cis-trans Peptide-Bond Isomerization in α-Methylproline Derivatives

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Dedicated to Professor *Dieter Seebach* on the occasion of his 75th birthday

α-Methyl-L-proline is an α-substituted analog of proline that has been previously employed to constrain prolyl peptide bonds in a *trans* conformation. Here, we revisit the *cis-trans* prolyl peptide bond equilibrium in derivatives of α-methyl-L-proline, such as *N*-Boc-protected α-methyl-L-proline and the hexapeptide H-Ala-Tyr-αMePro-Tyr-Asp-Val-OH. In Boc-α-methyl-L-proline, we found that both *cis* and *trans* conformers were populated, whereas, in the short peptide, only the *trans* conformer was detected. The energy barrier for the *cis-trans* isomerization in Boc-α-methyl-L-proline was determined by line-shape analysis of NMR spectra obtained at different temperatures and found to be 1.24 kcal/mol (at 298 K) higher than the corresponding value for Boc-L-proline. These findings further illuminate the conformationally constraining properties of α-methyl-L-proline.

Introduction. – Proline residues have a special significance in protein chemistry due to their effects on protein folding [1] and function [2]. The five-membered pyrrolidine ring places severe constraints upon rotation of the N–C(α) (φ angle) and C(α)–C_{CO} (ψ angle) bonds, greatly limiting the φ/ψ space accessible to the peptide backbone. In addition, proline is distinct from all other coded α-amino acids in that the barrier for *cis-trans* isomerization of its peptide bond is significantly lower. Typical values are in the range of 14 – 24 kcal/mol, which enables proline residues to function as molecular switches [2]. In one representative study, it was shown that *cis-trans* isomerization of a specific proline residue triggers conformational changes of a neurotransmitter-gated ion channel; *cis-trans* isomerization of this single proline acts as a switch for the interconversion between the open and closed states of the channel [3].

One elegant approach to influence the *cis-trans* equilibrium of prolines in peptides and proteins is based on modulating the strength of the $n_{CO} \rightarrow \pi^*_{CO}$ orbital interaction between the C=O moiety of the preceding residue and the C=O group of proline. For example, the configuration at C(4) of (2*S*,4*R*)-4-fluoroproline stabilizes the *exo* conformation of the ring *via* a *gauche* effect, which, in turn, leads to an enhanced $n \rightarrow \pi^*$ interaction and thus higher stability of the *trans*-prolyl conformer (6.7 : 1 *vs.* 4.6 : 1 for proline in the model compound Ac-Xaa-OMe [4]). This finding led *Raines* and co-workers to propose a stereoelectronic explanation for the high thermal stability of collagen, which was validated by chemical synthesis of an unnatural collagen analog that contained (4*R*)-4-fluoroproline and, as a result, possessed enhanced thermostability [5].

Population of either *cis* or *trans* conformers can be strongly enhanced by restricting the conformational freedom of proline's five-membered ring. For example, L-5,5′-

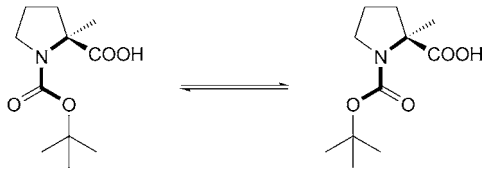
dimethylproline exists solely as the *cis* conformer [6], whereas the bicyclic derivative 2,4-methanoproline (2-carboxy-2,4-methanopyrrolidine) strongly favors the *trans* conformer [7]. α-Methylproline (αMePro) was shown to populate exclusively the *trans* conformer in the model system Ac-αMePro-NHMe [8]. In one pioneering study, *Robinson* and co-workers incorporated α-methylproline into the peptide hormone bradykinin and found that derivatives containing α-methylproline adopt a reverse-turn conformation, whereas wild-type bradykinin is disordered in solution [9].

Incorporation of *C(α)*-alkylated amino acids has long been recognized as a means of introducing local conformational constraints into peptides [10]; such amino acids can stabilize 3_{10} or α-helical structures [11][12], fully-extended conformations [13], as well as β-turns [14]. Among the *C(α)*-methylated standard 20 amino acids, α-methylproline is the most constrained residue. Its φ torsion angle is strongly restricted, the tertiary amide torsion angle ω is predicted to adopt the only *trans* conformation in linear peptides, and the side-chain χ^n torsion angles are also rigidified. Based on X-ray structural studies of several model dipeptides containing α-methylproline, it was recently shown that the conformational φ/ψ space of α-methylproline is restricted to two regions, namely the α-helix and the polyproline type-II structure [15][16].

Although the *trans* peptide-bond conformation is favored for α-methylproline, this preference is not absolute. The *cis* conformer was detected in solution studies of the heterochiral dipeptide Ac-L-αMePro-D-αMePro-NH^{i}Pr, where it constituted 17% of the mixture [16]. In this article, we report a study of *cis-trans* isomerization in Boc-α-methylproline, a derivative containing a moderately bulky urethane group that allows detection of both *cis* and *trans* forms, and hence determination of the energy barrier for the isomerization process (*Scheme 1*,*a*). To explore the conformational preferences in a more complex setting, we also incorporated α-methylproline in place of a proline residue in the hexapeptide H-Ala-Tyr-Pro-Tyr-Asp-Val-OH (*Scheme 1*,*b*). This peptide sequence was reported to display an anomalously high population (57%) of the *cis* conformation [17] and is, therefore, ideal to test the switching capabilities of the α-methylproline residue.

Scheme 1. *α-Methylproline as a Conformational Switch. a*) The tertiary Boc-urethane moiety undergoes *cis-trans* isomerization in Boc-α-(*S*)-methylproline. *b*) Amino acid sequence of the hexapeptide with the α-(*S*)-methylproline residue studied in this work. The corresponding peptide with an unmodified proline residue was reported to have an unusually high *cis*-prolyl bond content (57%) [17].

a)

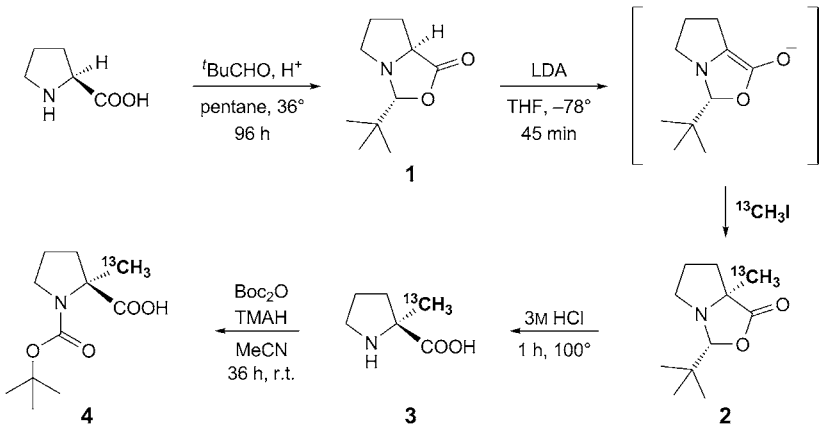


b) H-Ala-Tyr-**αMePro**-Tyr-Asp-Val-OH

Results and Discussion. – To enable convenient monitoring of the *cis-trans* equilibrium by NMR methods, we introduced a [^{13}C]-label at the Me position of α-

methylproline. The chemical synthesis of [$^{13}CH_3$]-labeled Boc-α-methylproline was performed according to a procedure developed by *Seebach* and co-workers [18][19] (*Scheme 2*). Briefly, proline and pivalaldehyde were condensed to generate a bicyclic adduct that was deprotonated and stereoselectively alkylated with commercially available [^{13}C]methyl iodide. The alkylation product was converted to α-[^{13}C]methyl-L-proline upon boiling with acid, and subsequently Boc-protected [20] to yield 1.471 g (20%) of Boc-α-[^{13}C]methyl-L-proline, a building block suitable for solid-phase peptide synthesis [21]. The product was characterized by elemental analysis, optical activity, and ^{1}H- and ^{13}C-NMR spectroscopy.

Scheme 2. *Chemical Synthesis of Boc-α-[^{13}C]Methylproline according to the Procedure Reported by* Seebach *and Co-workers* (see [18][19]). Total yield for the final product was 20%.



Inspection of the ^{1}H- and ^{13}C-NMR data indicates that Boc-α-methyl-L-proline adopts two conformations in solution, corresponding to the *cis* and *trans* geometries of the urethane moiety (*Figs. 1* and *2*), as is common for other Boc-protected amino acids [22]. We set out to determine the energy barrier for the *cis* → *trans* isomerization in this derivative and find out to what extent the introduction of an α-Me group alters the barrier. ^{1}H-NMR Spectra were recorded for Boc-α-methyl-L-proline and Boc-α-L-proline in DMSO at temperatures ranging from 293 to 343 K. Rate constants for *cis* → *trans* isomerization were extracted by line-shape analysis of the NMR spectra (*Fig. 1*). Fitting of the kinetics data to the *Eyring* equation yielded a *Gibbs* activation free energy for Boc-α-methyl-L-proline higher than that for Boc-α-L-proline by 1.24 kcal/mol at room temperature (*Fig. 3* and *Table*). This finding contradicts a previous theoretical study, which predicted that the barrier for *cis* → *trans* isomerization of acetyl-α-L-methylproline-methylamide would be 3.9 kcal/mol lower than the corresponding barrier for isomerization of the L-proline derivative [23]. Although the chemical structures are not identical, this disagreement is probably due to the inadequacy of the theoretical method used to calculate the barrier. The classical molecular-mechanics methodology used by the authors [23] does not properly describe the mechanism of this chemical transformation.

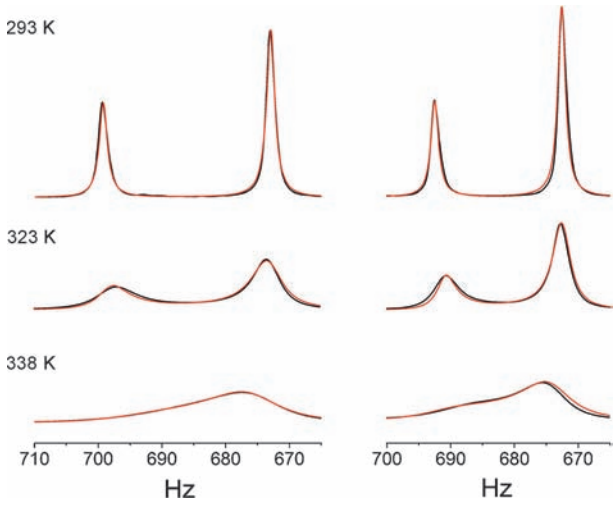


Fig. 1. *^{1}H-NMR Spectra at different temperatures for Boc-proline* (left column) *and Boc-α-methylproline* (right column). Full coalescence of the two resonances occurs for Boc-proline at 338 K (or 65°), while, at the same temperature, Boc-α-methylproline's signals have not fully coalesced. Experimental spectra are in black, and calculated line shapes are in red.

Table. cis *Content, Activation Parameters, and Rate Constants for* cis → trans *Isomerization of Boc-Pro and Boc-α-MePro*

	cis [%]	$\Delta H^{\ddagger}$ [kcal/mol]	$\Delta S^{\ddagger}$ [cal/mol · K]	$\Delta G^{\ddagger}_{298\,K}$ [kcal/mol]	$k_{c\to t}$ (at 293 K) [s^{-1}]
Boc-Proline	38	17.46	– 1.15	17.81	1
Boc-α-[^{13}C]Methylproline	35	18.28	– 2.53	19.05	0.5

To obtain crystals suitable for X-ray structure analysis, chemically synthesized Boc-α-methyl-L-proline was recrystallized from Et_2O. Well-defined crystals were obtained, one of which was analyzed by X-ray diffraction (see *Exper. Part* and *Fig. 4*). Surprisingly, the Boc urethane moiety was found to be locked in the *cis* conformation (*Fig. 4,a*). The backbone angles ($\varphi = -52.2°$ and $\psi = -32.9°$) correspond to α-helical conformation. The five-membered prolyl ring adopts the *exo* conformation; the *endo* conformation is presumably disfavored sterically in five-membered prolyl rings with an α,α′-tetrasubstituted C-atom.

Usually, the urethane moiety in *N*-protected α-methylproline derivatives adopts a *trans* conformation [15][16]. The only structure of an α,α-tetrasubstituted prolyl derivative with the Boc urethane group in a *cis* conformation was reported for a L-proline-derived spirolactam [24], which is structurally rather different than α-methylproline. *N*-Benzyl-α-methylproline, which more closely resembles Boc-α-methyl-L-proline, adopts the *trans* conformation in the solid state [16]. In the reported crystal structure [16], the five-membered prolyl ring is in an *exo* conformation, and the φ and ψ angles are -56 and $-33°$, respectively, similar to the values observed for Boc-α-methyl-L-proline (see above).

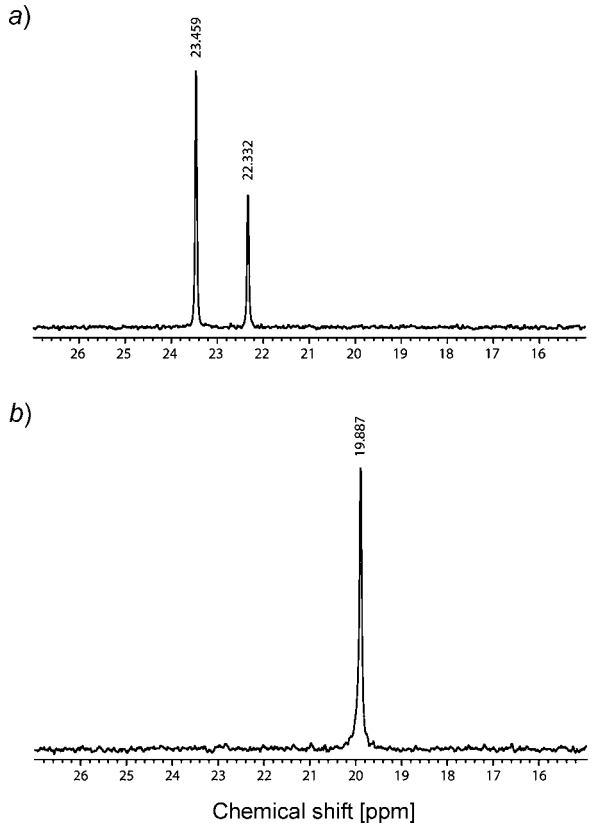


Fig. 2. *^{13}C-{^{1}H}-NMR Spectra of* a) *Boc-α-[^{13}C]methylproline in (D_6)DMSO, and* b) *H-Ala-Tyr-α-[$^{13}CH_3$]MePro-Tyr-Asp-Val-OH in 95% H_2O/5% D_2O with (D_6)DSS*

Analysis of the crystal structure of *N*-Boc-α-methylproline does not reveal an obvious reason for the preference for the *cis* amide conformation. The molecules in the crystals are arranged as H-bonded chains linked by a unit-cell translation in the *a* crystallographic direction between the COOH H-atom and the urethane C=O O-atom (*Fig. 4*, *b*). A rather similar molecular-chain arrangement was also observed in the crystal structure of *N*-benzyl-α-methylproline in its *trans* conformation. Individual molecules were also connected by H-bonds between neighboring COOH and urethane moieties, albeit related by a 2_1 screw axis of the $P2_12_12_1$ space group [16]. It is possible that, under different conditions, the *trans* conformer of *N*-Boc-α-methylproline can also be crystallized.

A short peptide with the sequence H-Ala-Tyr-Pro-Tyr-Asp-Val-OH was previously reported to exhibit an anomalously high population (57%) of the *cis* proline conformer [17]. It was hypothesized that stacking of the aromatic rings of the $i-1$ and $i+1$ residues against the proline ring stabilizes a compact conformation of the linear peptide, reinforcing the preference for the *cis* peptide bond conformation of the internal proline residue [25][26]. To test whether such a peptide sequence context can

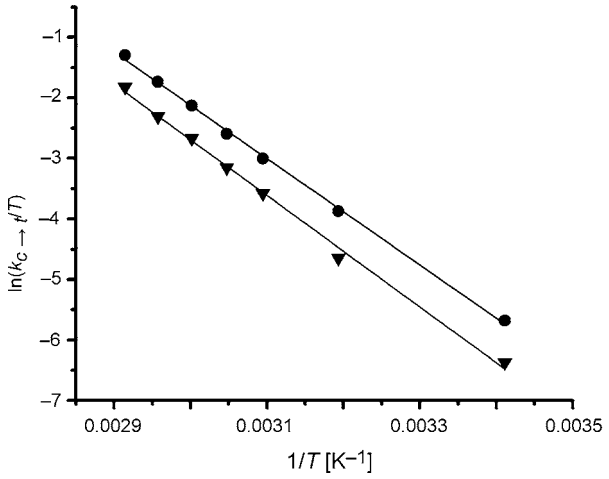


Fig. 3. Eyring *plot for the* cis-trans *isomerization of* (S)*-Boc-α-methylproline* (triangles) *and* (S)*-Boc-proline* (circles) *in DMSO*

still enable a *cis* prolyl conformation when proline is replaced by α-methylproline, we synthesized the corresponding peptide analog and studied its conformational properties by 2D-NMR.

The synthesis of the α-methylproline-containing polypeptide was accomplished by Boc-SPPS (solid-phase peptide synthesis) methodology [21]. In the ^{13}C-{^{1}H}-NMR spectrum, we observed only a single peak (*Fig. 2,b*), clearly indicating that only one conformer is populated. We further collected DQF-COSY, ^{1}H-TOCSY, and ^{1}H-ROESY data for this peptide molecule, allowing full assignment of the NMR resonances and determination of the local conformation of α-methylproline. A characteristic $^{1}H,^{1}H$-NOE peak was observed between the α-CH moiety of Tyr2 and the δ-CH_2 group of α-methylproline's five-membered ring (*Fig. 5*), unambiguously showing that the conformation of the prolyl amide bond in this peptide is *trans.*

Conclusions. – Previously, it was shown that α-methylproline is useful for constraining prolyl-amides in the *trans* conformation. Experimental studies exploring the energy barriers for *cis-trans* isomerization of α-methylproline derivatives have not been described, however. Recent theoretical study predicted counterintuitively that the barrier for isomerization of acetyl-α-methyl-L-proline-methylamide is lower than for the corresponding L-proline derivative [23]. In this work, we showed experimentally that the activation free energy barrier for the *cis-trans* isomerization of the prolyl amide bond is higher in α-methylproline than in unmodified proline. Measurements were carried out on *N*-Boc-derivatives of α-methylproline and proline, respectively, for which the *cis* and *trans* conformations were both directly observed by NMR. For these derivatives, the equilibrium concentration of *cis* and *trans* conformers varied insignificantly (35% *cis* for of *N*-Boc-α-methylproline and 38% *cis* for *N*-Boc-proline). Unexpectedly, however, only the *cis* amide isomer of an α-methylproline derivative crystallized.

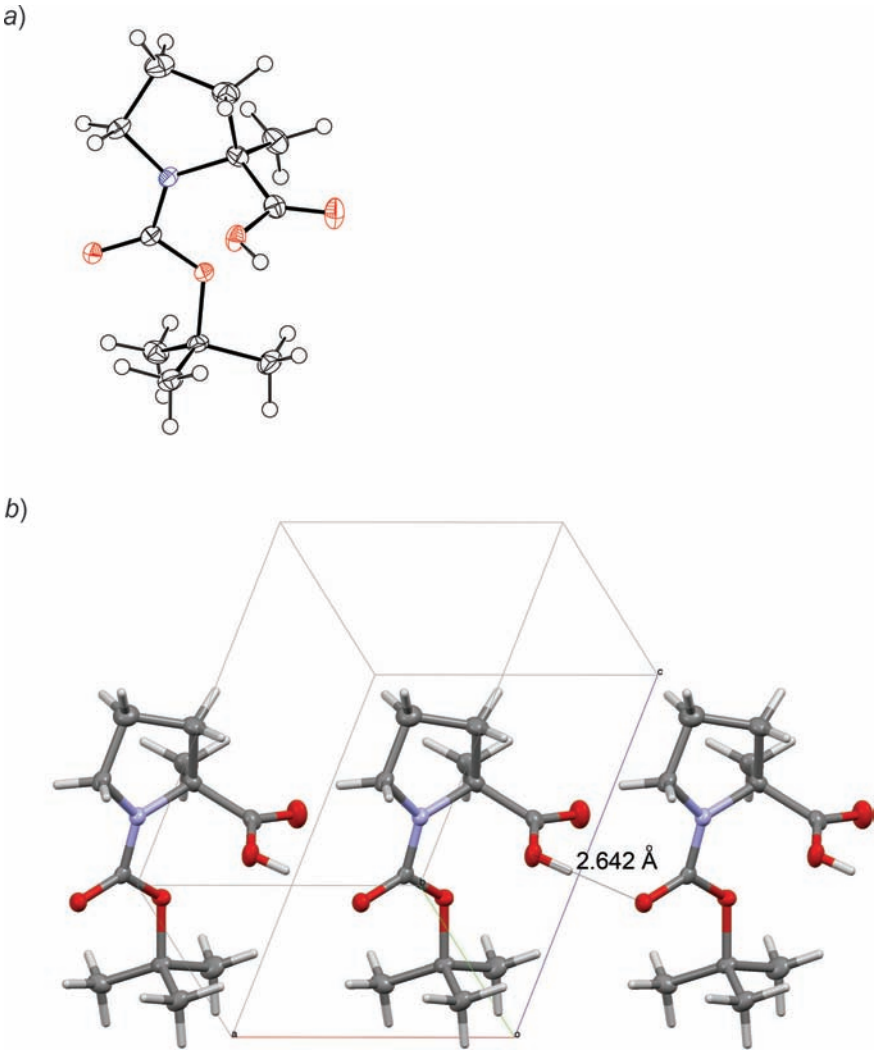


Fig. 4. *Crystal structure of (*S*)-*N*-Boc-α-methylproline as determined by X-ray diffraction* (space group $P2_1$. *a*) ORTEP Plot at 50% probability level of the molecular structure. *cis* Conformer was observed in crystals formed by recrystallization from Et_2O. *b*) Intermolecular H-bonding in the crystal between the C=O and urethane groups of adjacent molecules.

Nevertheless, when incorporated into a short linear hexapeptide, α-methylproline strongly favors the *trans*-prolyl-amide conformation. This bias can even override sequence constraints that normally encourage population of the *cis* isomer. In comparison to the Boc urethane derivative, the polypeptide structure is sterically more congested around its amide bonds, and this leads to a more pronounced preference for the *trans* conformer. The only previous study where the *cis* conformer was observed in a peptide by NMR involved a heterochiral dipeptide with a D-amino acid in its

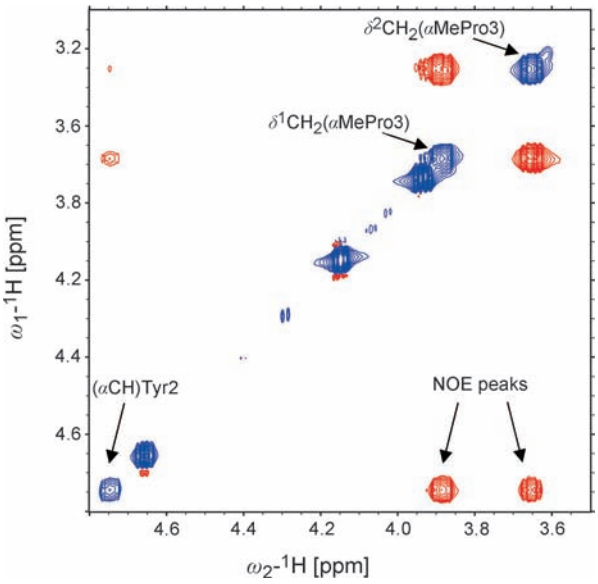


Fig. 5. *Section of the ^{1}H-ROESY spectrum of H-Ala-Tyr-α-[^{13}CH$_3$]MePro-Tyr-Asp-Val-OH in 95% H$_2$O/5% D$_2$O at pH 4.0 with 100 μM (D$_6$)DSS* ([peptide] = 6 mM). The presence of NOE peaks from the α-CH atom of Tyr2 residue to the δ-CH$_2$ moiety of α-methylproline provides strong support for the *trans* conformation of the peptide bond of α-methylproline.

sequence [16]. One can speculate that the conformational perturbation induced by the heterochiral nature of the peptide may be the cause for such an effect.

Experimental Part

General. L-Proline and pivalaldehyde (97%) were purchased from *ABCR*, Boc-amino acids from *Bachem*, biograde CF$_3$COOH (TFA) from *Halocarbon Products*, HF from *Linde Gas*, HBTU from *Peptides International*, HATU from *AAPPTEC*, DIEA (EtN^{i}Pr$_2$) from *Applied Biosystems*, Boc$_2$O from *Sigma-Aldrich*, and ^{13}C-labeled MeI from *Chembridge Isotope Laboratories.* Anal. HPLC was performed on a *Dionex Ultimate RS 3000* system. Prep. HPLC was performed on a *Waters* instrument equipped with *515* HPLC pumps and a *2487* UV absorbance detector. ^{1}H- and ^{13}C-NMR spectra were acquired on a *Varian Mercury 300* spectrometer operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C; δ in ppm rel. to Me$_4$Si as internal standard, *J* in Hz. Dynamic NMR studies were performed at seven different temps. ranging from 293 to 343 K on a *Bruker Avance III* instrument operating at 500 MHz. The temps. were adjusted with the help of an NMR tube fitted with a thermometer. Analysis of dynamic NMR data was performed with the help of iNMR (v. 5.1.2) software. The population of the two isomers and the rate constants of *cis* → *trans* isomerization $k_{c\to t}$ were determined by simulation. The populations did not significantly change in the temp. range of the recording. The derived rate constants were fitted to the *Eyring* equation to obtain the activation parameters and the rate constant of *cis* → *trans* isomerization at r.t. A series of 2D-NMR recordings were performed to elucidate the structure of the hexapeptide. DQF-COSY, TOCSY, and ROESY spectra were collected with the help of a *Bruker Avance III* 600 MHz instrument. Data were processed with TopSpin software and analyzed in Sparky software. LC/MS was conducted on the system composed from *Dionex Ultimate 3000 UPLC* integrated with a *ThermoFinnigan LCQdeca* mass-spectrometer; in *m*/*z*.

Synthesis of ^{13}C-Labeled α-Methylproline. (S)*-1-(*tert*-Butoxycarbonyl)-2-methylpyrrolidine-2-carboxylic Acid.* (2*R*,5*S*)-2-(*tert*-Butyl)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (**1**) was synthesized as described in [18][19]. (i-Pr)$_2$NH (13.6 mmol) and 1.6M BuLi in hexane (14.1 mmol) were added to THF (12 ml) at −78°, and the mixture was warmed to r.t. over 20 min. The mixture was recooled to −78° and added (as described in [27]) to a soln. of **1** (10.8 mmol) suspended in THF (60 ml) at −78°. After 45 min, commercially available ^{13}C-labeled MeI (14.0 mmol) was added to the mixture, which was then warmed to 0° over 3 h. The resulting soln. was successively washed with sat. NH_4Cl, NaCl, and Na_2CO_3 solns. (30 ml each). The product, *(2*R,5S*)-2-(*tert*-*butyl)*-5-[^{13}C]methyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one (**2**), was extracted from the mixture twice with AcOEt (20 ml), dried ($MgSO_4$), and concentrated under reduced pressure.

Compound **2** (7.813 mmol) was suspended in 3M HCl (40 ml) and heated at 100° for 1 h. The resulting product, *(*S*)-2-[^{13}C]methylpyrrolidine-2-carboxylic acid* (**3**), was concentrated under reduced pressure and washed four times with CH_2Cl_2 (20 ml). The combined org. phases were extracted with 3M HCl (20 ml), and the combined aq. phases were concentrated under reduced pressure at 60°. The residue was suspended in H_2O (50 ml) and purified on a *Dowex 50W* × *8* (H^+ form) column [28].

Compound **3** (8.9 mmol) was Boc-protected as described in [20], yielding 7.1 mmol of *(*S*)-1-(*tert*-*butoxycarbonyl)-2-[^{13}C]methylpyrrolidine-2-carboxylic acid* (**4**), which was further recrystallized from Et_2O at 4° (yield in the re-crystallization step 45%, the yield for compound **4** was 20% based on the amount of starting L-proline. $[\alpha]_D^{25} = -68.94$ ($c = 0.69$, $CHCl_3$). Anal. calc. for $C_{10}{}^{13}CH_{19}NO_4$ (230.27): C 57.81, H 8.32, N 6.08; found C 57.55, H 8.41, N 6.10.

Hexapeptide H-Ala-Tyr-α-*[^{13}C]*MePro-Tyr-Asp-Val-OH was prepared manually by stepwise solid-phase peptide synthesis using '*in situ* neutralization' Boc chemistry (Boc-SPPS) [21]. Side-chain protection for amino acids was as follows: Asp(OcHex), Tyr(Br-Z). The Boc-α-methylproline and Tyr2 residue were coupled with HATU (=2-(7-aza-1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate). After chain assembly was complete, the peptide was deprotected and simultaneously cleaved from the resin support by treatment with anh. HF containing 10% (*v*/*v*) *p*-cresol for 1 h at 0°. After evaporation of the HF under reduced pressure, the crude product was precipitated and triturated with chilled Et_2O, and subsequently dissolved in 50% aq. MeCN containing 0.1% CF_3COOH (TFA). Prep. HPLC of the crude peptide after SPPS was performed on a *Macherey-Nagel Nucleosil C$_{18}$* (250 × 20 mm, 200 Å, 7 μm) column using an appropriate shallow gradient of MeCN/0.08% TFA *vs.* H_2O/0.1% TFA. The fractions containing the desired purified peptide product were identified by anal. LC and LC/MS, combined and lyophilized. LC/MS: 742.40 Da (calc. 742.35 Da (monoisotopic)).

NMR Characterization of ^{13}C-Labelled Compounds. (2R,5S)*-2-(*tert*-Butyl)-5-[^{13}C]methyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one* (=*(3*R,7a*S)-3-*tert*-*Butyltetrahydro-7a-(^{13}C)methyl-1*H*-pyrrolo[1,2-c]*[1,3]oxazol-1-one*; **2**). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.89 (*s*, ^{t}Bu); 1.36 (*d*, ^1J(CH) = 128.4, $^{13}CH_3$); 1.62–1.85 (*m*, 3 H, $CH_2(\beta)$, $CH_2(\gamma)$); 2.09–2.19 (*m*, 1 H of $CH_2(\beta)$); 2.77–2.85 (*m*, 1 H of $CH_2(\delta)$); 3.06–3.14 (*m*, 1 H of $CH_2(\delta)$); 4.24 (*s*, ^{t}BuC*H*).

*α-[^{13}C]Methyl-*L*-proline* (**3**). ^{1}H-NMR (300 MHz, CD_3OD): 1.59 (*d*, ^1J(CH) = 128.3, $^{13}CH_3$); 1.80–2.10 (*m*, 3 H, $CH_2(\beta)$, $CH_2(\gamma)$); 2.34–2.46 (*m*, 1 H of $CH_2(\beta)$); 3.22–3.46 (*m*, 2 H of $CH_2(\delta)$).

*1-(*tert*-Butoxycarbonyl)-2-[^{13}C]methyl-*L*-proline* (**4**). ^{1}H-NMR (300 MHz, CD_3OD): 1.46 (*s*, 6 H, ^{t}Bu, conformer A); 1.48 (*s*, 3 H, ^{t}Bu, conformer B); 1.54 (*d*, ^3J(CH) = 128.4, 2 H, $^{13}CH_3$, conformer A); 1.56 (*d*, ^3J(CH) = 128.4, 1 H, $^{13}CH_3$, conformer B); 1.94–1.98 (*m*, 3 H, $CH_2(\beta)$, $CH_2(\gamma)$); 2.19–2.31 (*m*, 1 H of $CH_2(\beta)$); 3.49–3.54 (*m*, $CH_2(\delta)$).

X-Ray Analysis. Crystal data for **4**: $C_{10}{}^{13}CH_{19}NO_4$, M_r 230.27; crystal dimensions, 0.28 × 0.24 × 0.08 mm; clear colorless plate, monoclinic space group, $P2_1$, cell parameters at 100 K: $a = 6.2115(4)$, $b = 12.0649(6)$, $c = 8.5912(5)$ Å, $\beta = 108.568(2)°$, $V = 610.32(6)$ Å^3, $Z = 2$, $D_x = 1.248$ g·cm^{-3}, $F_{000} = 248$. The X-ray intensity data were collected on a *Bruker Nonius APEX-II CCD* system with MoK_α radiation ($\lambda = 0.71073$ Å) equipped with a graphite monochromator. Frame integration, data reduction, and cell refinement were performed with the *Bruker SAINT* software package [29]. The number of measured and unique reflexions are 7526 and 2679 (2519 with $I > 2\sigma(I)$), resp., in the range of $3.0° < \theta < 27.6°$, $R_{int} = 0.023$. The structures were solved and refined with SHELXS [30] and OLEX2 [31]. Non-H-atoms were localized by direct methods and refined anisotropically by full-matrix least-squares analysis. H-Atom positions could be localized in a difference electron-density map and were refined with isotropic

temp. factors. Final agreement factors for 221 parameters are $R[F^2 > 2\sigma(F^2)] = 0.033$, $wR(F^2) = 0.082$ ($w = 1/[\sigma^2(F_o^2) + (0.045(F_o^2 + 2\ F_c^2)/3)^2]$).

CCDC-894992 contains the supplementary crystallographic data for this article. This data can be obtained free of charge from *The Cambridge Crystallographic Data Centre via* www.ccdc.cam.ac.uk/data_request/cif.

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