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Peptidomimetic Synthesis: Utilization of N-Acyliminium Ion Cyclization Chemistry in the Generation of 7,6- and 7,5-Fused Bicyclic Lactams

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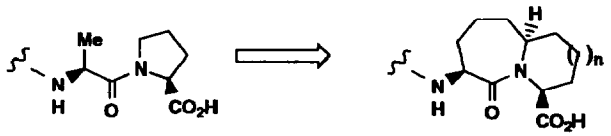
Abstract: A method for the stereoselective generation of 7,6- and 7,5-fused bicyclic lactams of type **1** has been developed. The key step involves intramolecular N-acyliminium ion cyclization of N-acyl enamine **2** to generate the core bicyclic framework. Lactams of type **1** may be viewed as conformationally restricted mimics of alanyl proline.

The generation of conformationally restricted peptides and their utilization in the synthesis of bioactive molecules has been a subject of considerable study over the last ten years.[1] As part of our efforts to generate novel metalloprotease inhibitors for the treatment of hypertension and congestive heart failure, our attention has centered on developing targets in which the alanyl-proline portion of an initial lead is replaced with a suitable conformationally restricted dipeptide surrogate. A potential peptidomimetic replacement for Ala-Pro is the fused bicyclic lactam **1** in which the alanine methyl group is joined to the C-5 position of the proline ring by a ethylene linker. A method for the generation of the 7,5-fused bicyclic lactam has been described by researchers at Merck[2] but the synthetic route is long (> 13 steps) and the stereochemistry at the three chiral centers is not controlled. In addition, the methodology would be difficult to apply towards the generation of the analogous 7,6-fused system.

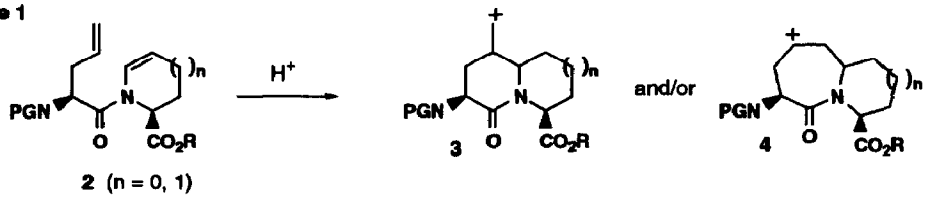
Figure 1



1 (n = 0, 1)

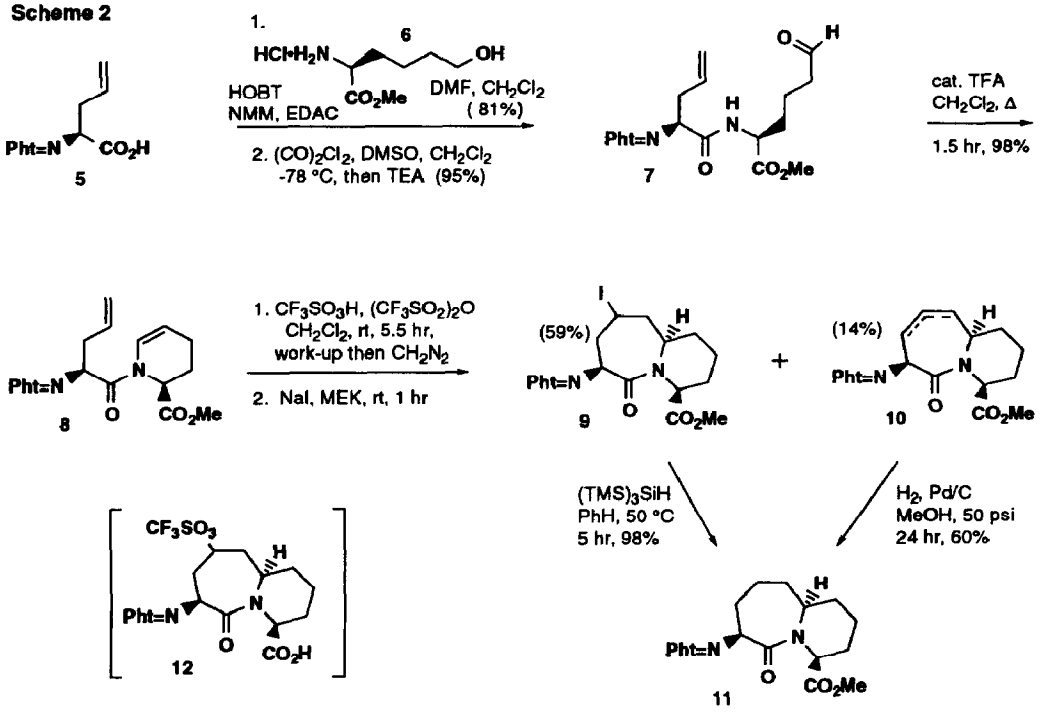
Because of these problems, we sought to developed a route to compounds of type **1** via N-acyliminium ion cyclization[3] of the corresponding monocyclic N-acyl enamide **2** (Scheme 1). In theory, olefin-iminium ion cyclization of **2** could lead to two regioisomeric lactams arising from carbonium ions **3** and **4**. Cyclization of **2** to give intermediate **4** was expected since the more stable secondary carbonium ion would be generated. Successful application of this methodology[4,5] has prompted us to disclose our results.

Scheme 1



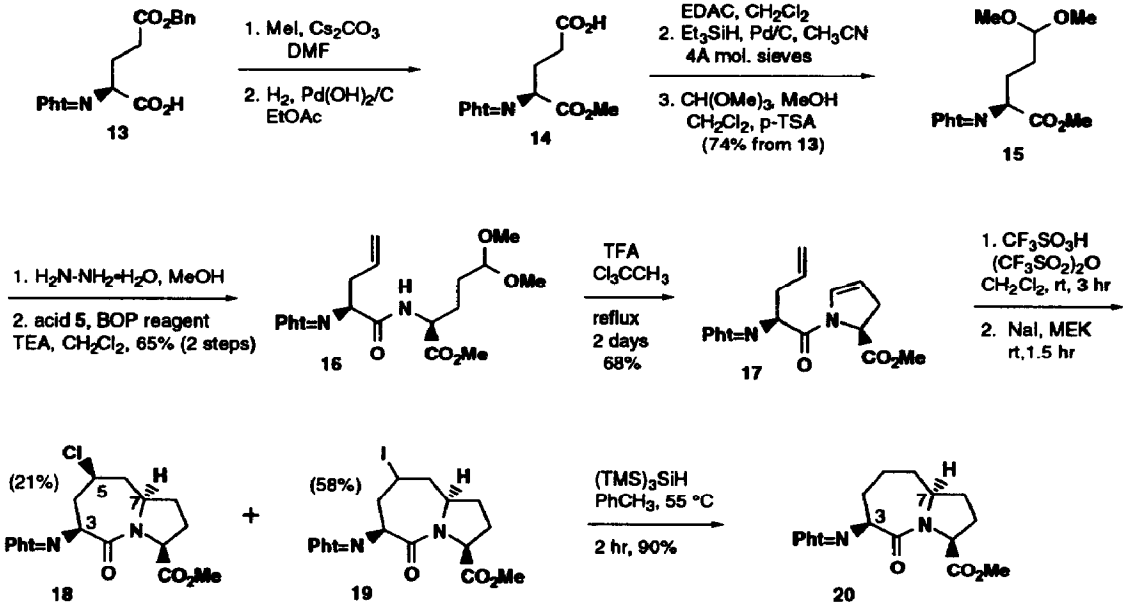
Water soluble carbodiimide coupling of N-phthaloyl-L-allylglycine (**5**)[6] with the HCl salt of L-ε-hydroxynorleucine methyl ester (**6**),[7] followed by Swern oxidation gave aldehyde **7**. Conversion of **7** to enamide **8** was rapid and essentially quantitative in the presence of catalytic TFA in refluxing dichloromethane. Addition of **8** in CH_2Cl_2 to trifluoromethanesulfonic acid[8] afforded triflate **12** as the major product as well as olefinic carboxylic acids related to **10**. No products in which the methyl ester group remained intact could be detected.[9] Re-esterification (CH_2N_2) and subsequent treatment of the crude mixture with NaI[10] resulted in the formation of **9** in 59% yield in addition to elimination products **10** in 14% yield.[11] Reduction of both **9** and **10** afforded the identical desired product **11** in 50% overall yield from **5**. Single crystal X-ray analysis of **11** indicated the S stereochemistry at the newly formed bridgehead center, thus confirming the assignments of compounds **9** and **10** as shown. No 6,6-fused lactam side-products arising from intermediate **3** were detected.

Scheme 2



Generation of the corresponding 7,5-fused bicyclic lactam was performed in a similar manner (Scheme 3). γ-Benzyl-N-phthaloyl-L-glutamate (**13**)[6] was methylated, then subjected to hydrogenolysis to afford acid **14**. Conversion of **14** to the ethyl thiol ester[12] followed by reduction with triethylsilane[13] gave the intermediate aldehyde which was protected as its dimethyl acetal. Deprotection of the phthalimido group (1.05 equivalents hydrazine, rt, 6 days) cleanly afforded the desired amine, which was subsequently coupled to acid **5**. Contrary to the cyclization of **7** to **8**, conversion of **16** to **17** was sluggish but eventually afforded the desired N-acyl enamine in 68% yield. Triflic acid induced cyclization of **17** generated a mixture of chloride **18** and the unstable triflate **22** (Scheme 4) which upon brief exposure[10] to NaI gave **19** and unreacted **18** in 58% and 21% yield respectively as single diastereomers. No carboxylic acid products were detected.[9] The desired 7,5-fused bicyclic lactam **20** was obtained in high yield and diastereomeric purity by free radical dehalogenation[14] of iodide **19**. Unable to obtain crystals of either **18** or **20** suitable for x-ray analysis, the stereochemical assignments shown were based on strong observed nOe's between the C-3 and C-7 protons in **20**, and between the C-3, C-5, and C-7 protons in **18**.

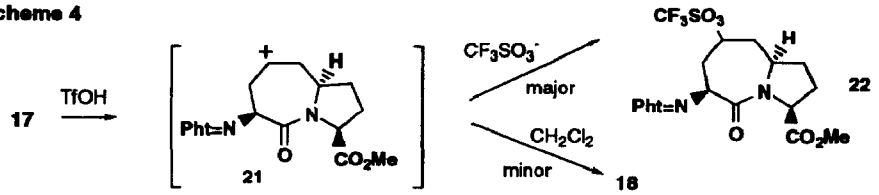
Scheme 3



Formation of chloride **18** in the N-acyliminium ion cyclization of **17** was unexpected although not without precedent. Olah[15] has reported cases in which dichloromethane can act as an effective source of nucleophilic chloride ion for carbocations. Consequently we believe that *in situ* generated carbonium ion **21** (Scheme 4), in the presence of the poorly nucleophilic triflate anion, abstracts chloride from the solvent to give **18** as a minor product.

Conversion of both **11** and **20** to their respective amines can readily be effected by treatment with hydrazine in MeOH/CH_2Cl_2. Utilization of these amines for the synthesis of metalloprotease inhibitors will be the subject of a future disclosure.

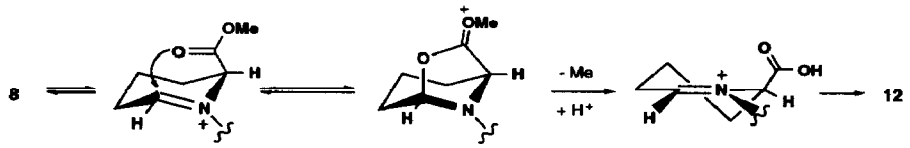
Scheme 4



Acknowledgments: Appreciation is expressed to Ms. Yolanda Pan and Ms. Alicia Kahle for performing the nOe experiments and Ms. Mary Malley for performing the crystallographic analysis of compound **11**. Thanks is also given to Professor George Olah for helpful discussions pertaining to the generation of compound **18**.

References and Notes:

1. For some recent examples see: a) Hirschmann, R. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1278. b) Smith, A. B. III; Keenan, T. P.; Holcomb, R. C.; Sprengeler, P. A.; Guzman, M. C.; Wood, J. L.; Carroll, P. J.; Hirschmann, R. *J. Am. Chem. Soc.* **1992**, *114*, 10672. c) Chackalamannil, S.; Wang, Y.; Haslanger, M. F. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1003. d) Deal, M. J.; Hagan, R. M.; Ireland, S. J.; Jordan, C. C.; McElroy, A. B.; Porter, B.; Ross, B. C.; Stephens-Smith, M.; Ward, P. *J. Med. Chem.* **1992**, *35*, 4195. e) de Laszlo, S. E.; Bush, B. L.; Doyle, J. J.; Greenlee, W. J.; Hangauer, D. G.; Halgren, T. A.; Lynch, R. J.; Schorn, T. W.; Siegl, P. K. S. *J. Med. Chem.* **1992**, *35*, 883. f) Williams, B. J.; Curtis, N. R.; McKnight, A. T.; Maguire, J. J.; Young, S. C.; Veber, D. F.; Baker, R. *J. Med. Chem.* **1993**, *36*, 2. g) Sreenivasan, U.; Mishra, R. K.; Johnson, R. L. *J. Med. Chem.* **1993**, *36*, 256. h) Genin, M. J.; Ojala, W. H.; Gleason, W. B.; Johnson, R. L. *J. Org. Chem.* **1993**, *58*, 2334. i) Flynn, G. A.; Beight, D. W.; Mehdi, S.; Koehl, J. R.; Giroux, E. L.; French, J. F.; Hake, P. W.; Dage, R. C. *J. Med. Chem.* **1993**, *36*, 2420.
2. Thorsett, E. D. *Actual. Chim. Ther.* **1986**, *13*, 257.
3. For two excellent reviews on N-acyliminium chemistry see a) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367. b) Hiemstra, H.; Speckamp, W. N. Additions to N-acyliminium Ions in *Comprehensive Organic Chemistry*; Vol. 2; Trost, B. M., Ed.; Pergamon Press: Oxford, **1991**, pp 1047-1082.
4. Related methodology in which a reactive N-acyliminuim ion underwent cyclization with a proximal aromatic ring has been described by Flynn, G. A.; Giroux, E. L.; Dage, R. C. *J. Am. Chem. Soc.* **1987**, *109*, 7914.
5. Recently Moeller et al have desribed the generation of related 7,5-fused lactams via N-acyliminium ion cyclization utilizing electrochemically reduced N-acylpyrrolidinones as starting materials: see Moeller, K. D.; Hanau, C. E. *Tetrahedron Lett.* **1992**, *33*, 6041 and Fobian, Y. M.; Moeller, K. D. 206th Meeting of the American Chemical Society, Chicago, IL, August 1993, Abstract ORG 297.
6. **5** and **13** were prepared from the corresponding amino acids by treatment with N-carboethoxyphthalimide in aqueous Na_2CO_3.
7. Compound **6** was formed by reaction of L-ε-hydroxynorleucine with HCl saturated methanol. L-ε-hydroxynorleucine was prepared according to the procedure outlined in Bodanszky, M.; Martinez, J.; Priestley, G. P.; Gardner, J. D.; Mutt, V. J. *Med. Chem.* **1978**, *21*, 1030.
8. In a typical experiment, a solution of the enamide (4 mmol) in CH_2Cl_2 (9 mL) is added at room temperature to a mixture of triflic acid (2.3 mL) and triflic anhydride (0.22 mL) under argon. After 3-6 hours the mixture is added to cold water and extracted with EtOAc. The organic extract is washed with water and brine, then dried (Na_2SO_4), filtered and evaporated. In the case of enamide **8**, the residue is first dissolved in MeOH/CH_2Cl_2 and treated with excess CH_2N_2 for 10 minutes. The solvent is removed and the residue is dissolved in methyl ethyl ketone and treated with 4-5 equivalents of NaI for 1-1.5 hours. Extractive work-up followed by flash chromatography affords the desired products.
9. We speculate that the carboxy methyl ester group undergoes addition to the electrophilic iminium center of protonated **8** resulting in hydrolysis of the ester and formation of the corresponding acid prior to addition of the olefin to give **12**. In the case of **17**, the greater distance between the carbonyl oxygen and the iminium center prevents this type of participation allowing the ester group to remain intact. In addition, iminium ion assisted hydrolysis of the ester group in **17** would have to proceed via a higher energy bicyclo [2.2.1] ring system, as compared to the less energetic [3.2.1] system depicted below.



10. Due to the lability of **12** (or **22**) and its corresponding Me ester, it is best to convert the intermediate triflate to the iodide without purification. Prolonged exposure of **19** to NaI results in the formation of a mixture of diastereomeric iodides, whereas chloride **18** is inert.
11. In addition a very small amount of the corresponding α,β-unsaturated lactam related to **10** could be detected.
12. Neises, B.; Steglich, W. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 522.
13. Fukuyama, T.; Lin, S-C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050.
14. Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188.
15. Olah, G. A.; Wu, A.; Farooq, O. *J. Org. Chem.* **1989**, *54*, 1463 and references therein.

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