Diastereofacial Selectivity in Reduction of Chiral Tetramic Acids[1]

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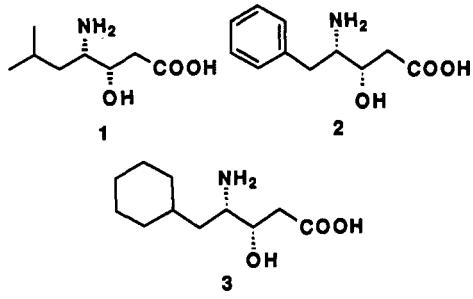
The reduction of (5*S*)-5-alkyl-2,4-dioxopyrrolidines, so-called tetramic acids, by $NaBH_4$ gives only partial diastereofacial selectivity in the case of the N-substituted analogues **9f–i**, unlike the carbamate derivatives **9a–e** which give the reduced *cis*-pyrrolidinones **10β a–e**. Increasing the steric hindrance of either the N- or C-5-substituents enhances the *re*-face selectivity. On the other hand, reduction of the heterobicyclic compound **9n** leads to a dramatic reversal of the stereoselectivity. Preliminary calculations show that the N-atom of the ring is slightly pyramidalized; the direction of hydride addition could be a consequence of this finding.

Introduction

Statine ((3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid) (**1**) and its congeners (3*S*,4*S*)-4-amino-3-hydroxy-5-phenylpentanoic acid (AHPPA) (**2**) and (3*S*,4*S*)-4-amino-3-hydroxy-5-cyclohexylpentanoic acid (ACHPA) (**3**) have been widely used in the design of pseudopeptides which inhibit renin and other aspartic proteases.[2] It is currently accepted that these γ-amino acids replace the scissile bond of the substrate as a mimetic transition state structure. In this context, only the γ-amino-β-hydroxy acids of the *syn* configuration can generally adopt a suitable conformation.



In a preceding report, we showed that *syn*-γ-amino-β-hydroxy acids can be prepared in good yield and high enantiomeric excess from chiral amino acids by a four-step procedure[3a] whose interest was recently underlined by Schmidt et al.[3b] The key step is the totally stereoselective $NaBH_4$ reduction of an intermediate *N*-(alkyloxycarbonyl)tetramic acid.[4]

In an earlier study, Katsuki and Yamaguchi[5a] claimed that the catalytic hydrogenation of the N-unsubstituted tetramic acid **9g** derived from leucine yielded, exclusively, the *cis*-alcohol **10βg**, a finding that was also reported by Klutchko et al.[5b] Similarly, Palomo et al. reported a totally stereoselective *cis* reduction of *N*-aryl-5-phenyl-2,4-dioxopyrrolidines.[5c] On the other hand, we indicated in a recent study[5d] that both diastereomeric alcohols (4*S*,5*S*)- and (4*R*,5*S*)-4-hydroxy-5-benzyl-2-pyrrolidinones **10αi** and **10βi** are formed by $NaBH_4$ reduction of the corresponding tetramic acid **9i**. A similar result was obtained by Schmidt et al. for compound **9h** using either catalytic hydrogenation or $NaBH_4$ reduction.[3b]

Given these contradicting results, $NaBH_4$ reduction or catalytic hydrogenation of the (5*S*)-5-isobutyl-2,4-dioxopyrrolidine (**9g**) was reexamined. In our hands, both $NaBH_4$ reduction and catalytic hydrogenation of this ketone afforded a mixture of the epimeric alcohols **10αg** and **10βg** in ratios of 32:68 and 14:86, respectively.

These results prompted us to elucidate the origin of the diastereofacial selectivity of reduction of (5*S*)-5-alkyl-2,4-dioxopyrrolidines. To this end, the reduction of compounds **9e–n** bearing various substituents on the N and the C-5 atoms was investigated.

Results

Preparation of the tetramic acids **9a–n** is outlined in Scheme I. The *N*-carbamoyl and *N*-acyl derivatives **9a–e** were obtained by cyclization of adducts **5a–e**, obtained by the addition of Meldrum's acid to the corresponding amino acid (route a).[3a] N-free tetramic acids **9f–i** resulted from trifluoroacetic acid treatment of the *N*-Boc derivatives. N-Alkylated compounds **9j–n** were obtained by Dieckmann cyclization of the *N*-malonyl intermediates **7j–n** (route b).[5d] Starting from Boc-MeLeu or Boc-MeVal, MeLeu-OMe (**6j**) and MeVal-OMe (**6k**) were obtained by esterification (Cs_2CO_3, MeI) followed by trifluoroacetic acid deprotection. *i*-PrAla-OtBu (**6l**) and *i*-PrLeu-OMe (**6m**) were prepared by reductive amination of Ala-OtBu and Leu-OMe, respectively, with acetone under catalytic hydrogenation conditions. The corresponding N-malonyl

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(1) Nomenclature, abbreviations, and symbols follow the recommendations of Nomenclature of Organic Chemistry (sections A, B, C, D, E, F, and H; Pergamon: Oxford, 1979) and of IUPAC-IUB Joint Commission on Biochemical Nomenclature (*Eur. J. Biochem.* **1984**, *138*, 9). In addition, the following abbrevations are used: BroP, tris(dimethylamino)bromophosphonium hexafluorophosphate; TEA, triethylamine.

(2) (a) Rich, D. H. In *Proteinase Inhibitors*; Barrett, A. J., Salvesen, G.; Eds.; Elsevier: Amsterdam, 1986; pp 179–217. (b) Hui, K. Y.; Carlson, W. D.; Bernatowicz, M. S.; Haber, E. *J. Med. Chem.* **1987**, *30*, 1287. (c) Maibaum, J.; Rich, D. H. *J. Med. Chem.* **1989**, *32*, 1571. (d) Dreyer, G. B.; Metcalf, B. W.; Tomaszek, T. A., Jr.; Carr, T. J.; Chandler, A. C., III; Hyland, L.; Fakhoury, S. A.; Magaard, V. W.; Moore, M. L.; Strickler, J. E.; Debouk, C.; Meek, T. D. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 9752.

(3) (a) Jouin, P.; Castro, B.; Nisato, D. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1177. (b) Schmidt, U.; Riedl, B.; Haas, G.; Griesser, H.; Vetter, A.; Weinbrenner, S. *Synthesis* **1993**, 216.

(4) For recent work on synthesis of tetramic acids see: Ley, S. V.; Smith, S. C.; Woodward, P. R. *Tetrahedron* **1992**, *48*, 1145 and refs cited therein.

(5) (a) Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3287. (b) Klutchko, S.; O'Brien, P.; Hodges, J. C. *Synth. Commun.* **1989**, *19*, 2573. (c) Palomo, C.; Cossio, F. P.; Rubiales, G.; Aparicio, D. *Tetrahedron Lett.* **1991**, *32*, 3115. (d) Poncet, J.; Jouin, P.; Castro, B.; Nicolas, L.; Boutar, M.; Gaudemer, A. *J. Chem. Soc., Perkin Trans. 1* **1990**, 611.

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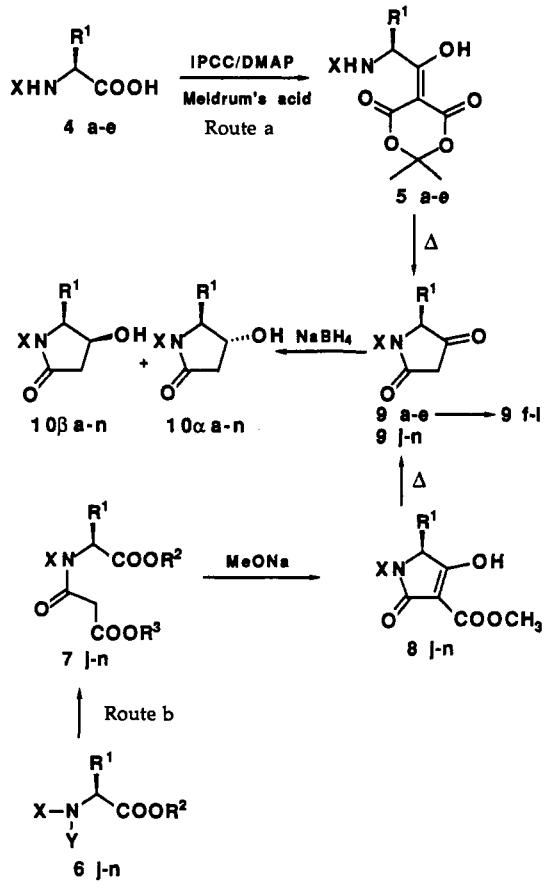
Scheme I



	X	R^1	R^2	Y	R^3
a	Z	Me	-	H	-
b	Boc	*i*-Bu	-	H	-
c	Boc	*i*-Pr	-	H	-
d	Boc	Bzl	-	H	-
e	Ac	*i*-Bu	-	H	-
f	H	Me	-	H	-
g	H	*i*-Bu	-	H	-
h	H	*i*-Pr	-	H	-
i	H	Bzl	-	H	-
j	Me	*i*-Bu	Me	Boc	Me
k	Me	*i*-Pr	Me	Boc	Me
l	*i*-Pr	Me	*t*-Bu	H	Et
m	*i*-Pr	*i*-Bu	Me	H	Me
n	$-(CH_2)_3-$		Me	H	Me

derivatives **7j,k,m,n** were synthesized by condensation of potassium ethyl malonate on **6j,k,m,n** using BroP as the coupling reagent.[6] Compound **7l** was obtained by reaction of **6l** with ethyl malonyl chloride. Cyclization of **7j–n** was achieved with sodium methoxide as described previously,[5d] leading to the N-substituted tetramic acids **9j–n**, after decarboxylation of intermediates **8j–n** in refluxing dilute sulfuric acid.

The *trans/cis* ratios obtained in the reduction of **9a–n** are given in Table I. This ratio was determined by ^1H NMR on the basis of following argument. The configurations of the diastereoisomers **10αg** and **10βg** were established by ^1H NMR studies: the NOE between protons H-4 and H-5 were 2.7–2.8% for the minor isomer and 7–8% for the major one. This led to the assignment of the *trans*

(6) Coste, J.; Dufour, M. N.; Pantaloni, A.; Castro, B. *Tetrahedron Lett.* **1990**, *31*, 669.

Table I. Stereoselectivity of the $NaBH_4$ Reduction of Compounds 9

			δ H-4, ppm		
tetramic acid	X	R^1	10α	10β	10α/10β ratio[a]
9a	Z	Me	-	4.82	0:100[b]
9b	Boc	*i*-Bu	-	4.30	0:100[b]
9c	Boc	*i*-Pr	-	4.46	0:100[b]
9d	Boc	Bzl	-	4.30	0:100[b]
9e	Ac	*i*-Bu	-	4.35	0:100[b]
9f	H	Me	3.86	4.15	34:66
9g	H	*i*-Bu	3.86	4.17	32:68
9h	H	*i*-Pr	3.95	4.18	4:96
9i	H	Bzl	3.95	4.10	18:82[c]
9j	Me	*i*-Bu	3.90	4.18	15:85
9k	Me	*i*-Pr	-	4.40	0:100
9l	*i*-Pr	Me	3.95	4.15	3:97[d]
9m	*i*-Pr	*i*-Bu	-	4.18	0:100
9n	$-(CH_2)_3-$		4.03[e]	4.20[e]	95:5
9n	$-(CH_2)_3-$		4.03[e]	4.20[e]	43:57[f]

[a] Determined by ^1H NMR on the H-4 signal (H-1 in the case of **10n**). [b] Reference 3a. [c] Reference 5d. [d] Determined on the H-3 signal, the H-4 signal of the *trans* isomer being masked by the CH proton of the isopropyl group. [e] H-4 corresponds to H-1 in this case. [f] Using K-selectride, in THF at −78 °C, as reducing agent.

configuration for the minor component **10αg** and the *cis* configuration for the major component **10βg**. This assumption was confirmed chemically; the major isomer was identical to the pure *cis*-alcohol **10βg** which was prepared independently from the pure *N*-(*tert*-butyloxycarbonyl) *cis* compound **10βb**[3a] by TFA treatment. In a previous report, the same demonstration was applied to **10αi** and **10βi**.[5d] In both cases, the H-4 proton of the *trans* isomer **10α** exhibits a lower field resonance (3.86 and 3.95 ppm, respectively) than that of the H-4 proton of the *cis* isomer **10β** (4.17 and 4.10 ppm, respectively). Configurations of the other alcohols were assigned by reasonable analogy with these findings (Table I); consequently, the *trans* configuration (compounds **10α**) was attributed to the isomer showing the lowest chemical shift for the H-4 proton.

As in the case of the pyrrolidonecarbamates,[3a] reduction of the *N*-acetyl compound **9e** led to a single alcohol. The H-4 chemical shift (4.35 ppm) is consistent with the *cis* configuration. Moreover, the H-4 and H-5 protons exhibited a NOE of 7%. Thus, we concluded that the reduction of **9e** afforded alcohol **10βe**. The *trans* stereoisomer **10αe** could not be detected by HPLC analysis or ^1H NMR.

In the case of the N-unsubstituted pyrrolidinones **9f–h**, the major products **10βf–i** arose from an attack of the less-hindered *re*-face; an increase in selectivity was observed for the bulkier isopropyl 5-substituent compared with the methyl substituent (Table I, entries f–i). Reduction of the benzyl derivative **9i** was more selective than that of the isobutyl derivative **9g**, which is not surprising since a phenyl group is considered to be larger than an isopropyl group.[7]

A priori, no greater selectivity was expected for the reduction of derivatives **9j–m** compared with the corresponding N–H derivatives **9f–h**. Surprisingly, as the size of the N-substituent X increased, the diastereofacial selection did also (compare entries g, j, and m, or f and l, or h and k in Table I).

Finally, reduction of the bicyclic compound **9n** led to a mixture of diastereoisomers in a 95:5 ratio (yield 83%).

(7) Hirsh, J. A. *Top. Stereochem.* **1967**, *1*, 199.

The diastereomerically pure major alcohol obtained by crystallization in ethyl acetate–hexane showed physical data identical to the *trans*-alcohol **10αn** prepared either by Hanson et al.[8a] or by Beckett et al.[8b,c] Therefore, in the case of **9n**, reduction of the carbonyl function proceeded with a dramatic reversal of stereoselectivity. This ratio can be partially reversed to 43:57 by using the bulky K-Selectride.

Discussion

Stereoselective additions to trigonal centers have been extensively studied using various models.[9] Among them, the Felkin–Ahn model supported by the *ab initio* calculations of Ahn and Eisenstein[10] which take into account the Bürgi–Dunitz trajectory[11] is well accepted. Recently, Lodge and Heathcock showed[12] that diastereofacial selection in nucleophilic addition to chiral aldehydes and ketones is related to this trajectory analysis, and this is consistent with the observation that asymmetric induction increases with steric effects.

This model accounts for the significant differences in diastereoselectivity observed in the reduction of the N-unsubstituted derivatives **9f–i**, but it does not fully explain the complete selectivity observed in the reduction of the corresponding carbamate derivatives **9a–d** or the *N*-acetyl compound **9e**. This stereochemical control might result from chelation of the reducing agent by the acyl group on the less-hindered *re*-face of the flat tetramic ring. The participation of the carbamoyl group in a transition state complex was envisioned in several other reports, such as in the reduction of chiral γ-amino β-keto esters,[13a,b] in the diastereocontrolled epoxidation of amino allylic alcohols derived from amino acids[14] as well as in numerous organometallic additions to α-amino aldehydes.[15]

The discrepancies in the diastereoselection obtained with the N-unsubstituted derivatives and the *N*-alkyl ones are more disturbing if we consider that the N-substituent participates, *a priori*, in a similar manner in the hindrance of the two faces of the ring. Moreover, the major isomer **10αn** obtained by reduction of **9n** is the result of an attack of the most crowded *si* face. Thus, since direct steric effects are not sufficient to explain our results, we considered the stereoelectronic involvement of the N-lone pair whose directing effects have already been postulated.[16a] A similar effect of the O-lone pairs was noticed by Seebach to account for remote stereoselectivity in dioxinones.[9a]

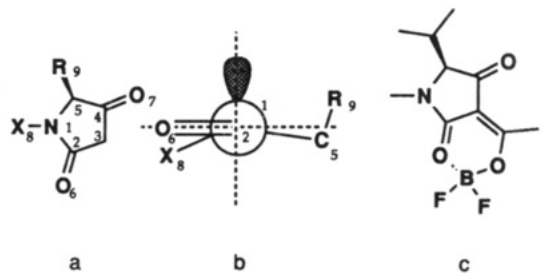


Figure 1.

Table II. Calculated Geometrical Parameters of Tetramic Acids 9[a]

entry	X	R	sum[b], deg	6–2–1–5, deg	6–2–1–8, deg	diff,[c] deg
1	H	H	360.00	180.0	0.0	180.0
2	H	Me	360.00	179.4	0.0	179.4
3	H	*i*-Bu	359.91	−179.2	−2.4	−176.8
4	Me	*i*-Bu	359.76	179.0	4.4	174.6
5	Me	*i*-Pr	359.84	179.3	3.7	175.6
6	*i*-Pr	Me	359.77	179.1	4.4	174.7
7	*i*-Pr	*i*-Bu	359.77	179.5	4.9	174.6
8	$-(CH_2)_3-$		352.42	−171.7	−24.0	−147.7
9[d]	Me	*i*-Pr	359.74	177.8	3.4	174.4

[a] See Figure 1a for numbering of atoms. [b] Sum of the three-bond angles around N. [c] Difference between 6–2–1–5 and 6–2–1–8. [d] Measured from the X-ray data of 3-[1-(difluoroboryloxy)ethylidene]-5-isopropyl-1-methylpyrrolidine-2,4-dione (Figure 1c) (ref 18).

Since an amide function is not rigorously planar and the N atom is slightly pyramidal,[17] and given the vicinal steric interaction between the C-5- and the N-substituents, we propose that the nitrogen atom of compounds **9a–m** adopts the preferred geometry with the lone pair rejected on the same face as the R_9 group (Figure 1b). In the case of the bicyclic compound **9n**, the configuration of the nitrogen atom must be reversed, due to the ring constraints.

To assess these hypotheses, preliminary calculations were carried out to determine the structure of the tetramic acids in the ground state. These compounds were built with the INSIGHT I molecular graphics program and the potential energies of the models were refined through molecular mechanics and molecular dynamics with DISCOVER using the CVFF force field (Biosym Technologies Inc., San Diego, CA). To determined the lowest energy conformation of the ring substituents, the initial models were submitted to 2 ps molecular dynamics at 900 K followed by 2 ps at 300 K. Then, a conjugate gradient minimization was performed until the root mean square of the gradients was 10^{-5} kcal/Å. During the last cycles a morse potential was used for the bond stretching term, and cross terms were added. The same procedure was repeated using three different starting conformations for each substituent with more than one carbon atom to ensure that the global minimum had been located. The results are listed in Table II.

The parameters used for the nitrogen atom correspond to an sp^2 nitrogen of an amide group and therefore tend

(8) (a) Hanson, G. J.; Baran, J. S.; Lindberg, T. *Tetrahedron Lett.* **1986**, *27*, 3577. (b) The syn isomer was described by Beckett, R. P.; Davies, S. G.; Mortlock, A. A. *Tetrahedron Asymm.* **1992**, *3*, 1123. (c) Our assumption concerning the NMR assignment of the configuration of alcohols **10** was also confirmed in the case of ref 8b.

(9) For interesting discussion see (a) Seebach, D.; Zimmermann, J.; Gysel, U.; Ziegler, R.; Ha, T. K. *J. Am. Chem. Soc.* **1988**, *110*, 4763. (b) Wu, Y. D.; Tucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5018 and refs cited therein.

(10) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61.

(11) (a) Bürgi, H. B.; Dunitz, J. D.; Shefter, J. D. *J. Am. Chem. Soc.* **1973**, *95*, 5065. (b) Bürgi, H. B.; Lehn, J. M.; Wipff, G. J. *J. Am. Chem. Soc.* **1974**, *96*, 1956. (c) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. J. *Tetrahedron* **1974**, *30*, 1563. (d) Liotta, C. L.; Burgess, E. M.; Eberhardt, W. H. *J. Am. Chem. Soc.* **1984**, *106*, 4849.

(12) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353.

(13) (a) Dufour, M.-N.; Jouin, P.; Poncet, J.; Pantaloni, A.; Castro, B. *J. Chem. Soc., Perkins Trans. 1* **1986**, 1895. (b) Harris, B. D.; Joullié, M. *Tetrahedron* **1988**, *44*, 3489.

(14) Kogen, H.; Nishi, T. J. *J. Chem. Soc. Chem. Commun.* **1987**, 311.

(15) (a) Vara Prasad, J. V. N.; Rich, D. H. *Tetrahedron Lett.* **1990**, *31*, 1803. (b) Reetz, M. T. *Pure Appl. Chem.* **1988**, *60*, 1607.

(16) (a) Meyers, A. I.; Wallace, R. H. *J. Org. Chem.* **1989**, *54*, 2509. (b) Curran, D. P.; Kim, B. H.; Daugherty, J.; Heffner, T. A. *Tetrahedron Lett.* **1988**, *29*, 3555. (c) Oppolzer, W.; Poli, G.; Starkemann, C.; Bernardinelli, G. *Tetrahedron Lett.* **1988**, *29*, 3559. (d) Seebach, D.; Juaristi, E.; Miller, D. D.; Schickli, C.; Weber, T. *Helv. Chim. Acta* **1987**, *70*, 237. (e) Magnus, P.; Gallagher, T.; Brown, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 2105.

(17) (a) Bennet, A. J.; Somayaji, V.; Brown, R. J.; Santarsiero, B. D. *J. Am. Chem. Soc.* **1991**, *113*, 7563. (b) Cieplak, A. S. *J. Am. Chem. Soc.* **1985**, *107*, 271.

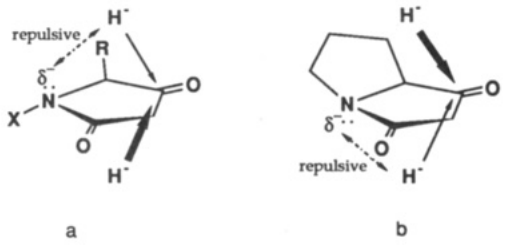


Figure 2. Direction of hydride attack in the case of electrostatic interactions.

to produce planar nitrogen. Indeed, the model of the unsubstituted tetramic acid shows a planar nitrogen with the sum of the valence angles around the nitrogen atom exactly equal to 360° (Table II, entry 1, column sum). The planarity can also be deduced from the difference between the dihedral angles formed between the amide CO bond and the two non-amide nitrogen bonds which are at 180° and 0° in the unsubstituted compound (Table II, entry 1, column diff). This indicates that deviations from planarity in the other model compounds are simply a consequence of the presence of steric hindrance or ring strain.

In all cases (Table II, entries 4–7), the nitrogen atom is always slightly nonplanar (columns sum and diff in Table II) with the top of the umbrella (the N-lone pair) directed toward the same side (*re*-face) of the tetramic acid plane as the C-5 substituent R_9 (Figure 1b). These results are supported by the observation of the same feature in the X-ray structure of 3-[1-(difluoroboryloxy)ethylidene]-5-isopropyl-1-methylpyrrolidine-2,4-dione (Table II, entry 9).[18] In the case of the N-unsubstituted compounds (entries 2, 3), the deviations from flatness are not really significant. Although there are no significant differences between all these compounds, we can reasonably assume that increasing the steric hindrance of the N-substituent will increase the pyramidalization of the nitrogen. In the bicyclic derivative **9n**, the nitrogen atom is markedly nonplanar with the top of the umbrella directed toward the *re*-face (Table II, entry 8).

Taking into account this pyramidalization and, consequently, the situation of the lone pair on one side of the ring, various theoretical models can be invoked to explain our results. Increasing the pyramidalization could enhance the electronic density on one side of the amide bond. Therefore, the inverted outcome observed for **9n** could be due to a predominant repulsive electrostatic interaction between the hydride and the negative charge on the nitrogen atom as already discussed by Houk and coworkers[9b] in the case of hydride addition to 4-substituted cyclohexanones. For **9f–m** the steric and the electrostatic effects act in the same direction, whereas for **9n** they act in opposite direction (Figure 2).

Given the frontier orbital approach developed by Ahn and Eisenstein,[10] interactions as depicted in Figures 3b,c can be envisaged. In this model, the nucleophile enters from the side that allows the best overlapping of the LUMO of the electrophile (π_{CO}*) and an antiperiplanar (with respect to the newly-formed CH bond) vicinal σ_{CG}*. Our calculations gave values of 17.5° and 28.5°, respectively, for the dihedral angles α and β of **9n** (Figure 3a), suggesting that addition of the hydride from the *si*-face requires less torsional energy. Moreover, a two-electron stabilizing

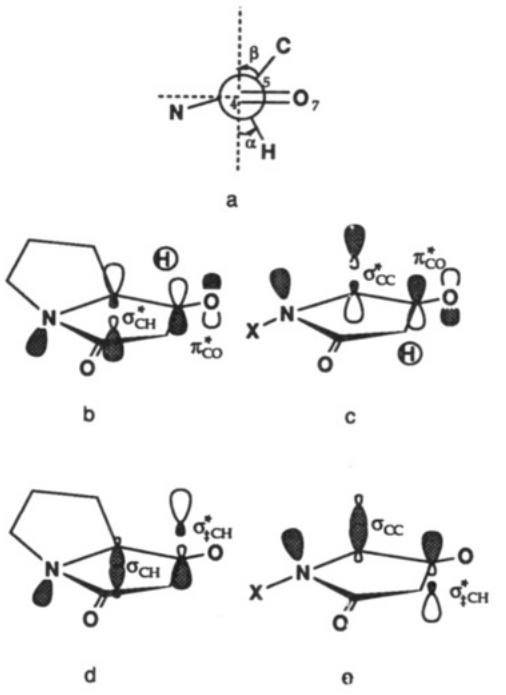


Figure 3. Transition states corresponding to the Ahn–Eisenstein model (b,c) or the Cieplak model (d,e).

interaction $n\sigma_{CH}$* could favor this geometry. In the case of **9l** the calculated values were 28.3° and 27.9° for α and β, respectively, whereas for the corresponding crystallized compound[18] an experimental value of 25.0° was found for β. The energy required to orient either the CH or the CC bond antiperiplanar to the forming bond is probably approximately the same, suggesting that the reaction could proceed through the transition state shown in Figure 3c to take into account the stabilizing effect of the N-lone pair. Increasing the size of X would increase the pyramidalization of the N-atom toward the *si*-face because of steric interactions between X and R^1, thus favoring the antiperiplanar attack from the *re*-face. As in the case of the preceding electrostatic model, both steric and electronic effects acts in the same direction for **9f–m**.

The controversial "Cieplak postulate" has been invoked in several examples.[9,16a,19] This qualitative model, developed by Cieplak[19a] to explain the preferred axial attack on cyclohexanone predicts that an incoming nucleophile will add to a carbonyl from the face that permits the best antiperiplanar hyperconjugative stabilization from an adjacent σ-bond [$\sigma \rightarrow \sigma_{\ddagger}^{*}$ donation] (*i.e.*, the attack is antiperiplanar to the best donor bond). The corresponding models for derivatives **9n** and **9f–m** are depicted in Figures 3, parts d and e. Taking into account the preceding comment concerning the values of the angles α and β, this model gives a good prediction for the reduction of **9n** if we assume that σ_{CH} bonds are better than σ_{CC} bonds as electron donors, which is generally admitted.[20] In the case of the other compounds, the increase of stereoselectivity from **9g** to **9h** or from **9j** to **9k**, for instance, is in agreement

(18) Jones, R. C. F.; Begley, M. J.; Peterson, G. E.; Sumaria, S. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1959.

(19) (a) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540. (b) Danishefsky, S.; Langer, M. E. *J. Org. Chem.* **1985**, *50*, 3674. (c) Chung, W. S.; Turro, N. J.; Srivastava, S.; Li, H.; Le Noble, W. J. *J. Am. Chem. Soc.* **1988**, *110*, 7882. (d) Macaulay, J. B.; Fallis, A. G. *J. Am. Chem. Soc.* **1990**, *112*, 1136. (e) Burgess, K.; van der Donk, W. A.; Jarstfer, M. B.; Ohlmeyer, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 6139. (f) Coxon, J. M.; McDonald, D. Q. *Tetrahedron Lett.* **1992**, *33*, 651. (g) Coxon, J. M.; McDonald, D. Q. *Tetrahedron* **1992**, *48*, 3353.

(20) See for example ref 19d and refs cited herein.

with an increase in the bulkiness of the C-5-substituent but also with an enhancement of the hyperconjugative power of the CC bond due to its greater substitution. However, the role of the N-substituent in this model appears less clear since one would expect that the effect of the N-lone pair is to act as a destabilizing rather than a stabilizing factor.

Finally, Seebach et al.,[21] on the basis of experimental data and computational calculations, suggested that pyramidalization of trigonal carbon could be used for predicting the stereoselective course of reactions. Nevertheless, in our case, C-4 was always found to be planar. This planarity was also observed in the solid state.[18]

Our findings show that the stereochemistry of the reduction of the carbonyl function of tetramic acids can be correlated with the pyramidalization of the nitrogen atom and accommodated within various established theoretical models. Further experiments are now under investigation to confirm this assumption and to try to validate one of them.

Experimental Section

General Procedures. "Usual workup" means washings of the organic phase with 1 M HCl, 5% $NaHCO_3$, and brine, drying over Na_2SO_4, filtration, and concentration of the solvent in vacuo. Analytical TLC was performed on silica gel $60F_{254}$ aluminum sheets (0.2 μm thick). Column chromatography was performed using silica gel 70–200 μm. Melting points were determined using a Buchi melting point apparatus. Optical rotations were measured at *c* 1 in MeOH. ^1H NMR data were recorded at 360 MHz in DMSO-d_6 unless specified otherwise. Mass spectra were obtained in the FAB+ mode from the Department of Physical Measurements of the University of Montpellier II. Elemental analyses were performed by the CNRS, at the Ecole Nationale Supérieure de Chimie de Montpellier. BroP reagent was synthesized according to Castro.[22]

Methyl *N*-Methyl-*N*-(*tert*-butoxycarbonyl)-L-leucinate (6j). To a solution of Boc-L-MeLeu[23] (3.68 g, 15 mmol) and MeI (1.88 mL, 30 mmol) in DMF (25 mL) was added Cs_2CO_3 (2.43 g, 7.5 mmol). The mixture was stirred for 90 min at rt. The solvent was then evaporated under reduced pressure and the residue dissolved in EtOAc (50 mL). Usual workup led to a yellow oily residue which was purified by chromatography (120 g; EtOAc/hexane, 20:80), yielding **6j** as a colorless oil (3.15 g, 81%): R_f 0.55 (EtOAc/hexane, 40:60); $[\alpha]^{20}_D$ −37°; ^1H NMR (two conformers 50:50) δ 0.80–0.93 (6 H, m), 1.36 and 1.39 (9 H, s), 1.51–1.62 (1 H, m), 1.64–1.76 (2 H, m), 2.70 (3 H, s), 3.63 (3 H, s), 4.39–4.50 and 4.63–4.74 (1 H, m); MS *m/z* (rel inten) 260 (MH^+, 7), 160 (65), 100 (63), 69 (100). Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.2; H, 9.7; N, 5.4. Found: C, 60.0; H, 9.7; N, 5.0.

Methyl *N*-Methyl-*N*-(*tert*-butoxycarbonyl)-L-valinate (6k). Ester **6k** was obtained as an oil from Boc-L-MeVal[23] by the preceding procedure (2.20 g, 78%): $[\alpha]^{20}_D$ +8°; ^1H NMR (two conformers, 50:50) δ 0.83 (3 H, d, *J* = 6.9 Hz), 0.89 (3 H, d, *J* = 6.8 Hz), 1.35 and 1.43 (9 H, s), 1.90–2.11 (1 H, m), 2.69 (3 H, s), 3.68 (3 H, s), 4.10 (0.5 H, d, *J* = 3.9 Hz) and 4.44 (0.5 H, d, *J* = 4 Hz); MS *m/z* (rel inten) 246 (MH^+, 5). Anal. Calcd for $C_{12}H_{23}NO_4$: C, 58.8; H, 9.5; N, 5.7. Found: C, 58.6; H, 9.5; N, 5.3.

tert-Butyl *N*-Isopropyl-L-alaninate (6l). To a solution of L-Ala-OtBu·HCl (4.54 g, 25 mmol), TEA (3.50 mL, 25 mmol), and acetone (1.83 mL, 35 mmol) in MeOH (100 mL) was added 10% Pd/C (1 g), and H_2 was bubbled through the mixture for 16 h. After filtration through Celite and concentration, the residue was triturated with Et_2O to precipitate the TEA hydrochloride. The organic phase was filtered and concentrated under reduced pressure to afford **6l** as a pale yellow oil homogeneous in TLC (2.30 g, 49%): R_f 0.80 ($MeOH/CH_2Cl_2$, 10:90); $[\alpha]^{20}_D$ −26°; ^1H NMR [($CDCl_3$)] δ 0.99 (3 H, d, *J* = 6.2 Hz), 1.02 (3 H, d, *J* = 6.2 Hz), 1.21 (3 H, d, *J* = 6.7 Hz), 1.44 (9 H, s), 1.66 (1 H, br), 2.73 (1 H, h, *J* = 6.2 Hz), 3.27 (1H, q, *J* = 6.9 Hz); MS *m/z* (rel inten), 188 (MH^+, 100), 146 (40), 132 (100), 90 (100), 57 (34). Anal. Calcd for $C_{10}H_{21}NO_2$: C, 64.1; H, 11.3; N, 7.5. Found: C, 63.9; H, 11.2; N, 7.4.

Methyl *N*-Isopropyl-L-leucinate (6m). Starting from L-Leu-OMe·HCl (2.96 g, 20 mmol) and using the preceding procedure, an oily residue was obtained which was purified by chromatography (100 g; EtOAc/hexane 50:50) to afford **6m** as an oil which crystallized from EtOAc/hexane (2.61 g, 70%): mp 122–124 °C; R_f 0.50 (EtOAc/hexane, 40:60); $[\alpha]^{20}_D$ 20°; ^1H NMR δ 0.90 (3 H, d, *J* = 5.0 Hz), 0.92 (3 H, d, *J* 5.0 = Hz), 1.24 (6 H, d, *J* 5.9 Hz), 1.64–1.73 (3 H, m), 3.22–3.35 (1 H, m), 3.79 (3 H, s), 3.94–4.04 (1 H, m), 9.07 (1 H, br); MS *m/z* (rel inten), 188 (MH^+, 100), 128 (10), 86 (15). Anal. Calcd for $C_{10}H_{21}NO_2$: C, 64.1; H, 11.3; N, 7.5. Found: C, 64.5; H, 11.3; N, 7.7.

Methyl *N*-Methyl-*N*-[(methoxycarbonyl)acetyl]-L-leucinate (7j). Compound **6j** was treated with TFA for 20 min at rt. The solvent was removed under vacuo yielding the trifluoroacetate salt as an oil which was used without further purification. To a solution of this salt (2.72 g, 10 mmol) and potassium methyl malonate (2.26 g, 10 mmol) in CH_2Cl_2 (20 mL) were added *N,N*-diisopropylethylamine (6 mL, 36 mmol) and BroP (4.65 g, 12 mmol). The mixture was stirred for 30 min at rt. The solvent was evaporated under reduced pressure and the residue dissolved in EtOAc (50 mL). Usual workup led to an oily residue which was chromatographed (120 g, EtOAc) yielding **7j** as a colorless oil (2.13 g, 82%): R_f 0.40 (EtOAc/hexane, 50:50); $[\alpha]^{20}_D$ −40°; ^1H NMR (two conformers, 89:11) major conformer, δ 0.84 (3 H, d, *J* = 6.4 Hz), 0.89 (3 H, d, *J* = 6.9 Hz), 1.40–1.53 (1 H, m), 1.53–1.63 (1 H, m), 1.68–1.79 (1 H, m), 2.86 (3 H, s), 3.63 (6 H, s), 3.52 and 3.64 (2 H, AB, *J* = 14.8 Hz), 5.06 (1 H, dd, J_1 = 10.8, J_2 = 4.9 Hz); minor conformer (distinguishable signals), δ 2.69 (3 H, s), 4.50 (1 H, t, *J* = 7.5 Hz); MS *m/z* (rel inten) 282 (MNa^+, 100), 260 (MH^+, 25), 200 (28), 100 (38). Anal. Calcd for $C_{12}H_{21}NO_5$: C, 55.6; H, 8.2; N, 5.4. Found: C, 55.2; H, 8.2; N, 5.5.

Methyl *N*-Methyl-*N*-[(methoxycarbonyl)acetyl]-L-valinate (7k). Starting from **6k** (2.20 g, 9 mmol) and using the same procedure as for **7j**, the title compound was obtained as an oil (1.80 g, 82%): R_f 0.40 (EtOAc/hexane, 50:50); $[\alpha]^{20}_D$ +30°; ^1H NMR (two conformers, 80:20) major conformer, δ 0.90 (3 H, d, *J* = 7 Hz), 1.00 (3 H, d, *J* = 6.9 Hz), 2.06–2.15 (1 H, m), 2.80 (3 H, s), 3.43 and 3.58 (2 H, AB, *J* = 16.0 Hz), 3.53 (3 H, s), 3.63 (3 H, s), 3.80 (1 H, d, *J* = 3.7 Hz); minor conformer (distinguishable signals), δ 2.71 (3 H, s); MS *m/z* (rel inten) 258 (MNa^+, 100), 246 (MH^+, 20), 186 (20), 86 (40). Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.9; H, 7.8; N, 5.7. Found: C, 54.2; H, 8.2; N, 5.8.

***tert*-Butyl *N*-Isopropyl-*N*-[(ethoxycarbonyl)acetyl]-L-alaninate (7l).** To an ice-cooled and stirred solution of **6l** (1.87 g, 10 mmol) and TEA (1.54 mL, 11 mmol) in CH_2Cl_2 (10 mL) was added dropwise with a syringe, over 5 min, ethyl malonyl chloride (1.41 mL, 11 mmol). The reaction was stirred for 30 min at rt. The mixture was diluted with EtOAc (50 mL), and worked up as usual. The oily residue (2.80 g) was chromatographed (120 g, EtOAc/hexane; 35:75) to yield **7l** which crystallized in cooled pentane (−20 °C) (1.95 g, 71%), mp 53–54 °C; R_f 0.50 (EtOAc/hexane, 40:60); $[\alpha]^{20}_D$ −16°; ^1H NMR δ 1.14 (3 H, d, *J* = 6.8 Hz), 1.16 (3 H, d, *J* = 6.8 Hz), 1.19 (3 H, t, *J* = 6.3 Hz), 1.26 (3 H, d, *J* = 6.7 Hz), 1.33 (9 H, s), 3.42 and 3.50 (2 H, AB, *J* = 15.5 Hz), 3.84 (1 H, q, *J* = 6.7 Hz), 3.98 (1 H, h, *J* = 6.8 Hz), 4.08 (2 H, 2q, *J* = 6.3 Hz); MS *m/z* (rel inten) 302 (MH^+, 100), 44 (40). Anal. Calcd for $C_{15}H_{27}NO_5$: C, 59.8; H, 9.0; N, 4.7. Found: C, 59.5; H, 8.7; N, 4.9.

Methyl *N*-Isopropyl-*N*-[(methoxycarbonyl)acetyl]-L-leucinate (7m). The title compound was obtained as an oil from **6m** (89%), using the same procedure as described for **7j**: R_f 0.50 (hexane–EtOAc, 50:50); $[\alpha]^{20}_D$ −54°; ^1H NMR δ 0.88 (3 H, d, *J* = 6.9 Hz), 0.90 (3 H, d, *J* = 6.9 Hz), 1.15 (3 H, d, *J* = 6.5 Hz), 1.20 (3 H, d, *J* = 6.5 Hz), 1.17–1.25 (2 H, m), 1.75–1.86 (1 H, m), 2.27–2.34 (1 H, m), 3.43 and 3.59 (2 H, AB, *J* = 15.5 Hz), 3.53 (3 H, s), 3.62 (3 H, s), 3.75 (1 H, dd, J_1 = 3.4, J_2 = 8.6 Hz), 4.00 (1 H, h, *J* = 6.5 Hz); MS *m/z* (rel inten) 288 (MH^+, 100), 228 (40), 186 (40), 128 (45), 86 (35). Anal. Calcd for $C_{14}H_{25}NO_5$: C, 58.5; H, 8.8; N, 4.9. Found: C, 58.3; H, 9.0; N, 5.1.

Methyl *N*-[(Methoxycarbonyl)acetyl]-L-prolinate (7n).

(21) Seebach, D.; Maetzke, T.; Peter, W.; Klötzer, B.; Plattner, D. A. *J. Am. Chem. Soc.* **1991**, *113*, 1781.
(22) Castro, B.; Dormoy, J.-R. *Tetrahedron Lett.* **1973**, 3243.
(23) Cheung, S. T.; Benoiton, N. L. *Can. J. Chem.* **1977**, *55*, 906.

This compound was prepared from L-proline methyl ester, using the same procedure as described for **7j** (oil, 95%): R_f 0.45 (EtOAc–hexane, 90:10); $[\alpha]^{20}_D$ –81°; ^{1}H NMR (two conformers, 80:20) major conformer, δ 1.81–1.95 (3 H, m), 2.10–2.26 (1 H, m), 3.47–3.50 (1 H, m), 3.47 and 3.56 (2 H, AB, J = 15.6 Hz), 3.56–3.58 (1 H, m), 3.62 (3 H, s), 3.63 (3 H, s), 4.30 (1 H, dd, J_1 = 4.4, J_2 = 9.3 Hz); minor conformer (distinguishable signals), δ 3.35–3.42 (1 H, m), 3.51 and 3.57 (2 H, AB, J = 10.3 Hz), 3.61 (3 H, s), 3.68 (3 H, s), 4.67 (1 H, dd, J_1 = 2.4, J_2 = 8.9 Hz); MS m/z (rel inten) 252 (MNa^+, 100), 230 (MH^+, 7), 170 (10), 130 (17), 70 (25). Anal. Calcd for $C_{10}H_{15}NO_5$: C, 52.4; H, 6.6; N, 6.1. Found: C, 52.4; H, 6.6; N, 6.1.

(5*S*)-5-Methyl-2,4-dioxopyrrolidine (9f). The corresponding *N*-Z compound **9b** was synthesized from Z-L-Ala (2.23 g, 10 mmol) according to a previously described procedure[3a] and then hydrogenolyzed in MeOH using 10% Pd/C as catalyst. After filtration on Celite, the solvent was removed under reduced pressure and the residue purified by chromatography (acetone/CH_2Cl_2, 30:70) to yield **9f** which crystallized by triturating with Et_2O (0.30 g, 27%): mp 75–85 °C dec; $[\alpha]^{20}_D$ –2°; ^{1}H NMR (keto–enol equilibrium 70:30) keto form, δ 1.16 (3 H, d, J = 7.0 Hz), 2.96 and 3.15 (2 H, AB, J = 21.7 Hz), 3.97 (1 H, q, J = 7.0 Hz), 8.30 (1 H, br), enol form, δ 1.17 (3 H, d, J = 6.7 Hz), 3.88 (1 H, q, J = 6.7 Hz), 4.67 (1 H, s), 7.14 (1 H, br), 11.18 (1 H, s); MS m/z (rel inten) 114 (MH^+, 100). Anal. Calcd for $C_5H_7NO_2$: C, 53.1; H, 6.2; N, 12.4. Found: C, 52.9; H, 6.6; N, 12.2.

(5*S*)-5-Isobutyl-2,4-dioxopyrrolidine (9g). Compound **9b**[3a] was treated by TFA (2 mL) for 15 min. The solvent was removed under reduced pressure and the residue was crystallized as pale yellow crystals, triturating with hexane/Et_2O (1.03 g, 85%): mp 97–98 °C (lit.[3b] 99–101 °C); R_f 0.61 (CH_2Cl_2–MeOH, 90:10); $[\alpha]^{20}_D$ –55° (lit.[3b] –40.8° (*c* 0.87 in CH_2Cl_2); ^{1}H NMR (keto–enol equilibrium, 68:32) keto form, δ 0.85–0.91 (6 H, m), 1.30–1.47 (2 H, m), 1.70–1.83 (1 H, m), 2.97 and 3.01 (2 H, AB, J = 22.1 Hz), 3.87–3.97 (1 H, m), 8.49 (1H, s); enol form (distinguishable signals), δ 1.17–1.27 (1 H, m), 1.47–1.58 (1 H, m), 4.75 (1 H, s), 11.10 (1 H, s). Anal. Calcd for $C_8H_{13}NO_2$: C, 61.9; H, 8.4; N, 9.0. Found: C, 61.6; H, 8.6; N, 8.8.

(5*S*)-5-Isopropyl-2,4-dioxopyrrolidine (9h). Using the preceding procedure, **9h** was obtained from Boc-L-Val as an off-white solid, triturating with Et_2O (0.65 g, 46%): R_f 0.36 (acetone–CH_2Cl_2, 20:80); mp 131–136 °C (lit.[3b] 145 °C); $[\alpha]^{20}_D$ –67° (lit.[3b] –85.6° (*c* 0.97 in CH_2Cl_2); ^{1}H NMR (keto–enol equilibrium, 70:30) keto form, δ 0.80 (3 H, d, J = 6.6 Hz), 0.93 (3 H, d, J = 6.6 Hz), 1.93–2.02 (1 H, m), 2.95 (2 H, s), 3.79 (1 H, s), 8.41 (1 H, br); enol form, δ 0.71 (3 H, d, J = 6.6 Hz), 0.94 (3 H, d, J = 6.6 Hz), 1.93–2.02 (1 H, m), 3.79 (1 H, s), 4.72 (1 H, s), 7.13 (1 H, br), 11.14 (1 H, s); MS m/z (rel inten) 283 (M_2H^+, 12), 142 (MH^+, 100). Anal. Calcd for $C_7H_{11}NO_2$: C, 59.6; H, 7.9; N, 9.9. Found: C, 59.2; H, 8.1; N, 9.8.

Dieckmann Cyclization of 7 (route b). Typical Procedure. To a stirred solution of **7** (1 equiv) in MeOH (1 mL/mmol) was added sodium methoxide [prepared from sodium (1 equiv) and anhydrous MeOH (0.4 mL/mmol)]. The mixture was stirred for 1 h at rt. The solvent was concentrated (0.5 mL/mmol). The sodium salt was precipitated as a white powder by dropwise addition of Et_2O (10 mL/mmol)). The sodium salt of **8** was collected, washed twice with Et_2O, and dried in vacuo. A solution of this compound in water (4 mL/mmol) and 1 M H_2SO_4 (1.1 equiv) was refluxed for 1 h. The solution was cooled and extracted three times with EtOAc. The organic phase was dried and concentrated yielding **9**.

(5*S*)-1-Methyl-5-isobutyl-2,4-dioxopyrrolidine (9j): oil (1.16 g, 95%); R_f 0.53 (EtOAc–MeOH, 95:5); $[\alpha]^{20}_D$ 0°; ^{1}H NMR (keto–enol equilibrium, 76:24) keto form, δ 0.89 (3 H, d, J = 6.0 Hz), 0.91 (3 H, d, J = 6.0 Hz), 1.54–1.63 (2 H, m), 1.65–1.77 (1 H, m), 2.82 (3 H, s), 2.96 and 3.15 (2 H, AB, J = 15.8 Hz), 3.92 (1 H, t, J = 6.8 Hz); enol form (distinguishable signals), δ 2.73 (3 H, s), 3.86 (1 H, t, J = 6.4 Hz), 4.78 (1 H, s), 11.30 (1 H, s); MS m/z (rel inten) 321 ($M_2H^+ - H_2O$, 100), 170 (MH^+, 25), 100 (15). Anal. Calcd for $C_9H_{15}NO_2$: C, 63.9; H, 8.9; N, 8.3. Found: C, 63.5; H, 9.3 N, 8.4.

(5*S*)-1-Methyl-5-isopropyl-2,4-dioxopyrrolidine (9k): white solid (0.68 g, 70%); mp 71–73 °C (Et_2O); R_f 0.50 (MeOH–CH_2Cl_2, 5:95); $[\alpha]^{20}_D$ +12°; ^{1}H NMR (keto–enol equilibrium, 80:20) keto form, δ 0.85 (3 H, d, J = 6.8 Hz), 0.90 (3 H, d, J = 6.9 Hz), 1.80–1.99 (1 H, m), 2.80 (3 H, s) 2.92 and 3.16 (2 H, AB, J = 19.8 Hz), 4.01 (1 H, d, J = 3.8 Hz); enol form (distinguishable signals), δ 2.72 (3 H, s), 4.75 (1 H, s), 11.40 (1 H, s); FAB MS m/z (rel inten) 311 (M_2H^+, 5), 293 ($M_2H^+ - H_2O$, 30), 156 (MH^+, 100). Anal. Calcd for $C_8H_{13}NO_2$: C, 61.9; H, 8.4; N, 9.0. Found: C, 61.7; H, 8.7 N, 9.1.

(5*S*)-1-Isopropyl-5-methyl-2,4-dioxopyrrolidine (9l): white solid (0.16 g, 78%); mp 190 °C dec (Et_2O); R_f 0.80 (MeOH–CH_2Cl_2, 5:95); $[\alpha]^{20}_D$ +16°; ^{1}H NMR (keto–enol equilibrium, 68:32) keto form, δ 1.23 (3 H, d, J = 7.0 Hz), 1.26 (3 H, d, J = 7.0 Hz), 1.27 (3 H, d, J = 6.4 Hz), 3.00 (1 H, *AB*, J = 21.9 Hz), 3.14 (1 H, d*AB*, J_1 = 21.9, J_2 = 1.6 Hz), 3.99 (1 H, h, J = 6.7 Hz), 4.63 (1 H, br q, J = 6.4 Hz); enol form, δ 1.21 (3 H, d, J = 6.9 Hz), 1.24 (3 H, d, J = 6.8 Hz), 1.35 (3 H, d, J = 6.6 Hz), 4.03 (1 H, q, J = 6.6 Hz), 4.16 (1 H, h, J = 6.9 Hz), 6.15 (1 H, s) 11.40 (1 H, s); MS m/z (rel inten) 156 (MH^+, 100). Anal. Calcd for $C_8H_{13}NO_2$: C, 61.9; H, 8.4; N, 9.0. Found: C, 61.7; H 8.5; N, 8.8.

(5*S*)-1-Isopropyl-5-isobutyl-2,4-dioxopyrrolidine (9m): white solid (1.02 g, 80%); mp 80 °C; R_f 0.55 (EtOAc/hexane, 50:50); $[\alpha]^{20}_D$ +35°; ^{1}H NMR (keto–enol equilibrium, 75:25) keto form, δ 0.88 (3 H, d, J = 6.0 Hz), 0.89 (3 H, d, J = 6.9 Hz), 1.24 (3 H, d, J = 7.0 Hz), 1.27 (3 H, d, J = 7.0 Hz), 1.55–1.60 (2 H, m), 1.72–1.87 (1 H, m), 2.90 (1 H, *AB*, J = 21.9 Hz), 3.26 (1 H, d*AB*, J_1 = 21.9, J_2 = 1.7 Hz), 3.94–4.00 (1 H, m), 3.96 (1 H, h, J = 7.0 Hz); enol form (distinguishable signals), δ 1.17 (3 H, d, J = 6.9 Hz), 1.21 (3 H, d, J = 6.9 Hz), 3.83 (1 H, h, J = 6.9 Hz), 4.70 (1 H, s), 11.30 (1 H, s); FAB MS m/z (rel inten) 377 ($M_2H^+ - H_2O$, 10), 198 (MH^+, 100). Anal. Calcd for $C_{11}H_{19}NO_2$: C, 67.0; H, 9.7; N, 7.1. Found: C, 67.1; H, 9.8 N, 7.3.

(8*S*)-Pyrrolizidine-1,3-dione (9n): oil (1.10 g, 82); R_f 0.5 (MeOH/CH_2Cl_2, 5:95); $[\alpha]^{20}_D$ –44°; ^{1}H NMR (keto–enol equilibrium, 50:50) keto form, δ 1.59–1.71 (1 H, m), 1.89–1.99 (3 H, m), 2.89 (1 H, dd, J_1 = 21.0 Hz, J_2 = 1.0 Hz), 3.01–3.08 (1H, m), 3.52 (1 H, dd, J_1 = 21.0 Hz, J_2 = 0.5 Hz), 3.66–3.73 (1 H, m), 4.18–4.22 (1 H, m); enol form, δ 1.24–1.40 (2 H, m), 1.96–2.07 (2 H, m), 2.89–2.95 (1 H, m), 3.25–3.33 (1 H, m), 4.02–4.06 (1 H, m), 4.66 (1 H, s), 11.70 (1 H, s); MS m/z (rel inten) 261 ($M_2H^+ - H_2O$, 100), 140 (MH^+, 50), 70 (70).

Reduction of 9 to 10. Typical Procedure. To a cooled (0 °C) solution of compounds **9** (1 mmol) in CH_2Cl_2/AcOH (90:10; 5 mL/mmol) was added $NaBH_4$ (2 mmol) in three batches. The reaction was stirred for 1 h. The solvent was evaporated and the residue dissolved in EtOAc (15 mL). The organic phase was washed with 5% $NaHCO_3$ (3 × 5 mL), dried, and concentrated to dryness. The mixture of **10α** and **10β** was purified (but not separated) by flash chromatography, and the ratio **10α**/**10β** was assayed by integration of the 4-H signal in the ^{1}H NMR spectrum.

(4*S*,5*S*)-*N*-Acetyl-2-oxo-4-hydroxy-5-isobutylpyrrolidine (10βe). Compound **9e** was prepared from Ac-L-Leu, following the procedure described by Jouin et al.,[3a] and reduced, without purification, according to the general procedure: yield 51% (from Ac-Leu); mp 40 °C (EtOAc–hexane); R_f 0.50 (EtOAc–hexane 40:60); $[\alpha]^{20}_D$ –3°; ^{1}H NMR δ 0.81–0.96 (6 H, m), 1.23–1.39 (1 H, m), 1.62–1.81 (2 H, m), 2.33 (3 H, s), 2.53 (1 H, *ABX*, J_1 = 16.0, J_2 9.0 Hz), 2.62 (1 H, *ABX*, J_1 = 16.0, J_2 = 6.8 Hz), 4.14–4.22 (1 H, m), 4.25–4.44 (1 H, m), 5.31 (1 H, d, J = 4.9 Hz); FAB MS m/z (rel inten) 400 (M_2H^+, 5), 200 (MH^+, 100), 158 (50). Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.3; H, 8.6; N, 7.0. Found: C, 60.2; H, 8.7 N, 7.1.

(5*S*)-5-Methyl-4-hydroxyl-2-oxopyrrolidine (10f): yield 88%; R_f 0.50 (MeOH–CH_2Cl_2, 15:85); ^{1}H NMR **10αf**/**10βf** mixture, 34:66; **10βf** δ 1.03 (3 H, d, J = 6.6 Hz), 1.96 (1 H, *ABX*, J_1 = 16.5, J_2 = 3.2 Hz), 2.39 (1 H, *ABX*, J_1 = 16.5, J_2 = 6.6 Hz), 3.54–3.60 (1 H, m), 4.10–4.19 (1 H, m), 4.92 (1 H, br), 7.47 (1 H, br); **10αf** δ 1.07 (3 H, d, J = 6.5 Hz), 1.94 (1 H, *ABX*, J_1 = 16.8, J_2 = 4.7 Hz), 2.39 (1 H, *ABX*, J_1 = 16.8, J_2 = 6.6 Hz), 3.25–3.37 (1 H, m), 3.77–3.95 (1 H, m), 5.15 (1 H, br), 7.57 (1 H, br); MS m/z (rel inten) 231 (M_2H^+, 20), 116 (MH^+, 100), 98 (5). Anal. Calcd for $C_5H_9NO_2$: C, 52.2; H, 7.9; N, 12.2. Found: C, 52.3; H, 7.8; N, 12.3.

(5*S*)-5-Isobutyl-4-hydroxyl-2-oxopyrrolidine (10g): yield 74% as a colorless oil; R_f 0.53 (CH_2Cl_2–MeOH, 90:10); ^{1}H NMR **10αg**/**10βg** mixture, 32:68; **10βg** δ 0.86 (3 H, d, J = 6.8 Hz), 0.89 (3 H, d, J = 6.8 Hz), 1.13–1.45 (2 H, m), 1.61–1.76 (m), 1.96 (1 H, *ABX*, J_1 = 16.4, J_2 = 2.7 Hz), 2.40 (1 H, *ABX*, J_1 = 16.4, J_2 = 6.1 Hz), 3.46–3.54 (1 H, m), 4.14–4.20 (1 H, m), 4.89 (1 H, d,

J = 4.9 Hz), 7.56 (1 H, br); **10αg** (distinguishable signals) δ 0.87 (3 H, d, J = 6.8 Hz), 0.90 (3 H, d, J = 6.8 Hz), 1.91 (1 H, *A*BX, J_1 = 17.1, J_2 = 3.4 Hz), 2.45 (1 H, A*B*X, J_1 = 17.1, J_2 = 6.8 Hz), 3.23–3.29 (1 H, m), 3.83–3.89 (1 H, m), 5.13 (1 H, d, J = 4.4 Hz), 7.73 (1 H, br). Anal. Calcd for $C_8H_{15}NO_2$: C, 61.1; H, 9.6; N, 8.9. Found: C, 59.9; H, 10.0; N, 9.1.

Reduction of 9g by Catalytic Hydrogenation. To a solution of **9g** (465 mg, 3.00 mmol) in EtOAc (50 mL) was added PtO_2 (50 mg). The mixture was hydrogenated at 200 psi and 25 °C for 24 h to afford a mixture of **10αg** and **10βg** (ratio 14:86) (430 mg, 85%).

Preparation of 10βg from 10βb. Compound **10βb** (257 mg, 1.00 mmol) prepared according to Jouin et al.[3a] was treated by TFA (1 mL) for 15 min. After removal of the solvent, the residue was purified by flash chromatography to afford **10βg** as a colorless oil (133 mg, 85%). Anal. Calcd for $C_8H_{15}NO_2$: C, 61.1; H, 9.6; N, 8.9. Found: C, 61.1; H, 9.9; N, 9.1.

(5*S*)-5-Isopropyl-4-hydroxyl-2-oxopyrrolidine (10h): yield 74%; R_f 0.40 (MeOH–CH_2Cl_2, 10:90); ^{1}H NMR **10αh/10βh** mixture, 4:96; **10βh** δ 0.86 (3 H, d, J = 6.9 Hz), 0.91 (3 H, d, J = 7.3 Hz), 1.75–1.86 (1 H, m), 1.93 (1 H, *A*BX, J_1 = 16.5 J_2 = 2.5 Hz), 2.43 (1 H, A*B*X, J_1 = 16.5, J_2 = 7.2 Hz), 3.01–3.05 (1 H, m), 4.17–4.19 (1 H, m), 5.00 (1 H, br), 7.70 (1 H, br); **10αh** (distinguishable signals) δ 3.20–3.24 (1 H, m), 3.98–4.01 (1 H, m), 7.73 (1 H, br); MS m/z (rel inten) 287 (M_2H^+, 27), 144 (MH^+, 100), 126 (5). Anal. Calcd for $C_7H_{13}NO_2$: C, 58.7; H, 9.2; N, 9.8. Found: C, 58.7; H, 9.5; N, 10.0.

(5*S*)-1-Methyl-5-isobutyl-4-hydroxy-2-oxopyrrolidine (10j): yield 82%; R_f 0.50 (CH_2Cl_2–MeOH, 90:10); ^{1}H NMR **10αj/10βj** mixture, 15:85; **10βj** δ 0.91 (6 H, d, J = 6.0 Hz), 1.25–1.34 (1 H, m), 1.56–1.67 (1 H, m), 1.67–1.84 (1 H, m), 2.06 (1 H, *A*BX, J_1 = 16.5, J_2 = 2.6 Hz), 2.45 (1 H, A*B*X, J_1 = 16.5, J_2 = 6.0 Hz), 2.62 (3 H, s), 3.44 (1 H, td, J_1 = 4.3, J_2 = 9.9 Hz), 4.14–4.22 (1 H, m), 4.94 (1 H, d, J = 5.1 Hz); **10αj** (distinguishable signals) δ 1.34–1.42 (1 H, m), 2.67 (3 H, s), 3.22 (1 H, ddd, J_1 = 1.5, J_2 = 4.2 J_3 = 10.3 Hz), 3.89–3.94 (1 H, m), 5.17 (1 H, d, J = 3.7 Hz); MS m/z (rel inten) 343 (M_2H^+, 10), 172 (MH^+, 100), 154 (5), 100 (10). Anal. Calcd for $C_9H_{17}NO_2$: C, 63.1; H, 10.0; N, 8.2. Found: C, 63.2; H, 10.0; N, 7.9.

(4*S*,5*S*)-1-Methyl-5-isopropyl-4-hydroxy-2-oxopyrrolidine (10βk): yield 77%; R_f 0.50 (CH_2Cl_2–MeOH, 90:10); $[\alpha]^{20}_D$ +21°; ^{1}H NMR δ 0.96 (3 H, d, J = 6.9 Hz), 1.01 (3 H, d, J = 7.2 Hz), 2.07–2.18 (1 H, m), 2.11 (1 H, *A*BX, J_1 = 16.3, J_2 = 7.2 Hz), 2.36 (1 H, A*B*X, J_1 = 16.3, J_2 = 6.8 Hz), 3.80 (1 H, dd, J_1 = 3.8 J_2 = 6.6 Hz), 4.35–4.42 (1 H, m), 5.50 (1 H, d, J = 4.6 Hz); MS m/z (rel inten) 315 (M_2H^+, 12), 297 ($M_2H^+ - H_2O$, 5), 158 (MH^+, 100). Anal. Calcd for $C_8H_{15}NO_2$: C, 61.1; H, 9.6; N, 8.9. Found: C, 59.9; H, 9.9; N, 9.0.

(5*S*)-1-Isopropyl-5-methyl-4-hydroxy-2-oxopyrrolidine (10l): yield 80%; oil; R_f 0.50 (CH_2Cl_2–MeOH, 85:15); ^{1}H NMR **10αl/10βl** mixture, 3:97; **10βl** δ 1.09 (3 H, d, J = 6.7 Hz), 1.10 (3 H, d, J = 6.6 Hz), 1.12 (3 H, d, J = 6.7 Hz), 2.13 (1 H, *A*BX, J_1 = 16.2, J_2 = 7.3 Hz), 2.30 (1 H, A*B*X, J_1 = 16.2, J_2 = 7.2 Hz), 3.65 (1 H, qd, J_1 = 6.6, J_2 = 6.6 Hz), 3.95 (1 H, h, J = 6.7 Hz), 4.16 (1 H, q, J = 6.7 Hz), 5.20 (1 H, br); **10αl** (distinguishable signals) δ 2.52 (1 H, *A*BX, J_1 = 16.5, J_2 = 6.0 Hz); MS m/z (rel inten) 158 (MH^+, 100). Anal. Calcd for $C_8H_{15}NO_2$: C, 61.1; H, 9.6; N, 8.9. Found: C, 59.8; H, 9.8; N, 8.9.

(4*S*,5*S*)-1-Isopropyl-5-isobutyl-4-hydroxy-2-oxopyrrolidine (10βm): yield 93%; mp 85–87 °C; R_f 0.45 (CH_2Cl_2–MeOH, 90:10); ^{1}H NMR δ 0.90 (3 H, d, J = 6.8 Hz), 0.92 (3 H, d, J = 6.8 Hz), 1.14 (3 H, d, J = 6.8 Hz), 1.19 (3 H, d, J = 6.8 Hz), 1.21–1.28 (1 H, m), 1.72–1.81 (2H, m), 2.10 (1 H, *A*BX, J_1 = 16.1, J_2 = 4.4 Hz), 2.34 (1 H, A*B*X, J_1 = 16.1 J_2 = 6.8 Hz), 3.53–3.58 (1 H, m), 3.86 (1 H, h, J = 6.8 Hz), 4.14–4.21 (1 H, m), 4.97 (1 H, d, J = 5.4 Hz); MS m/z (rel inten) 200 (MH^+, 100). Anal. Calcd for $C_{11}H_{21}NO_2$: C, 66.3; H, 10.6; N, 7.0. Found: C, 66.1; H, 10.5; N, 7.0.

(1*R*,8*S*)-1-Hydroxypyrrolizidin-3-one (10αn): yield 83%; ^{1}H NMR **10αn/10βn** mixture, 95:5; **10αn**, δ 1.33–1.44 (1 H, m), 1.84–1.93 (2 H, m), 1.93–2.03 (1 H, m), 2.47 (2 H, *AB*X), 2.82–2.89 (1 H, m), 3.33–3.41 (1 H, m), 3.52–3.58 (1 H, m), 3.99–4.07 (1 H, m), 5.36 (1 H, d, J = 5.1 Hz); **10βn** (distinguishable signals), δ 1.57–1.68 (1 H, m), 3.85–3.91 (1 H, m), 4.16–4.24 (1 H, m), 5.03 (1 H, d, J = 5.1 Hz); MS m/z (rel inten) 283 (M_2H^+, 10), 142 (MH^+, 100), 70 (5). Successive crystallizations in EtOAc–hexane led to a pure sample of the major product **10αn**: mp 79–81 °C (lit. 84–86 °C,[8a] 81–82 °C[8b]); $[\alpha]^{20}_D$ = −90° (*c* 1 in $CHCl_3$) (lit. −91.5°,[8a] −97°[8b]), R_f 0.45 (MeOH/CH_2Cl_2, 10:90).

Reduction of 9n with K-Selectride. To a cooled (−78 °C) solution of **9n** (100 mg, 0.72 mmol) in anhydrous THF (1.5 mL) was added a 1 M solution of K-Selectride in THF (1.5 mL). The reaction was stirred at −78 °C for 4 h and then at rt for 24 h. After workup the yield was 40% as a 43:57 mixture of **10αn/10βn**.

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