPA induced cyclization of quinoline

derivative **12** (PPA, 120 °C, 2 hours) was considerably more sluggish than its indoline counterpart and unexpectedly produced the "conjugated" acid **13** as the major product (58%) along with a small amount of the expected "unconjugated" ester **14** (5%). The low optical rotation of **13** and it's subsequent reduction product (i.e. **15**) indicated that nearly complete racemization of the carboxylic acid functionality had occurred. The presence of **14** in a small but steady-state concentration (as observed by TLC) during the reaction indicated that this compound was a likely intermediate in the formation of **13**. In addition, brief exposure of pure **14** to hot PPA resulted in the formation of acids **13** and **21** in a 4:1 ratio (see Scheme 3).

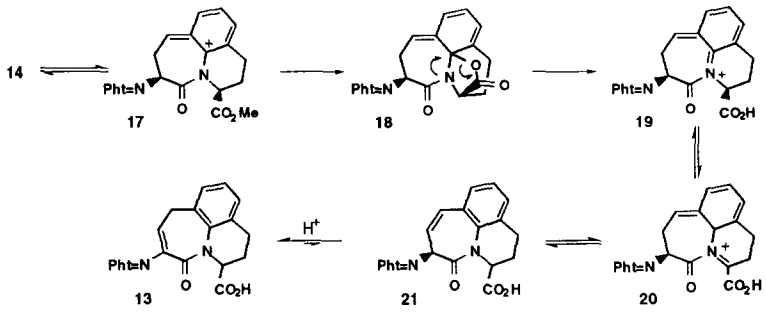
Scheme 2



a)PCl_5, Et_2O b) amine **10**, aq. $NaHCO_3$, toluene, rt, 18 hrs (86%). c) H_2, $Pd(OH)_2/C$, EtOAc, rt, (100%). d) EtSH, EDAC, DMAP, CH_2Cl_2, (88%). e) Et_3SiH, Pd/C, CH_3CN, (69%). f) $CH(OMe)_3$, TsOH, MeOH, CH_2Cl_2, (100%). g) PPA, 100 °C, 2 hr (**11**, 58%; **12**, 5%). h) PPA, 100 °C, 1.5 hr. i) CH_2N_2, Et_2O, CH_2Cl_2. j) H_2, Pd/C, MeOH, DMF, 55 °C, 50 psi (48%). k) H_2, Pd/C, MeOH, THF (88%), l) H_2N-NH_2•H_2O MeOH, rt, (78%)

Based on these results, a putative mechanism for the generation of **13** from **14** is proposed in Scheme 3. Protonation of **14** generates carbonium ion **17** which is trapped by the carbomethoxy group to give lactone **18**. Acid catalyzed opening of the lactam, assisted by the amide nitrogen, gives **19** which isomerizes to **20** and in the process destroys the stereochemistry at the carboxyl center. Subsequent prototropic shifts give **21** and eventually the thermo-dynamic product **13**. The observation that no "conjugated" methyl ester

Scheme 3



product was formed in these reactions indicate that the free carboxylic acid likely assists in the migration of the olefin in **21**. Although unexpected, a similar difference in reactivity was observed in the formation of related 7,5- and 7,6-fused azepinones generated via N-acyl iminium ion cyclization methodology,[9] although in that case destruction of the stereocenters was not observed.

We were pleased to discover that hydrogenation of the methyl ester of **13** afforded azepinone (±)-**15** as a single isomer in modest yield[10] which was identical in every respect to (-)-**15** (obtained via hydrogenation of **14**) except for the magnitude of it's optical rotation (Scheme 2). Hydrazine promoted removal of the phthalimido protecting group afforded racemic amine (±)-**16**. The relative stereochemistry of this amine was confirmed by single crystal X-ray analysis.

Application of dipeptide surrogates **9** and (±)-**16** in the synthesis of homochiral inhibitors **1** and **2** was performed utilizing our previously described method.[1,2] *In vitro*, compound **1** demonstrated activity against both ACE and NEP with IC_{50}'s of 13 nM and 50 nM respectively. The 7,6-fused inhibitor **2** displayed equivalent activity *in vitro* against ACE (IC_{50} = 9.9 nM) but was 3-fold more potent versus NEP (IC_{50} = 17 nM). A more detailed pharmacological profile of these compounds will be described elsewhere.

In summary, we have described a convenient route for generating benzo-fused bicyclic azepinones via an intramolecular acid catalyzed addition of an oxonium ion to an indole or tetrahydroquinoline ring. A dramatic difference in product formation was observed which was dependent on the size of the ring fusion adducts (7,5- or 7,6-fused). The azepinones described proved to be suitable dipeptide mimetics in the generation of dual ACE/NEP inhibitors **1** and **2**.

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References and Notes:

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2. A complete description of the synthesis of compounds **1** and **2** as well as other closely related inhibitors was described by us in European Patent Application 0595610A, filing date October 27, 1993.
3. In a recent Letter, workers from Ciba-Giegy described an alternate synthetic route for the synthesis of the 7,5-fused peptidomimetic present in structure **1** (i.e. methyl ester of compound **9**). Synthesis of the related 7,6-fused analog was not discussed. See DeLombaert, S.; Blanchard, L.; Stamford, L. B.; Sperbeck, D. M.; Grim, M. D.; Jensen, T. M.; Rodriguez, H. R. *Tetrahedron Lett.* **1994**, *35*, 7513.
4. Compound **3** was conveniently prepared in 79% yield by reaction of γ-benzyl-L-aspartic acid with N-carbethoxy phthalimide in aqueous $NaHCO_3$/dioxane followed by isolation via its dicyclohexylamine salt.
5. The acyl fluoride of **3** was prepared utilizing the method of Carpino. See Carpino, L. A.; Mansour, E. M. E.; Sadat-Aalaee, D. *J. Org. Chem.* **1994**, *56*, 2611.
6. Fukuyama, T.; Lin, S-C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050.
7. Amine **10** was prepared from quinoline-2-carboxylic acid as follows; a) Raney Ni-Al alloy, 2.5 N NaOH, rt, 2.5 hr. b) Cbz-Cl, pH 8.5-9.0, then isolate via DCHA salt. c) resolve free acid via S-(-)-α-methylbenzylamine salt (according to U. S. Patent 4,461,896). d) esterification of the free acid with MeI, K_2CO_3, DMF. e) H_2, Pd/C, 1 equiv. $TsOH•H_2O$, MeOH.
8. In addition, the reaction also proceeded in good (85%) yield and high (99.3%) diastereomeric purity by reaction of the acid chloride with the amine•TsOH salt in the presence of di-tert-butylpyridine in CH_2Cl_2 (0 °C to rt). The use of N-methyl morpholine as base under identical conditions lead to a 1:1 mixture of diastereomers.
9. Robl, J. R. *Tetrahedron Lett.* **1994**, *35*, 393-396.
10. The major side product of this reaction (19%) was the methanol adduct of (±)-**15** arising from addition of methanol to the imide protecting group under the forcing conditions of the reaction. Re-conversion of this side-product to (±)-**15** was effected by refluxing in toluene in the presence of $TsOH•H_2O$ (85% yield).

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