42. An 'Umpolung' Route to Peptide Mimetics of Thyrotropin-Releasing Hormone Based on a Cyclohexane Framework

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Dedicated to Prof. Dr. *W. Fleischhacker* on the occasion of his 60th birthday

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Peptide mimetics of thyrotropin-releasing hormone (TRH) in which the peptide backbone is replaced by cyclohexane were synthesized from the cyclohexenone precursor **7**. The aromatic side chains of the mimetics were derived from the corresponding aldehydes which were attached to the cyclohexenone *via* the *Wittig* reagent **8**. The TRH mimetics are active in a mouse model of cognitive performance.

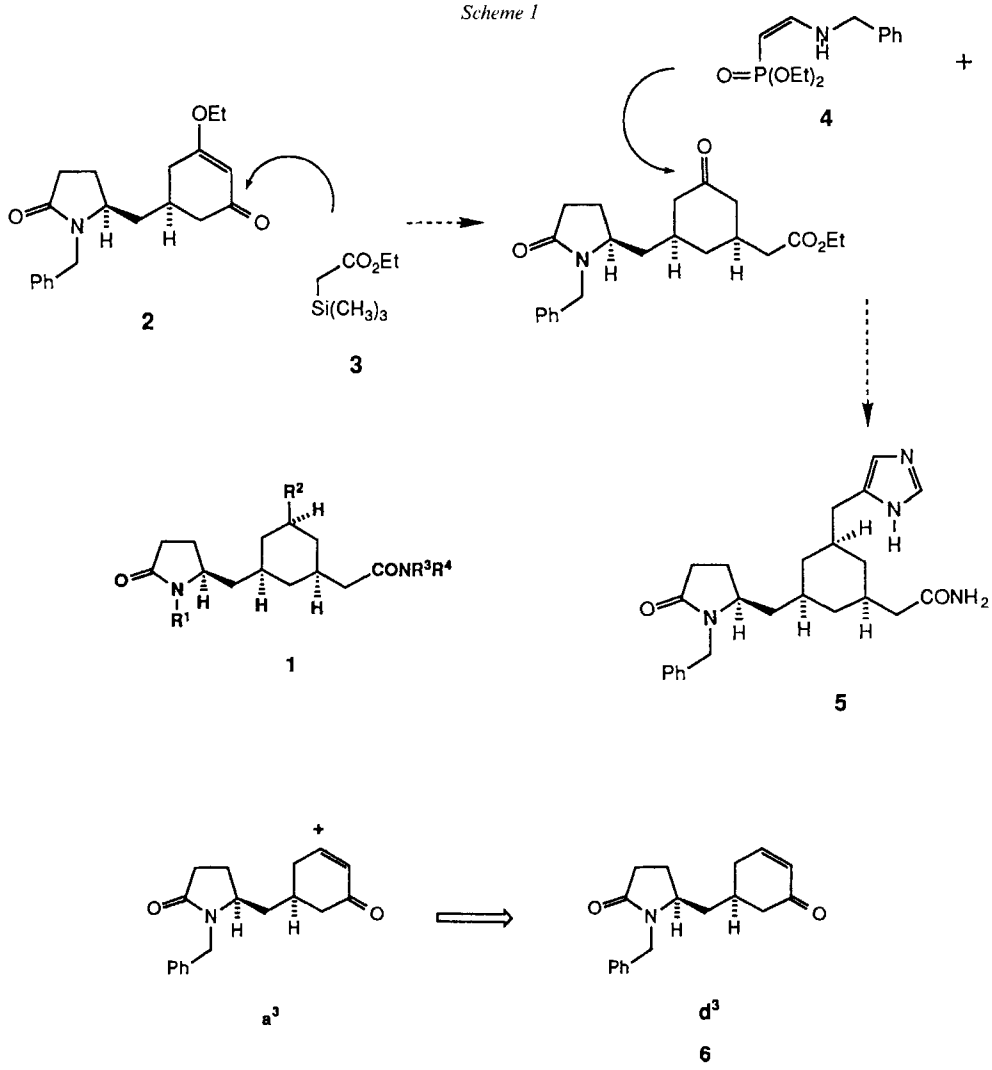
1. Introduction. – Thyrotropin-releasing hormone (TRH) is a tripeptide (pGlu-His-ProNH_2) which displays a variety of biological activities [1]. In addition to the stimulation of pituitary-hormone release, TRH is a potent neuromodulator that facilitates cholinergic and monoaminergic neurotransmission [2], and is an analeptic agent which also has trophic effects on neurons. The CNS-related effects would suggest the TRH could be used for the treatment of disorders such as *Alzheimer*'s disease, age-associated memory impairment, cerebral ischemia, and spinal injury [3]. However, endocrine effects, a short half-life and poor bioavailability are limitations for its use as a drug.

Olson et al. have developed peptide mimetics of TRH and TRH analogs [4], in which a cyclohexane framework replaces the peptide backbone (generic structure **1**). Unlike TRH and TRH peptide analogs, which are active in cognitive performance models but lack oral activity and produce endocrine side effects [5], the peptide mimetics are orally active and devoid of endocrine effects.

The synthesis of the cyclohexane mimetics follows a protocol [4] in which the substituents are added to the framework (corresponding to the enone **2**) as nucleophilic reagents. Thus, the mimetic **5** was derived from **2** and the d^2-reagents **3** and **4** (*Scheme 1*). However, the scope of this synthetic approach is limited because of the low reactivity of the vinylogous ester group. Reactive anionic reagents such as benzyllithium give only low yields of the desired addition products. Furthermore, the central imidazole ring of **5** was synthesized from TosMIC (*Scheme 1*). This procedure does not give access to mimetics with 1-alkyl-1*H*-imidazol-4-yl or 1*H*-imidazol-2-yl groups. Therefore, we studied alternatives which would allow the addition of the aromatic side chain to the cyclohexane in a single step.

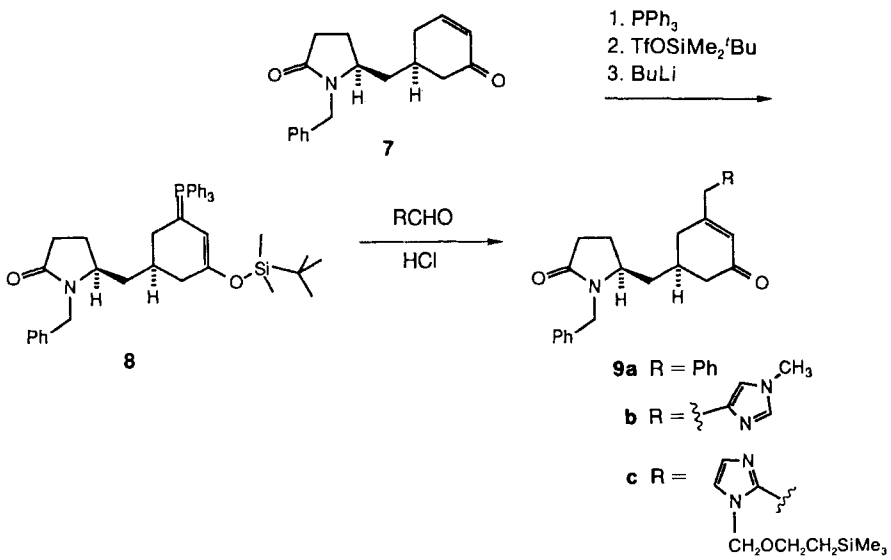
The following results describe an approach in which the reactivity of the framework (a^3-synthon) and the substituent groups is reversed, with the synthon **6** (d^3-synthon) serving as the nucleophile and the application to the synthesis of novel analogs. The ability of these compounds to enhance cognitive performance is demonstrated by their activity in the *Morris* water maze test.

Scheme 1



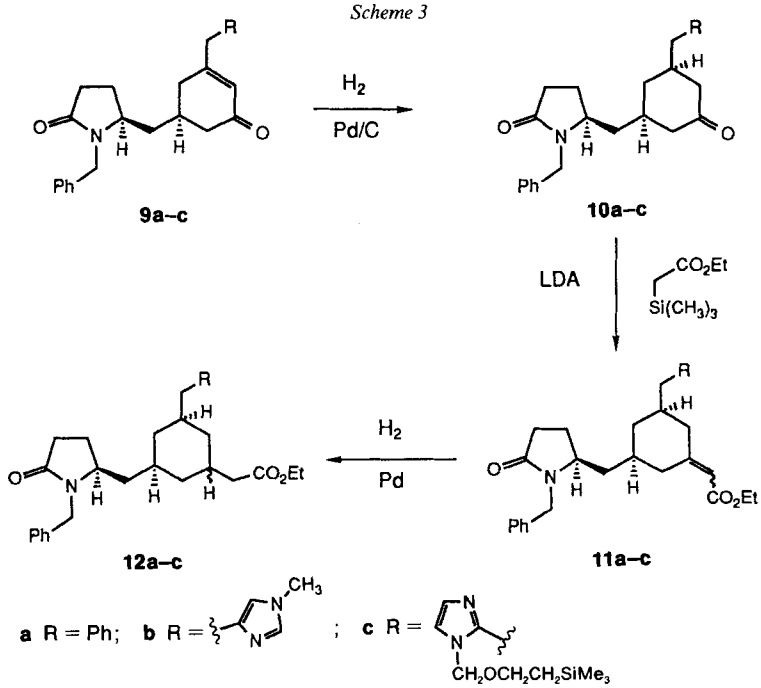
2. Results. – 2.1. *Synthesis.* The reagent corresponding to synthon **6** was generated from enone **7** by *Kozikowski*'s method for the β-functionalization of enones [6]. Enone **7** was prepared from the C(1')-epimer of **2** by $NaBH_4/CeCl_3$ [7] reduction and subsequent hydrolysis with 6N HCl. In a one-pot sequence, **7** underwent phosphoniosilylation, followed by deprotonation to give ylide **8**. *Wittig* reaction with an appropriate aldehyde and silyl enol ether hydrolysis gave the substituted enones **9** (*Scheme 2*). For the synthesis of a [Phe^2]TRH mimetic, benzaldehyde was employed to give 67% of the corresponding enone **9a**. The precursor **9b** of the [His(τ-Me)^2]TRH mimetic was derived from 1-methyl-1*H*-imidazole-4-carboxaldehyde [8] and the intermediate **9c** for the synthesis of the 1*H*-imidazol-2-yl mimetic was accessible from the [2-(trimethylsilyl)ethoxy]methyl ($Me_3SiCH_2CH_2OCH_2$)-protected 1*H*-imidazole-2-carboxaldehyde [9].

Scheme 2



Hydrogenation of the enones over Pd/C gave predominantly the *cis*-configurated cyclohexanones **10a–c**. The introduction of the C_2 fragment of the acetic-acid side chain was accomplished *via* a *Peterson* olefination to give a 1:1 mixture of the (*E*/*Z*) esters **11a–c** (*Scheme 3*). The unsaturated esters **11a–c** were resistant to hydrogenation under

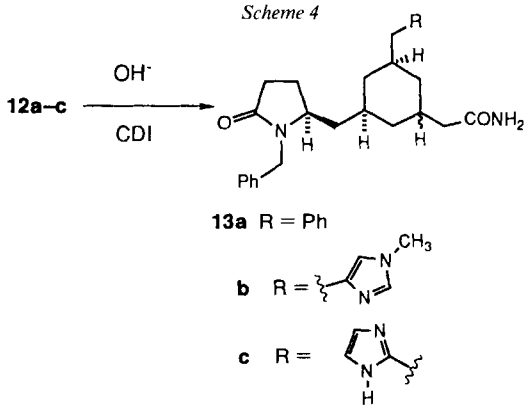
Scheme 3



standard conditions and required high pressure (500 psi) at 70° to produce a diastereoisomer mixture of the saturated compounds **12a–c**.

For the synthesis of the [Phe^2]TRH mimetic **13a** and the [His(τ-Me)^2]TRH mimetic **13b**, the esters **12a** and **12b**, respectively, were hydrolyzed and the acids activated with 1,1′-carbonylbis(1*H*-imidazole) (CDI) and reacted with ammonia. Isomer **13c** of **5** was prepared from **12c** by hydrolysis, removal of the $Me_3SiCH_2CH_2OCH_2$ group from the imidazole ring with HCl, followed by amide formation with CDI and ammonia (*Scheme 4*).

Scheme 4



Since none of the novel analogs was more active than the mimetic **5** (*vide infra*), no separation of the diastereoisomer mixtures was attempted.

2.2. *Pharmacology*. The ability of the TRH mimetics **13a–c** to enhance cognitive performance was determined in the *Morris* water maze test [10] using C57Bl/10 mice, a strain deficient in learning the water maze task [11]. This task requires an animal to attend to spatial cues in order to locate a hidden platform. The time required for each animal to locate the platform (latency) on each of four trials was recorded. The mean total latency was recorded as a function of dose. The test compounds and TRH were dissolved in saline or suspended in acacia and administered by the intraperitoneal route 30 min prior to

Table. *Effects of TRH and Compounds* **5** *and* **13a–c** *on the* Morris *Water Maze Performance in C57BL/10 Mice*

Compound	Dose [mg/kg]	Mean latency [s]	±s.e.m.	Compound	Dose [mg/kg]	Mean latency [s]	±s.e.m.
TRH	0.001	50.59	0.94	**13a**	0.001	67.88	1.55
	0.003	43.08	0.67		0.01	53.86	2.62
	0.01	37.97	0.79		0.1	26.65	7.44
	0.03	32.69	0.74		1.0	33.96	1.12
	0.1	25.76	2.20	**13b**	0.0001	57.76	1.63
	0.3	20.85	0.53		0.001	32.86	3.65
	1.0	28.87	0.74		0.01	33.87	2.23
	3.0	33.57	0.90		0.1	22.14	0.60
	10.0	46.00	2.15		1.0	27.10	1.79
5	0.0003	33.29	0.52	**13c**	0.001	49.99	0.63
	0.003	22.24	1.02		0.01	39.89	0.46
	0.03	15.65	0.45		0.1	19.88	0.38
	0.3	17.62	0.60		1.0	27.86	0.89
	3.0	31.62	0.96				

testing. Because of the tendency for compounds of the related series to bind to glass vessels, all solutions were made in plastic apparatus. One group of mice received a total of 10 ml/kg of body weight. One group of mice in each experiment with test compounds received a 0.1 mg/kg dose of TRH as a positive control. The results are summarized in the *Table* and show that the compounds are all active in the test at doses comparable to TRH, but less potent than the reference compound **5**. Because of the lower potency, **5** was judged to be a more suitable candidate for further study. The lower potencies for the compounds described here show the relative importance of the properly oriented unsubstituted imidazole ring in TRH mimetics.

Experimental Part

General. All laboratory glassware was flame-dried under vacuum and purged with dry Ar. THF was distilled from sodium benzophenone ketyl and then transferred *via* a syringe. Column chromatography (CC): silica gel (230–400 mesh; *Merck*); 0.3–1.0 bar pressure. IR Spectra (cm^{-1}): *Digilab FTS-15E.* ^{1}H-NMR Spectra (δ in ppm rel. to internal or external Me_4Si, coupling constants J in Hz): *Varian XL-200* and *XL-400*, HR-MS: *VG-7070HF.*

(5S,1'R)-5-[(5'-Oxocyclohex-3'-en-1'-yl)methyl]-1-(phenylmethyl)pyrrolidin-2-one (**7**). A soln. of (5*S*,1'*S*)-5-[(3'-ethoxy-5'-oxocyclohex-3'-en-1'-yl)methyl]-1-(phenylmethyl)pyrrolidin-2-one (2 g, 6.1 mmol) [4] and cerium chloride heptahydrate (4 g, 10.7 mmol) in MeOH (45 ml) was cooled to 0° and $NaBH_4$ (418 mg, 11 mmol) was added in small portions. The mixture was stirred for 1 h and extracted with 6N HCl (20 ml) and CH_2Cl_2. The combined org. layers were dried (Na_2SO_4) and evaporated: 1.68 g (97%) of **7**. Colorless oil.

IR ($CHCl_3$): 3030, 1672. ^{1}H-NMR ($CDCl_3$): 7.35–7.21 (*m*, 5 H); 6.94 (*m*, 1 H); 6.01 (*d*, J = 11, 1 H); 4.99, 3.94 (*AB*, J = 15, 2 H); 2.55–2.33 (*m*, 4 H); 2.17–1.93 (*m*, 4 H); 1.80 (*m*, 1 H); 1.66 (*m*, 1 H); 1.37 (*m*, 1 H). HR-MS: 283.1572 (M^+, $C_{18}H_{21}NO_2^+$, calc. 283.1572).

(5S,1'R)-5-{[5'-Oxo-3'-(phenylmethyl)cyclohex-3'-en-1'-yl]methyl}-1-(phenylmethyl)pyrrolidin-2-one (**9a**). To a soln. of **7** (700 mg, 2.4 mmol) and PPh_3 (590 mg, 2.4 mmol) in THF (20 ml) was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (TfOSiMe$_2$(*t*-Bu)) (0.53 ml, 2.4 mmol). After stirring for 1.5 h at r.t., the soln. was cooled to −78° and BuLi (2.4 mmol in hexane) added. The red soln. was stirred for 30 min at −78° and a soln. of benzaldehyde (300 mg, 2.8 mmol) in THF (10 ml) added. The mixture was kept at −78° for 45 min and then warmed to r.t. within 1 h. THF was evaporated and the residue chromatographed (silica gel, AcOEt/hexane 6:4): (*E*)- and (*Z*)(silyloxy)dienes (720 mg). This mixture was dissolved in THF (10 ml), and 6N HCl (2 ml) was added. After stirring for 15 min, the THF was removed and the residue extracted with CH_2Cl_2. The combined layers were dried (Na_2SO_4) and evaporated: 610 mg (66.5%) of **9a**. Colorless oil. IR ($CHCl_3$): 3020, 1670. ^{1}H-NMR ($CDCl_3$): 7.36–7.09 (*m*, 10 H); 5.85 (*s*, 1 H); 4.93, 3.89 (*AB*, J = 15, 2 H); 3.47 (*s*, 2 H); 3.39 (*m*, 1 H); 2.52–1.49 (*m*, 10 H); 1.26 (*m*, 1 H). HR-MS: 373.2042 (M^+, $C_{25}H_{27}NO_2^+$, calc. 373.2040).

(5S,1'R)-5-{{3'-[(1-Methyl-1H-imidazol-4-yl)methyl]-5'-oxocyclohex-3'-en-1'-yl}methyl}-1-(phenylmethyl)pyrrolidin-2-one (**9b**). As described for **9a**, with **7** (1.7 g, 5.6 mmol), PPh_3 (1.46 g, 5.6 mmol), THF (30 ml), TfOSiMe$_2$(*t*-Bu) (1.3 ml, 5.6 mmol), BuLi (5.6 mmol in hexane), 1-methyl-1*H*-imidazol-4-carboxaldehyde (610 mg, 5.5 mmol) [7], and THF (10 ml). Before workup, H_2O (5 ml) and 6N HCl (10 ml) were added, and the mixture was stirred overnight. THF was removed, the soln. basified with 5% NaOH soln. and extracted with CH_2Cl_2. The combined org. phase dried (Na_2SO_4) and evaporated, and the residue subjected to CC (silica gel, $CHCl_3$/MeOH/AcOH 60:10:1): 1.24 g (55%) of **9b**. Colorless oil. IR ($CHCl_3$): 3020, 1670. ^{1}H-NMR ($CDCl_3$): 7.37 (*s*, 1 H); 7.35–7.15 (*m*, 5 H); 6.66 (*s*, 1 H); 5.84 (*s*, 1 H); 4.94, 3.91 (*AB*, J = 15, 2 H); 3.64 (*s*, 3 H); 3.42 (*s*, 2 H); 3.39 (*m*, 1 H): 2.49–1.50 (*m*, 10 H); 1.33 (*m*, 1 H). HR-MS: 377.2083 (M^+, $C_{23}H_{27}N_3O_2^+$, calc. 377.2103).

(5S,1'R)-5-{{5'-Oxo-[3'-{{1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazol-2-yl}methyl}cyclohex-3'-en-1'-yl}methyl}-1-(phenylmethyl)pyrrolidin-2-one (**9c**). As described for **9a**, with **7** (1.8 g, 6 mmol), PPh_3 (1.75 g, 6 mmol), THF (30 ml), TfOSiMe$_2$(*t*-Bu) (1.4 ml, 6 mmol), BuLi (6 mmol in hexane), 1-[2-(trimethylsilyl)ethoxy]methyl-1*H*-imidazole-2-carbaldehyde [8] (1.35 g, 6 mmol), and THF (10 ml). Before workup, H_2O (5 ml) and 6N HCl (10 ml) were added, the mixture was stirred at 50° for 1 h. THF was removed, and the mixture worked up as described for **9b**. CC (silica gel, AcOEt/MeOH 9:1) gave 1.9 g (64%) of **9c**. Yellow oil. IR ($CHCl_3$): 3020, 1678. ^{1}H-NMR ($CDCl_3$): 7.28 (*m*, 3 H); 7.17 (*m*, 2 H); 6.97 (*d*, J = 1.5, 1 H); 6.94 (*d*, J = 1.5, 1 H); 5.77 (*s*, 1 H); 4.96, 3.92 (*AB*, J = 15, 2 H); 3.68 (*s*, 2 H); 3.45 (*dd*, J = 8.5, 10, 2 H); 3.42 (*m*, 1 H); 2.50–2.24 (*m*, 4 H); 2.20–2.0 (*m*, 3 H); 1.94–1.53 (*m*, 3 H); 1.42–1.23 (*m*, 1 H); 0.86 (*dd*, J = 8.5, 10, 2 H); −0.06 (*s*, 9 H). HR-MS: 493.2779 (M^+, $C_{28}H_{39}N_3O_3Si^+$, calc. 493.2761).

General Procedure for the Hydrogenation of **9**. A soln. of the enone **9** (2 mmol) in EtOH (20 ml) and 2N HCl (5 ml) was hydrogenated over 10% Pd/C (30 mg) at 40 psi for 2 h. The mixture was filtered, basified with 5% NaOH soln., and extracted with CH_2Cl_2. The combined org. layers were dried (Na_2SO_4) and evaporated to give a mixture of diastereoisomers. This mixture was subjected to CC (AcOEt/MeOH 9:1) to give the major *cis*-isomer in 90% yield. Colorless oils.

(5S,1R,5S)-5-{[3'-Oxo-5'-(phenylmethyl)cyclohex-1'-yl]methyl}-1-(phenylmethyl)pyrrolidin-2-one (**10a**). IR ($CHCl_3$): 1702, 1670, 1600. ^{1}H-NMR ($CDCl_3$): 7.35–7.08 (*m*, 10 H); 4.98, 3.92 (*AB*, *J* = 15, 2 H); 3.36 (*m*, 1 H); 2.62–2.48 (*m*, 2 H); 2.44–1.85 (*m*, 7 H); 1.69–1.48 (*m*, 5 H); 1.38–1.04 (*m*, 2 H). HR-MS: 375.2179 (M^+, $C_{25}H_{29}NO_2^+$, calc. 375.2198).

(5S,1'R,5'S)-5-{{3'-Oxo-5'-[(1-methyl-1H-imidazol-4-yl)methyl]cyclohex-1'-yl}methyl}-1-(phenylmethyl)-pyrrolidin-2-one (**10b**). IR ($CHCl_3$): 1705, 1672. ^{1}H-NMR ($CDCl_3$): 7.34–7.14 (*m*, 6 H); 6.57 (*s*, 1 H); 4.96, 3.89 (*AB*, *J* = 15, 2 H); 3.61 (*s*, 1 H); 3.36 (*m*, 1 H); 2.53–1.05 (*m*, 16 H). HR-MS: 379.2261 (M^+, $C_{23}H_{29}N_3O_2^+$, calc. 379.2260).

(5S,1'R,5'S)-5-{{3'-Oxo-5'-{{1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazol-2-yl}methyl}cyclohex-1'-yl}methyl}-1-(phenylmethyl)pyrrolidin-2-one (**10c**). IR ($CHCl_3$): 1708, 1672, 838. ^{1}H-NMR ($CDCl_3$): 7.33 (*m*, 3 H); 7.19 (*m*, 2 H); 6.98 (*s*, 1 H); 6.93 (*s*, 1 H); 5.20 (*s*, 2 H); 4.99, 3.92 (*AB*, *J* = 15, 2 H); 3.48 (*dd*, *J* = 7.5, 9, 2 H); 3.39 (*m*, 1 H); 2.77 (*d*, *J* = 6.5, 2 H); 2.50–1.50 (*m*, 12 H); 1.38 (*m*, 1 H); 1.25 (*m*, 1 H); 0.89 (*dd*, *J* = 7.5, 9, 2 H); −0.06 (*s*, 9 H). HR-MS: 495.2914 (M^+, $C_{28}H_{41}N_3O_3Si^+$, calc. 495.2917).

General Procedure for the Peterson-*Olefination of* **10**. To a soln. of freshly prepared lithium diisopropylamide (LDA; 3.5 mmol) in THF (20 ml) was added ethyl (trimethylsilyl)acetate (0.6 ml, 3.2 mmol) at −40°. After stirring for 1 h at −40°, a soln. of ketone **10** (3 mmol) in THF (10 ml) was added. The mixture was slowly warmed to r.t. and extracted with H_2O and CH_2Cl_2. The combined org. phase was dried (Na_2SO_4) and evaporated and the residue subjected to CC (AcOEt/MeOH 9:1): 1:1 mixture of the (*E*/*Z*)-esters **11**.

Ethyl {(E/Z,3S,5R,2'S)-3-{[5'-Oxo-1'-(phenylmethyl)pyrrolidin-2'-yl]methyl}-5-(phenylmethyl)cyclohexylidene}acetate (**11a**). Yield 67.5%. IR ($CHCl_3$): 3020, 1700, 1670. ^{1}H-NMR ($CDCl_3$): 7.30–7.07 (*m*, 10 H); 5.53, 5.50 (*s*, 1 H); 4.97, 4.92, 3.95, 3.87 (*AB*, *J* = 15, 2 H); 4.08, 4.06 (*q*, *J* = 7, 2 H); 2.78–1.10 (*m*, 15 H); 3.55, 3.37 (*m*, 1 H); 1.19 (*t*, *J* = 7, 3 H); 0.87 (*m*, 1 H). HR-MS: 445.2610 (M^+, $C_{29}H_{35}NO_3^+$, calc. 445.2617).

Ethyl {(E/Z,3S,5R,2'S)-5-[(1-Methyl-1H-imidazol-4-yl)methyl]-3-{[5'-oxo-1'-(phenylmethyl)pyrrolidin-2'-yl]methyl}cyclohexylidene}acetate (**11b**). Yield 76%. IR ($CHCl_3$): 3000, 1700, 1672. ^{1}H-NMR ($CDCl_3$): 7.33–7.18 (*m*, 6 H); 6.61, 6.57 (*s*, 1 H); 5.56, 5.50 (*s*, 1 H); 4.97, 4.92, 3.96, 3.90 (*AB*, *J* = 15, 2 H); 4.12, 4.09 (*q*, *J* = 7, 2 H); 3.63 (*s*, 3 H); 3.58, 3.42 (*m*, 1 H); 2.63–1.92 (*m*, 7 H); 1.87–1.35 (*m*, 6 H); 1.35–1.10 (*m*, 2 H); 1.21, 1.23 (*t*, *J* = 3 H); 0.90 (*m*, 1 H). HR-MS: 449.2695 (M^+, $C_{27}H_{35}N_3O_3^+$, calc. 449.2678).

Ethyl {(E/Z,3S,5R,2'S)-3-{[5'-Oxo-1'-(phenylmethyl)pyrrolidin-2'-yl]methyl}-5-{{1-{[2-(trimethylsilyl)-ethoxy]methyl}-1H-imidazol-2-yl}methyl}cyclohexylidene}acetate (**11c**). Yield 72.5%. IR ($CHCl_3$): 2960, 1700, 1672, 838. ^{1}H-NMR ($CDCl_3$): 7.29–7.14 (*m*, 5 H); 6.91 (*d*, *J* = 1.3, 1 H); 6.86 (*d*, *J* = 1.3, 1 H); 5.35, 5.47 (*s*, 1 H); 5.14 (*s*, 2 H); 4.92, 4.88, 3.85 (*AB*, *J* = 15, 2 H); 4.03, 4.02 (*q*, *J* = 7, 2 H); 3.80 (*m*, 2 H); 3.55, 3.35 (*m*, 1 H); 3.42 (*dd*, *J* = 8.3, 6.7, 2 H); 2.63 (*m*, 2 H); 2.42–1.30 (*m*, 10 H); 1.21, 1.18 (*t*, *J* = 7, 3 H); 1.19 (*m*, 3 H); 0.98 (*m*, 1 H); 0.86 (*dd*, *J* = 8.3, 6.7, 2 H); −0.06 (*s*, 9 H). HR-MS: 565.3344 (M^+, $C_{32}H_{47}N_3O_4Si^+$, calc. 565.3336).

General Procedure for the Hydrogenation of **11**. A soln. of ester **11** (1.0 mmol) in EtOH (50 ml) was hydrogenated over Pd black (40 mg) at 500 psi and 70°. The solvent was removed to give colorless oil of **12**.

Ethyl (1RS,3S,5R,2'S)-3-{[5'-Oxo-1'-(phenylmethyl)pyrrolidin-2'-yl]methyl}-5-(phenylmethyl)cyclohexaneacetate (**12a**). Yield 97%. IR ($CHCl_3$): 2925, 1725, 1672. ^{1}H-NMR ($CDCl_3$): 7.34–7.06 (*m*, 10 H); 4.96, 3.90 (*AB*, *J* = 15, 2 H); 4.07, 4.02 (*q*, *J* = 7, 2 H); 3.40 (*m*, 1 H); 2.57–0.32 (*m*, 19 H); 1.19 (*t*, *J* = 7, 3 H). HR-MS: 447.2773 (M^+, $C_{29}H_{37}NO_3^+$, calc. 447.2773).

Ethyl (1RS,3S,5R,2'S)-5-[(1-Methyl-1H-imidazol-4-yl)methyl]-3-{[5'-oxo-1'-(phenylmethyl)pyrrolidin-2'-yl]methyl}cyclohexaneacetate (**12b**). Yield 95%. IR ($CHCl_3$): 1725, 1672. ^{1}H-NMR ($CHCl_3$): 7.73 (*s*, 1 H); 7.32–7.12 (*m*, 5 H); 6.58 (*s*, 1 H); 4.92, 3.89, 3.87 (*AB*, *J* = 15, 2 H); 4.06, 4.02 (*q*, *J* = 7, 2 H); 3.67 (*s*, 3 H); 3.40 (*m*, 1 H); 2.5–0.3 (*m*, 19 H); 1.18, 1.16 (*t*, *J* = 7, 3 H). HR-MS: 451.2831 (M^+, $C_{27}N_{37}N_3O_3^+$, calc. 451.2835).

Ethyl (1RS,3S,5R,2'S)-3-{[5'-Oxo-1'-(phenylmethyl)pyrrolidin-2'-yl]methyl}-5-{{1-{[2-(trimethylsilyl)-ethoxy]methyl}-1H-imidazol-2-yl}methyl}cyclohexaneacetate (**12c**). Yield 91%. IR ($CHCl_3$): 2950, 1725, 1672, 838. ^{1}H-NMR ($CHCl_3$): 7.25–7.11 (*m*, 5 H); 6.87 (*s*, 1 H); 6.83 (*s*, 1 H); 5.11 (*s*, 2 H); 4.87, 3.85, 3.83 (*AB*, *J* = 15, 2 H); 4.01 (*q*, *J* = 7, 2 H); 3.40 (*dd*, *J* = 8.3, 8.3, 2 H); 3.35 (*m*, 1 H); 1.14 (*t*, *J* = 7, 3 H); 0.82 (*dd*, *J* = 8.3, 8.3, 2 H); 0.73–0.30 (*m*, 2 H); −0.07 (*s*, 9 H). HR-MS: 567.3507 (M^+, $C_{32}H_{49}N_3O_4Si^+$, calc. 567.3492).

(1RS,3S,5R,2'S)-3-{[5'-Oxo-1'-(phenylmethyl)pyrrolidin-2'-yl]methyl}-5-(phenylmethyl)cyclohexaneacetamide (**13a**). A soln. of **12a** (340 mg, 0.76 mmol) in EtOH (10 ml) and 1N NaOH (2 ml) was heated to 80° for 30 min. EtOH was removed, the pH adjusted to 3 with 1N HCl, and the mixture evaporated. After the addition of

1,1′-carbonylbis(1*H*-imidazole) (125 mg, 0.77 mmol) and THF (10 ml), the mixture was refluxed for 1 h. The soln. was saturated with ammonia at 5–10°, stirred for 2 h at 20°, and extracted with H_2O and CH_2Cl. The combined org. phase was dried (Na_2SO_4) and evaporated and the residue purified by CC ($CHCl_3$/MeOH 9:1): 200 mg (63%) of **13a**. Colorless oil. IR ($CHCl_3$): 3525, 3410, 1673. ^{1}H-NMR ($CDCl_3$): 7.32–7.07 (*m*, 10 H); 5.76, 5.52 (*s*, 2 H); 4.39, 3.89 (*AB*, *J* = 15, 2 H); 3.44 (*m*, 1 H); 2.55–0.32 (*m*, 19 H). HR-MS: 418.2623 (M^+, $C_{27}H_{34}N_2O_2^+$, calc. 418.2620).

*(1*RS,*3*S,*5*R,*2′*S*)-5-[(1-Methyl-1*H*-imidazol-4-yl)methyl]-3-{[5′-oxo-1′-(phenylmethyl)pyrrolidin-2′-yl]cyclohexaneacetamide* (**13b**). As described for **13a**, with **12b** (225 mg, 0.5 mmol), EtOH (10 ml), 1N NaOH (2 ml), 1,1′-carbonylbis(1*H*-imidazole) (85 mg, 0.52 mmol), and THF (10 ml): 200 mg (95%) of **13b**. Colorless oil. IR ($CHCl_3$): 3525, 3405, 1670. ^{1}H-NMR ($CDCl_3$): 7.34–7.15 (*m*, 6 H); 6.53, 6.54 (*s*, 1 H); 4.90, 3.89 (*AB*, *J* = 15, 2 H); 3.60, 3.61 (*s*, 3 H); 3.43 (*m*, 1 H); 2.51–2.23 (*m*, 6 H); 2.15–1.78 (*m*, 3 H); 1.85–0.80 (*m*, 8 H); 0.70–0.33 (*m*, 2 H). HR-MS: 422.689 (M^+, $C_{25}H_{34}N_4O_2^+$, calc. 422.2682).

*(1*RS,*3*S,*5*R,*2*S*)-5-[(1*H*-Imidazol-2-yl)methyl]-3-{[5′-oxo-1′-(phenylmethyl)pyrrolidin-2′-yl]methyl}cyclohexaneacetamide Hydrochloride* (**13c**·HCl). A soln. of **12c** (400 mg, 0.7 mmol) in EtOH (20 ml) and 1N NaOH (5 ml) was heated to 80° for 30 min. EtOH was removed, the pH adjusted to 3, and the mixture extracted with CH_2Cl_2 to give 375 mg of an orange oil. The oil was dissolved in 6N HCl (10 ml) and refluxed for 4 h. The solvent was evaporated to give 240 mg (88%) of the deprotected acid. After the addition of 1,1′-carbonylbis(1*H*-imidazole) (100 mg, 0.6 mmol) and 6 ml of DMF, the mixture was refluxed for 1 h. The soln. was saturated with ammonia at 5–10° and stirred for 2 h at r.t. The mixture was filtered and the solvent evaporated: The residue was dissolved in dioxane (3 ml) and 5% aq. NaOH soln. (1 ml), (*t*-BuO)C(O)OC(O)(*t*-BuO) (130 mg, 0.6 mmol) added, and the mixture stirred for 1 h. The soln. was extracted with CH_2Cl_2 and H_2O. The combined org. layers were dried (Na_2SO_4) and evaporated. The resulting Boc derivative was purified by CC ($CHCl_3$/MeOH 9:1): 150 mg of a colorless oil. A soln. of this oil was dissolved in CH_2Cl_2 (3 ml) and CF_3COOH (1 ml) and stirred for 2 h at r.t. The solvent was removed, the residue taken up in 2N HCl, and the soln. evaporated: 100 mg (32%) of **13c**·HCl. IR (neat): 2950, 1650. ^{1}H-NMR (CD_3OD): 7.29 (*s*, 2 H); 7.23–7.09 (*m*, 5 H); 4.72, 4.00 (*AB*, *J* = 15.4, 2 H); 3.43 (*m*, 1 H); 2.73 (*m*, 1 H); 2.40–0.29 (*m*, 17 H). HR-MS: 408.2526 (M^+, $C_{24}H_{32}N_4O_2^+$, calc. 408.2525).

Morris *Water Maze Test.* C57BL/10 Male mice weighing 15–18 g at the start of the experiment were group housed, 10 per box, for at least 1 week prior to the experiment and had *ad libitum* access to food and H_2O. The maze consisted of a 60 cm × 60 cm × 60 cm transparent plexiglas chamber filled to the depth of 30 cm, leaving 30 cm of wall extending up from the H_2O surface. The H_2O was made opaque by the addition of powdered milk. The H_2O temp. was maintained at 20°. Both distal cues (*i.e.*, standard room objects) and proximal cues (*i.e.*, 20 cm × 22 cm unique black and white patterns attached to the center of each of the four walls of the maze) were used. The submerged platform, 8×8 cm, 1 cm below the H_2O surface, was positioned 10 cm from the walls near one corner of the maze. Each animal was given 4 trials (maximum of 2 min/trial, 20 s intertrial interval) to locate the position of the hidden platform. On each trial the mouse was placed into the H_2O at the opposite corner to that of the submerged platform. Between trials, mice were removed from the H_2O and placed on a dry surface under a heat lamp for 20 to 30 s before the start of the next trial. The mean time (latency) for the 4 trials was used as the score for a given animal. Drug or vehicle was administered *i.p.*, 30 min prior to the first trial.

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