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Further Studies on the Chemistry of Piperazic Acids: New Building Blocks for β-Hydroxy-α-Aminoacids through the Aza-Achmatowicz Reaction

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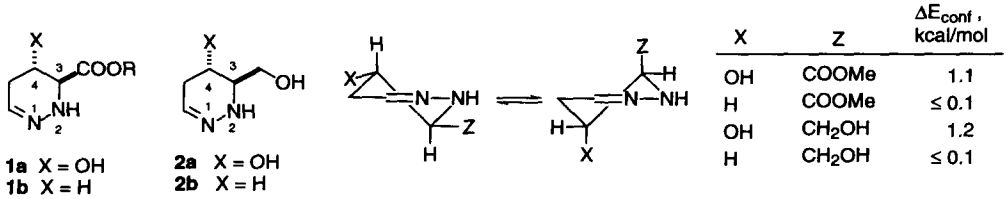
ABSTRACT: The abnormal reluctance of piperazic acids to undergo N-2 acylation seems to be due to an electronic effect, not a steric / conformational problem. A system suitable for probing these issues was assembled by methods that have produced a versatile building block for β-hydroxy-α-aminoacids of either relative stereochemistry and of either (L) or (D) configuration. © 1997 Elsevier Science Ltd.

The unusual 4-hydroxy-2,3,4,5-tetrahydropyridazine carboxylic acid **1a** ("HPCA", R = H) and its esters are extraordinarily reluctant to undergo acylation at the N-2 position. Acylation of reduced analogs of **1a** may be induced, with marginal success, through the use of acid chlorides, but anhydrides are insufficiently reactive.[1] HPCA is a key subunit of the antitumor and anti-HIV peptide antibiotics, luzopeptins,[2] a synthesis of which must necessarily overcome this difficulty. We wished to clarify, both computationally and experimentally, whether the abnormal behavior of piperazic acids may be ascribed primarily to steric / conformational factors, or whether subtler electronic effect may be involved. Accordingly, we required a probe system that would be sterically and conformationally similar to **1a**, but that displayed substantially different electronic properties. Compound **2a** seemed to satisfy these requirements. The steric demand of the CH_2OH unit is comparable to that of a COOMe group, as gauged from experimental A-values in cyclohexanes (1.7 vs. 1.3 kcal/mol, respectively)[3] and from molecular mechanics calculations (MM+ field, Scheme 1)[4] on **1a-b** and **2a-b**. However, the powerful electron-withdrawing effect of the COOR group is absent in **2**. It thus appeared that a study of the acylation chemistry of a system of the type **2a** might produce considerable insight in the matter. Our results are summarized below.

Both experiment and calculations indicate that the COOR unit in N-2 acyl derivatives of esters of **1a** strongly favors the axial position, as expected of a generic N-acyl piperidine-like molecule.[1,5] Adverse conformational effects might undermine the feasibility of direct N-2 acylation of HPCA, if attainment of the axial conformation were required prior to N-acylation, and if the energy demand of this conformer were excessive. However, calcu-

Scheme 1

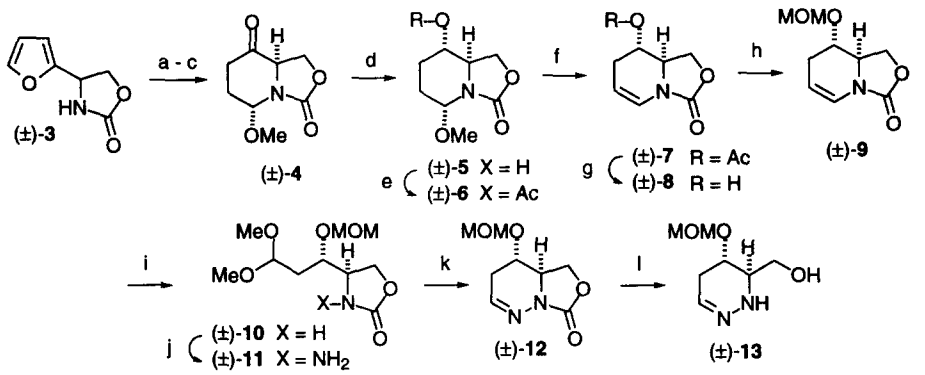


1a X = OH
1b X = H

2a X = OH
2b X = H

X	Z	ΔE_{conf}, kcal/mol
OH	COOMe	1.1
H	COOMe	≤ 0.1
OH	CH_2OH	1.2
H	CH_2OH	≤ 0.1

Scheme 2



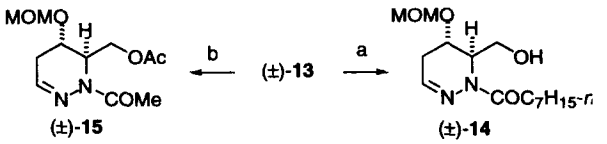
(a) Br_2, MeOH, Et_2O, –40°C, then $NH_3(g)$, 91%; (b) RaNi, H_2, 1500 psi, 50°C, 97%; (c) 15 mol% TfOH, 2 eq. H_2O, THF, RT, 86 % chrom.; (d) $NaBH_4$, EtOH, –78°C, 92%; (e) Ac_2O, pyridine, RT, 97-99%; (f) 15 mol% QCS, PhH, reflux, 85%; (g) K_2CO_3, MeOH, 82%; (h) MOMCl, Hünig base, CH_2Cl_2, reflux, 71%; (i) i. O_3, MeOH, CH_2Cl_2, –78°C, then Me_2S; ii. evaporate; iii MeOH, $HC(OMe)_3$, $CeCl_3 \cdot 7H_2O$, 60%; (j) NaH, H_2N-OP(O)Ph_2, DMF; (k) cat. aq. HCl, MeCN, 73 % j-k; (l) 0.1N aq. NaOH (cpd. **12** is water-soluble), RT, 90 min, then Amberlite IRC-50 to pH 7, 97%.

lations (MM+) revealed that the ΔE between axial and equatorial states of **1a** (R = Me) is only 1.1 kcal/mol; moreover, this difference seems to be due solely to the presence of the ring OH group, since the axial and equatorial conformers of 4-desoxy structure **1b** (R = Me) are calculated to be isoenergetic (ΔE ≤ 0.1 kcal/mol). This notwithstanding, N-2 acylation of **1b** is also problematic,[6] already suggesting that steric / conformational effects are not likely to play a significant role here. Finally, the calculated ΔE's between axial and equatorial conformers of **2a** and **2b** are 1.2 and ≈ 0.0 kcal/mol, respectively. These values are similar to those calculated for **1** (Scheme 1), therefore, it is reasonable to anticipate that whatever steric or conformational problems might hamper acylation of **1** will also oppose acylation of **2**.

Our route to **2** relied on aza-Achmatowicz methodology,[7] rather than reduction of esters of HPCA, in order to avoid several projected problems. Rearrangement of oxazolone (±)-**3** afforded **4**. Stereoselective reduction of the ketone ($NaBH_4$)[5] gave an equatorial alcohol that was acetylated and advanced to enamide **7** [cat. quinolinium camphorsulfonate (QCS)[8]]. Compound **7** was best converted to MOM ether **9** prior to ozonolysis and protection of the emerging aldehyde as a methyl acetal under Luche conditions.[9] Subsequent Klotzer[10] N-amination of **10** afforded **11**, cyclization of which to **12** occurred promptly upon exposure to cat. aq. HCl. Hydrolysis of the oxazolone in **12** occurred quite readily under mild conditions to afford (±)-**13**: the MOM ether of **2a** (Scheme 2).

In stark contrast to HPCA and related systems, compound **13** underwent facile N-2 acylation. Even weak acylating agents such as 4-nitrophenyl esters in the presence of N-hydroxy-benzotriazole (HOBt) converted **13** to

Scheme 3

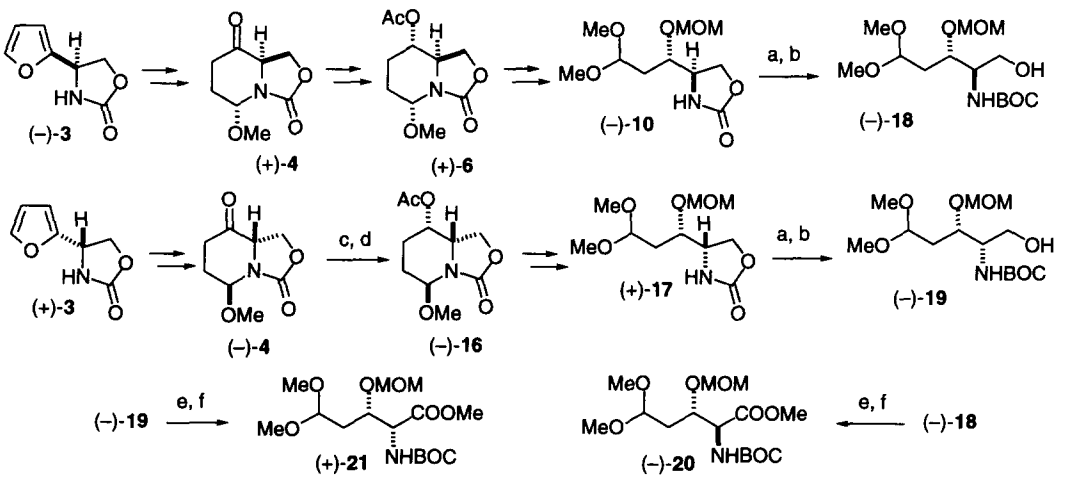


(a) 4-Nitrophenyl-*n*-octanoate, 10 mol% HOBt, MeCN, RT, 58% after rough chrom.;[15] (b) Ac_2O, pyr., 56% chrom.

N-2 amides, e.g., **14**. In light of this, one must conclude that N-2 acylation of piperazic acids **1** and congeners is unlikely to fail because of steric effects. It rather seems that this may be due to inductive erosion of the nucleophilicity of the N-2 atom promoted by the COOR unit. Almost nothing is known in the literature regarding the acylation of cyclic hydrazones[11] of the type **2**, so it is also worthy of note that reaction with Ac_2O/pyridine produced only **15**, with no evidence of N-1 acylation and consequent enamide formation (Scheme 3).

As a useful spin-off of these investigations, optically active materials of the type **10** emerged as versatile building blocks for β-hydroxy-α-aminoacids of either *syn* or *anti* relative stereochemistry, and of either *D* or *L* configuration. To illustrate, oxazolones (–)-**3** and (+)-**3** are readily available in high optical purity by a simple chemoenzymatic protocol.[5,12] Rearrangement to (+)-**4** and (–)-**4** (Scheme 4) and stereoselective reduction of the ketone to an equatorial ($NaBH_4$) or an axial (L-Selectride)[5] carbinol, set the stage for advancement to compounds (*L*)-(–)-**10** and (*D*)-(+)-**17** by the same procedure detailed earlier for the racemic series. Kunieda-type opening of the oxazolones[13] delivered N-BOC protected aminoalcohols *anti*-(*L*)-(–)-**18** and *syn*-(*D*)-(–)-**19**, which were oxidized to carboxylic acids as described by Garner[14] and esterified (CH_2N_2) to *anti*-(*L*)-(–)-**20** and *syn*-(*D*)-(+)-**21**, respectively, with only marginal loss of optical integrity. Richly functionalized **18** - **21** should be useful for the preparation of sphingobases, hydroxyaminoacids, peptidomimetics, and other nitrogenous substances.[15]

Scheme 4



(a) BOC_2O, 4-DMAP, Et_3N, THF; (b) Cs_2CO_3, MeOH, rt, 93% a-b; (c) L-Selectride, THF, –78°C, 88%; (d) Ac_2O, pyr, 97%; (e) $KMnO_4$, aq. NaOH, RT; (f) CH_2N_2, Et_2O, 51% chrom. e-f.

In summary, the reluctance of compounds **1** to undergo N-2 acylation is most likely due to an inductive, not a steric, effect. Therefore, little or nothing can be done to overcome this inherent molecular property of those systems. Fortunately, alternative methods for the *indirect* formation of peptides containing piperazic acids are now available.[1a] These conclusions should provide useful guidelines for charting future syntheses of oligopeptides incorporating piperazic acids and related building blocks.

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References and Footnotes

1. (a) Ciufolini, M. A.; Xi, N. *J. Org. Chem.* **1997**, *62*, 2320; (b) Ciufolini, M. A.; Xi, N. *J. Chem. Soc., Chem. Commun.* **1994**, 1867; (c) Hale, K. J.; Delisser, V. M.; Yeh, L.-K.; Peak,S. A.; Manaviazar, S.; Bhatia, G. S. *Tetrahedron Lett.* **1994**, *35*, 7685; (d) Schmidt, U.; Riedl, B. *Synthesis* **1993**, 809; (e) Rebert, N. W. *Dissertation*, Utah State University, 1987.
2. Konishi, M.; Ohkuma, H.; Sakai, F.; Tsuno, T.; Koshiyama, H.; Naito, T.; Kawaguchi, H. *J. Am. Chem. Soc.* **1981**, *103*, 1241; Arnold, E.; Clardy, J. *J. Am. Chem. Soc.* **1981**, *103*, 1243.
3. Cf. Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, NY, 1994; pp. 696-697 and references cited therein.
4. All calculations described here were carried out with the PC-based Hyperchem® 4.0 package, by Hypercube, Inc, Ontario, Canada.
5. Cf. Ciufolini, M. A.; Hermann, C. Y. W.; Whitmire, K. H.; Byrne, N. E. *J. Am. Chem. Soc.* **1989**, *111*, 3473, and references cited therein.
6. Xi, N. unpublished results from these laboratories.
7. Ciufolini, M. A.; Wood, C. Y. *Tetrahedron Lett.* **1986**, *27*, 5085.
8. This reagent, developed by Prof. T. Fukuyama, formerly of this Department, is especially useful for enamide formation from mixed amidals of the type **16**: cf. ref. 7.
9. Luche, J. L.; Gemal, A. L. *J. Chem. Soc., Chem. Commun.* **1978**, 976.
10. a. Klotzer, W. *Synthesis* **1982**, 592; b. Harger, M. J. P. *J. Chem. Soc., Chem. Commun.* **1981**, 3284.
11. Cf. Curtius, T.; Zinkeisen, E. *J. Prakt. Chem.* **1898**, *58*, 310.
12. Drueckhammer. D. G.; Barbas, III, C. F.; Nozaki, K.; Wong, C. H.; Wood, C. Y., Ciufolini, M. A. *J. Org. Chem.* **1988**, *53*, 1607.
13. Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.* **1987**, *28*, 4185.
14. Garner, P. *Tetrahedron Lett.* **1984**, *25*, 5855.
15. All cpds. except **11** and **15** were fully characterized (^{1}H & ^{13}C NMR, IR, low and high res. mass spec.), and all except **11** (sensitive) and **14** (contam. HOBt) were purified to homogeneity (NMR, TLC). Data for represent. cpds. (^{1}H and ^{13}C [250, 75 MHz] in $CDCl_3$, δ, ppm; opt. rot. with Na D line, 25°C, in EtOH): (*L*)-(–)-**10**: oil; [α] = –6° (c=0.64). ^{1}H: 5.76 (br.s, 1H), 4.69 (d, 1H, J=7.0 Hz), 4.62 (d, 1H, J=7.0 Hz), 4.53 (t, 1H, J=5.3 Hz), 4.45 (dd, 1H, J1≈J2=8.8 Hz), 4.27 (dd, 1H, J=8.8, 5.3 Hz), 3.92 (ddd, 1H, J=8.8, 4.5, 1.0 Hz), 3.71(quintet, 1H, J=5.4 Hz), 3.38 (s, 3H), 3.34 (s, 3H), 3.32 (s, 3H), 1.84 (t, 2H, J=5.4 Hz). ^{13}C: 159.4, 101.3, 96.5, 76.2, 67.2, 56.0, 55.0, 53.7, 52.7, 34.1. (±)-**13**: ^{1}H: 6.70 (t, 1H; J=2.7 Hz), 5.86 (br.s, 1H), 4.70 (d, 1H; J=6.8Hz), 4.65 (d, 1H; J=6.8 Hz), 3.88 (dd, 1H; J=7.6, 1.7 Hz), 3.82 (dd, 1H; J=6.4, 2.5 Hz), 3.67 (dd, 1H; J=11.3, 6. 5Hz), 3.36 (s, 3H), 2.98 (dt, 1H; J=5.9, 3.1 Hz), 2.60, (ddd, 1H; J=18.6, 6.7, 3.0 Hz), 2.21 (ddd, 1H; J=18.6, 7.9, 1.7 Hz). ^{13}C: 139.3, 95.4, 68.7, 61.3, 57.6, 55.6, 31.8. (±)-**14**: ^{1}H: 7.25 (br. s, 1H), 4.77 (d, 1H; J=6.8 Hz), 4.74 (d, 1H; J=7.0 Hz), 4.06 (dd, 1H; J=12.1, 3.8 Hz), 3.92 (dd, 1H; J=12.1, 2.6Hz), 3.39 (s, 3H), 2.85(m, 1H), 2.55 (dt, 1H; J=16.3, 8.1 Hz), 2.26 (ddd, 1H; J=14.0, 10.0, 6.5 Hz), 1.60-1.47 (br.m, 2H), 1.30-1.16 (br. m, 10H), 0.84 (t, 3H; J=6.70 Hz). (*D*)-(+)-**17**: oil; [α] =+32° (c=0.24). ^{1}H: 6.47 (br.s, 1H), 4.68 (d, 1H; J=7.1 Hz), 4.64 (d, 1H; J=7.1), 4.50 (t, 1H; J=5.4 Hz), 4.39 (dd, 1H; J_1≈J_2=8.8 Hz), 4.12 (dd, 1H; J=8.8, 5.9 Hz), 3.90 (dt; 1H; J=8.6, 6.2, Hz), 3.59 (quintet, 1H; J= 6.0 Hz), 3.37 (s, 3H), 3.30 (s, 6H), 1.74 (t, 2H; J=5.6 Hz). ^{13}C: 159.5, 101.4, 97.2, 78.2, 66.6, 55.9, 55.6, 53.3, 34.3. (*L*)-(–)-**20**: oil; [α] = –22° (c=0.52). ^{1}H: 5.73 (br.d, 1H; J=8.9 Hz), 4.69 (d, 1H; J=7.0 Hz), 4.62 (d, 1H; J=7.0 Hz), 4.53 (dd, 1H; J=7.5,4.2 Hz), 4.43 (dd, 1H; J=8.8, 2.6 Hz), 3.93 (1H, ddd; J=4.5, 4.4, 3.0 Hz), 3.76 (S, 3H), 3.41 (s, 3H), 3.30 (s, 3H), 1.92 (m, 2H). ^{1}H: 170.5, 155.5, 101.5, 97.1, 79.8, 76.8, 56.7, 56.0, 53.1, 52.5, 52.2, 35.3, 28.3.

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