A Novel Synthesis of Highly Substituted Perhydropyrrolizines, Perhydroindolizines, and Pyrrolidines: Inhibition of the Peptidyl-Prolyl *cis*/*trans* Isomerase (PPIase) Pin1

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In this paper, we describe the synthesis and biological evaluation of highly substituted perhydropyrrolizines that inhibit the peptidyl-prolyl *cis*/*trans* isomerase (PPIase) Pin1, an oncogenic target. The enzyme selectively catalyzes the *cis*/*trans* isomerization of peptide bonds between a phosphorylated serine or threonine, and proline, thereby inducing a conformational change. Such structural modifications play an important role in many cellular events, such as cell-cycle progression, transcriptional regulation, RNA processing, as well as cell proliferation and differentiation. Based on computer modeling (*Fig. 2*), the new perhydropyrrolizinone derivatives (−)-**1a**,**b**, decorated with two substituents, were selected and synthesized (*Schemes 1–3*). While enzymatic assays showed no biological activity, ^{15}N,^{1}H-HSQC-NMR spectroscopy revealed that (−)-**1a**,**b** bind to the WW recognition domain of Pin1, apparently in a mode that does not inhibit PPIase activity. To enforce complexation into the larger active site rather than into the tighter WW domain of Pin1 and to enhance the overall binding affinity, we designed a perhydropyrrolizine scaffold substituted with additional aromatic residues (*Fig. 5*). A novel, straightforward synthesis towards this class of compounds was developed (*Schemes 4* and *5*), and the racemic compounds (±)-**22a**–**22d** were found to inhibit Pin1 with K_i values (K_i = inhibition constant) in the micromolar range (*Table 2*). To further enhance the potency of these inhibitors, the optically pure ligands (+)-**22a** and (+)-**33b**,**c** were prepared (*Schemes 6* and *7*) and shown to inhibit Pin1 with K_i values down to the single-digit micromolar range. According to ^{15}N,^{1}H-HSQC-NMR spectroscopy and enzymatic activity assays, binding occurs at both the WW domain and the active site of Pin1. Furthermore, the new synthetic protocol towards perhydropyrrolizines was extended to the preparation of highly substituted perhydroindolizine ((±)-**43**; *Scheme 8*) and pyrrolidine ((±)-**48a**,**b**; *Scheme 9*) derivatives, illustrating a new, potentially general access to these highly substituted heterocycles.

1. Introduction. – Rotation about peptide bonds is energetically demanding, due to their partial double-bond character and, consequently, the *cis*/*trans* isomerization of prolyl bonds is a slow process. However, this step is catalyzed by a family of enzymes called the peptidyl-prolyl *cis*/*trans* isomerases (PPIases). Since the discovery of the first PPIase in 1984 by *Fischer et al.* [1], three families differing in the amino acid

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sequence of their catalytic domain, their substrate specificity, and their sensitivity for inhibitors have emerged [2]: the cyclophilins (Cyps), the FK506 binding proteins (FKBPs), and, more recently, a family divided into two subclasses, the Pin1-PPIases, which recognize phosphorylated substrates, and the parvulin-like-PPIases, which do not [3][4].

Pin1, a member of the third family, selectively binds and isomerizes specific peptide bonds between a phosphorylated serine or threonine and proline (*p*Ser/*p*Thr-Pro motif), thereby inducing conformational changes. Such modifications play an essential role in several cellular events, notably in the proper cell-cycle progression. Thus, Pin1 has been found to regulate several cell-cycle regulators such as cyclin D1 [5] and the Cdc25 phosphatase [6][7], the transcription factors *c*-Jun [8], β-catenin [9], and *c*-Myc [10], or the tumor suppressor p53 [11][12]. Deregulation of Pin1 plays an important role in the development of numerous human cancers. In malignant cells, Pin1 is overexpressed, hyperactive, and seems to favor tumor growth. Additionally, the overexpression of Pin1 in cancer cells correlates with that of cyclin D1, β-catenin, and *c*-Myc [13].

Pin1 is for several reasons an attractive new drug target for cancer therapy. Depletion of Pin1 from yeast induces mitotic arrest [14], and inhibition of the enzyme triggers tumor cells to enter apoptosis [15]. Moreover, Pin1 knockout mice develop normally to adulthood [16], suggesting that Pin1 inhibition might not have general toxic effects. To date, several reversible inhibitors of the enzyme Pin1 have been reported [17]. These enclosed notably the natural product juglone [18], polycyclic aromatic derivatives [19], or peptides and peptide derivatives [20–22].

In this paper, we describe the synthesis and *in vitro* evaluation of new perhydropyrrolizine derivatives, targeting the inhibition of Pin1. Whereas the first-generation ligands, based on a central perhydropyrrolizinone core decorated with two vectors, show no biological activity towards Pin1, preparation of highly substituted perhydropyrrolizines leads to the development of a new generation of nonpeptidic inhibitors of Pin1, exhibiting K_i values (K_i = inhibition constant) down to the single-digit micromolar range. Furthermore, the new synthetic protocol towards the perhydropyrrolizines is further amenable to the preparation of other highly substituted heterocycles, such as perhydroindolizines and pyrrolidines.

2. Results and Discussion. – 2.1.1. *Design of the Perhydropyrrolizinone Lead Structure (–)*-**1a**. Pin1, a rather small enzyme (163 amino acids), isolated in 1996 [14], is composed of two domains, the WW and the PPIase domain, connected by a flexible loop, as revealed by the 1.35-Å-resolution X-ray crystal structure of a co-crystal with a non-natural dipeptide and a sulfate anion (PDB-code 1PIN; *Fig. 1*,*a*) [23]. The PPIase domain is responsible for the catalytic activity of the enzyme, the *cis*/*trans* isomerization of the peptide bond to specific proline residues in the substrate, while the WW domain displays recognition function only. Importantly, both domains have the same specificity for *p*Ser/*p*Thr-Pro motifs.

On the basis of the crystal structure of Pin1, we used the molecular-modeling package MOLOC [24] to design small molecules that should exhibit good steric and electronic complementarity with the active site of the enzyme. The active site is located at the surface of the enzyme. The residues Leu122, Met130, and Phe134 build a hydro-

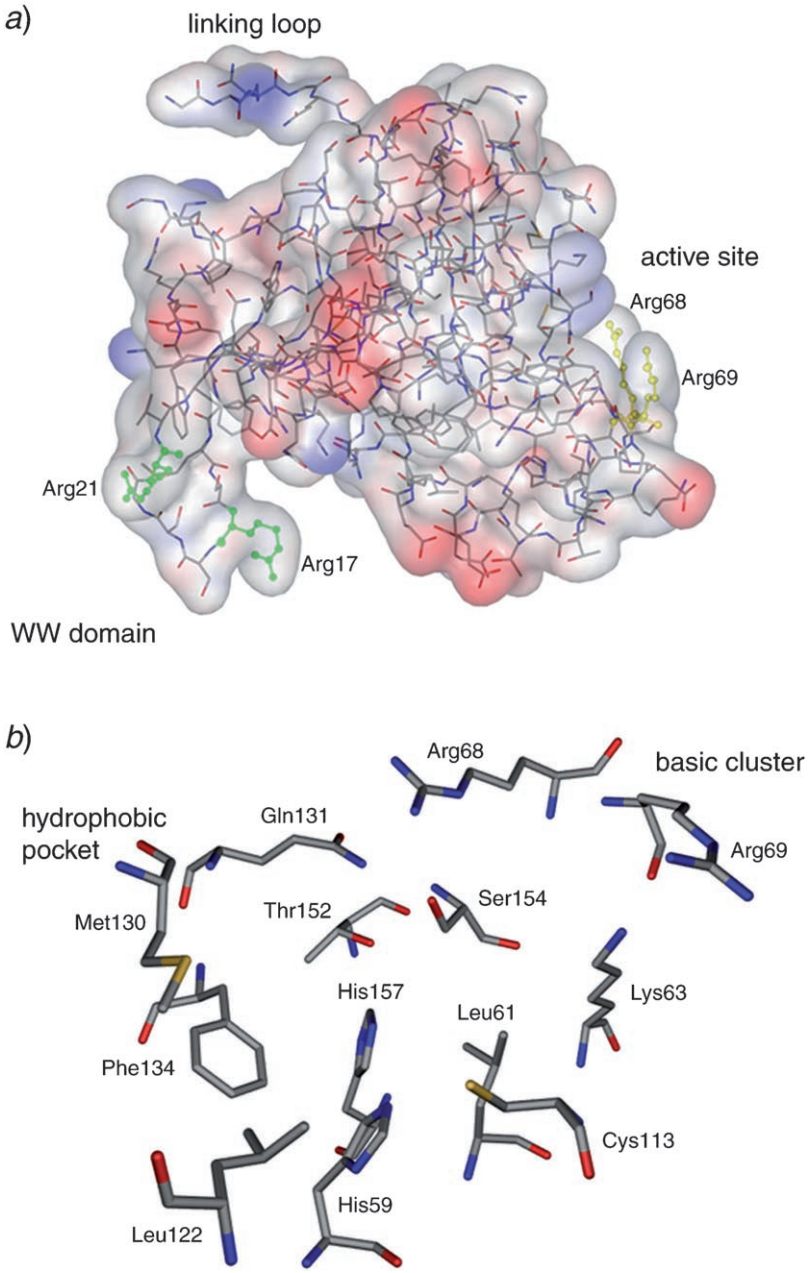


Fig. 1. a) *Structure of the enzyme Pin1 featuring the catalytic PPIase domain, the recognition WW domain, and the connecting loop* (PDB-code: 1PIN) [23]. The loop is apparently quite flexible, and residues 40–44 are disordered and not visible in the electron density map [23]. b) *View on the catalytic site.* A non-natural dipeptide and a sulfate anion bound in the active site in the co-crystal are not shown.

phobic pocket, which binds the cyclic side chain of the prolyl residue of the substrate (*Fig. 1*,*b*). His59, Cys113, Ser154, and His157 surround the peptide bond undergoing the catalyzed *cis*/*trans* isomerization. Finally, Lys63, Arg68, and Arg69 form a basic cluster, which binds the phosphorylated Ser/Thr of the substrate. A perhydropyrrolizinone (2,3,5,6,7,7a-hexahydro-1*H*-pyrrolizin-3-one) scaffold, decorated with two vectors, seemed to fit well into the active site, and compound (−)-**1a** was chosen as a lead compound. The i-Pr group should fill the hydrophobic pocket, whereas the phosphate moiety was positioned to ensure binding into the basic cluster (*Fig. 2*). To assess the influence of the alkyl substituent on the biological activity of the perhydropyrrolizinone, methyl derivative (−)-**1b** and analog (+)-**1c** lacking an alkyl chain were also targeted.

2.1.2. *Synthesis of (−)-***1a**,**b** *and (+)-***1c**. Based on preliminary studies [25], we envisioned preparing (−)-**1a** from the *trans*-alkylated prolinol (−)-**2a**, which, in turn, could be prepared taking advantage of the *Garner*'s aldehyde (+)-**3** [26][27]. The synthesis started from D-serine ((−)-**4**), which was esterified and *N*-protected (*Scheme 1*). Ester (−)-**5** was converted to the corresponding oxazolidine (+)-**6** upon treatment with 1,3-dimethoxypropane and TsOH (see *Scheme* captions for abbreviations). The resulting ester (+)-**6** was reduced with DIBAL-H, and the crude aldehyde (+)-**3** was *in situ* subjected to *Wittig* olefination with ylide **7a**. The α,β-unsaturated ketone (+)-**8a** was catalytically hydrogenated (→ (+)-**9a**). Alternatively, treatment of aldehyde (+)-**3** with ylide **7b** (→ (+)-**8b**) afforded the methyl derivative (+)-**9b** after catalytic hydrogenation.

Acidic treatment of (+)-**9a**,**b** resulted in global deprotection and concomitant cyclization to the imines **10a**,**b** (*Scheme 1*). It was anticipated to use the free OH group to control the hydride delivery and thus to obtain only the *trans*-products (−)-**2a**,**b**. However, conducting the reduction at low temperature, as previously reported [28a], yielded a mixture of the *cis*- and *trans*-prolinols (−)-**11a**,**b** and (−)-**2a**,**b** (*Table 1*). The assignment of the *cis*- and *trans*-prolinols was achieved by NMR analysis and unambiguously confirmed by converting *cis*-prolinol (−)-**11a** into the α,β-unsaturated lactones (+)-**12** and (+)-**13** (*Scheme 1*), using ylide **14**. By slow evaporation of a concentrated solution in hexane, suitable crystals of the (*Z*)-isomer (+)-**12** were obtained to carry out an X-ray crystal structure analysis (*Fig. 3*), which confirmed the configurational assignment.

Table 1. *Reduction of Imines* **10a**,**b** *to the* trans-*Prolinols (−)-***2a**,**b**

Imine	Conditions	Yields [%]	
		(−)-**11a**,**b**	(−)-**2a**,**b**
10a	$NaBH(OAc)_3$, PhMe, −10°, 48 h	33	16
10a	$NaBH_4$, AcOH, PhMe, −10°, 19 h	26	31
10a	$NaBH(OAc)_3$, PhMe, Δ, 48 h	0	24
10a	$NaBH(OAc)_3$, PhMe, Δ, 12 h	0	41
10b	$NaBH(OAc)_3$, PhMe, Δ, 12 h	0	19
10b	$NaBH_4$, AcOH, PhMe, Δ, 15 h	0	13

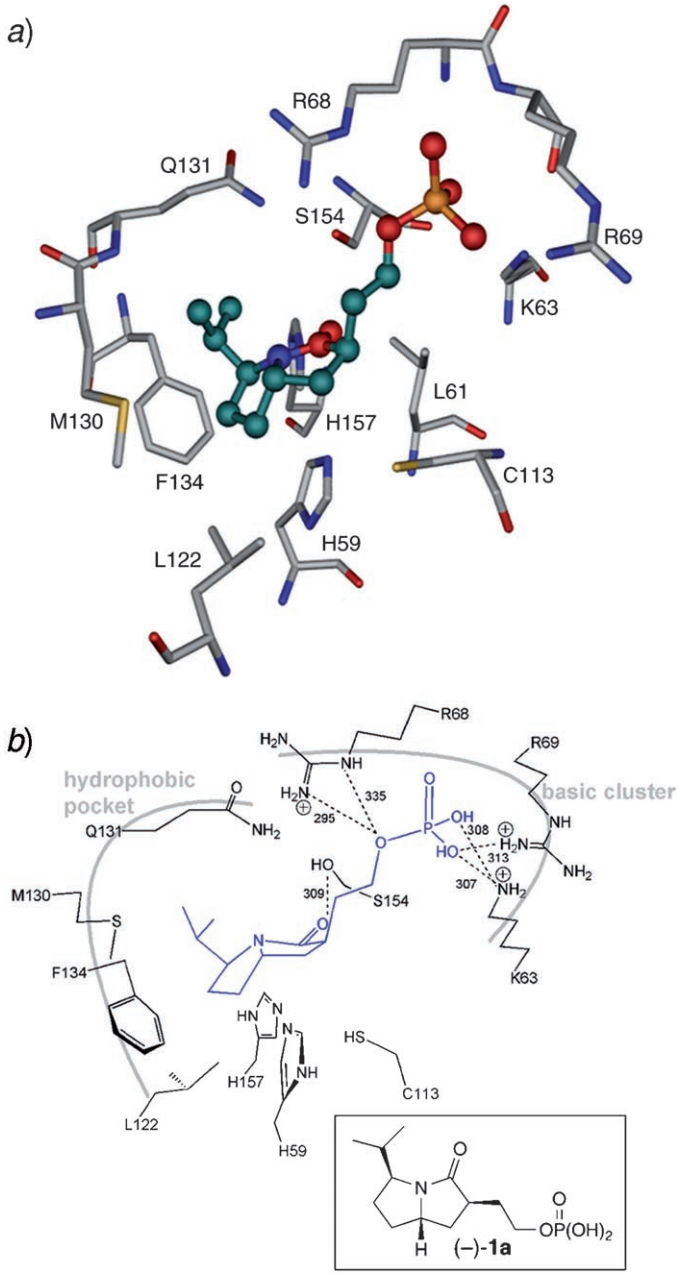
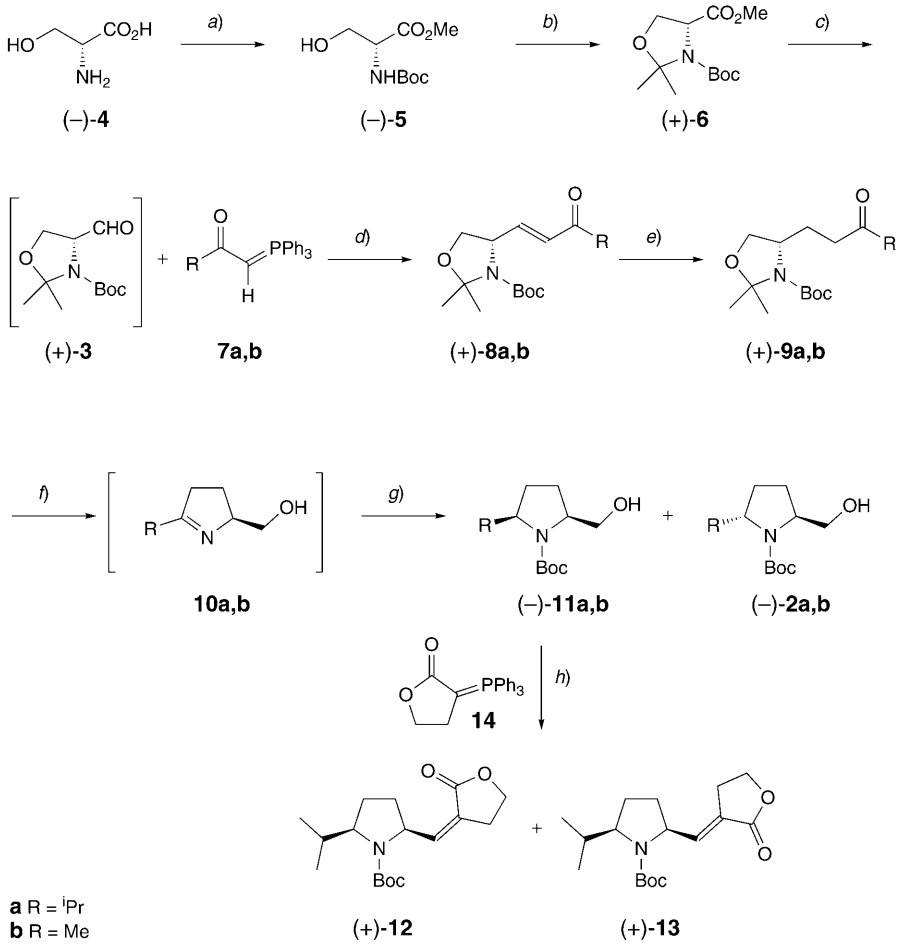


Fig. 2. a) *Computer model* (MOLOC) [24] *prediction of the binding of (–)-***1a** *to the active site of Pin1*. Color code: C-skeleton of (–)-**1a**: *green*, C-skeleton of the protein: *grey*, N-atoms: *blue*, O-atoms: *red*, P-atom: *orange*, S-atoms: *yellow*. b) *Schematic representation of the predicted interactions of* (–)-**1a** *at the active site of Pin1*. Distances are given in pm.

Scheme 1. *Synthesis of Prolinols (−)-***11a**,**b** *and (−)-***2a**,**b**



a) 1. AcCl, MeOH, 0° → Δ, 2 h; 97%; 2. Boc_2O, Et_3N, CH_2Cl_2, 0° → 20°, 3 h; 98%. *b*) DMP, TsOH, CH_2Cl_2, 20°, 13 h; 67%. *c*) DIBAL-H, toluene, −78°, 2 h. *d*) THF, Δ, 13 h; 86% ((+)-**8a**, over 2 steps); 89% ((+)-**8b**, over 2 steps). *e*) H_2, Pd/C, AcOEt, 20°, 21 h; 100% ((+)-**9a**); 91% ((+)-**9b**). *f*) TFA, TsOH, CH_2Cl_2, Δ, 17 h. *g*) 1. See *Table 1*; 2. $(Boc)_2O$, K_2CO_3, MeCN, 20°, 24 h; 41% ((−)-**2a**, over 3 steps); 19% ((−)-**2b**, over 3 steps). *h*) 1. $SO_3 \cdot Py$, Me_2SO, 10°, 3 h; 2. **14**, THF, 50°, 37 h; 29% ((+)-**12**); 60% ((+)-**13**). Boc = (*tert*-butoxy)carbonyl, TsOH = *para*-toluenesulfonic acid, DIBAL-H = diisobutylaluminium hydride, DMP = 1,3-dimethoxypropane, THF = tetrahydrofuran, TFA = trifluoroacetic acid.

Variations of the reduction conditions were then screened in order to selectively obtain solely the *trans*-prolinols (−)-**2a**,**b** (*Table 1*). *In situ* preparation of the reducing agent from $NaBH_4$ and AcOH, and subsequent reduction at low temperature resulted in a *ca.* 1:1 mixture of *cis*- and *trans*-product. In a next attempt, the reduction was conducted under reflux [28b] and, pleasantly, only the *trans*-products (−)-**2a**,**b** were obtained in low yield, which could be improved by decreasing the reaction time. Fur-

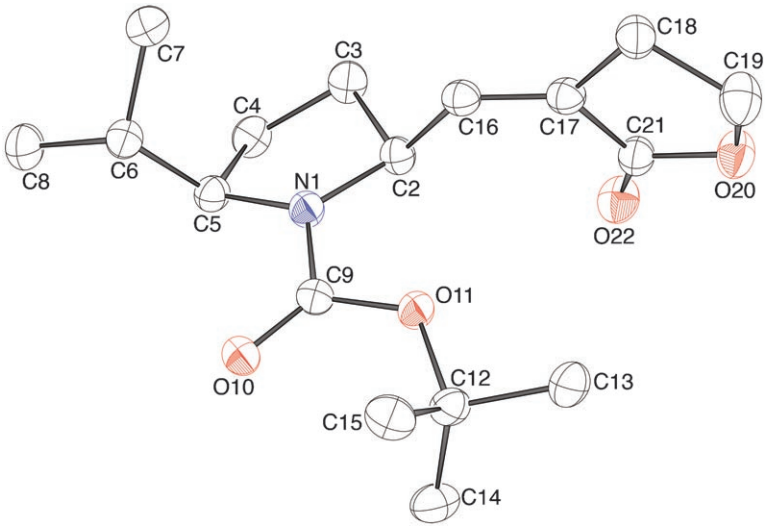


Fig. 3. *X-Ray crystal structure of (+)-***12**. Arbitrary numbering. Atomic displacement parameters obtained at 223 K are drawn at the 30% probability level.

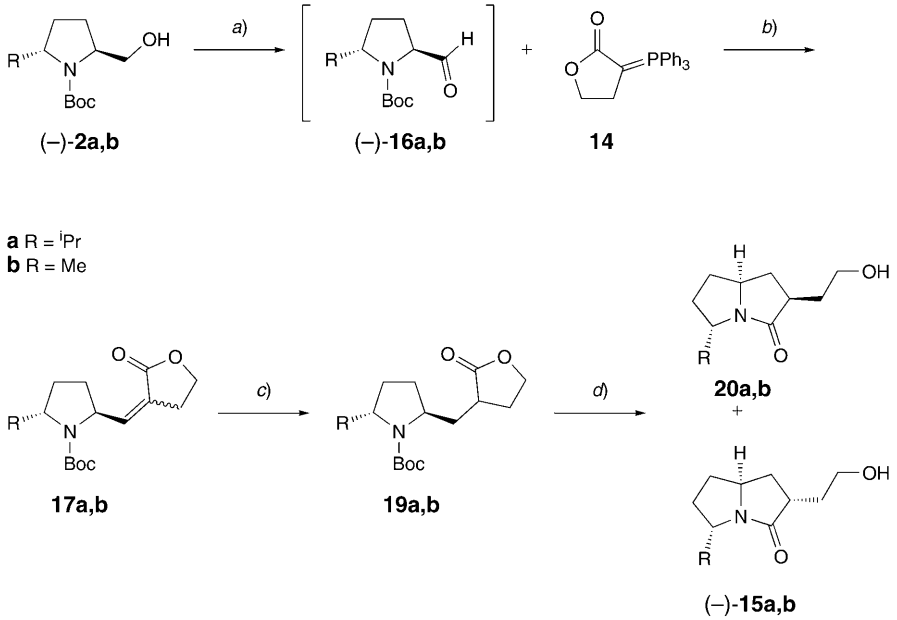
ther variations of the reaction conditions, aiming at enhanced yields, were not successful.

The prolinols (−)-**2a**,**b** were then converted to the perhydropyrrolizinones (−)-**15a**,**b** *via* the route we previously developed [25]. Thus, alcohols (−)-**2a**,**b** were oxidized, and the resulting aldehydes (−)-**16a**,**b** were subjected *in situ* to *Wittig* olefination with ylide **14**, affording the α,β-unsaturated lactones **17a**,**b** as an unseparable mixture of (*E*)- and (*Z*)-diastereoisomers (*Scheme 2*). The mixtures were catalytically hydrogenated. Unlike the series derived from L-proline ((−)-**18**) [25], the resulting saturated lactones **19a**,**b** were isolated as a mixture of unseparable diastereoisomers, which were then converted to the perhydropyrrolizinones (−)-**15a**,**b** and **20a**,**b**. At this stage, the bicyclic systems were separated by column chromatography, affording the perhydropyrrolizinones (−)-**15a**,**b** as pure diastereoisomers.

To install a phosphate group at the end of the alkyl chain, the alcohols (−)-**15a**,**b** and (−)-**15c** [25] were converted *via Mitsunobu* reaction to the Bn-protected phosphates (−)-**21a**–**21c** [29], which were hydrogenated to yield the desired target compounds, dihydrogen phosphates (−)-**1a**,**b** and (+)-**1c** (*Scheme 3*). The Bn-protected phosphate **21a** was isolated together with triphenylphosphine oxide and subjected as a mixture to the subsequent hydrogenolysis.

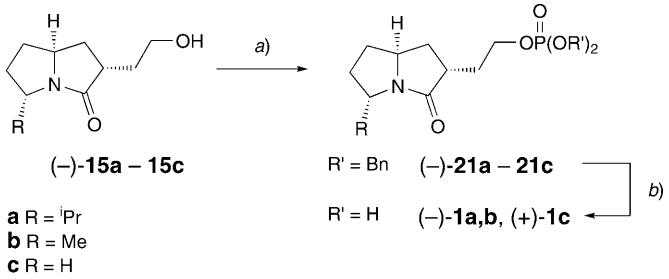
2.1.3. *Biological and* $^{15}N,^{1}H$*-HSQC-NMR Spectroscopic Results.* The inhibitory affinity (K_i values) of (−)-**1a**,**b** and (+)-**1c** towards Pin1 was determined by a previously reported enzyme activity assay [30]. Disappointingly, compounds (−)-**1a**,**b** and (+)-**1c** exhibited no detectable activity within the sensitivity limits of the assay. On the other hand, $^{15}N,^{1}H$-HSQC-NMR spectroscopy (*Fig. 4*,*a*) [31] clearly revealed that (−)-**1a**,**b** bind to the WW domain of Pin1, however, apparently in a non-inhibitory mode. The superimposition of the spectra for Pin1 in the presence and absence of the ligand indicates binding-induced changes in chemical shift of the residues Glu12, Ser16, Ser18,

Scheme 2. *Synthesis of Pyrrolizidinones (−)-***15a**,**b** *and* **20a**,**b**



a) $SO_3 \cdot Py$, Me_2SO, 5°, 2.5 h. *b*) THF, 50°, 22 h; 69% (**17a**, over 2 steps); 55% (**17b**, over 2 steps). *c*) H_2, Pd/C, AcOEt, 20°, 14 h; 99% (**19a**); 67% (**19b**). *d*) 1. TFA, CH_2Cl_2, 0°, 1 h; 2. DMAP (cat.), pyr, Δ, 16 h; 51% ((−)-**15a**); 36% ((−)-**15b**). DMAP = 4-(Dimethylamino)pyridine, pyr = pyridine.

Scheme 3. *Synthesis of Dihydrogen Phosphates (−)-***1a**,**b** *and (+)-***1c**



a) Dibenzyl phosphate, PPh_3, DIAD, Et_3N, THF, 20°, 3 h; 86% ((−)-**21b**); 84% ((−)-**21c**). *b*) H_2, Pd/C, EtOH or MeOH, 20°, 15 h; 72% ((−)-**1a**, over 2 steps); 94% ((−)-**1b**); 100% ((+)-**1c**). DIAD = Diisopropyl azodicarboxylate.

Tyr23, Phe25, Asn30, and Ser32 located in the WW domain (*Fig. 4*,*b*). Notably, Ser16 and Tyr23 are residues involved in the recognition of the phosphate moiety of Pin1 substrates, indicating that the phosphate group of (−)-**1a**,**b** is recognized in a similar fashion to the one of the natural substrates [32]. A computer-model (MOLOC) prediction of the binding of (−)-**1a** to the WW domain is shown in *Fig. 4*,*c*.

2.2.1. *Design of the Perhydropyrrolizine Lead Structure.* To enforce complexation into the larger active site rather than into the tighter WW domain of Pin1 and to

enhance the overall binding affinity, we designed a perhydropyrrolizine scaffold decorated with additional aromatic residues. Compound (+)-**22a** (*Fig. 5*) was chosen as new lead compound. The phosphate moiety was expected to ensure binding into the basic cluster, whereas the perhydropyrrolizine should fill the hydrophobic pocket. The naphthalene residue was selected to interact, as reported for patented phenylalaninol derivatives [33], with the side chain or backbone atoms of Cys113, Ser114, Ser115, Ala118, and Leu122, whereas the Bn group was introduced to target the substrate-entry groove of the active site of Pin1 (*Fig. 5*).

2.2.2. *Synthesis of the Racemic Ligands (±)-***22a**–**22d**. The synthesis of the target compounds (±)-**22a**–**22d** relied on a 1,3-dipolar cycloaddition between *N*-benzylmaleimide (**23**) or *N*-piperonylmaleimide (piperonyl = (1,3-benzodioxol-5-yl)methyl; **24**), and the azomethine ylide, generated from an aromatic aldehyde **25**–**27** and L-proline ((−)-**18**; *Scheme 4*). During the cycloaddition, the two *trans*-isomers, namely the desired (±)-*endo*-**28** and (±)-*exo*-**29** were formed and subsequently separated by column chromatography in modest-to-good overall yield (*endo* refers to the orientation of the aryl (*e.g.*, naphthalenyl) substituent with respect to the perhydropyrrolo[3,4-*c*]pyrrole scaffold and *trans* to the position of this substituent with respect to the configuration of C(8a) at the fusion of the two five-membered rings in the perhydropyrrolizine bicycle; for numbering, see *Scheme 4*). The assignment of the relative configuration was achieved by NMR analysis and comparison with data previously published for thrombin inhibitors featuring this tricyclic skeleton [34].

Regioselective hydrolysis of (±)-*endo*-**28a**–**28d** under very mild conditions (0.05M NaOH in THF/H_2O 2:1, 20°) [35], followed by esterification of the crude sodium carboxylates with MeOH in the presence of $SOCl_2$, afforded esters (±)-**30a**–**30d**, which were subsequently reduced to alcohols (±)-**31a**–**31d** with DIBAL-H (*Scheme 5*). The formation of the tricylic derivatives (±)-**28a**–**28d** as by-products, resulting from back-cyclization of (±)-**30a**–**30d**, accounted for the low yield of this step. Finally, introduction of the protected phosphate group using standard phosphoramidite techniques (→ (±)-**32a**–**32d**) [36] and subsequent hydrogenolysis provided inhibitors (±)-**22a**–**22d**.

2.2.3. *Biological Results of the Racemic Series.* Ligands (±)-**22a**–**22d** were subsequently subjected to the enzyme-activity assay [30] and shown to be active inhibitors of Pin1, with K_i values varying between 15 ((±)-**22a**) and 44 μM ((±)-**22b**) (*Table 2*). These encouraging biochemical results prompted us to prepare optically pure derivatives, since molecular modeling hinted at chiral discrimination in the active binding site of Pin1. The most active derivative of the racemic series, (±)-**22a**, was chosen as new lead and, according to molecular modeling, the enantiomer (+)-**22a** was targeted.

2.2.4. *Synthesis of the Optically Pure Ligands (+)-***22a** *and (+)-***33b**,**c**. 1,3-Dipolar cycloaddition between (2*S*,4*R*)-4-hydroxyproline ((−)-**34**) and the azomethine ylide generated from *N*-benzylmaleimide (**23**) and naphthalene-2-carbaldehyde (**25**) afforded (−)-**35** as a single enantiomer after fractional crystallization (*Scheme 6*). The assigned absolute configuration was confirmed by X-ray crystallography (*Fig. 6*,*a*). The crystal packing of (−)-**35** reveals several interesting intermolecular contacts (*Fig. 6*,*b*): the OH group forms a H-bond ($d(O\cdots N) = 2.95$ Å) with the tertiary amine of an adjacent ligand molecule. In addition, a short intermolecular face-to-face contact

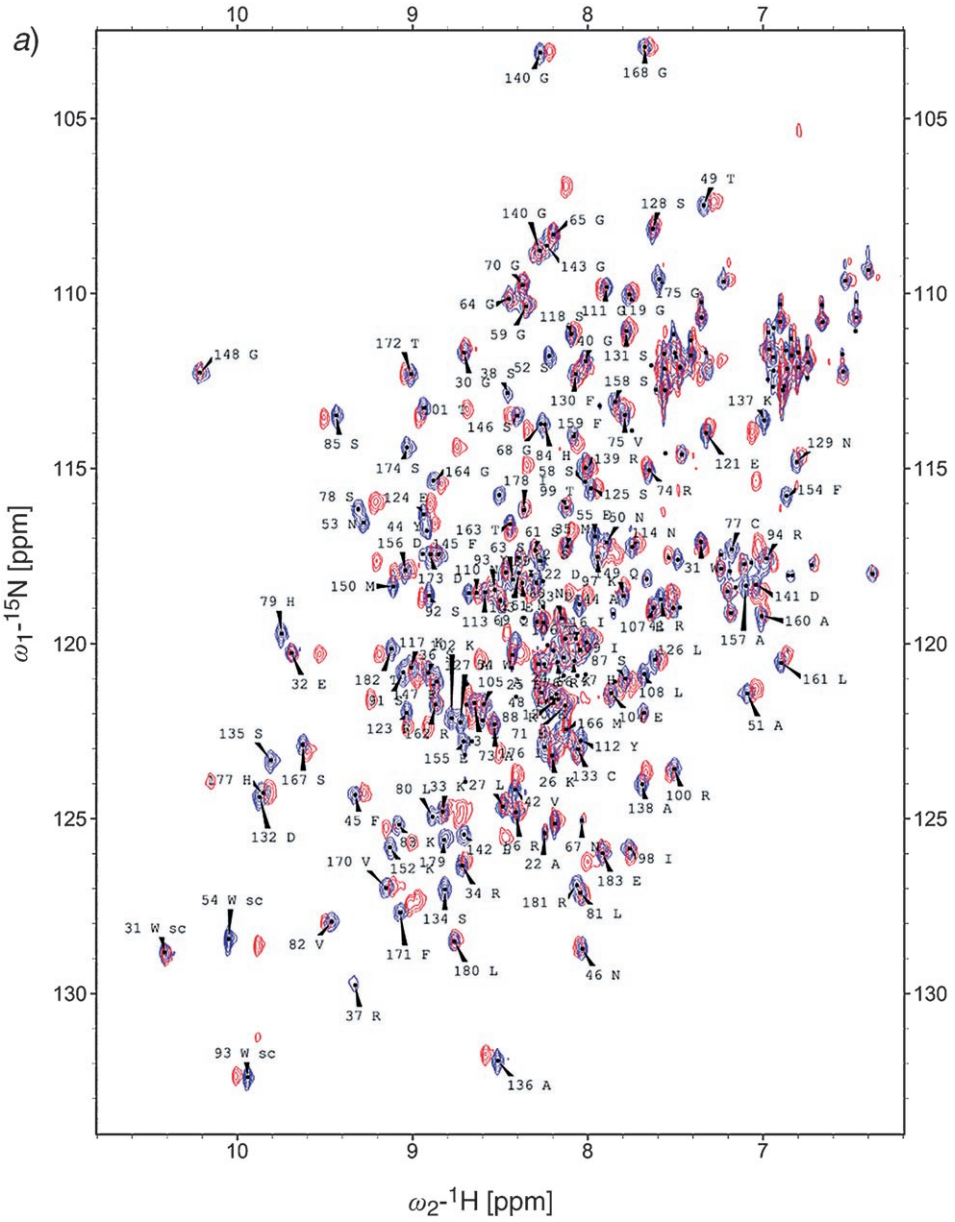


Fig. 4. a) *Superposition of $^{15}N,^1H$ correlation spectra at 700 MHz of U-^{15}N-labeled Pin1 in the free form* (*blue*) *and in complex with (−)-***1a**. The peak assignment according to *Jacobs et al.* is indicated [31a]. b) *Mapping of the NMR chemical-shift changes upon binding of (−)-***1a** *on the crystal structure of Pin1*. Red regions correspond to a binding-induced disappearance of the signals or shifts far apart to another spectral region, yellow ones to shifts stronger than the linewidth. c) *Computer model* (MOLOC) *prediction of the binding of (−)-***1a** *to the WW domain of Pin1*. Color code: C-skeleton of (−)-**1a**: *green*, C-skeleton of the protein: *grey*, N-atoms: *blue*, O-atoms: *red*, P-atoms: *orange*. Distances are given in pm.

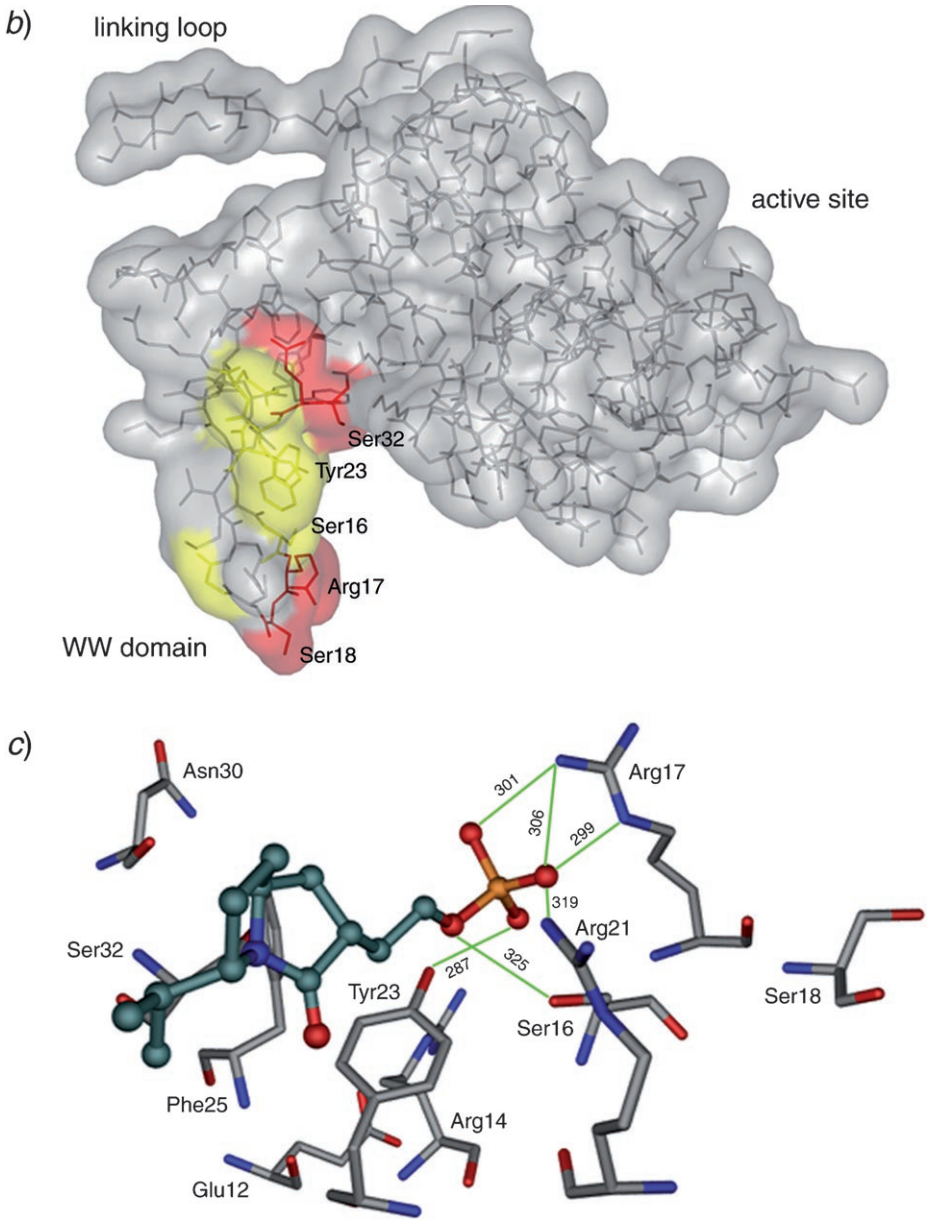


Fig. 4 (cont.)

between the imide ring and the naphthalenyl unit of a neighboring molecule is indicated [37].

Removal of the OH group was accomplished *via* a *Barton–McCombie* deoxygenation to yield imide (−)-**28a** [38]. Compound (−)-**35** was also converted into the fluoro

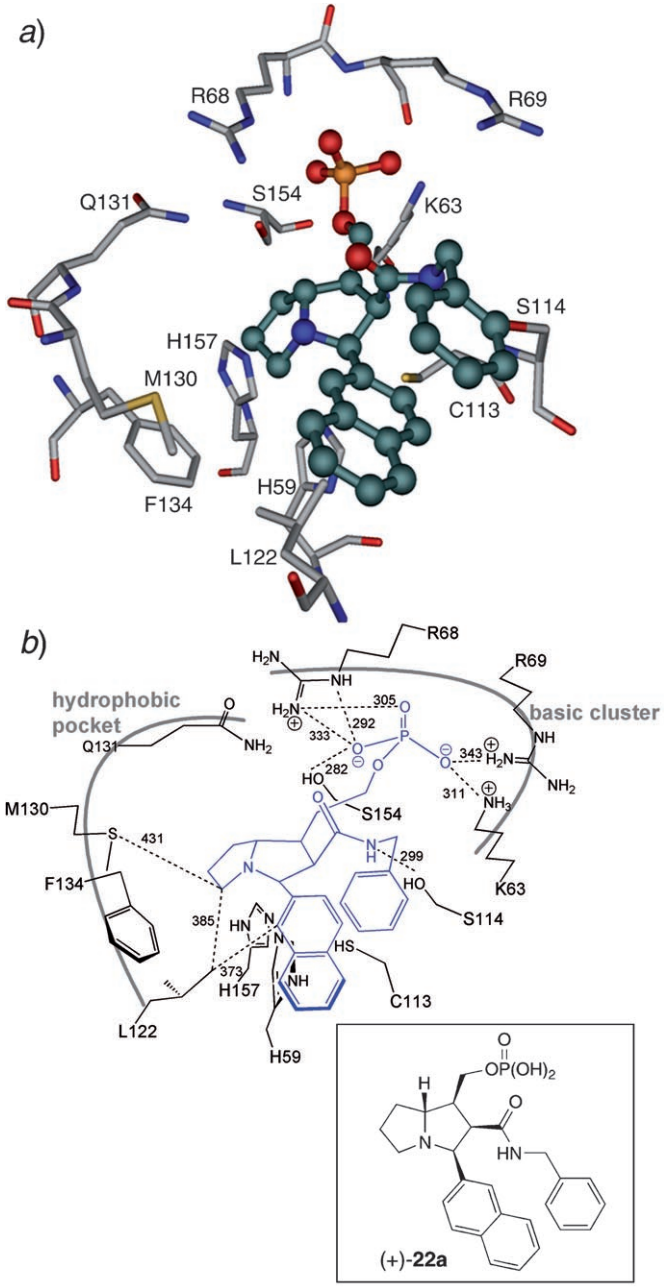
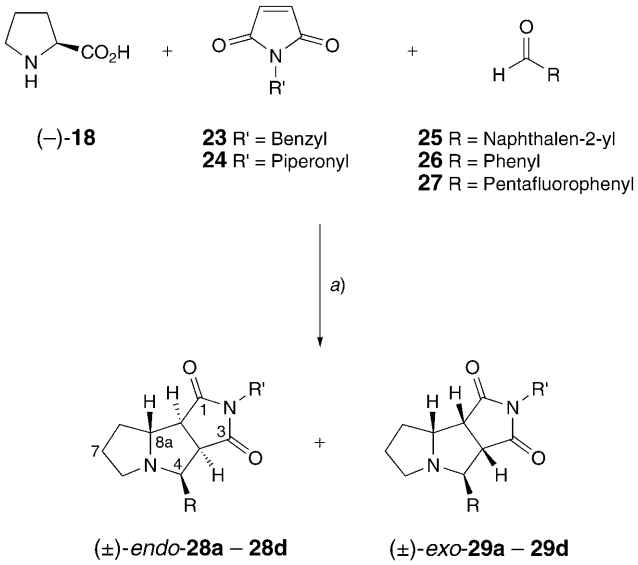


Fig. 5. a) *Computer model* (MOLOC) *prediction of the binding of (+)-***22a** *to the active site of Pin1*. Color code: C-skeleton of ligand:*green*, C-skeleton of the protein: *grey*, N-atoms: *blue*, O-atoms: *red*, P-atom: *orange*, S-atoms: *yellow*. b) *Schematic representation of the predicted interactions of (+)-***22a** *at the active site of Pin1*. Distances are given in pm.

Scheme 4. *1,3-Dipolar Cycloaddition between* L-*Proline* ((−)-**18**) *and Azomethine Ylides Obtained from Maleimides* **23** *or* **24**, *and Aromatic Aldehydes* **25**–**27**.



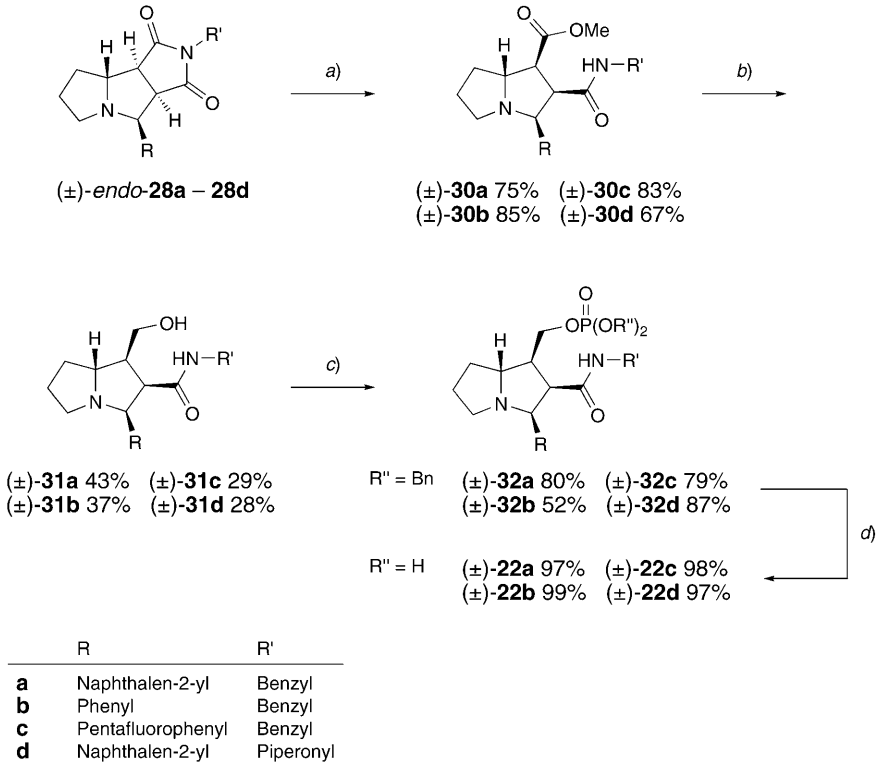
	R	R'	*endo*	*exo*
a	Naphthalen-2-yl	Benzyl	31%	41%
b	Phenyl	Benzyl	16%	22%
c	Pentafluorophenyl	Benzyl	32%	44%
d	Naphthalen-2-yl	Piperonyl	32%	44%

a) MeCN, 85°, 15 h. Piperonyl = (1,3-benzodioxol-5-yl)methyl.

derivative (−)-**36b** by treatment with DAST. Alternatively, it was transformed into the methoxy derivative (−)-**36c**. The three optically pure tricycles (−)-**28a**, and (−)-**36b**,**c** were subsequently converted into phosphates (+)-**22a** and (+)-**33b**,**c**, *via* esters (−)-**30a** and (−)-**37b**,**c**, alcohols (−)-**31a** and (−)-**38b**,**c**, and Bn-protected phosphates (−)-**32a** and (−)-**39b**,**c**, as depicted in *Scheme 7*. On the way to (+)-**33c**, an X-ray crystal structure of the methanol precursor (−)-**38c** was obtained, verifying the absolute configuration of the trisubstituted perhydropyrrolizine scaffold (*Fig. 6*, *b*). The structural analysis also confirmed retention of the configuration during the entire sequence, as well as the regioselectivity of the imide hydrolysis. Furthermore, analysis of the crystal packing showed that the Bn and naphthalenyl moieties are disordered over two orientations. The OH groups of neighboring molecules form an intermolecular H-bond (d(O···O) = 2.74 Å), while a second intermolecular H-bond (d(N···O) = 3.01 Å) is observed between amide NH and C=O of neighboring molecules.

2.2.5. *Biological and* ^{15}N,^{1}H-*HSQC-NMR-Spectroscopic Results with (+)-***22a** *and (+)-***33b**,**c**. In the enzymatic assay, inhibitor (+)-**22a** was found to be far less active (K_i = 139 μM) than racemic (±)-**22a** (K_i = 15 μM), indicating that the other enantiomer (−)-**22a** should be the more potent one (*Table 2*). On the other hand, the fluoro (*i.e.*, (+)-**33b**, K_i = 26 μM) and methoxy (*i.e.*, (+)-**33c**, K_i = 9 μM) derivatives were found to

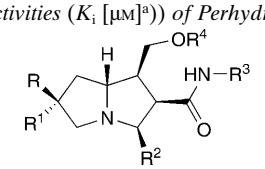
Scheme 5. *Synthesis of the Racemic Phosphates* (±)-**22a**–**22d**



	R	R'
a	Naphthalen-2-yl	Benzyl
b	Phenyl	Benzyl
c	Pentafluorophenyl	Benzyl
d	Naphthalen-2-yl	Piperonyl

a) 1. 0.05M NaOH in THF/H_2O 2:1, 20°, 15 h; 2. $SOCl_2$, MeOH, 20°, 15 h. *b*) DIBAL-H, THF, 0°, 2 h. *c*) 1. Dibenzyl *N,N*-diisopropylphosphoramidite, 1*H*-tetrazole, MeCN, 20°, 3 h; 2. *m*CPBA, 20°, 30 min. *d*) H_2, Pd/C, MeOH, 20°, 15 h. *m*CPBA = *meta*-Chloroperbenzoic acid.

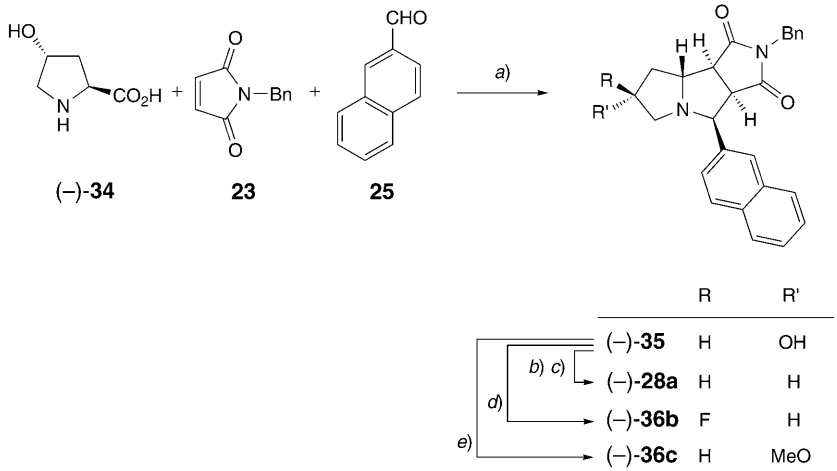
Table 2. *Structures and Biological Activities* (K_i [μM][a])) *of Perhydropyrrolizine-Based Inhibitors of Pin1*



Inhibitor	R	R^1	R^2	R^3	R^4	K_i [μM]
(±)-**22a**	H	H	naphthalen-2-yl	$PhCH_2$	$P(O)(OH)_2$	15
(±)-**22b**	H	H	Ph	$PhCH_2$	$P(O)(OH)_2$	44
(±)-**22c**	H	H	pentafluorophenyl	$PhCH_2$	$P(O)(OH)_2$	16
(±)-**22d**	H	H	naphthalen-2-yl	piperonyl[b])	$P(O)(OH)_2$	32
(+)-**22a**	H	H	naphthalen-2-yl	$PhCH_2$	$P(O)(OH)_2$	139
(+)-**33b**	F	H	naphthalen-2-yl	$PhCH_2$	$P(O)(OH)_2$	26
(+)-**33c**	H	MeO	naphthalen-2-yl	$PhCH_2$	$P(O)(OH)_2$	9
(−)-**38c**	H	MeO	naphthalen-2-yl	$PhCH_2$	H	inactive

[a]) Uncertainties in K_i: ±10–20%. [b]) Piperonyl = (1,3-benzodioxol-5-yl)methyl.

Scheme 6. *Synthesis of the Tricyclic Compounds (−)-***28a** *and (−)-***36b**,**c**



a) 1. DMF, 85°, 20 h; 2. fractional crystallization from MeOH; 17%. *b*) 1. NaH, THF, 20°, 3 h; 2. CS_2, 20°, 1 h; 3. MeI, 20°, 17 h ; 84%. *c*) Bu_3SnH, AIBN, toluene, Δ, 1 h; 88%. *d*) DAST, CH_2Cl_2, −78° → 20°; 89%. *e*) NaH, [15]crown-5, MeI, THF, 20°; 63%. AIBN = azobis[isobutyronitrile], DAST = diethylaminosulfur trifluoride

be significantly more active than (+)-**22a**. The non-phosphorylated alcohol (−)-**38c** (*Table 2*) showed no activity towards Pin1, underlining that the phosphate moiety is crucial for measurable binding affinity [21b].

The enzymatic activity of (+)-**33c** towards a Pin1 construct lacking the WW domain (Pin1ΔWW) was also determined, and a K_i value of 12 μM was obtained. Furthermore, the activity of (+)-**33c** towards Pin1ΔWW dropped when GST-WW domain (GST = glutathione-S-transferase, a protein tag) was added, providing evidence for the affinity of compound (+)-**33c** for *both* the PPIase and the WW domain. The binding of (+)-**33c** to the WW domain was further confirmed by ^{15}N,^{1}H-HSQC-NMR spectroscopy. The comparison of the spectra of Pin1 in presence and absence of (+)-**33c** demonstrated that the inhibitor interacts mainly with Met15, Ser16, Arg17, Ser18, Gly20, Tyr23, Phe25, Asn30, Ala31, Ser32, Gln33, Trp34, and Glu35 (*Fig. 7*). All these residues are located in the WW domain of Pin1 and involved in the binding of phosphoprotein to Pin1. Interestingly, ^{15}N,^{1}H-HSQC-NMR spectroscopy showed no interaction between inhibitor (+)-**33c** and the PPIase binding site.

The discrepancy between the results of the NMR and enzymatic assays could possibly be rationalized by the inherently different experimental conditions of the two methods used. For instance, the NMR studies were performed in the absence of the peptide substrate. Additionally, whereas both domains have the same specificity towards *p*Ser/*p*Thr-Pro motifs, the WW domain exhibits a stronger affinity towards this motif than the PPIase one [39]. This may explain why the ^{15}N,^{1}H-HSQC-NMR data indicate binding in the WW domain only. Finally, both (−)-**1a** and (+)-**33c** were found to bind only into the WW domain in the ^{15}N,^{1}H-HSQC-NMR spectra, but (−)-**1a** showed no inhibitory activity. We believe that compound (−)-**1a** is too small to com-

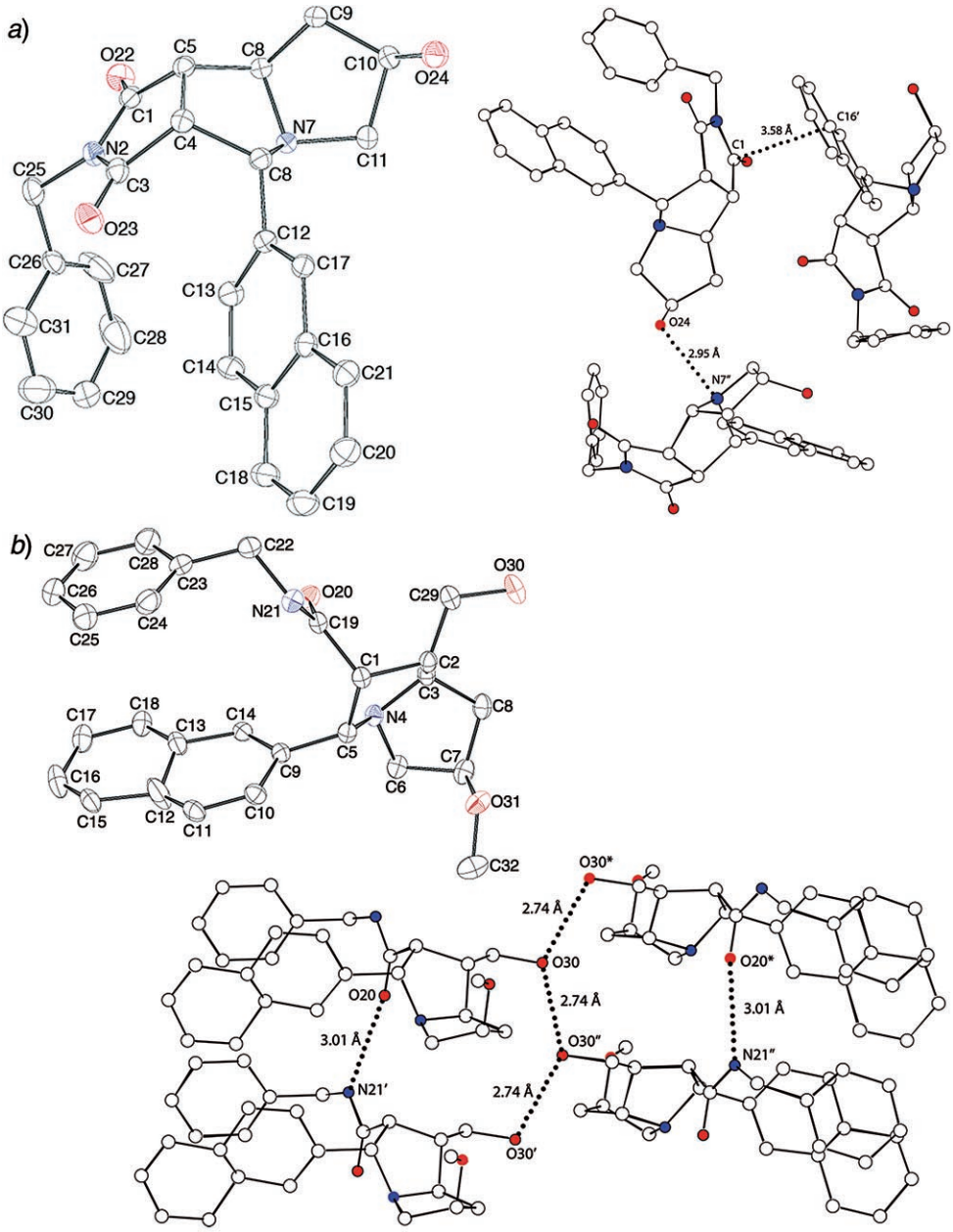
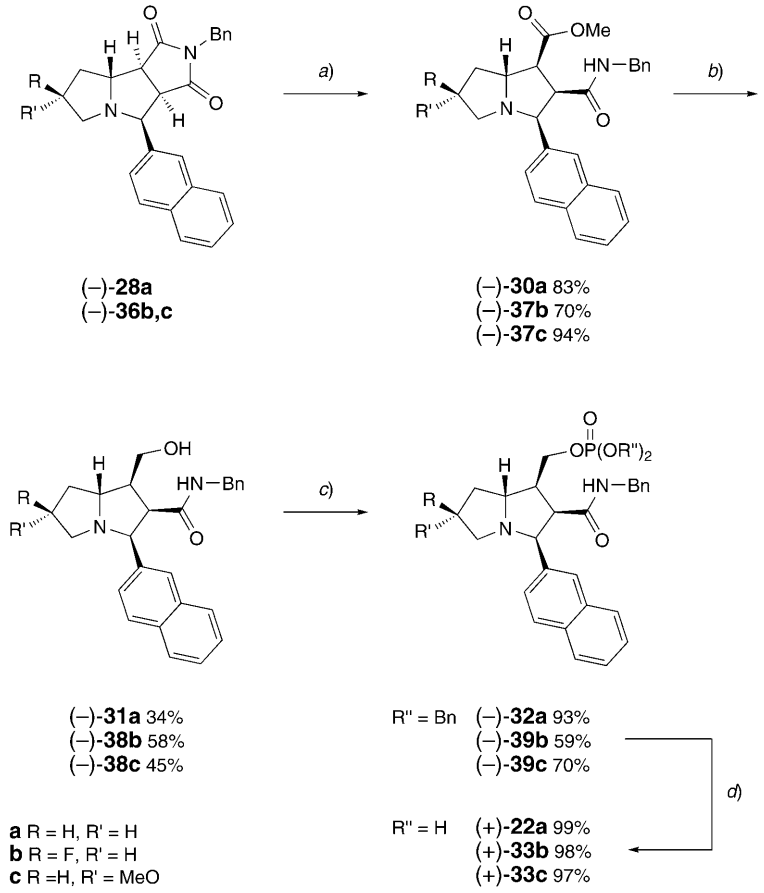


Fig. 6. a) *X-Ray crystal structure of (−)-***35** (*left*) *with short intermolecular contacts* (*right*). b) *X-Ray crystal structure of (−)-***38c** (*top*) *with short intermolecular contacts* (*bottom*). Note that the structure of (−)-**38c** is partially disordered over two orientations, but only one orientation is shown for clarity. Arbitrary numbering. Atomic displacement parameters obtained at 223 K are drawn at the 30% probability level.

Scheme 7. *Synthesis of the Optically Pure Phosphates (+)-***22a** *and (+)-***33b**,**c**



a) 1. 0.05M NaOH in THF/H_2O 2:1, 20°, 15 h; 2. $SOCl_2$, MeOH, 20°, 15 h. *b*) DIBAL-H, THF, 0°, 2 h. *c*) 1. Dibenzyl *N*,*N*-diisopropylphosphoramidite, 1*H*-tetrazole, MeCN, 20°, 3 h; 2. *m*CPBA, 20°, 30 min. *d*) H_2, Pd/C, MeOH, 20°, 15 h.

pete with the Suc-Ala-Glu-Pro-Phe-pNa peptide used in the biological assay. For example, the dipeptide *p*Ser-D-Pro is 1000-fold less active than longer peptides [21b]. In contrast, the large aromatic and hydrophobic rings present in (+)-**33c** should enhance the overall binding affinity of this compound.

2.3. *Synthesis of Highly Substituted Perhydroindolizines and Pyrrolidines.* The 1,3-dipolar cycloaddition is not limited to the cyclic amino acid proline (–)-**18**, but can be extended to primary, secondary, α,α-disubstituted, cyclic, or acyclic α-amino acids. Only tertiary α-amino acids cannot be used [40]. Thus, the previously described synthetic pathway is amenable to the preparation of other heterocyclic systems. Engaging racemic pipecolinic acid (±)-**40** in the 1,3-dipolar cycloaddition led to the tricyclic derivatives (±)-*endo*-**41** and (±)-*exo*-**42**. Compound (±)-**41** was converted to perhydroindolizine (±)-**43** *via* ester (±)-**44** (*Scheme 8*).

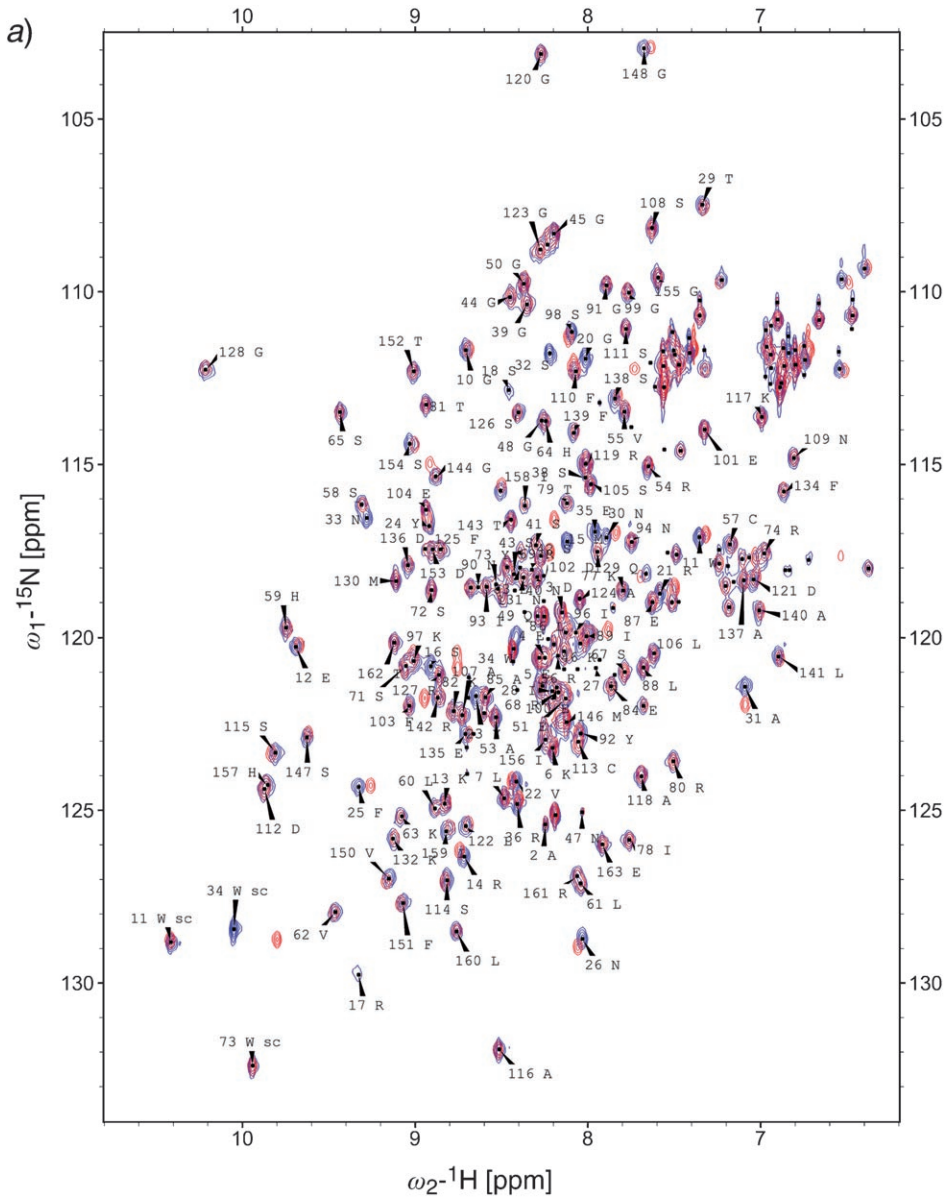


Fig. 7. a) *Superposition of $^{15}N,^1H$ correlation spectra at 700 MHz of U-^{15}N-labeled Pin1 in the free form* (*blue*) *and in complex with (+)*-**33c**. The peak assignment according to *Jacobs et al.* is indicated [31a]. b) *Mapping of the NMR chemical-shift changes upon binding of (+)*-**33c** *on the crystal structure of Pin1*. Red regions correspond to a binding-induced disappearance of the signals or shifts far apart to another spectral region, yellow ones to shifts stronger than the linewidth. c) *Computer model* (MOLOC) *prediction of the binding of (+)*-**33c** *to the WW domain of Pin1*. Color code: C-skeleton of (+)-**33c**: *green*, C-skeleton of the protein: *grey*, N-atoms: *blue*, O-atoms: *red*, P-atoms: *orange*. Distances are given in pm.

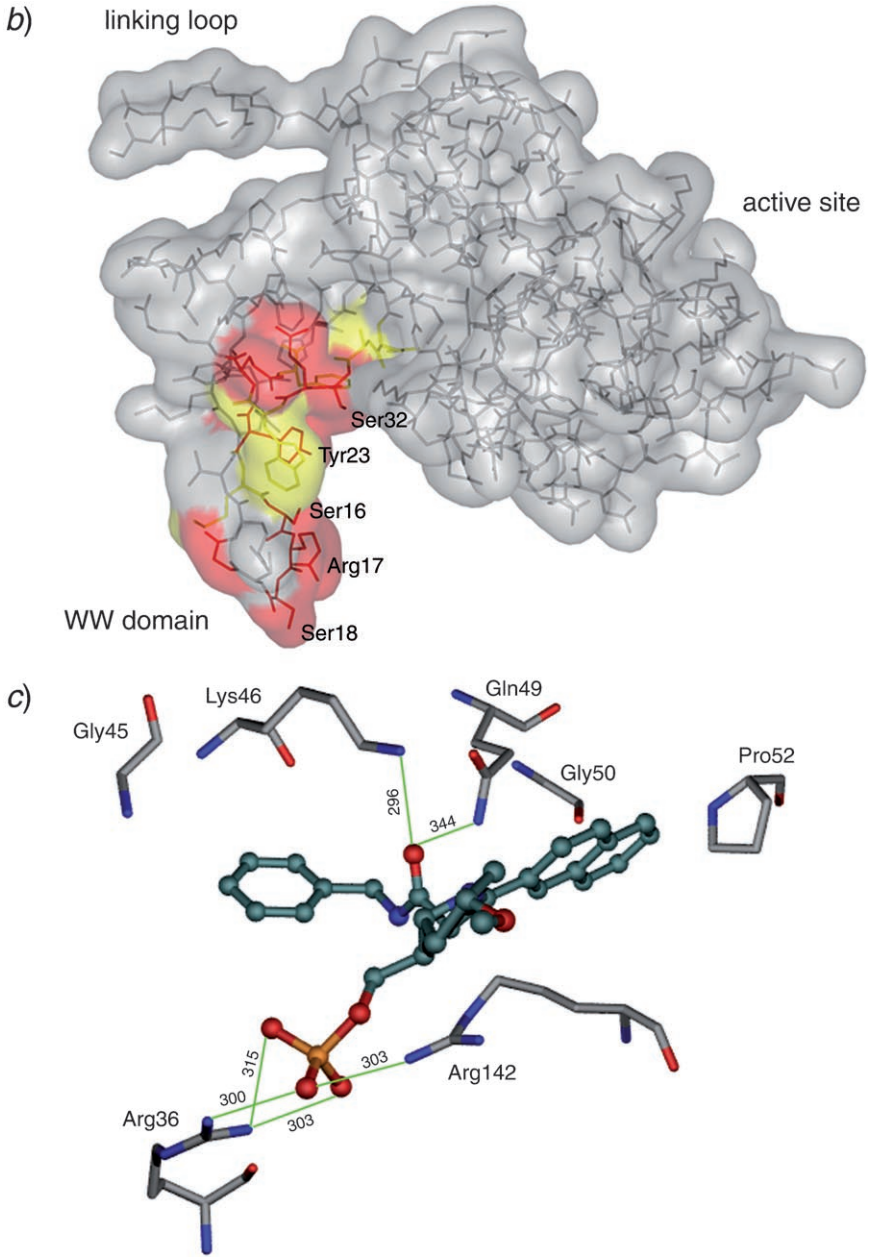
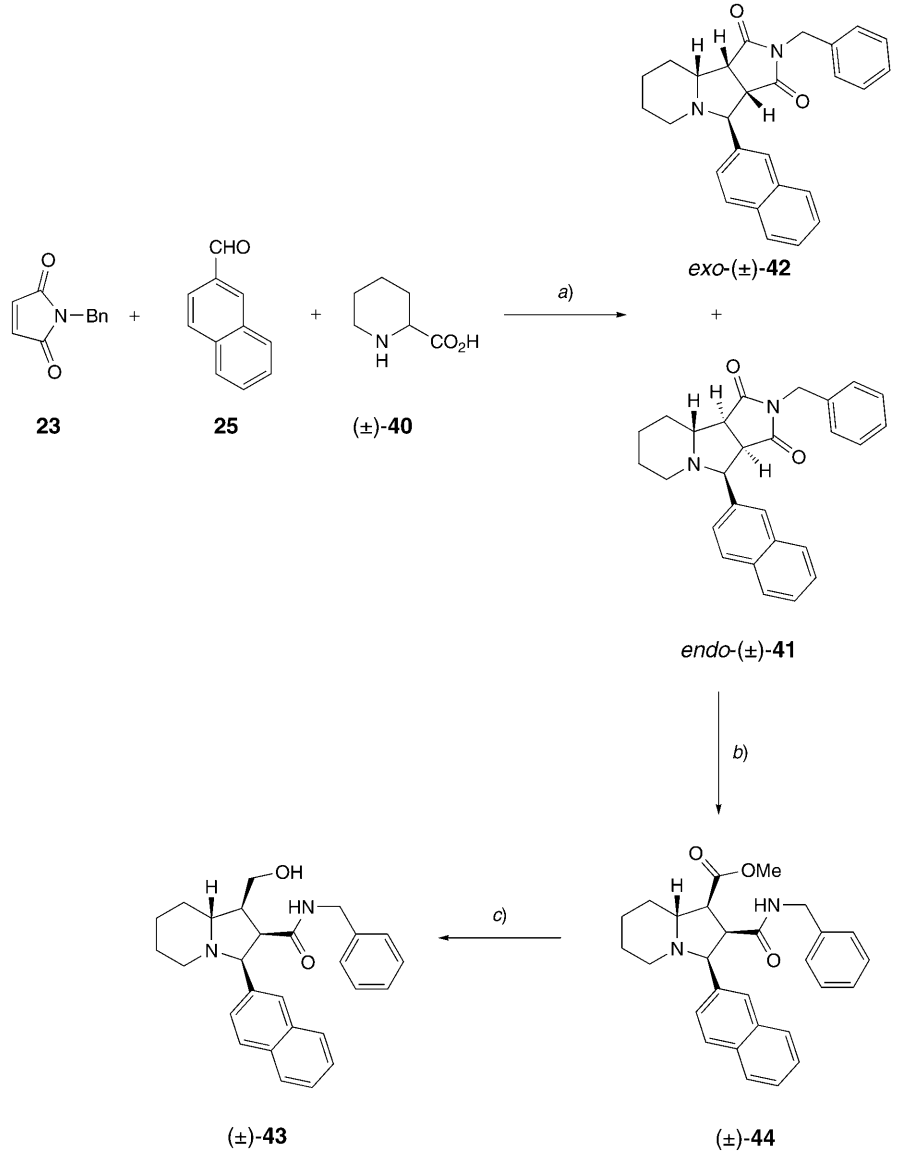


Fig. 7 (cont.)

Alternatively, the use of acyclic amino acids permitted the isolation of pyrrolidines. Starting from L-phenylalanine ((−)-**45a**) or L-valine ((+)-**45b**) led to the formation of the bicyclic derivatives (±)-*endo*-**46a**,**b**, which were hydrolyzed and esterified, afford-

Scheme 8. *Synthesis of Perhydroindolizine (±)*-**43**

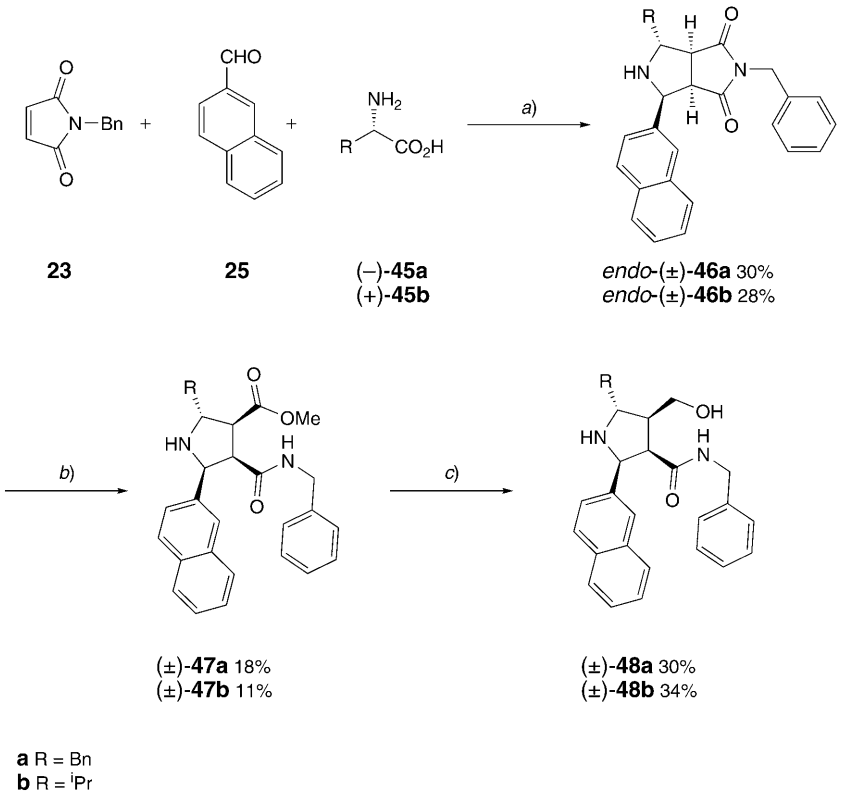


a) MeCN, 85°, 17 h; 17% ((±)-**41**); 32% ((±)-**42**). *b*) 1. 0.05M NaOH in THF/H_2O 2:1, 20°, 15 h; 2. $SOCl_2$, MeOH, 20°, 15 h; 54%. *c*) DIBAL-H, THF, 0°, 2 h; 32%.

ing (±)-**47a**,**b** (*Scheme 9*). Reduction afforded the pyrrolidines (±)-**48a**,**b** (for highly substituted perhydropyrrolizines, perhydroindolizines, and pyrrolidines, see [41–43]).

3. Conclusions. – We described in this paper the development of a new generation of nonpeptidic inhibitors of the PPIase Pin1, an oncogenic target of substantial interest,

Scheme 9. *Synthesis of Pyrrolidines* (±)-**48a**,**b**



a) MeCN, 85°, 17 h. *b*) 1. 0.05M NaOH in THF/H_2O 2:1, 20°, 15 h; 2. $SOCl_2$, MeOH, 20°, 15 h. *c*) DIBAL-H, THF, 0°, 2 h.

and of versatile synthetic protocols towards highly substituted heterocycles, including perhydropyrrolizines, perhydroindolizines, and pyrrolidines. The first generation of perhydropyrrolizinone derivatives was found to be biologically inactive. In contrast, the synthesis of highly substituted perhydropyrrolizine derivatives led to a series of active compounds. The K_i values of the new inhibitors, determined by an enzyme-activity assay, are in the low micromolar range. According to the biological assays, the ligands bind to both the WW recognition domain and the active PPIase site. On the other hand, ^{15}N,^{1}H-HSQC-NMR spectra provided evidence only for WW domain binding, which could be a result of the differences in the experimental conditions applied in the NMR and enzymatic-activity assays. Nevertheless, the power of the NMR binding analysis is nicely demonstrated in this study, which provides clear evidence for WW domain recognition. Clearly, assigning inhibition of Pin1 to ligand binding at the catalytic PPIase site only – even if supported by extensive molecular modeling – is rather dangerous in the absence of experimental structural evidence. Future work will focus on the elucidation of the exact mechanism of action of the new perhydropyrrolizine inhibitors, as well as the development of more potent analogs.

Financial support by the *Roche Research Foundation* (doctoral fellowship for *R. S.*) and by *F. Hoffmann-La Roche, Ltd.*, Basel, is gratefully acknowledged. We also thank Dr. *Carlo Thilgen* for help with the nomenclature and *Ralf Schmitt* for technical assistance.

Experimental Part

General. Solvents and reagents were reagent-grade, purchased from commercial suppliers, and used without further purification unless otherwise stated. The following compounds were prepared according to literature procedures: oxazolidine (+)-**6** [44], ylides **7a** [45], **7b** [46], and **14** [47], *N*-benzylmaleimide (**23**) [48], and N-*piperonylmaleimide* (piperonyl = (1,3-benzodioxol-5-yl)methyl; **24**) [34a]. THF was freshly distilled from sodium benzophenone ketyl, CH_2Cl_2 from CaH_2. Evaporation *in vacuo* was conducted at H_2O aspirator pressure. All products were dried under high vacuum (10^{-2} Torr) before anal. characterization. Column chromatography (CC): SiO_2 *60* (40–63 μm) from *Fluka*, 0–0.3 bar pressure. TLC: SiO_2 *60* F_{245}, *Merck*, visualization by UV light at 245 nm or staining with a soln. of $KMnO_4$ (3 g) and K_2CO_3 (20 g) in 5% aq. NaOH soln. (5 ml) and H_2O (300 ml). M.p.: *Büchi B540* melting-point apparatus; uncorrected. Optical rotations: *Perkin-Elmer 241* polarimeter, 1-dm cell, $\lambda = 589$ nm (Na D-line). IR Spectra [cm^{-1}]: *Perkin-Elmer 1600-FTIR* spectrometer. NMR spectra (^1H, ^{13}C, and ^{31}P): *Varian Gemini-300*, *Varian Gemini-400*, and *Bruker AMX-500*; spectra were recorded at 20°–23° unless otherwise stated, with solvent peak as reference; the signals for the pentafluorophenyl group were not observed by ^{13}C-NMR spectroscopy. High-resolution mass spectra (HR-MS): MALDI: *IonSpec Ultima* spectrometer, 2,5-dihydroxybenzoic acid (DHB) as matrix; EI: *VG-TRIBRID* spectrometer at 70 eV; ESI: *Finnigan Newstar TSQ 7000* instrument, positive-ion mode. Elemental analyses were performed by the Mikrolabor at the *Laboratorium für Organische Chemie*, *ETH-Zürich*.

General Procedure A for the Reduction of an Ester to an Aldehyde and Subsequent Wittig *Olefination.* To a soln. of an ester (1.0 equiv.) in toluene cooled to −78°, 20 wt.-% DIBAL-H in toluene (1.7 equiv.) was added at a rate to keep the internal temp. below −65°. The mixture was stirred at −78° for 2 h. The reaction was carefully quenched with MeOH, the mixture was allowed to warm to 20°, and poured into a soln. of potassium sodium tartrate (2 g per 1 mmol) in H_2O (5 ml per 1 mmol). The biphasic system was stirred at 20° for 2 h. The layers were separated. The aq. phase was extracted with Et_2O (2 × 5 ml per 1 mmol). The comb. org. phases were dried ($MgSO_4$) and concentrated *in vacuo*. To a soln. of the resulting aldehyde in THF (4 ml per 1 mmol), an ylide (2.0 equiv.) was added. The mixture was heated to reflux for 13 h. The mixture was cooled to 20° and filtered. The filtrate was concentrated *in vacuo*.

General Procedure B for the Catalytic Hydrogenation of an α,β-Unsaturated Lactone, Ester, or Ketone. To a soln. of a lactone, an ester, or a ketone (1 equiv.) in AcOEt (10 ml per 1 mmol), 10% Pd/C (10% (*w*/*w*)) was added under Ar. The flask was evacuated and refilled with H_2 (3×). The black suspension was stirred at 20° for 21 h under an H_2 atmosphere (atmospheric pressure), filtered over *Celite*, and the *Celite* was washed with AcOEt. The filtrate was concentrated *in vacuo*.

General Procedure C for the Preparation of a 5-trans-*Substituted Prolinol.* A ketone (1.0 equiv.) and $TsOH \cdot H_2O$ (1.0 equiv.) were dissolved in CH_2Cl_2 (6 ml per 1 mmol) and TFA (1.5 ml per 1 mmol). The mixture was heated to reflux for 17 h, cooled to 20°, and concentrated *in vacuo*. The residue was treated with MeOH (1 × 5 ml per 1 mmol) and hexane (3 × 5 ml per 1 mmol). The resulting iminium salt was dissolved in $CHCl_3$ (7 ml per 1 mmol), washed with sat. aq. K_2CO_3 soln. (1 × 7 ml per 1 mmol), dried ($MgSO_4$), and concentrated *in vacuo*. To a soln. of the residue in toluene (4 ml per 1 mmol), $NaHB(OAc)_3$ (1.5 equiv.) was added under Ar. The mixture was heated to reflux for 15 h, cooled to 20°, quenched with conc. HCl, and concentrated *in vacuo*. The residue was suspended in MeOH, filtered, and the filtrate was concentrated *in vacuo*. To a soln. of the residue in MeCN (4 ml per 1 mmol), Boc_2O (2.0 equiv.) and K_2CO_3 (2.2 equiv.) were added. The mixture was stirred at 20° for 24 h, filtered, and the filtrate concentrated *in vacuo*.

General Procedure D for the Intramolecular Cyclization of a Lactone. To an ice-cooled soln. of a lactone (1 equiv.) in CH_2Cl_2 (4 ml per 1 mmol), TFA (1 ml per 1 mmol) was added. The mixture was stirred

at 0° for 1 h, then concentrated *in vacuo*. The resulting residue was dissolved in pyridine (6 ml per 1 mmol). After addition of a cat. amount of DMAP, the mixture was heated to reflux for 16 h. The solvent was removed *in vacuo*.

General Procedure E for the Introduction of a Protected Phosphate via *a* Mitsunobu *Reaction.* To a soln. of an alcohol (1.0 equiv.), Ph_3P (1.5 equiv.), dibenzyl phosphate (1.5 equiv.), and Et_3N (5 equiv.) in THF (10 ml per 1 mmol), DIAD (1.5 equiv.) was added. The mixture was stirred at 20° for 3 h, then concentrated *in vacuo*.

General Procedure F for the Deprotection of a Dibenzyl-Protected Phosphate. To a soln. of a dibenzyl-protected phosphate (1.0 equiv.) in EtOH or MeOH (*ca.* 20 ml per 1 mmol), 10% Pd/C (10% (*w*/*w*)) was added under Ar. The flask was evacuated and refilled with H_2 (3×). The black suspension was stirred at 20° under an H_2 atmosphere (atmospheric pressure) for 15 h. The mixture was filtered over *Celite*, the *Celite* was washed with MeOH, and the filtrate was concentrated *in vacuo*. The residue was dissolved in H_2O (60 ml per 1 mmol), washed with CH_2Cl_2 (1×60 ml per 1 mmol), and lyophilized.

General Procedure G for the 1,3-Dipolar Cycloaddition. A suspension of an aromatic aldehyde (1.05 equiv.), an amino acid (1.05 equiv.), and an *N*-substituted maleimide (1.00 equiv.) in MeCN or DMF (2 ml per 1 mmol) was stirred at 85° for 15–20 h (TLC control). The resulting mixture was cooled to 20° and concentrated *in vacuo*.

General Procedure H for the Imide Ring Opening and the in situ *Formation of a Methyl Ester*. A soln. of an imide (1 equiv.) in 0.05M NaOH in THF/H_2O 2:1 (40 ml per 1 mmol) was stirred at 20° for 15 h (TLC control). The solvent was removed *in vacuo*, and the resulting solid was shortly dried under high vacuum. The solid was taken up in MeOH (15 ml per 1 mmol) and cooled to 0°. $SOCl_2$ (5 equiv.) was slowly added. The mixture was stirred at 20° for 15 h, then concentrated *in vacuo*.

General Procedure I for the Reduction of a Methyl Ester to the Corresponding Alcohol. To an ice-cooled soln. of a methyl ester (1 equiv.) in THF (15 ml per 1 mmol), 20 wt.-% DIBAL-H in toluene (3 equiv.) was slowly added. The mixture was stirred at 0° for 2 h, and then the reaction was quenched with MeOH. The soln. was poured in a soln. of potassium sodium tartrate (4 g per 1 mmol) in H_2O (20 ml per 1 mmol) and AcOEt (50 ml per 1 mmol). The biphasic system was stirred at 20° for 2 h. The layers were separated. The aq. phase was extracted with AcOEt. The combined org. phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo*.

General Procedure J for the Introduction of a Dibenzyl-Protected Phosphate. To a suspension of an alcohol (1.0 equiv.) in MeCN (10 ml per 1 mmol), 0.45M 1*H*-tetrazole in MeCN (3.0 equiv.) and dibenzyl *N*,*N*-diisopropylphosphoramidite (1.5 equiv.) were added. The suspension was stirred at 20° for 3 h. *m*CPBA (70% pure, 2.4 equiv.) was added, and the mixture was stirred at 20° for 30 min. After addition of AcOEt, the mixture was washed with sat. aq. $NaHSO_3$ soln., sat. aq. $NaHCO_3$ soln., and H_2O, dried ($MgSO_4$), filtered, and concentrated *in vacuo*.

General Procedure K for the Deprotection of a Dibenzyl-Protected Phosphate. To a soln. of a dibenzyl-protected phosphate (1 equiv.) in MeOH (25 ml per 1 mmol), 10% Pd/C (10% (*w*/*w*)) was added under Ar. The flask was evacuated and refilled with H_2 (3×). The black suspension was stirred at 20° under a H_2 atmosphere (atmospheric pressure) for 15 h. The mixture was filtered over *Celite*, the *Celite* was washed with MeOH, and the filtrate was concentrated *in vacuo*. A small amount was purified by HPLC (*RP18*, H_2O/MeCN 95:5 → 40:60 in 60 min). The fractions containing product were lyophilized.

(+)-tert-*Butyl (4*S*)-2,2-Dimethyl-4-[(*E*)-4-methyl-3-oxopent-1-en-1-yl]-1,3-oxazolidine-3-carboxylate* ((+)-**8a**). *General Procedure A* with (+)-**6** (3.70 g, 14.25 mmol, 1.0 equiv.), toluene (35 ml), 20 wt.-% DIBAL-H in toluene (20.2 ml, 24.23 mmol, 1.7 equiv.), MeOH (10 ml), ylide **7a** (9.87 g, 28.50 mmol, 2.0 equiv.), and THF (60 ml) to afford, after purification by CC (SiO_2; hexane/AcOEt 9:1), (+)-**8a** (3.65 g, 86%). White solid. M.p. 57–59°. $[\alpha]_D^{20} = +69.6$ ($c = 1.00$, $CHCl_3$). IR (neat): 2977*w*, 2934*w*, 2885*w*, 1693*s*, 1629*m*, 1464*w*, 1364*s*, 1252*m*, 1224*m*, 1210*m*, 1168*m*, 1145*m*, 1080*m*, 1050*s*, 986*m*, 858*m*, 844*m*, 766*m*. ^{1}H-NMR (300 MHz, 363 K, $C_2D_2Cl_4$): 1.07 (*d*, $J = 6.9$, 6 H); 1.41 (*s*, 9 H); 1.49 (*s*, 3 H); 1.57 (*s*, 3 H); 2.74 (*sept.*, $J = 6.9$, 1 H); 3.74 (*dd*, $J = 9.0$, 2.5, 1 H); 4.04 (*dd*, $J = 9.0$, 6.5, 1 H); 4.41–4.44 (*m*, 1 H); 6.21 (*dd*, $J = 15.7$, 1.1, 1 H); 6.66 (*dd*, $J = 15.7$, 6.7, 1 H). ^{13}C-NMR (75 MHz, 363 K, $C_2D_2Cl_4$): 18.4; 18.5; 24.6; 27.1; 28.7; 39.3; 58.5; 67.8; 80.5; 94.6; 128.6; 144.0; 152.0; 203.3. HR-MALDI-MS: 320.1828 ($[M+Na]^+$, $C_{16}H_{27}NNaO_4^+$; calc. 320.1832). Anal. calc. for $C_{16}H_{27}NO_4$ (297.39): C 64.62, H 9.15, N 4.71; found: C 64.60, H 9.17, N 4.77.

(+)-tert-*Butyl (4*S*)-2,2-Dimethyl-4-[(*E*)-3-oxobut-1-en-1-yl]-1,3-oxazolidine-3-carboxylate* ((+)-**8b**). *General Procedure A* with (+)-**6** (11.00 g, 42.3 mmol, 1.0 equiv.), toluene (115 ml), 20 wt.-% DIBAL-H in toluene (59.9 ml, 71.8 mmol, 1.7 equiv.), MeOH (30 ml), ylide **7b** (26.90 g, 84.5 mmol, 2.0 equiv.), and THF (180 ml) to yield, after purification by CC (SiO_2; hexane/AcOEt 8:2), (+)-**8b** (10.17 g, 89%). White solid. M.p. 75–80°. $[\alpha]_D^{20} = +58.2$ ($c = 0.61$, $CHCl_3$). IR (neat): 2984*m*, 1691*s*, 1671*s*, 1648*m*, 1479*w*, 1456*w*, 1384*s*, 1363*s*, 1266*m*, 1255*m*, 1242*m*, 1159*m*, 1100*m*, 1068*m*, 1053*m*, 980*m*, 851*m*, 771*m*, 668*m*. ^{1}H-NMR (300 MHz, 363K, $C_2D_2Cl_4$): 1.41 (*s*, 9 H); 1.49 (*s*, 3 H); 1.57 (*s*, 3 H); 2.20 (*s*, 3 H); 3.74 (*dd*, $J = 9.0$, 2.5, 1 H); 4.05 (*dd*, $J = 9.0$, 6.5, 1 H); 4.40–4.44 (*m*, 1 H); 6.10 (*dd*, $J = 15.9$, 1.0, 1 H); 6.59 (*dd*, $J = 15.9$, 6.9, 1 H). ^{13}C-NMR (75 MHz, 363 K, $C_2D_2Cl_4$): 24.7; 27.2; 27.5; 28.8; 58.4; 67.7; 80.6; 94.6; 131.7; 144.8; 151.8; 197.6. Anal. calc. for $C_{14}H_{23}NO_4$ (269.34): C 62.43, H 8.61, N 5.20; found: C 62.50, H 8.48, N 5.23.

(+)-tert-*Butyl (4*S*)-2,2-Dimethyl-4-(4-methyl-3-oxopentyl)-1,3-oxazolidine-3-carboxylate* ((+)-**9a**). *General Procedure B* with (+)-**8a** (3.32 g, 11.16 mmol, 1 equiv.), 10% Pd/C (330 mg), and AcOEt (75 ml) to give, after purification by CC (SiO_2; hexane/AcOEt 8:2), (+)-**9a** (3.33 g, quant.). Colorless oil. $[\alpha]_D^{20} = +26.0$ ($c = 1.00$, $CHCl_3$). IR (neat): 2975*w*, 2936*w*, 2875*w*, 1690*s*, 1456*w*, 1386*s*, 1365*s*, 1257*m*, 1206*w*, 1173*m*, 1148*m*, 1087*s*, 1022*w*, 849*w*, 769*w*. ^{1}H-NMR (300 MHz, 363 K, $C_2D_2Cl_4$): 1.05 (*d*, $J = 6.9$, 6 H); 1.44 (*s*, 12 H); 1.53 (*s*, 3 H); 1.72–1.97 (*m*, 2 H); 2.40 (*t*, $J = 7.4$, 2 H); 2.54 (*sept.*, $J = 6.9$, 1 H); 3.58–3.64 (*m*, 1 H); 3.81–3.91 (*m*, 2 H). ^{13}C-NMR (75 MHz, 363 K, $C_2D_2Cl_4$): 18.4; 18.5; 24.4; 27.5; 28.1; 28.7; 36.8; 41.1; 57.2; 67.5; 80.0; 93.9; 152.4; 213.5. HR-MALDI-MS: 322.1982 ($[M+Na]^+$, $C_{16}H_{29}NNaO_4^+$; calc. 322.1989).

(+)-tert-*Butyl (4*S*)-2,2-Dimethyl-4-(3-oxobutyl)-1,3-oxazolidine-3-carboxylate* ((+)-**9b**). *General Procedure B* with (+)-**8b** (2.27 g, 8.43 mmol, 1 equiv.), 10% Pd/C (227 mg), and AcOEt (50 ml). The crude product was purified by CC (SiO_2; hexane/AcOEt 9:1) to yield (+)-**9b** (2.09 g, 91%). White solid. M.p. 34–39°. $[\alpha]_D^{20} = +22.4$ ($c = 1.01$, $CHCl_3$). IR (neat): 2976*w*, 2875*w*, 1689*s*, 1478*w*, 1453*w*, 1388*s*, 1362*s*, 1304*w*, 1249*m*, 1167*m*, 1145*m*, 1078*s*, 1048*m*, 1024*m*, 851*m*, 769*m*. ^{1}H-NMR (300 MHz, 363 K, $C_2D_2Cl_4$): 1.44 (*s*, 12 H); 1.53 (*s*, 3 H); 1.73–1.90 (*m*, 2 H); 2.09 (*s*, 3 H); 2.38 (*t*, $J = 7.5$, 2 H); 3.62 (*d*, $J = 7.5$, 1 H); 3.83–3.91 (*m*, 2 H). ^{13}C-NMR (75 MHz, 363 K, $C_2D_2Cl_4$): 24.4; 27.5; 28.2; 28.8; 29.8; 40.3; 57.0; 67.4; 79.9; 93.8; 152.2; 207.1. HR-ESI-MS: 294.1672 ($[M+Na]^+$, $C_{14}H_{25}NNaO_4^+$; calc. 294.1676). Anal. calc. for $C_{14}H_{25}NO_4$ (271.36): C 61.97, H 9.29, N 5.16; found: C 62.07, H 9.30, N 5.17.

(−)-tert-*Butyl (2*S*,5*R*)-2-(Hydroxymethyl)-5-(1-methylethyl)pyrrolidine-1-carboxylate* ((−)-**2a**). *General Procedure C* with (+)-**9a** (6.68 g, 22.32 mmol, 1.0 equiv.), $TsOH \cdot H_2O$ (4.25 g, 22.32 mmol, 1.0 equiv.), CH_2Cl_2 (120 ml), TFA (30 ml), $NaHB(OAc)_3$ (5.97 g, 28.15 mmol, 1.5 equiv.), toluene (100 ml), Boc_2O (8.19 g, 37.54 mmol, 2.0 equiv.), K_2CO_3 (5.71 g, 41.29 mmol, 2.2 equiv.), and MeCN (100 ml). The crude product was purified by CC (SiO_2; hexane/AcOEt 9:1) to afford (−)-**2a** (2.25 g, 41%). Colorless oil. $[\alpha]_D^{20} = -44.4$ ($c = 1.00$, $CHCl_3$). IR (neat): 3406*w*, 2961*w*, 2873*w*, 1689*m*, 1663*s*, 1472*w*, 1380*s*, 1365*s*, 1288*w*, 1254*w*, 1172*s*, 1122*m*, 1104*m*, 1046*m*, 966*w*, 924*w*, 892*m*, 871*w*, 854*w*, 826*w*, 775*m*. ^{1}H-NMR (300 MHz, 363 K, $C_2D_2Cl_4$): 0.75 (*d*, $J = 6.9$, 3 H); 0.83 (*d*, $J = 6.9$, 3 H); 1.43 (*s*, 9 H); 1.54–1.68 (*m*, 2 H); 1.72–1.96 (*m*, 2 H); 2.25–2.31 (*m*, 1 H); 3.55 (*dd*, $J = 11.2$, 4.1, 1 H); 3.63 (*dd*, $J = 11.2$, 5.9, 1 H); 3.71 (*ddd*, $J = 8.1$, 4.7, 2.8, 1 H); 3.82–3.89 (*m*, 1 H). HR-ESI-MS: 266.1720 ($[M+Na]^+$, $C_{13}H_{25}NNaO_3^+$; calc. 266.1727). Anal. calc. for $C_{13}H_{25}NO_3$ (243.35): C 64.17, H 10.35, N 5.76; found: C 64.28, H 10.29, N 5.60.

(−)-tert-*Butyl (2*S*,5*R*)-2-(Hydroxymethyl)-5-methylpyrrolidine-1-carboxylate* ((−)-**2b**). *General Procedure C* with (+)-**9b** (10.00 g, 36.9 mmol, 1.0 equiv.), $TsOH \cdot H_2O$ (7.00 g, 36.9 mmol, 1.0 equiv.), CH_2Cl_2 (225 ml), TFA (75 ml), $NaHB(OAc)_3$ (11.70 g, 55.3 mmol, 1.5 equiv.), toluene (120 ml), Boc_2O (16.1 g, 73.7 mmol, 2.0 equiv.), K_2CO_3 (11.2 g, 71.1 mmol, 2.2 equiv.), and MeCN (120 ml). The crude product was purified by CC (SiO_2; hexane/AcOEt 8:2) to yield (−)-**2b** (1.51 g, 19%). Colorless oil. $[\alpha]_D^{20} = -46.7$ ($c = 1.01$, $CHCl_3$). IR (neat): 3411*w* (br.), 2968*m*, 2876*w*, 1690*s*, 1666*s*, 1477*w*, 1456*w*, 1386*s*, 1365*s*, 1253*w*, 1169*s*, 1131*m*, 1110*m*, 1082*m*, 1052*m*, 1021*m*, 956*w*, 922*w*, 872*w*, 854*w*, 773*m*. ^{1}H-NMR (300 MHz, 363 K, $C_2D_2Cl_4$): 1.12 (*d*, $J = 6.2$, 3 H); 1.43 (*s*, 9 H); 1.46–1.52 (*m*, 1 H); 1.59–1.64 (*m*, 1 H); 1.90–2.10 (*m*, 2 H); 3.48–3.62 (*m*, 2 H); 3.85–3.93 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 20.4; 26.7; 28.9; 31.5; 54.7; 59.9; 68.1; 80.4; 156.8. HR-ESI-MS: 238.1399 ($[M+Na]^+$, $C_{11}H_{21}NNaO_3^+$; calc. 238.1414).

(+)-tert-*Butyl (2*R,*5*S*)-2-(1-Methylethyl)-5-[(*E*)-(2-oxo-4,5-dihydrofuran-3(2*H*)-ylidene)methyl]pyrrolidine-1-carboxylate* ((+)-**12**) *and (+)*-tert-*Butyl (2*R,*5*S*)-2-(1-Methylethyl)-5-[(*Z*)-(2-oxo-4,5-dihydrofuran-3(2*H*)-ylidene)methyl]pyrrolidine-1-carboxylate* ((+)-**13**). To a soln. of (−)-**11a** (771 mg, 3.17 mmol, 1.0 equiv.) in Me_2SO (15 ml), Et_3N (1.54 ml, 11.09 mmol, 3.5 equiv.) was added. The mixture was stirred at 20° for 15 min, then cooled to 15°. $SO_3 \cdot Py$ complex (1.77 g, 11.09 mmol, 3.5 equiv.) was added portionwise. The mixture was stirred at 10° for 3 h. Ice was added, and the resulting mixture was extracted with CH_2Cl_2 (4×30 ml). The combined org. phases were washed with 50% aq. citric acid soln. (1×60 ml), H_2O (1×60 ml), sat. aq. $NaHCO_3$ soln. (1×60 ml), H_2O (1×60 ml), and concentrated *in vacuo*. The residue was dissolved in THF (50 ml). Ylide **14** (2.20 g, 6.34 mmol, 2.0 equiv.) was added, and the mixture was stirred at 50° for 37 h. The mixture was cooled to 20°, filtered, and the filtrate was concentrated *in vacuo*. The crude product was purified by CC (SiO_2; hexane/AcOEt 8:2) to afford (+)-**12** (287 mg, 29%) and (+)-**13** (587 mg, 60%).

Data of (+)-**12**. White solid. M.p. 112–113°. $[\alpha]_D^{20} = +34.7$ ($c = 1.00$, $CHCl_3$). IR (neat): 2959*w*, 2906*w*, 1746*s*, 1680*s*, 1471*m*, 1443*w*, 1393*m*, 1381*s*, 1352*s*, 1342*s*, 1329*m*, 1318*m*, 1223*m*, 1206*m*, 1171*s*, 1135*m*, 1123*s*, 1111*s*, 1077*s*, 1055*w*, 1022*s*, 995*w*, 933*m*, 862*m*, 783*m*. ^{1}H-NMR (300 MHz, 363 K, $C_2D_2Cl_4$): 0.85 (*d*, *J* = 6.8, 3 H); 0.91 (*d*, *J* = 6.8, 3 H); 1.37 (*s*, 9 H); 1.45–1.60 (*m*, 1 H); 1.66–1.82 (*m*, 2 H); 1.90 (*ddd*, *J* = 13.5, 6.6, 6.6, 1 H); 2.16–2.27 (*m*, 1 H); 2.83–2.89 (*m*, 2 H); 3.69 (*ddd*, *J* = 7.2, 3.2, 3.2, 1 H); 4.26 (*dt*, *J* = 7.2, 1.3, 2 H); 5.30–5.38 (*m*, 1 H); 6.11 (*dt*, *J* = 8.1, 2.3, 1 H). ^{13}C-NMR (125 MHz, 363 K, $C_2D_2Cl_4$): 18.6; 20.0; 26.6; 28.7; 29.1; 31.0; 31.6; 56.2; 64.8; 65.7; 79.4; 122.5; 147.1; 155.7; 169.6. HR-MALDI-MS: 332.1836 ($[M+Na]^+$, $C_{17}H_{27}NNaO_4^+$; calc. 332.1832). Anal. calc. for $C_{17}H_{27}NO_4$ (309.40): C 65.99, H 8.80, N 4.53; found: C 65.93, H 8.57; N 4.72.

Data of (+)-**13**. Colorless oil. $[\alpha]_D^{20} = +42.8$ ($c = 1.00$, $CHCl_3$). IR (neat): 2969*w*, 1766*s*, 1680*s*, 1471*w*, 1379*s*, 1364*s*, 1258*w*, 1167*s*, 1110*m*, 1035*m*, 1029*m*, 1016*w*, 962*w*, 934*w*, 862*w*, 768*w*, 726*w*, 631*s*. ^{1}H-NMR (300 MHz, 363 K, $C_2D_2Cl_4$): 0.85 (*d*, *J* = 6.9, 3 H); 0.91 (*d*, *J* = 6.9, 3 H); 1.39 (*s*, 9 H); 1.59–2.09 (*m*, 5 H); 2.73–2.85 (*m*, 1 H); 3.01–3.12 (*m*, 1 H); 3.66–3.72 (*m*, 1 H); 4.24–4.40 (*m*, 3 H); 6.55 (*dt*, *J* = 8.6, 2.9, 1 H). HR-MALDI-MS: 332.1831 ($[M+Na]^+$, $C_{17}H_{27}NNaO_4^+$, 332.1832). Anal. calc. for $C_{17}H_{27}NO_4$ (309.40): C 65.99, H 8.80, N 4.53; found: C 65.97, H 8.60, N 4.38.

*(−)-(2*R,*5*S,*7a*S*)-Hexahydro-2-(2-hydroxyethyl)-5-(1-methylethyl)-1*H*-pyrrolizin-3-one* ((−)-**15a**). *General Procedure D* with **19a** (780 mg, 2.50 mmol, 1 equiv.). The two diastereoisomers were separated twice by CC (SiO_2; hexane/THF 4:6). Only the desired isomer (−)-**15a** was isolated in pure form (270 mg, 51%). Pale yellow oil. $[\alpha]_D^{20} = -72.2$ ($c = 1.00$, $CHCl_3$). IR (neat): 3383*w*, 2958*w*, 2871*w*, 1656*s*, 1463*w*, 1409*m*, 1387*m*, 1370*w*, 1348*w*, 1289*w*, 1261*w*, 1183*w*, 1154*w*, 1119*w*, 1055*m*, 945*w*, 906*w*, 865*w*, 796*w*, 728*w*, 665*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.89 (*d*, *J* = 6.5, 3 H); 0.93 (*d*, *J* = 6.5, 3 H); 1.25 (*ddd*, *J* = 22.3, 11.4, 8.3, 1 H); 1.66–2.20 (*m*, 8 H); 2.68–2.78 (*m*, 1 H); 3.65 (*dd*, *J* = 14.9, 7.5, 1 H); 3.79 (*dd*, *J* = 6.5, 4.7, 2 H); 3.86 (*ddd*, *J* = 10.6, 7.5, 5.3, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 18.2; 19.6; 30.3; 31.8; 32.6; 32.9; 35.8; 44.9; 60.5; 60.7; 62.0; 179.1. HR-MALDI-MS: 212.1644 ($[M+H]^+$, $C_{12}H_{22}NO_2^+$; calc. 212.1645). Anal. calc. for $C_{12}H_{21}NO_2$ (211.30): C 68.21, H 10.02, N 6.63; found: C 68.07, H 10.03, N 6.79.

*(−)-(2*R,*5*R,*10*S*)-Hexahydro-2-(2-hydroxyethyl)-5-methyl-1*H*-pyrrolizin-3-one* ((−)-**15b**). *General Procedure D* with **19b** (670 mg, 2.36 mmol, 1 equiv.). The two diastereoisomers were separated twice by CC (SiO_2; hexane/THF 4:6 and CH_2Cl_2/MeOH 95:5). Only the desired isomer (−)-**15b** was isolated in pure form (155 mg, 36%). Colorless oil. $[\alpha]_D^{20} = -77.1$ ($c = 1.09$, $CHCl_3$). IR (neat): 3376*w* (br.), 2962*w*, 2932*w*, 2868*w*, 1656*s*, 1418*m*, 1375*w*, 1346*w*, 1297*w*, 1181*w*, 1162*w*, 1049*m*, 712*w*, 667*m*, 608*m*. ^{1}H-NMR (300 MHz, $CDCl_3 + D_2O$): 1.22 (*d*, *J* = 6.2, 3 H); 1.24–1.39 (*m*, 1 H); 1.54–1.67 (*m*, 1 H); 1.74–1.84 (*m*, 1 H); 1.87–1.99 (*m*, 4 H); 2.29–2.38 (*m*, 1 H); 2.69–2.79 (*m*, 1 H); 3.72–3.81 (*m*, 2 H); 3.88–4.02 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.2; 32.5; 32.8; 35.4; 36.0; 45.4; 50.0; 59.8; 61.7; 177.9. HR-ESI-MS: 206.1149 ($[M+Na]^+$, $C_{10}H_{17}NNaO_2^+$; calc. 206.1152).

*(−)-2-[(2*R,*5*R,*7a*S*)-Hexahydro-5-methyl-3-oxo-1*H*-pyrrolizin-2-yl]ethyl Bis(phenylmethyl) Phosphate* ((−)-**21b**). *General Procedure E* with (−)-**15b** (145 mg, 0.8 mmol, 1.0 equiv.), PPh_3 (312 mg, 1.2 mmol, 1.5 equiv.), dibenzyl phosphate (331 mg, 1.2 mmol, 1.5 equiv.), Et_3N (0.55 ml, 4.0 mmol, 5.0 equiv.), DIAD (0.23 ml, 1.2 mmol, 1.5 equiv.), THF (8 ml). The crude product was purified by CC (SiO_2; hexane/AcOEt/MeOH 3:7:0.2) to yield (−)-**21b** (300 mg, 86%). Orange oil. $[\alpha]_D^{20} = -28.2$ ($c = 1.02$, $CHCl_3$). IR (neat): 2965*w*, 2894*w*, 1674*s*, 1497*w*, 1455*w*, 1409*w*, 1347*w*, 1266*m*, 1214*w*, 1006*s*, 993*s*, 918*w*, 879*w*, 735*s*, 696*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.20 (*d*, *J* = 6.5, 3 H); 1.22–1.38 (*m*, 1 H);

1.51–1.64 (*m*, 1 H); 1.75–2.16 (*m*, 5 H); 2.22–2.35 (*m*, 1 H), 2.54–2.63 (*m*, 1 H); 3.81–3.96 (*m*, 2 H); 4.13 (*ddd*, *J* = 13.8, 6.6, 1.2, 2 H); 4.98–5.10 (*m*, 4 H); 7.32–7.37 (*m*, 10 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.4; 31.4; 32.6 (*d*, ^3J(C,P) = 7.3); 32.9; 36.0; 43.3; 50.1; 59.6; 66.2 (*d*, ^2J(C,P) = 6.1); 69.3 (*d*, ^2J(C,P) = 4.3); 127.9; 128.4; 128.5; 135.8 (*d*, ^3J(C,P) = 7.4); 176.5. HR-ESI-MS: 444.1927 ($[M+H]^+$, $C_{24}H_{31}NO_5P^+$; calc. 444.1934).

*(−)-2-[(2*R*,7a*S*)-Hexahydro-3-oxo-1*H*-pyrrolizin-2-yl]ethyl Dibenzy Phosphate* ((−)-**21c**). *General Procedure E* with (−)-**15c** (349 mg, 2.1 mmol, 1.0 equiv.), PPh_3 (811 mg, 3.1 mmol, 1.5 equiv.), dibenzyl phosphate (861 mg, 3.1 mmol, 1.5 equiv.), Et_3N (1.44 ml, 10.3 mmol, 5.0 equiv.), DIAD (0.60 ml, 3.1 mmol, 1.5 equiv.), THF (20 ml). The crude product was purified by CC (SiO_2; cyclohexane/AcOEt/MeOH 1:1:0.1) to afford (−)-**21c** (740 mg, 84%). Yellow oil. $[\alpha]_D^{20} = -7.2$ (*c* = 1.01, $CHCl_3$). IR (neat): 2958*w*, 2890*w*, 1682*s*, 1456*w*, 1418*w*, 1273*m*, 994*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.18–1.29 (*m*, 1 H); 1.76–2.15 (*m*, 7 H); 2.57–2.67 (*m*, 1 H); 3.03 (*ddd*, *J* = 11.8, 8.8, 3.5, 1 H); 3.55 (*ddd*, *J* = 11.8, 7.9, 7.9, 1 H); 3.73–3.83 (*m*, 1 H); 4.09–4.16 (*m*, 2 H); 4.98–5.10 (*m*, 4 H); 7.32–7.37 (*m*, 10 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 26.8; 31.6; 32.0; 32.5 (*d*, ^3J(C,P) = 6.7); 41.4; 43.4; 60.4; 66.1 (*d*, ^2J(C,P) = 5.5); 69.3 (*d*, ^2J(C,P) = 5.5); 127.9; 128.4; 128.5; 135.7 (*d*, ^3J(C,P) = 6.7); 176.5. ^{31}P-NMR (120 MHz, $CDCl_3$): −0.6. HR-MALDI-MS: 452.1603 ($[M+Na]^+$, $C_{23}H_{28}NNaO_5P^+$; calc. 452.1603). Anal. calc. for $C_{23}H_{28}NO_5P$ (429.45): C 64.33, H 6.57, N 3.26; found: C 64.43, H 6.52, N 3.31.

*(−)-2-[(2*R*,5*S*,7a*S*)-Hexahydro-5-(1-methylethyl)-3-oxo-1*H*-pyrrolizin-2-yl]ethyl Dihydrogen Phosphate* ((−)-**1a**). *General Procedure E* with (−)-**15a** (235 mg, 1.09 mmol, 1.0 equiv.), Ph_3P (430 mg, 1.64 mmol, 1.5 equiv.), dibenzyl phosphate (456 mg, 1.64 mmol, 1.5 equiv.), Et_3N (0.76 ml, 5.44 mmol, 5.0 equiv.), DIAD (0.32 ml, 1.64 mmol, 1.5 equiv.), THF (10 ml). The crude product was purified by CC (SiO_2; hexane/AcOEt/MeOH 1:1:0.1). *General Procedure F* starting from **21a** contaminated with triphenylphosphine oxide, 10% Pd/C (32 mg), and EtOH (30 ml) yielded (−)-**1a** (227 mg, 72%). White foam. $[\alpha]_D^{20} = -11.0$ (*c* = 0.40, MeOH). IR (neat): 3359*w*, 2962*w*, 1651*m*, 1434*w*, 1389*w*, 1370*w*, 1185*m*, 1119*w*, 1012*s*, 973*s*, 773*w*, 668*w*. ^{1}H-NMR (CD_3OD, 300 MHz): 0.89 (*d*, *J* = 6.5, 3 H); 0.91 (*d*, *J* = 6.5, 3 H); 1.24–1.37 (*m*, 1 H); 1.73–1.90 (*m*, 3 H); 1.96–2.22 (*m*, 5 H); 2.68–2.78 (*m*, 1 H); 3.59 (*dd*, *J* = 14.9, 7.5, 1 H); 3.89–4.12 (*m*, 3 H). ^{13}C-NMR (75 MHz, CD_3OD): 17.3; 18.7; 30.0; 30.6; 32.3; 32.7; 32.9; 43.2; 60.5; 61.1; 64.2; 179.1. HR-MALDI-MS: 292.1309 ($[M+H]^+$, $C_{12}H_{23}NO_5P^+$; calc. 292.1308).

*(−)-2-[(2*R*,5*R*,7aS)-Hexahydro-5-methyl-3-oxo-1*H*-pyrrolizin-2-yl]ethyl Dihydrogen Phosphate* ((−)-**1b**). *General Procedure F* with (−)-**21b** (290 mg, 0.65 mmol, 1 equiv.), 10% Pd/C (29 mg), and EtOH (10 ml) afforded (−)-**1b** (168 mg, 94%). Colorless foam. $[\alpha]_D^{20} = -42.9$ (*c* = 1.01, MeOH). IR (neat): 2966*w*, 2359*w*, 2339*w*, 1652*m* (br.), 1441*m*, 1377*w*, 1346*w*, 1165*m*, 962*s* (br.), 827*m*, 781*m*, 735*m*, 712*m*, 668*m*. ^{1}H-NMR (300 MHz, CD_3OD): 1.21 (*d*, *J* = 6.3, 3 H); 1.27–1.41 (*m*, 1 H); 1.61–1.74 (*m*, 1 H); 1.83–2.16 (*m*, 5 H); 2.33–2.42 (*m*, 1 H); 2.70–2.79 (*m*, 1 H); 3.84 (*m*, 1 H); 4.02–4.14 (*m*, 3 H). ^{13}C-NMR (75 MHz, CD_3OD): 21.1; 32.6; 33.6; 37.1; 45.2; 47.7; 51.3; 61.6; 65.6 (*d*, ^2J(C,P) = 4.7); 178.8. HR-ESI-MS: 286.0813 ($[M+Na]^+$, $C_{10}H_{18}NNaO_5P^+$; calc. 286.0815).

*(+)-2-[(2*R*,7a*S*)-Hexahydro-3-oxo-1*H*-pyrrolizin-2-yl]ethyl Dihydrogen Phosphate* ((+)-**1c**). *General Procedure F* with (−)-**21c** (139 mg, 0.3 mmol, 1 equiv.), 10% Pd/C (14 mg), MeOH (7 ml) afforded (+)-**1c** (80 mg, quant.). White foam. $[\alpha]_D^{20} = +10.7$ (*c* = 1.01, MeOH). IR (neat): 2957*w*, 2889*w*, 2360*w*, 1652*s*, 1458*m*, 1177*m*, 943*s*. ^{1}H-NMR (500 MHz, CD_3OD): 1.29–1.38 (*m*, 1 H); 1.89 (br. *s*, 1 H); 1.97–2.20 (*m*, 6 H); 2.78 (br. *s*, 1 H); 3.05–3.10 (*m*, 1 H); 3.44–3.50 (*m*, 1 H); 3.99–4.05 (*m*, 3 H). ^{13}C-NMR (125 MHz, CD_3OD): 27.8; 32.6; 32.8; 33.6; 42.2; 45.5; 62.4; 65.2; 179.3. ^{31}P-NMR (120 MHz, CD_3OD): 1.6. HR-MALDI-MS: 250.0837 ($[M+H]^+$, $C_9H_{17}NO_5P^+$; calc. 250.0844).

*(±)-(3a*RS*,4*SR*,8a*RS*,8b*SR*)-Hexahydro-4-(naphthalen-2-yl)-2-(phenylmethyl)pyrrolo[3,4-*a*]pyrrolizine-1,3(2*H*,4*H*)-dione* ((±)-*endo*-**28a**) *and (±)-(3a*SR*,4*SR*,8a*RS*,8b*RS*)-Hexahydro-4-(naphthalen-2-yl)-2-(phenylmethyl)pyrrolo[3,4-*a*]pyrrolizine-1,3(2*H*,4*H*)-dione* ((±)-*exo*-**29a**). *General Procedure G* with *N*-benzylmaleimide (**23**) (9.36 g, 50.0 mmol, 1.00 equiv.), L-proline ((−)-**18**; 6.04 g, 52.5 mmol, 1.05 equiv.), naphthalene-2-carbaldehyde (**25**; 8.20 g, 52.5 mmol, 1.05 equiv.), and MeCN (100 ml) yielded, after purification by CC (SiO_2; CH_2Cl_2/Et_2O 98:2 → 1:1), (±)-**28a** (6.05 g, 31%) and (±)-**29a** (8.00 g, 41%).

Data of (±)-endo-**28a**. White solid. M.p. 150–153°. IR (neat): 3058*w*, 2947*w*, 2880*w*, 1769*w*, 1694*s*, 1601*w*, 1509*w*, 1495*w*, 1429*m*, 1398*m*, 1349*m*, 1316*m*, 1233*w*, 1202*w*, 1171*m*, 1154*m*, 1124*w*, 1074*m*, 1061*m*, 896*m*, 861*m*, 825*m*, 743*s*, 698*s*, 631*m*, 618*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.64–1.86 (*m*, 2 H);

1.97–2.22 (*m*, 2 H); 2.73 (*ddd*, *J* = 12.6, 8.4, 4.0, 1 H); 2.91 (*ddd*, *J* = 12.6, 8.7, 7.3, 1 H); 3.31 (*d*, *J* = 8.5, 1 H); 3.58 (*dd*, *J* = 8.5, 8.5, 1 H); 3.83 (*dd*, *J* = 9.8, 7.4, 1 H); 4.22 (*d*, *J* = 8.5, 1 H); 4.52 (*AB*, *J* = 3.3, 2 H); 7.24–7.31 (*m*, 6 H); 7.41–7.46 (*m*, 2 H); 7.71–7.74 (*m*, 3 H); 7.77–7.82 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 23.5; 29.7; 42.5; 49.1; 50.6; 50.9; 68.0; 68.9; 125.6; 125.7; 126.3; 126.6; 127.5; 127.6; 127.7; 127.9; 128.4; 128.7; 133.0; 133.1; 135.3; 135.6; 175.0; 177.9. HR-MALDI-MS: 397.1917 ($[M+H]^+$, $C_{26}H_{25}N_2O_2^+$; calc. 397.1911). Anal. calc. for $C_{26}H_{24}N_2O_2$ (396.49): C 78.76, H 6.10, N 7.07; found: C 78.61, H 6.12, N 7.14.

*Data of (±)-*exo-**29a**. White solid. M.p. 101–103°. IR (neat): 3055*w*, 2950*w*, 2875*w*, 2358*w*, 1766*w*, 1694*s*, 1602*w*, 1583*w*, 1508*w*, 1493*w*, 1455*w*, 1430*m*, 1391*m*, 1335*m*, 1311*m*, 1286*w*, 1250*w*, 1166*m*, 1153*m*, 1105*w*, 1067*m*, 912*w*, 900*w*, 860*w*, 822*m*, 808*m*, 790*m*, 749*s*, 701*s*, 661*m*, 617*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.56–1.82 (*m*, 3 H); 1.93–2.04 (*m*, 1 H); 2.61 (*ddd*, *J* = 11.2, 7.2, 7.2, 1 H); 2.98 (*ddd*, *J* = 11.2, 8.3, 5.3, 1 H); 3.46 (*dd*, *J* = 9.0, 5.3, 1H); 3.57 (*dd*, *J* = 9.0, 9.0, 1 H); 3.94–4.02 (*m*, 1 H); 4.30 (*d*, *J* = 5.3, 1 H); 4.68 (*s*, 2 H); 7.26–7.37 (*m*, 3 H); 7.42–7.50 (*m*, 4 H); 7.60 (*dd*, *J* = 8.6, 1.7, 1 H); 7.81–7.89 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 24.3; 26.3; 42.6; 48.1; 52.2; 55.5; 66.5; 69.8; 125.0; 125.2; 125.8; 126.1; 127.5; 127.9; 128.0; 128.4; 128.6; 129.0; 132.7; 133.2; 135.3; 139.3; 176.6; 177.7. HR-EI-MS: 396.1833 (M^+, $C_{26}H_{24}N_2O_2^+$; calc. 396.1832). Anal. calc. for $C_{26}H_{24}N_2O_2$ (396.49): C 78.76, H 6.10, N 7.07; found: C 78.83, H 5.89, N 7.18.

*(±)-Methyl (1*RS*,2*SR*,3*RS*,7a*SR*)-Hexahydro-3-(naphthalen-2-yl)-2-{[(phenylmethyl)amino]carbonyl}-1*H*-pyrrolizine-1-carboxylate* ((±)-**30a**). *General Procedure H* with (±)-*endo*-**28a** (2.38 g, 6.0 mmol, 1 equiv.), 0.05M NaOH in THF/H_2O 2:1 (240 ml), MeOH (120 ml), and $SOCl_2$ (2.18 ml, 30 mmol, 5 equiv.). The crude product was taken up in sat. aq. $NaHCO_3$ soln. (300 ml) and AcOEt/i-PrOH 4:1 (500 ml). The layers were separated. The aq. phase was extracted with AcOEt/i-PrOH 4:1 (3 × 500 ml). The comb. org. phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a solid, which was purified by CC (SiO_2; AcOEt/hexane/Et_3N 60:40:1 → AcOEt/Et_3N 100:1) to yield (±)-**30a** (1.94 g, 75%). White solid. M.p. 173–175°. IR (neat): 3281*m*, 3062*w*, 2954*m*, 2918*m*, 2856*m*, 2723*w*, 2625*w*, 2359*m*, 2343*m*, 2217*w*, 1742*s*, 1671*m*, 1648*s*, 1603*m*, 1558*m*, 1452*m*, 1435*m*, 1361*m*, 1331*m*, 1266*m*, 1234*m*, 1246*m*, 1192*m*, 1176*s*, 1135*m*, 1116*m*, 1081*m*, 1054*m*, 1029*m*, 992*w*, 953*m*, 896*m*, 856*m*, 824*m*, 809*m*, 743*m*, 724*s*, 694*m*, 642*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.70 (*ddd*, *J* = 19.1, 6.2, 6.2, 1 H); 1.91–2.00 (*m*, 2 H); 2.18 (*ddd*, *J* = 19.1, 6.8, 6.8, 1 H); 2.56–2.64 (*m*, 1 H); 3.04–3.15 (*m*, 2 H); 3.65 (*dd*, *J* = 6.8, 5.7, 1 H); 3.72 (*s*, 3 H); 3.96 (*dd*, *J* = 15.0, 5.6, 1 H); 4.09 (*dd*, *J* = 15.0, 5.6, 1 H); 4.34–4.41 (*m*, 2 H); 6.23 (*dd*, *J* = 5.6, 5.6, 1 H); 6.58 (*d*, *J* = 7.4, 2 H); 6.86–6.91 (*m*, 2 H); 7.03 (*dd*, *J* = 7.4, 7.4, 1 H); 7.39–7.52 (*m*, 3 H); 7.74–7.86 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 26.4; 33.0; 43.4; 52.1; 53.0; 54.1; 57.7; 65.5; 71.9; 125.0; 125.5; 125.7; 126.1; 126.8; 127.3; 127.6; 127.9; 128.0; 128.2; 132.8; 133.3; 136.8; 137.6; 169.2; 171.5. HR-MALDI-MS: 429.2165 ($[M+H]^+$, $C_{27}H_{29}N_2O_3^+$; calc. 429.2173). Anal. calc. for $C_{27}H_{28}N_2O_3$ (428.53): C 75.68, H 6.59, N 6.54; found C 75.86, H 6.60, N 6.48.

*(±)-(1*RS*,2*SR*,3*RS*,7a*SR*)-Hexahydro-1-(hydroxymethyl)-3-(naphthalen-2-yl)-*N*-(phenylmethyl)-1*H*-pyrrolizine-2-carboxamide* ((±)-**31a**). *General Procedure I* with (±)-**30a** (1.88 g, 4.39 mmol, 1 equiv.), 20 wt.-% DIBAL-H in toluene (10.9 ml, 13.2 mmol, 3 equiv.), THF (65 ml). The crude product was purified by CC (SiO_2; Et_2O/MeOH/Et_3N 95:5:1) to yield (±)-**31a** (760 mg, 43%). Beige solid. M.p. 141–144°. IR (neat): 3305*w* (br.), 3059*w*, 2950*w*, 2865*w*, 1648*s*, 1602*w*, 1537*m*, 1495*w*, 1454*m*, 1423*w*, 1379*w*, 1358*w*, 1322*w*, 1262*m*, 1247*m*, 1220*m*, 1158*w*, 1136*m*, 1079*m*, 1028*s*, 953*w*, 862*m*, 809*m*, 738*s*, 724*s*, 693*s*, 638*m*, 622*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.68–1.76 (*m*, 1 H); 1.85–2.06 (*m*, 3 H); 2.53–2.63 (*m*, 1 H); 2.67–2.74 (*m*, 1 H); 3.11–3.19 (*m*, 2 H); 3.37–3.42 (*m*, 1 H); 3.55–3.66 (*m*, 1 H); 3.71–3.80 (*m*, 2 H); 4.00 (*dd*, *J* = 15.0, 4.8, 1 H); 4.30–4.36 (*m*, 2 H); 6.55–6.57 (*m*, 2 H); 6.82 (*dd*, *J* = 7.5, 7.5, 2 H); 6.99 (*dd*, *J* = 7.5, 7.5, 1 H); 7.39 (*dd*, *J* = 8.6, 1.7, 1 H); 7.45–7.52 (*m*, 2 H); 7.56–7.62 (*m*, 1 H); 7.68–7.72 (*m*, 1 H); 7.76–7.79 (*m*, 2 H); 7.82–7.85 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 25.9; 32.1; 43.0; 51.5; 54.0; 56.7; 62.8; 65.8; 70.0; 124.9; 125.0; 125.7; 126.2; 126.8; 127.0; 127.6; 127.9; 128.1; 128.4; 132.5; 133.4; 137.2; 137.5; 171.5. HR-MALDI-MS: 401.2223 ($[M+H]^+$, $C_{26}H_{29}N_2O_2^+$; calc. 401.2224). Anal. calc. for $C_{26}H_{28}N_2O_2$ (400.52): C 77.97, H 7.05, N 6.99; found: C 77.89, H 7.24, N 6.91.

*(±)-((1*RS*,2*SR*,3*RS*,7a*SR*)-Hexahydro-3-(naphthalen-2-yl)-2-{[(phenylmethyl)amino]carbonyl}-1*H*-pyrrolizin-1-yl)methyl Bis(phenylmethyl) Phosphate* ((±)-**32a**). *General Procedure J* with (±)-**31a** (401 mg, 1.0 mmol, 1.0 equiv.), 0.45M 1*H*-tetrazole in MeCN (6.7 ml, 3.0 mmol, 3.0 equiv.), dibenzyl-*N*,

N-diisopropylphosphoramidite (0.5 ml, 1.5 mmol, 1.5 equiv.), MeCN (10 ml), and 70% pure *m*CPBA (591 mg, 2.4 mmol, 2.4 equiv.) afforded, after purification by CC (SiO_2; AcOEt/hexane/Et_3N 90:10:1), (±)-**32a** (530 mg, 80%). White solid. M.p. 138–140°. IR (neat): 3267*w*, 3055*w*, 2937*w*, 2905*w*, 2856*w*, 1641*m*, 1549*m*, 1496*w*, 1453*m*, 1366*w*, 1281*s*, 1260*m*, 1187*w*, 1128*w*, 1069*w*, 1012*s*, 908*m*, 872*m*, 835*m*, 812*m*, 758*m*, 739*s*, 726*s*, 696*s*, 642*m*, 607*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.63–1.71 (*m*, 1 H); 1.87–2.05 (*m*, 3 H); 2.42–2.52 (*m*, 1 H); 2.58–2.65 (*m*, 1 H); 3.09–3.20 (*m*, 1 H); 3.42 (*dd*, *J* = 5.7, 5.7, 1 H); 3.60–3.74 (*m*, 1 H); 3.92–4.16 (*m*, 3 H); 4.25–4.35 (*m*, 2 H); 5.03–5.12 (*m*, 4 H); 6.52 (*d*, *J* = 7.5, 2 H); 6.78 (*dd*, *J* = 7.5, 7.5, 2 H); 6.97 (*dd*, *J* = 7.5, 7.5, 1 H); 7.09 (*dd*, *J* = 5.6, 5.6, 1 H); 7.33–7.51 (*m*, 13 H); 7.69–7.83 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 26.3; 32.6; 43.1; 48.3 (*d*, ^2J(C,P) = 7.3); 53.9; 56.6; 67.6; 67.7; 69.4 (*d*, ^2J(C,P) = 4.9); 71.0; 124.9; 125.3; 125.7; 126.0; 126.7; 127.1; 127.4; 127.5; 127.9; 128.0; 128.2; 128.5; 128.5; 132.6; 133.2; 135.7; 135.8; 137.6; 169.2. HR-MALDI-MS: 661.2837 ($[M+H]^+$, $C_{40}H_{42}N_2O_5P^+$; calc. 661.2826). Anal. calc. for $C_{40}H_{41}N_2O_5P$ (660.75): C 72.71, H 6.25, N 4.24; found: C 72.74, H 6.27, N 4.25.

*(±)-((1*RS*,2*SR*,3*RS*,7a*S*R)-Hexahydro-3-(naphthalen-2-yl)-2-{[(phenylmethyl)amino]carbonyl}-1*H*-pyrrolizin-1-yl)methyl Dihydrogen Phosphate* ((±)-**22a**). *General Procedure K* with (±)-**32a** (500 mg, 0.76 mmol, 1 equiv.), cat. Pd/C (50 mg), and MeOH (30 ml) yielded (±)-**22a** (356 mg, 97%). White solid. M.p. 155–165° (dec.). IR (neat): 3278*w*, 3060*w*, 3028*w*, 2944*w*, 2861*w*, 1748*m*, 1662*s*, 1644*s*, 1603*m*, 1564*m*, 1509*m*, 1496*m*, 1453*m*, 1435*m*, 1388*m*, 1360*m*, 1248*m*, 1195*m*, 1175*s*, 1127*m*, 1093*m*, 1051*s*, 1037*s*, 912*m*, 899*m*, 862*m*, 823*m*, 744*m*, 730*m*, 696*m*, 660*w*. ^{1}H-NMR (300 MHz, CD_3OD): 2.00–2.22 (*m*, 4 H); 2.78–2.88 (*m*, 1 H); 2.98–3.04 (*m*, 1 H); 3.25–3.34 (*m*, 1 H); 3.60 (*dd*, *J* = 5.4, 5.4, 1 H); 3.69 (*d*, *J* = 15.2, 1 H); 3.82–3.95 (*m*, 2 H); 4.29 (*d*, *J* = 15.2, 1 H); 4.31–4.40 (*m*, 1 H); 4.65 (*d*, *J* = 5.4, 1 H); 6.34 (*d*, *J* = 7.5, 2 H); 6.52 (*dd*, *J* = 7.5, 7.5, 2 H); 6.76 (*dd*, *J* = 7.5, 1 H); 7.38–7.48 (*m*, 3 H); 7.73–7.81 (*m*, 3 H); 7.88 (*s*, 1 H). ^{13}C-NMR (75 MHz, CD_3OD): 26.5; 31.9; 40.5; 43.7; 54.9; 55.7; 66.0; 73.1; 74.1; 125.6; 127.6; 127.9; 128.0; 128.2; 128.4; 129.0; 129.2; 129.4; 130.3; 134.6; 135.0; 138.9; 170.6 (one arom. signal missing due to overlap). HR-MALDI-MS: 481.1879 ($[M+H]^+$, $C_{26}H_{30}N_2O_5P^+$; calc. 481.1887).

*(±)-(3a*RS*,4*SR*,8a*RS*,8b*SR*)-Hexahydro-4-phenyl-2-(phenylmethyl)pyrrolo[3,4-*a*]pyrrolizine-1,3-(2*H*,4*H*)-dione* ((±)-*endo*-**28b**) *and (±)-(3a*RS*,4*RS*,8a*SR*,8b*SR*)-Hexahydro-4-phenyl-2-(phenylmethyl)-pyrrolo[3,4-*a*]pyrrolizine-1,3(2*H*,4*H*)-dione* ((±)-*exo*-**29b**). *General Procedure G* with **23** (9.36 g, 50.0 mmol, 1.00 equiv.), (−)-**18** (6.04 g, 52.5 mmol, 1.05 equiv.), *benzaldehyde* (**26**) (5.34 ml, 52.5 mmol, 1.05 equiv.), MeCN (100 ml) afforded, after purification by CC (SiO_2; CH_2Cl_2/Et_2O 97:3 → AcOEt), (±)-**28b** (2.80 g, 16%) and (±)-**29b** (3.80 g, 22%).

Data of (±)-endo-**28b**. White solid. M.p. 175–178°. IR (neat): 3034*w*, 2956*w*, 2879*w*, 2836*w*, 1774*w*, 1698*s*, 1495*w*, 1452*w*, 1418*m*, 1396*m*, 1338*m*, 1307*m*, 1174*s*, 1101*m*, 1091*m*, 1072*m*, 1045*w*, 1026*w*, 968*w*, 922*w*, 893*m*, 764*w*, 746*w*, 694*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.60–1.81 (*m*, 2 H); 2.00–2.17 (*m*, 2 H); 2.70 (*ddd*, *J* = 12.6, 8.4, 4.1, 1 H); 2.87 (*ddd*, *J* = 12.6, 8.9, 7.3, 1 H); 3.28 (*dd*, *J* = 8.1, 0.9, 1 H); 3.49 (*dd*, *J* = 8.1, 8.1, 1 H); 3.79 (*dd*, *J* = 9.6, 7.5, 1 H); 4.07 (*d*, *J* = 8.1, 1 H); 4.54 (*s*, 2 H); 7.20–7.34 (*m*, 10 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 23.4; 29.6; 42.4; 49.0; 50.6; 50.7; 67.8; 68.7; 127.6; 127.9; 128.0; 128.3; 128.7; 135.6; 137.7; 175.0; 177.8 (one arom. signal missing due to overlap). HR-MALDI-MS: 347.1749 ($[M+H]^+$, $C_{22}H_{23}N_2O_2^+$; calc. 347.1754). Anal. calc. for $C_{22}H_{22}N_2O_2$ (346.43): C 76.28, H 6.40, N 8.09; found: C 76.55, H 6.47, N 8.10.

Data of (±)-exo-**29b**. White solid. M.p. 72–74°. IR (neat): 3274*w*, 2967*w*, 2932*w*, 2869*w*, 2360*w*, 1769*w*, 1694*s*, 1644*m*, 1601*w*, 1585*w*, 1556*w*, 1494*m*, 1452*m*, 1427*m*, 1391*m*, 1341*s*, 1314*m*, 1205*m*, 1169*s*, 1150*m*, 1106*m*, 1095*m*, 1078*m*, 1054*m*, 1030*m*, 1020*m*, 963*w*, 913*m*, 896*m*, 861*w*, 821*w*, 758*m*, 748*s*, 703*s*, 644*m*, 628*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.53–1.78 (*m*, 3 H); 1.90–2.00 (*m*, 1 H); 2.39–2.48 (*m*, 1 H); 2.94 (*ddd*, *J* = 11.4, 8.3, 5.3, 1 H); 3.38 (*dd*, *J* = 9.0, 5.5, 1 H); 3.45–3.57 (*m*, 1 H); 3.92 (*dd*, *J* = 16.5, 7.3, 1 H); 4.15 (*d*, *J* = 5.5, 1 H); 4.66 (*s*, 2 H); 7.24–7.48 (*m*, 10 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 24.2; 26.2; 42.5; 48.1; 52.1; 55.5; 66.3; 69.5; 126.6; 127.2; 127.9; 128.4; 128.4; 128.9; 135.2; 141.9; 176.5; 177.6. HR-MALDI-MS: 347.1749 ($[M+H]^+$, $C_{22}H_{23}N_2O_2^+$; calc. 347.1754).

*(±)-Methyl (1*RS*,2*SR*,3*RS*,7a*S*R)-Hexahydro-3-phenyl-2-{[(phenylmethyl)amino]carbonyl}-1*H*-pyrrolizine-1-carboxylate* ((±)-**30b**). *General Procedure H* with (±)-*endo*-**28b** (1.67 g, 4.8 mmol, 1 equiv.), 0.05M NaOH in THF/H_2O 2:1 (193 ml), MeOH (115 ml), and $SOCl_2$ (1.75 ml, 24.0 mmol, 5 equiv.). The crude product was taken up in sat. aq. $NaHCO_3$ soln. (250 ml) and CH_2Cl_2 (250 ml). The layers were separated. The aq. phase was extracted with CH_2Cl_2 (2 × 200 ml). The comb. org. phases were

dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a solid, which, after purification by CC (SiO_2; CH_2Cl_2/MeOH/Et_3N 99:1:1), yielded (±)-**30b** (1.55g, 85%). White solid. M.p. 142–144°. IR (neat): 3274*m*, 3064*w*, 2957*w*, 2866*w*, 2360*w*, 1733*s*, 1668*m*, 1643*s*, 1555*m*, 1493*m*, 1451*m*, 1435*m*, 1418*m*, 1361*m*, 1282*m*, 1248*m*, 1186*m*, 1174*m*, 1132*m*, 1118*m*, 1094*m*, 1055*m*, 1026*m*, 928*w*, 897*w*, 867*w*, 826*w*, 748*m*, 724*s*, 694*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.60–1.71 (*m*, 1 H); 1.84–1.98 (*m*, 2 H); 2.08–2.19 (*m*, 1 H); 2.54 (*ddd*, *J* = 10.8, 6.3, 6.3, 1 H); 2.98–3.06 (*m*, 2 H); 3.55 (*dd*, *J* = 5.9, 5.9, 1 H); 3.71 (*s*, 3 H); 4.04 (*dd*, *J* = 15.0, 5.7, 1 H); 4.13–4.20 (*m*, 2 H); 4.29 (*dd*, *J* = 15.5, 6.8, 1 H); 6.34–6.40 (*m*, 1 H); 6.87–6.90 (*m*, 2 H); 7.18–7.36 (*m*, 8 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 26.3; 32.8; 43.2; 52.0; 52.9; 53.8; 57.8; 65.3; 71.6; 126.9; 126.9; 127.2; 127.6; 128.3; 128.5; 138.1; 139.3; 169.4; 171.7. HR-MALDI-MS: 379.2009 ($[M+H]^+$, $C_{23}H_{27}N_2O_3^+$; calc. 379.2016). Anal. calc. for $C_{23}H_{26}N_2O_3$ (378.47): C 72.99, H 6.92, N 7.40; found: C 72.81, H 7.10, N 7.34.

*(±)-(1*RS*,2*SR*,3*RS*,7a*SR*)-Hexahydro-1-(hydroxymethyl)-3-phenyl*-N-*(phenylmethyl)-1*H*-pyrrolizine-2-carboxamide* ((±)-**31b**). *General Procedure I* with (±)-**30b** (2.25 g, 5.94 mmol, 1 equiv.), 20 wt.-% DIBAL-H in toluene (14.7 ml, 17.8 mmol, 3 equiv.), and THF (90 ml) afforded, after purification by CC (SiO_2; Et_2O/MeOH/Et_3N 95:5:1), (±)-**31b** (780 mg, 37%). White solid. M.p. 154–157°. IR (neat): 3620*w*, 3251*m*, 3066*w*, 2915*m*, 2860*m*, 1638*s*, 1551*m*, 1493*m*, 1451*m*, 1414*m*, 1362*m*, 1284*m*, 1263*m*, 1187*w*, 1122*m*, 1026*m*, 1006*m*, 908*w*, 750*m*, 725*s*, 698*s*, 647*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.67–1.72 (*m*, 1 H); 1.80–2.20 (*m*, 3 H); 2.42–2.57 (*m*, 1 H); 2.60–2.63 (*m*, 1 H); 3.00–3.09 (*m*, 1 H); 3.12–3.42 (*m*, 2 H); 3.55–3.75 (*m*, 3 H); 4.10–4.20 (*m*, 2 H); 4.32 (*dd*, *J* = 14.7, 6.3, 1 H); 6.74–6.85 (*m*, 2 H); 7.19–7.32 (*m*, 8 H); 7.68 (br. *s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 26.0; 32.1; 43.0; 51.3; 53.7; 56.8; 62.7; 65.7; 69.7; 126.4; 126.6; 126.7; 127.1; 128.2; 128.4; 137.6; 139.4; 171.3. HR-MALDI-MS: 351.2062 ($[M+H]^+$, $C_{22}H_{27}N_2O_2^+$; calc. 351.2067). Anal. calc. for $C_{22}H_{26}N_2O_2$ (350.46): C 75.40, H 7.48, N 7.99; found: C 75.26, H 7.63, N 7.94.

*(±)-Bis(phenylmethyl) ((1*RS*,2*SR*,3*RS*,7a*SR*)-Hexahydro-3-phenyl-2-{[(phenylmethyl)amino]carbonyl}-1*H*-pyrrolizin-1-yl)methyl Phosphate* ((±)-**32b**). *General Procedure J* with (±)-**31b** (350 mg, 1.0 mmol, 1.0 equiv.), 0.45M 1*H*-tetrazole in MeCN (6.7 ml, 3.0 mmol, 3.0 equiv.), dibenzyl-*N*,*N*-diisopropylphosphoramidite (0.5 ml, 1.5 mmol, 1.5 equiv.), MeCN (10 ml), and 70% pure *m*CPBA (591 mg, 2.4 mmol, 2.4 equiv.) yielded, after purification by CC (SiO_2; AcOEt/hexane/Et_3N 90:10:1), (±)-**32b** (320 mg, 52%). White solid. M.p. 118–121°. IR (neat): 3244*w*, 3065*w*, 2957*w*, 2910*w*, 2865*w*, 2783*w*, 1666*w*, 1638*m*, 1555*m*, 1494*w*, 1452*m*, 1417*w*, 1379*w*, 1361*w*, 1330*w*, 1008*s* (br.), 892*m*, 877*m*, 822*w*, 736*s*, 726*s*, 694*s*, 606*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.61–1.68 (*m*, 1 H); 1.83–2.00 (*m*, 3 H); 2.35–2.53 (*m*, 2 H); 2.95–3.10 (*m*, 1 H); 3.27–3.40 (*m*, 1 H); 3.44–3.65 (*m*, 1 H); 3.93–4.14 (*m*, 4 H); 4.28 (*ddd*, *J* = 10.2, 6.9, ^3J(H,P) = 6.9, 1 H); 5.05 (*dd*, *J* = 8.1, 2.2, 4 H); 6.76–6.80 (*m*, 2 H); 7.15 (*dd*, *J* = 4.8, 1.8, 2 H); 7.21–7.30 (*m*, 7 H); 7.34–7.38 (*m*, 10 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 26.2; 32.5; 43.0; 48.1 (*d*, ^2J(C,P) = 7.3); 53.6; 56.7; 67.6; 67.7; 69.3 (*d*, ^2J(C,P) = 3.5); 70.6; 126.7; 126.9; 127.0; 127.4; 128.0; 128.3; 128.4; 128.5; 128.5; 135.8; 135.9; 138.0; 169.6. HR-MALDI-MS: 611.2657 ($[M+H]^+$, $C_{36}H_{40}N_2O_5P^+$; calc. 611.2669).

*(±)-((1*RS*,2*SR*,3*RS*,7a*SR*)-Hexahydro-3-phenyl-2-{[(phenylmethyl)amino]carbonyl}-1*H*-pyrrolizin-1-yl)methyl Dihydrogen Phosphate* ((±)-**22b**). *General Procedure K* with (±)-**32b** (270 mg, 0.44 mmol, 1 equiv.), cat. Pd/C (27 mg), and MeOH (20 ml) afforded (±)-**22b** (189 mg, 99%). White solid. M.p. 219–224° (dec.). IR (neat): 3259*w* (br.), 3061*w*, 1944*w*, 2798*w* (br.), 1640*s*, 1546*m*, 1496*w*, 1454*m*, 1400*w*, 1226*m*, 1190*m*, 1130*m*, 1091*m*, 1051*m*, 1024*m*, 998*m*, 939*m*, 913*m*, 855*m*, 733*m*, 697*s*. ^{1}H-NMR (300 MHz, CD_3OD): 2.11–2.34 (*m*, 4 H); 2.88–2.99 (*m*, 1 H); 3.12–3.18 (*m*, 1 H); 3.33–3.42 (*m*, 2 H); 3.61–3.64 (*m*, 1 H); 3.90–4.04 (*m*, 3 H); 4.43–4.54 (*m*, 2 H); 6.80–6.83 (*m*, 2 H); 7.14–7.16 (*m*, 3 H); 7.38–7.48 (*m*, 5 H). ^{13}C-NMR (75 MHz, CD_3OD): 25.9; 31.3; 40.1; 43.3; 54.2; 55.4; 64.2; 72.6; 73.5; 127.5; 127.8; 128.0; 128.9; 129.8; 130.0; 132.0; 138.7; 170.3. HR-MALDI-MS: 431.1724 ($[M+H]^+$, $C_{22}H_{28}N_2O_5P^+$; calc. 431.1730).

*(±)-(3a*RS*,4*SR*,8a*RS*,8b*SR*)-Hexahydro-4-(pentafluorophenyl)-2-(phenylmethyl)pyrrolo[3,4-*a*]pyrrolizine-1,3(2*H*,4*H*)-dione* ((±)-*endo*-**28c**) *and (±)-(3a*RS*,4*RS*,8a*SR*,8b*SR*)-Hexahydro-4-(pentafluorophenyl)-2-(phenylmethyl)pyrrolo[3,4-*a*]pyrrolizine-1,3(2*H*,4*H*)-dione* ((±)-*exo*-**29c**). *General Procedure G* with **23** (9.36 g, 50.0 mmol, 1.00 equiv.), (−)-**18** (6.04 g, 52.5 mmol, 1.05 equiv.), *pentafluorobenzaldehyde* (**27**) (10.00 g, 51.0 mmol, 1.02 equiv.), and MeCN (100 ml) yielded, after purification by CC (SiO_2; CH_2Cl_2/Et_2O 97:3), (±)-**28c** (7.03 g, 32%) and (±)-**29c** (9.60 g, 44%).

Data of (±)-endo-**28c**. White solid. M.p. 141–144°. IR (neat): 2955*w*, 2906*w*, 2883*w*, 1777*w*, 1698*s*, 1654*m*, 1524*m*, 1504*s*, 1450*w*, 1425*m*, 1399*m*, 1359*m*, 1340*m*, 1308*m*, 1246*w*, 1216*w*, 1177*m*, 1144*m*, 1102*m*, 1078*m*, 1042*m*, 1017*m*, 980*s*, 924*m*, 892*m*, 871*m*, 858*m*, 832*w*, 734*m*, 722*m*, 696*m*, 686*m*, 639*m*, 619*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.60–1.88 (*m*, 2 H); 1.99–2.22 (*m*, 2 H); 2.66 (*ddd*, *J* = 12.5, 8.0, 4.7, 1 H); 2.90 (*ddd*, *J* = 12.5, 8.6, 7.0, 1 H); 3.31 (*dd*, *J* = 8.4, 1.5, 1 H); 3.54 (*dd*, *J* = 8.4, 8.4, 1 H); 3.82 (*dd*, *J* = 8.4, 8.4, 1 H); 4.43 (*d*, *J* = 8.4, 1 H); 4.62 (*AB*, *J* = 10.2, 2 H); 7.24–7.37 (*m*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 23.6; 29.8; 42.9; 48.8; 49.3; 51.6; 60.5; 67.9; 128.0; 128.6; 128.9; 135.2; 175.4; 177.1. HR-MALDI-MS: 437.1276 ($[M+H]^+$, $C_{22}H_{18}F_5N_2O_2^+$; calc. 437.1283). Anal. calc. for $C_{22}H_{17}F_5N_2O_2$ (436.38): C 60.55, H 3.93, N 6.42; found: C 60.46, H 3.99, N 6.29.

Data of (±)-exo-**29c**. White solid. M.p. 76–79°. IR (neat): 2967*w* (br.), 2361*w*, 1774*w*, 1699*s*, 1654*w*, 1586*w*, 1522*m*, 1499*s*, 1456*w*, 1432*w*, 1393*m*, 1341*m*, 1305*m*, 1267*w*, 1235*w*, 1169*m*, 1120*m*, 1071*w*, 1027*m*, 996*m*, 972*m*, 947*w*, 926*w*, 896*m*, 824*w*, 736*m*, 699*m*, 625*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.50–1.69 (*m*, 3 H); 1.81–1.95 (*m*, 1 H); 2.32–2.41 (*m*, 1 H); 2.85–2.93 (*m*, 1 H); 3.62–3.71 (*m*, 2 H); 3.90–3.96 (*m*, 1 H); 4.63 (*d*, *J* = 3.6, 1 H); 4.65 (*AB*, *J* = 2.7, 2 H); 7.26–7.35 (*m*, 3 H); 7.38–7.42 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 24.7; 26.3; 42.8; 49.0; 53.0; 53.1; 60.5; 66.9; 128.1; 128.6; 129.0; 135.0; 176.1; 177.1. HR-MALDI-MS: 437.1275 ($[M+H]^+$, $C_{22}H_{18}F_5N_2O_2^+$; calc. 437.1283).

*(±)-Methyl (1*RS,*2*SR,*3*RS,*7a*SR*)-Hexahydro-3-(pentafluorophenyl)-2-{[(phenylmethyl)amino]carbonyl}-1*H*-pyrrolizine-1-carboxylate* ((±)-**30c**). *General Procedure H* with (±)-*endo*-**28c** (6.11 g, 14 mmol, 1 equiv.), 0.05M NaOH in THF/H_2O 2:1 (560 ml), MeOH (70 ml), and $SOCl_2$ (5.1 ml, 70 mmol, 5 equiv.). The crude product was taken up in sat. aq. $NaHCO_3$ soln. (500 ml) and CH_2Cl_2/i-PrOH 3:1 (500 ml). The layers were separated. The aq. phase was extracted with CH_2Cl_2/i-PrOH 3:1 (2 × 250 ml). The comb. org. phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a solid, which was purified by CC (SiO_2; CH_2Cl_2/MeOH/Et_3N 99.5:0.5:1) to afford (±)-**30c** (5.47 g, 83%). White solid. M.p. 192–194°. IR (neat): 3311*w*, 3091*w*, 2980*w*, 2950*w*, 2803*w*, 1725*s*, 1649*s*, 1557*m*, 1519*m*, 1495*s*, 1455*m*, 1435*m*, 1376*m*, 1302*m*, 1221*s*, 1208*s*, 1140*m*, 1121*m*, 1096*m*, 1030*m*, 1001*s*, 973*s*, 950*m*, 888*w*, 872*w*, 826*w*, 734*m*, 696*s*, 656*m*, 644*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.57–1.68 (*m*, 1 H); 1.84–2.04 (*m*, 2 H); 2.08–2.19 (*m*, 1 H); 2.49–2.57 (*m*, 1 H); 2.98–3.08 (*m*, 2 H); 3.64–3.70 (*m*, 1 H); 3.69 (*s*, 3 H); 4.16–4.37 (*m*, 4 H); 7.12–7.15 (*m*, 2 H); 7.23–7.29 (*m*, 3 H); 7.48–7.54 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 26.3; 32.2; 43.3; 51.8; 52.2; 53.3; 56.1; 64.9; 65.1; 127.3; 127.8; 128.4; 138.2; 168.9; 170.9. HR-MALDI-MS: 469.1548 ($[M+H]^+$, $C_{23}H_{22}F_5N_2O_3^+$; calc. 469.1545). Anal. calc. for $C_{23}H_{21}N_2O_3F_5$ (468.42): C 58.98, H 4.52, N 5.98; found: C 59.08, H 4.58, N 5.91.

*(±)-(1*RS,*2*SR,*3*RS,*7a*SR*)-Hexahydro-1-(hydroxymethyl)-3-(pentafluorophenyl)*-N-*(phenylmethyl)-1*H*-pyrrolizine-2-carboxamide* ((±)-**31c**). *General Procedure I* with (±)-**30c** (5.51 g, 11 mmol, 1 equiv.), 20 wt.-% DIBAL-H in toluene (27.3 ml, 33 mmol, 3 equiv.), and THF (180 ml) yielded, after purification by CC (SiO_2; Et_2O/MeOH/Et_3N 98:1:1), (±)-**31c** (1.40 g, 29%). Pale yellow solid. M.p. 144–147°. IR (neat): 3330*m* (br.), 3058*w*, 3028*w*, 2966*w*, 2941*w*, 2910*w*, 2872*w*, 2713*w*, 2628*w*, 2330*w*, 2222*w*, 1765*m*, 1731*m*, 1670*s*, 1652*s*, 1602*m*, 1558*m*, 1523*s*, 1495*s*, 1454*m*, 1431*w*, 1386*w*, 1328*w*, 1306*m*, 1287*w*, 1249*m*, 1223*m*, 1151*s*, 1114*m*, 1080*m*, 1030*s*, 1001*m*, 969*s*, 941*m*, 908*m*, 899*m*, 858*m*, 822*m*, 806*m*, 739*s*, 696*s*, 634*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.81–2.04 (*m*, 4 H); 2.46–2.58 (*m*, 2 H); 2.84 (*dd*, *J* = 10.7, 4.1, 1 H); 2.99 (*ddd*, *J* = 10.7, 6.5, 6.5, 1 H); 3.27 (*dd*, *J* = 14.7, 6.6, 1 H); 3.50–3.75 (*m*, 3 H); 4.21 (*dd*, *J* = 14.4, 5.7, 1 H); 4.28 (*d*, *J* = 3.9, 1 H); 4.49 (*dd*, *J* = 14.4, 6.6, 1 H); 7.11–7.15 (*m*, 2 H); 7.24–7.27 (*m*, 3 H); 8.46–8.54 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 26.3; 32.1; 43.3; 50.5; 52.8; 55.7; 62.8; 64.5; 65.2; 127.3; 127.7; 128.4; 138.0; 170.7. HR-MALDI-MS: 441.1590 ($[M+H]^+$, $C_{22}H_{22}F_5N_2O_2^+$; calc. 441.1596). Anal. calc. for $C_{22}H_{21}F_5N_2O_2$ (440.41): C 60.00, H 4.81, N 6.36; found: C 60.22, H 5.06, N 6.32.

*(±)-(1*RS,*2*SR,*3*RS,*7a*SR*)-Hexahydro-3-(pentafluorophenyl)-2-{[(phenylmethyl)amino]carbonyl}-1*H*-pyrrolizin-1-yl)methyl Bis(phenylmethyl) Phosphate* ((±)-**32c**). *General Procedure J* with (±)-**31c** (440 mg, 1.0 mmol, 1.0 equiv.), 0.45M 1*H*-tetrazole in MeCN (6.7 ml, 3.0 mmol, 3.0 equiv.), dibenzyl-*N*,*N*-diisopropylphosphoramidite (0.5 ml, 1.5 mmol, 1.5 equiv.), MeCN (10 ml), and 70% pure *m*CPBA (591 mg, 2.4 mmol, 2.4 equiv.) yielded, after purification by CC (SiO_2; AcOEt/hexane/Et_3N 50:50:1), (±)-**32c** (557 mg, 79%). White solid. M.p. 106–108°. IR (neat): 3302*w*, 3066*w*, 3033*w*, 2951*w*, 2896*w*, 2818*w*, 1647*m*, 1554*m*, 1519*m*, 1493*m*, 1455*m*, 1375*w*, 1338*w*, 1303*w*, 1272*m*, 1236*m*, 1215*m*, 1189*w*, 1154*w*, 1140*w*, 1120*w*, 1048*m*, 1032*m*, 1017*s*, 999*s*, 974*s*, 900*m*, 882*m*, 816*w*, 791*w*, 770*w*, 736*s*, 695*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.52–1.61 (*m*, 1 H); 1.79–2.01 (*m*, 3 H); 2.29–2.39 (*m*, 1 H); 2.45–2.53 (*m*,

1 H); 2.93–3.01 (*m*, 1 H); 3.35–3.48 (*m*, 2 H); 3.89 (*ddd*, *J* = 10.3, 8.7, 7.5, 1 H); 4.13 (*dd*, *J* = 14.4, 5.6, 1 H); 4.18–4.26 (*m*, 2 H); 4.35 (*dd*, *J* = 14.4, 6.6, 1 H); 4.99–5.11 (*m*, 4 H); 7.06–7.10 (*m*, 2 H); 7.20–7.25 (*m*, 3 H); 7.33–7.38 (*m*, 10 H); 8.07–8.11 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 26.5; 32.3; 43.2; 47.1 (*d*, ^2J(C,P) = 7.3); 52.9; 55.3; 64.8; 66.9; 67.5; 69.4 (*d*, ^2J(C,P) = 5.4); 127.3; 127.8; 128.1; 128.1; 128.5; 128.6; 135.8 (*d*, ^3J(C,P) = 6.7); 138.3; 169.0. HR-MALDI-MS: 701.2185 ($[M+H]^+$, $C_{36}H_{35}F_5N_2O_2P^+$; calc. 701.2198). Anal. calc. for $C_{36}H_{34}F_5N_2O_2P$ (700.64): C 61.71, H 4.89, N 4.00; found: C 61.59, H 4.95, N 4.05.

*(±)-(1*RS*,2*SR*,3*RS*,7a*SR*)-Hexahydro-3-(pentafluorophenyl)-2-{[(phenylmethyl)amino]carbonyl}-1*H*-pyrrolizin-1-yl)methyl Dihydrogen Phosphate* ((±)-**22c**). *General Procedure K* with (±)-**32c** (270 mg, 0.44 mmol, 1 equiv.), cat. Pd/C (27 mg), and MeOH (20 ml) afforded (±)-**22c** (362 mg, 98%). White solid. M.p. 134–150° (dec.). IR (neat): 3227*w* (br.), 3056*w*, 3028*w*, 2950*w*, 2903*w*, 1759*w*, 1722*w*, 1658*m*, 1652*m*, 1585*w*, 1567*w*, 1525*m*, 1496*s*, 1455*w*, 1429*w*, 1359*w*, 1299*w*, 1204*m*, 1165*m*, 1153*m*, 1038*s*, 1010*m*, 976*s*, 949*m*, 921*s*, 829*w*, 818*w*, 771*w*, 750*m*, 734*m*, 698*m*, 634*w*, 613*w*. ^{1}H-NMR (300 MHz, CD_3OD): 2.04–2.32 (*m*, 4 H); 2.87–2.97 (*m*, 1 H); 3.44–3.53 (*m*, 1 H); 3.79 (*dd*, *J* = 5.4, 5.4, 1 H); 3.88–3.97 (*m*, 2 H); 3.90 (*d*, *J* = 14.5, 1 H); 4.34–4.42 (*m*, 2 H); 4.47 (*d*, *J* = 14.7, 1 H); 5.02–5.03 (*m*, 1 H); 6.98–7.01 (*m*, 2 H); 7.18–7.20 (*m*, 3 H). ^{13}C-NMR (75 MHz, CD_3OD): 26.4; 31.6; 43.8; 47.9; 54.1; 55.1; 64.8; 66.6; 73.1; 128.0; 128.5; 129.1; 139.8; 170.4. HR-MALDI-MS: 521.1251 ($[M+H]^+$, $C_{22}H_{23}F_5N_2O_5P^+$; calc. 521.1259).

*(±)-(3aRS,4SR,8aRS,8bSR)-2-[(1,3-Benzodioxol-5-yl)methyl]hexahydro-4-(naphthalen-2-yl)pyrrolo[3,4-*a*]pyrrolizine-1,3(2*H*,4*H*)-dione* ((±)-**28d**) *and (3a*RS*,4*RS*,8a*SR*,8b*SR*)-2-[(1,3-Benzodioxol-5-yl)methyl]hexahydro-4-(naphthalen-2-yl)pyrrolo[3,4-*a*]pyrrolizine-1,3(2*H*,4*H*)-dione* ((±)-**29d**). *General Procedure G* with **24** (11.56 g, 50.0 mmol, 1.00 equiv.), (–)-**18** (6.04 g, 52.5 mmol, 1.05 equiv.), **25** (8.20 g, 52.5 mmol, 1.05 equiv.), and MeCN (100 ml) afforded, after purification by CC (SiO_2; CH_2Cl_2/Et_2O 95 : 5 → 1 : 1), (±)-**28d** (7.04 g, 32%) and (±)-**29d** (9.60 g, 44%).

*Data of (±)-*endo-**28d**. White-off solid. M.p. 173–175°. IR (neat): 3050*w*, 2954*w*, 2903*w*, 1773*w*, 1698*s*, 1609*w*, 1499*m*, 1443*m*, 1426*m*, 1401*m*, 1374*m*, 1340*m*, 1301*w*, 1274*w*, 1248*s*, 1210*m*, 1172*m*, 1124*w*, 1096*m*, 1034*s*, 971*w*, 956*w*, 926*m*, 897*m*, 866*m*, 828*m*, 808*m*, 776*m*, 752*m*, 740*m*, 649*m*, 624*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.65–1.87 (*m*, 2 H); 1.98–2.23 (*m*, 2 H); 2.74 (*ddd*, *J* = 12.5, 8.3, 4.0, 1 H); 2.92 (*ddd*, *J* = 12.5, 8.0, 8.0, 1 H); 3.31 (*d*, *J* = 8.3, 1 H); 3.58 (*dd*, *J* = 8.3, 8.3, 1 H); 3.84 (*dd*, *J* = 9.3, 7.5, 1 H); 4.23 (*d*, *J* = 8.3, 1 H); 4.98 (*AB*, *J* = 5.0, 2 H); 5.94 (*s*, 2 H); 6.67–6.82 (*m*, 3 H); 7.31–7.34 (*m*, 1 H); 7.43–7.46 (*m*, 2 H); 7.75–7.83 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 23.5; 29.8; 42.3; 49.2; 50.7; 50.9; 67.9; 69.0; 101.0; 108.1; 109.5; 122.5; 125.7; 125.8; 126.3; 126.7; 127.5; 127.7; 128.0; 129.4; 133.1; 133.2; 135.4; 147.0; 147.5; 175.1; 177.9. HR-MALDI-MS: 441.1801 ($[M+H]^+$, $C_{27}H_{25}N_2O_4^+$; calc. 441.1809). Anal. calc. for $C_{27}H_{24}N_2O_4$ (440.5): C 73.62, H 5.49, N 6.36; found: C 73.65, H 5.68, N 6.43.

*Data of (±)-*exo-**29d**. White solid. M.p. 110–111°. IR (neat): 2941*w*, 2873*w*, 1774*w*, 1698*s*, 1631*w*, 1601*w*, 1501*m*, 1488*m*, 1444*m*, 1431*m*, 1393*m*, 1370*m*, 1327*m*, 1272*w*, 1246*s*, 1167*m*, 1121*m*, 1101*m*, 957*w*, 920*m*, 882*m*, 864*m*, 826*m*, 786*m*, 749*m*, 662*m*, 636*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.57–1.81 (*m*, 3 H); 1.94–2.05 (*m*, 1 H); 2.52 (*ddd*, *J* = 11.2, 7.2, 7.2, 1 H); 3.00 (*ddd*, *J* = 11.2, 6.9, 6.9, 1 H); 3.42 (*dd*, *J* = 9.0, 5.4, 1 H); 3.55 (*dd*, *J* = 9.0, 9.0, 1 H); 3.93–4.01 (*m*, 1 H); 4.29 (*d*, *J* = 5.4, 1 H); 4.57 (*s*, 2 H); 5.94 (*s*, 2 H); 6.76 (*d*, *J* = 7.8, 1 H); 6.92–6.95 (*m*, 2 H); 7.44–7.50 (*m*, 2 H); 7.59–7.62 (*m*, 1 H); 7.81–7.89 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 24.5; 26.5; 42.5; 48.2; 52.3; 55.7; 66.7; 70.0; 101.3; 108.5; 109.8; 123.0; 125.3; 125.5; 126.1; 126.4; 127.8; 128.2; 128.8; 129.4; 133.1; 133.5; 139.7; 147.6; 147.9; 177.0; 178.1. HR-MALDI-MS: 441.1800 ($[M+H]^+$, $C_{27}H_{25}N_2O_4^+$; calc. 441.1809). Anal. calc. for $C_{27}H_{24}N_2O_4$ (440.50): C 73.62, H 5.49, N 6.36; found: C 73.63, H 5.56, N 6.37.

*(±)-Methyl (1*RS*,2*SR*,3*RS*,7a*SR*)-2-({[(1,3-Benzodioxol-5-yl)methyl]amino}carbonyl)hexahydro-3-(naphthalen-2-yl)-1*H*-pyrrolizine-1-carboxylate* ((±)-**30d**). *General Procedure H* with (±)-*endo*-**28d** (4.40 g, 10 mmol, 1 equiv.), 0.05M NaOH in THF/H_2O 2 : 1 (400 ml), MeOH (230 ml), and $SOCl_2$ (3.63 ml, 50 mmol, 5 equiv.). The crude product was taken up in sat. aq. $NaHCO_3$ soln. (400 ml), H_2O (100 ml), and CH_2Cl_2 (500 ml). The layers were separated. The aq. phase was extracted with CH_2Cl_2 (2 × 500 ml). The comb. org. phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a solid, which was purified by CC (SiO_2; CH_2Cl_2/MeOH/Et_3N 99 : 1 : 1) to afford (±)-**30d** (3.17 g, 67%). White-off solid. M.p. 101–103°. IR (neat): 3337*w*, 3053*w*, 2951*w*, 2871*w*, 1720*m*, 1644*m*, 1566*w*, 1504*m*, 1491*m*, 1439*m*, 1398*w*, 1371*w*, 1330*w*, 1238*s*, 1217*s*, 1188*m*, 1141*w*, 1117*w*, 1092*w*, 1018*s*, 958*w*, 931*m*, 916*m*, 857*m*, 809*m*, 734*m*, 644*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.64–1.74 (*m*, 1 H); 1.90–1.99 (*m*, 2

H); 2.18 (*ddd*, *J* = 19.3, 6.9, 6.9, 1 H); 2.59 (*ddd*, *J* = 11.2, 5.9, 5.9, 1 H); 3.04–3.15 (*m*, 2 H); 3.61–3.65 (*m*, 1 H); 3.73 (*s*, 3 H); 3.80 (*dd*, *J* = 14.6, 5.3, 1 H); 4.01 (*dd*, *J* = 14.6, 6.2, 1 H); 4.32–4.38 (*m*, 2 H); 5.82 (*dd*, *J* = 5.6, 1.6, 2 H); 6.01–6.03 (*m*, 1 H); 6.24–6.30 (*m*, 3 H); 7.37–7.40 (*m*, 1 H); 7.44–7.49 (*m*, 2 H); 7.72–7.82 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 26.4; 33.0; 43.1; 52.1; 53.0; 54.0; 57.7; 65.5; 72.0; 100.8; 107.8; 108.2; 120.7; 125.1; 125.6; 125.7; 126.1; 127.7; 127.9; 128.2; 131.7; 132.9; 133.4; 136.8; 146.4; 147.4; 169.3; 171.7. HR-MALDI-MS: 473.2063 ($[M+H]^+$, $C_{28}H_{29}N_2O_5^+$; calc. 473.2071).

*(±)-(1*RS*,2*SR*,3*RS*,7a*SR*)*-N-*[(1,3-Benzodioxol-5-yl)methyl]hexahydro-1-(hydroxymethyl)-3-(naphthalen-2-yl)-1*H*-pyrrolizine-2-carboxamide* ((±)-**31d**). *General Procedure I* with (±)-**30d** (2.36 g, 5 mmol, 1 equiv.), 20 wt.-% DIBAL-H in toluene (12.35 ml, 15 mmol, 3 equiv.), and THF (75 ml) afforded, after purification by CC (SiO_2; Et_2O/MeOH/Et_3N 95 : 5 : 1), (±)-**31d** (620 mg, 28%). White solid. M.p. 149–150°. IR (neat): 3236*w*, 3055*w*, 2890*w*, 1638*m*, 1550*m*, 1502*m*, 1490*m*, 1442*m*, 1404*w*, 1368*w*, 1318*w*, 1250*s*, 1209*m*, 1101*m*, 1082*m*, 1037*s*, 926*m*, 859*m*, 806*m*, 770*m*, 742*m*, 653*m*, 617*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.66–1.74 (*m*, 1 H); 1.86–2.06 (*m*, 3 H); 2.51–2.62 (*m*, 1 H); 2.65–2.73 (*m*, 1 H); 3.10–3.20 (*m*, 2 H); 3.34–3.42 (*m*, 1 H); 3.53–3.62 (*m*, 1 H); 3.70–3.79 (*m*, 2 H); 3.85 (*dd*, *J* = 14.6, 4.7, 1 H); 4.23–4.30 (*m*, 2 H); 5.79 (*dd*, *J* = 10.6, 1.6, 2 H); 6.00–6.03 (*m*, 1 H); 6.17–6.21 (*m*, 2 H); 7.35–7.38 (*m*, 1 H); 7.42–7.49 (*m*, 2 H); 7.55–7.64 (*m*, 1 H); 7.66–7.69 (*m*, 1 H); 7.74–7.82 (*m*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 26.1; 32.2; 42.9; 51.5; 54.0; 56.6; 62.9; 70.1; 96.0; 96.1; 100.7; 107.6; 107.8; 120.3; 124.7; 124.9; 125.5; 126.0; 127.5; 127.7; 128.3; 131.3; 132.4; 133.1; 146.2; 147.2; 171.2. HR-MALDI-MS: 445.2116 ($[M+H]^+$, $C_{27}H_{29}N_2O_4^+$; calc. 445.2122).

*(±)-[(1*RS*,2*SR*,3*RS*,7a*SR*)-2-({[(1,3-Benzodioxol-5-yl)methyl]amino}carbonyl)hexahydro-3-(naphthalen-2-yl)-1*H*-pyrrolizin-1-yl]methyl Bis(phenylmethyl) Phosphate* ((±)-**32d**). *General Procedure J* with (±)-**31d** (445 mg, 1.0 mmol, 1.0 equiv.), 0.45M 1*H*-tetrazole in MeCN (6.7 ml, 3.0 mmol, 3.0 equiv.), dibenzyl-*N*,*N*-diisopropylphosphoramidite (0.5 ml, 1.5 mmol, 1.5 equiv.), MeCN (10 ml), and 70% pure *m*CPBA (591 mg, 2.4 mmol, 2.4 equiv.) yielded, after purification by CC (SiO_2; AcOEt/hexane/Et_3N 90 : 10 : 1), (±)-**32d** (611 mg, 87%). White solid. M.p. 97–99°. IR (neat): 3270*w*, 3061*w*, 2903*w*, 2863*w*, 1643*m*, 1546*w*, 1489*m*, 1440*w*, 1380*w*, 1326*w*, 1261*m*, 1234*m*, 1184*w*, 1126*w*, 1008*s*, 998*s*, 941*m*, 917*m*, 868*m*, 810*m*, 739*s*, 696*s*, 644*w*. ^{1}H-NMR ($CDCl_3$): 1.63–1.69 (*m*, 1 H); 1.88–2.03 (*m*, 3 H); 2.41–2.51 (*m*, 1 H); 2.58–2.61 (*m*, 1 H); 3.04–3.16 (*m*, 1 H); 3.37–3.41 (*m*, 1 H); 3.56–3.64 (*m*, 1 H); 3.73–3.79 (*m*, 1 H); 3.99 (*ddd*, *J* = 10.3, 7.8, 7.8, 1 H); 4.06–4.13 (*m*, 1 H); 4.23–4.24 (*m*, 1 H); 4.30 (*ddd*, *J* = 10.3, 6.8, 6.8, 1 H); 5.04–5.08 (*m*, 4 H); 5.77 (*dd*, *J* = 9.6, 1.6, 2 H); 5.98–6.01 (*m*, 1 H); 6.17–6.20 (*m*, 2 H); 7.11–7.18 (*m*, 1 H); 7.31–7.39 (*m*, 11 H); 7.41–7.48 (*m*, 2 H); 7.66–7.81 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 26.2; 32.6; 42.7; 48.1 (*d*, ^2J(C,P) = 7.3); 53.7; 56.5; 67.5; 67.7; 69.3 (*d*, ^2J(C,P) = 4.9); 70.8; 100.6; 107.6; 107.9; 120.4; 124.9; 125.2; 125.5; 125.9; 127.5; 127.8; 127.9; 128.1; 128.5; 128.5; 131.6; 132.5; 133.1; 135.7; 135.8; 146.2; 147.2; 169.3. HR-MALDI-MS: 705.2710 ($[M+H]^+$, $C_{41}H_{42}N_2O_7P^+$; calc. 705.2724). Anal. calc. for $C_{41}H_{41}N_2O_7P$ (704.76): C 69.88, H 5.86, N 3.97; found: C 69.62, H 6.03, 3.92.

*(±)-[(1*RS*,2*SR*,3*RS*,7a*SR*)-2-({[(1,3-Benzodioxol-5-yl)methyl]amino}carbonyl)hexahydro-3-(naphthalen-2-yl)-1*H*-pyrrolizin-1-yl]methyl Dihydrogen Phosphate* ((±)-**22d**). *General Procedure K* with (±)-**32d** (572 mg, 0.81 mmol, 1 equiv.), cat. Pd/C (57 mg), and MeOH (35 ml) afforded (±)-**22d** (412 mg, 97%). White solid. M.p. 189–190° (dec.). IR (neat): 3258*w*, 2883*w*, 1790*w*, 1756*w*, 1700*w*, 1653*w*, 1642*w*, 1576*w*, 1528*w*, 1501*w*, 1489*m*, 1444*w*, 1399*w*, 1329*w*, 1234*m*, 1155*m*, 1129*m*, 1097*m*, 1037*s*, 915*s*, 861*m*, 807*m*, 794*m*, 770*m*, 742*m*, 665*m*. ^{1}H-NMR (300 MHz, CD_3OD): 2.12–2.35 (*m*, 4 H); 2.92–2.99 (*m*, 1 H); 3.14–3.20 (*m*, 1 H); 3.34–3.44 (*m*, 1 H); 3.67–3.70 (*m*, 1 H); 3.74 (*d*, *J* = 14.9, 1 H); 3.95–4.02 (*m*, 2 H); 4.32 (*d*, *J* = 14.9, 1 H); 4.46–4.55 (*m*, 1 H); 4.98 (*d*, *J* = 4.7, 1 H); 5.74 (*s*, 2 H); 5.97 (*dd*, *J* = 8.1, 1.2, 1 H); 6.07 (*d*, *J* = 8.1, 1 H); 6.23 (*d*, *J* = 1.2, 1 H); 7.48–7.59 (*m*, 3 H); 7.81–7.94 (*m*, 4 H). ^{13}C-NMR (75 MHz, CD_3OD): 26.4; 32.0; 43.5; 54.8; 56.0; 64.8; 72.7; 74.1; 102.1; 108.7; 108.8; 121.4; 125.8; 127.5; 127.9; 128.9; 129.2; 130.0; 133.1; 134.6; 134.8; 147.8; 148.8; 171.0 (one aliph. signal missing due to solvent overlap; two arom. signals missing due to overlap). HR-MALDI-MS: 525.1782 ($[M+H]^+$, $C_{27}H_{30}N_2O_7P^+$; calc. 525.1785).

*(−)-(3a*R*,4*S*,7*R*,8a*R*,8b*S*)-Hexahydro-7-hydroxy-4-(naphthalen-2-yl)-2-(phenylmethyl)pyrrolo[3,4-*a*]pyrrolizine-1,3(2*H*,4*H*)-dione* ((−)-*endo*-**35**). *General Procedure G* with ((−)-**23** (9.36 g, 50.0 mmol, 1.00 equiv.), *(2*S*,4*R*)-hydroxyproline* ((−)-**34**) (6.88 g, 52.5 mmol, 1.05 equiv.), **25** (8.20 g, 52.5 mmol, 1.0 equiv.), and DMF (100 ml) yielded, after purification by CC (SiO_2; hexane/AcOEt 3 : 7 → AcOEt),

followed by recrystallization from MeOH, (−)-**35** (3.51 g, 17%). White crystals. M.p. 188–191°. $[\alpha]_D^{20} = -81.1$ ($c = 1.00$, $CHCl_3$). IR (neat): 3512*m*, 3052*w*, 2930*w*, 2895*w*, 1772*w*, 1685*s*, 1602*w*, 1511*w*, 1498*w*, 1453*w*, 1428*m*, 1403*m*, 1360*m*, 1341*m*, 1297*w*, 1286*w*, 1240*w*, 1202*w*, 1175*m*, 1155*m*, 1126*w*, 1112*w*, 1087*m*, 1059*m*, 1044*m*, 1027*m*, 1002*w*, 969*m*, 953*m*, 931*m*, 907*w*, 885*w*, 820*s*, 811*m*, 747*m*, 726*s*, 694*m*, 659*m*, 647*m*, 635*m*, 616*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.81–1.95 (*m*, 2 H); 2.58–2.67 (*m*, 1 H); 2.78 (*d*, $J = 13.7$, 1 H); 3.05–3.12 (*m*, 1 H); 3.40 (*d*, $J = 8.5$, 1 H); 3.70 (*dd*, $J = 8.5$, 8.5, 1 H); 3.89–3.95 (*m*, 1 H); 4.51 (*AB*, $J = 4.0$, 2 H); 4.63–4.65 (*m*, 1 H); 4.93 (*d*, $J = 8.5$, 1 H); 7.25–7.32 (*m*, 6 H); 7.44 (*ddd*, $J = 9.7$, 3.4, 3.4, 2 H); 7.70–7.74 (*m*, 3 H); 7.78–7.82 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 40.8; 42.6; 49.6; 50.6; 60.3; 67.4; 69.9; 75.0; 125.7; 125.8; 126.3; 126.8; 127.5; 127.7; 128.0; 128.4; 128.8; 133.1; 133.1; 135.3; 135.5; 175.0; 177.8 (one arom. signal missing due to overlap). HR-MALDI-MS: 435.1672 ($[M+Na]^+$, $C_{26}H_{24}N_2NaO_3^+$; calc. 435.1679). Anal. calc. for $C_{26}H_{24}N_2O_3$ (412.49): C 75.71, H 5.86, N 6.79; found: C 75.59, H 5.94, N 6.99.

*(−)-*S*-Methyl* O*-[(3a*R*,4*S*,7*R*,8a*R*,8b*S*)-Decahydro-4-(naphthalen-2-yl)-1,3-dioxo-2-(phenylmethyl)-pyrrolo[3,4-*a*]pyrrolizin-7-yl] Dithiocarbonate*. To an ice-cooled suspension of (−)-**35** (2.15 g, 5.21 mmol, 1.0 equiv.) in THF (15 ml), 60% NaH in mineral oil (313 mg, 7.82 mmol, 1.5 equiv.) was added. The mixture was stirred at 20° for 3 h, then cooled to 0°. CS_2 (2.61 ml, 35.52 mmol, 8.3 equiv.) was added. The yellow mixture was stirred at 20° for 1 h. MeI (0.97 ml, 15.63 mmol, 3 equiv.) was added. The mixture was stirred at 20° for 17 h. H_2O (80 ml) and ice were added. The layers were separated. The aq. phase was extracted with AcOEt (3 × 80 ml). The combined org. phases were washed with H_2O (1 × 80 ml) and sat. aq. NaCl soln. (1 × 80 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by CC (SiO_2; hexane/AcOEt 7:3) to yield the title compound (190 mg, 84%). White solid. M.p. 89–93°. $[\alpha]_D^{20} = -175.6$ ($c = 1.00$, $CHCl_3$). IR (neat): 3044*w*, 2922*w*, 2287*w*, 2052*w*, 1772*w*, 1699*s*, 1496*w*, 1429*m*, 1398*m*, 1339*m*, 1283*w*, 1209*m*, 1173*m*, 1051*s*, 957*m*, 895*m*, 860*m*, 817*m*, 745*m*, 723*m*, 699*m*, 659*m*, 622*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.10 (*ddd*, $J = 14.7$, 10.5, 4.3, 1 H); 2.53 (*s*, 3 H); 2.83 (*ddd*, $J = 14.7$, 7.5, 7.5, 1 H); 3.05 (*d*, $J = 15.0$, 1 H); 3.23 (*dd*, $J = 15.0$, 6.2, 1 H); 3.40 (*d*, $J = 8.6$, 1 H); 3.69 (*dd*, $J = 8.6$, 8.6, 1 H); 3.97 (*dd*, $J = 10.5$, 7.5, 1 H); 4.54 (*AB*, $J = 2.1$, 2 H); 4.64 (*d*, $J = 8.6$, 1 H); 5.95–6.01 (*m*, 1 H); 7.26–7.29 (*m*, 6 H); 7.44 (*d*, $J = 3.3$, 1 H); 7.46 (*d*, $J = 3.3$, 1 H); 7.70–7.74 (*m*, 3 H); 7.81 (*dd*, $J = 6.0$, 3.6, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 19.3; 37.5; 42.6; 49.3; 50.4; 57.1; 67.1; 69.2; 86.7; 125.9; 126.3; 127.0; 127.8; 127.9; 128.1; 128.6; 128.9; 133.3; 133.3; 134.7; 135.6; 174.8; 177.5; 214.9 (two arom. signals missing due to overlap). HR-MALDI-MS: 503.1451 ($[M+H]^+$, $C_{28}H_{27}N_2O_3S_2^+$; calc. 503.1458). Anal. calc. for $C_{28}H_{26}N_2O_3S_2$ (502.66): C 66.91, H 5.21, N 5.57; found: C 66.63, H 5.20, N 5.44.

*(−)-(3a*R*,4*S*,8a*R*,8b*S*)-Hexahydro-4-(naphthalen-2-yl)-2-(phenylmethyl)pyrrolo[3,4-*a*]pyrrolizine-1,3(2*H*,4*H*)-dione* ((−)-**28a**). To a soln. of the dithiocarbonate described above (2.422 g, 4.82 mmol, 1 equiv.) and a cat. amount of AIBN in toluene (50 ml), Bu_3SnH (1.94 ml, 7.23 mmol, 1.5 equiv.) was added. The mixture was heated to reflux for 1 h, then concentrated *in vacuo*. The crude product was purified by CC (SiO_2; CH_2Cl_2 → CH_2Cl_2/Et_2O 98:2) to afford (−)-**28a** (1.68 g, 88%). White solid. M.p. 151–154°. $[\alpha]_D^{20} = -196.8$ ($c = 1.03$, $CHCl_3$). IR (neat): 3049*w*, 2946*w*, 2863*w*, 1771*w*, 1699*s*, 1601*w*, 1507*w*, 1495*w*, 1455*w*, 1429*m*, 1397*m*, 1343*m*, 1315*m*, 1283*m*, 1207*m*, 1171*m*, 1125*m*, 1073*m*, 1050*m*, 957*m*, 925*m*, 895*m*, 860*m*, 817*m*, 745*m*, 724*m*, 698*m*, 657*m*, 630*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.64–1.86 (*m*, 2 H); 1.97–2.22 (*m*, 2 H); 2.73 (*ddd*, $J = 12.6$, 8.5, 4.1, 1 H); 2.91 (*ddd*, $J = 12.6$, 8.8, 7.1, 1 H); 3.32 (*d*, $J = 8.1$, 1 H); 3.59 (*dd*, $J = 8.7$, 8.1, 1 H); 3.83 (*dd*, $J = 10.0$, 7.1, 1 H); 4.22 (*d*, $J = 8.7$, 1 H); 4.52 (*AB*, $J = 3.6$, 2 H); 7.24–7.33 (*m*, 6 H); 7.41–7.46 (*m*, 2 H); 7.71–7.73 (*m*, 3 H); 7.77–7.82 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 23.4; 29.6; 42.4; 49.1; 50.6; 50.8; 67.9; 69.0; 125.7; 125.8; 126.4; 126.7; 127.6; 127.8; 128.0; 128.5; 128.8; 133.2; 133.3; 135.4; 135.7; 175.2; 178.1 (one arom. signal missing due to overlap). HR-MALDI-MS: 397.1906 ($[M+H]^+$, $C_{26}H_{25}N_2O_2^+$; calc. 397.1911). Anal. calc. for $C_{26}H_{24}N_2O_2$ (396.49): C 78.76, H 6.10, N 7.07; found: C 78.48, H 5.93, N 6.89.

*(−)-Methyl (1*S*,2*R*,3*S*,7a*R*)-Hexahydro-3-(naphthalen-2-yl)-2-{[(phenylmethyl)amino]carbonyl}-1*H*-pyrrolizine-1-carboxylate* ((−)-**30a**). *General Procedure H* with (−)-*endo*-**28a** (1.68 g, 4.24 mmol, 1 equiv.), 0.05M NaOH in THF/H_2O 2:1 (170 ml), MeOH (100 ml), and $SOCl_2$ (1.54 ml, 21.2 mmol, 5 equiv.). The crude product was taken up in sat. aq. $NaHCO_3$ soln. (100 ml), H_2O (25 ml), and AcOEt (100 ml). The layers were separated. The aq. phase was extracted with AcOEt (3 × 100 ml). The comb.

org. phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a solid, which was purified by CC (SiO_2; CH_2Cl_2/MeOH/Et_3N 98:2:1) to afford (−)-**30a** (1.51 g, 83%). White solid. $[\alpha]_D^{20} = -97.2$ ($c = 1.00$, MeOH).

(−)-(1S,2R,3S,7aR)-Hexahydro-1-(hydroxymethyl)-3-(naphthalen-2-yl)-N-*(phenylmethyl)-1*H-*pyrrolizine-2-carboxamide* ((−)-**31a**). *General Procedure I* with (−)-**30a** (1.49 g, 3.49 mmol, 1 equiv.), 20 wt.-% DIBAL-H in toluene (8.61 ml, 10.46 mmol, 3 equiv.), and THF (50 ml) afforded, after purification by CC (SiO_2; Et_2O/MeOH/Et_3N 95:5:1), (−)-**31a** (475 mg, 34%). White solid. $[\alpha]_D^{20} = -86.0$ ($c = 1.00$, $CHCl_3$).

*(−)-[(1S,2R,3S,7aR)-Hexahydro-3-(naphthalen-2-yl)-2-{[(phenylmethyl)amino]carbonyl}-1*H-*pyrrolizin-1-yl]methyl Bis(phenylmethyl) Phosphate* ((−)-**32a**). *General Procedure J* with (−)-**31a** (470 mg, 1.17 mmol, 1.0 equiv.), 0.45M 1*H*-tetrazole in MeCN (7.8 ml, 3.52 mmol, 3.0 equiv.), dibenzyl-*N*,*N*-diisopropylphosphoramidite (0.58 ml, 1.76 mmol, 1.5 equiv.), MeCN (15 ml), and 70% pure *m*CPBA (693 mg, 2.4 mmol, 2.4 equiv.) yielded, after purification by CC (SiO_2; AcOEt/hexane/Et_3N 9:1:0.1), (−)-**32a** (718 mg, 93%). Pale yellow solid. $[\alpha]_D^{20} = -43.1$ ($c = 1.00$, $CHCl_3$).

*(+)-[(1S,2R,3S,7aR)-Hexahydro-3-(naphthalen-2-yl)-2-{[(phenylmethyl)amino]carbonyl}-1*H-*pyrrolizin-1-yl]methyl Dihydrogen Phosphate* ((+)-**22a**). *General Procedure K* with (−)-**32a** (330 mg, 0.5 mmol, 1 equiv.), cat. Pd/C (35 mg), and MeOH (15 ml) gave (+)-**22a** (239 mg, 99%). White solid. $[\alpha]_D^{20} = +47.9$ ($c = 1.00$, MeOH).

(−)-(3aR,4S,7S,8aR,8bS)-7-Fluorohexahydro-4-(naphthalen-2-yl)-2-(phenylmethyl)pyrrolo[3,4-a]-pyrrolizine-1,3(2H,4H)-dione ((−)-**36b**). To a soln. of (−)-**35** (2.98 g, 7.23 mmol, 1 equiv.) in CH_2Cl_2 (150 ml) cooled to −78°, DAST (3.67 g, 21.7 mmol, 3 equiv.) was slowly added. The mixture was stirred at −78° for 15 min and further at 20° for 3 h. MeOH (60 ml) was carefully added to the orange soln. The mixture was stirred at 20° for 15 min, then poured into a sat. aq. $NaHCO_3$ soln. (200 ml) and ice, and stirred at 20° for 30 min. The layers were separated. The aq. phase was extracted with CH_2Cl_2 (2×200 ml). The comb. org. phases were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified by CC (SiO_2; AcOEt/hexane 1:1) to yield (−)-**36b** (2.66 g, 89%). Pale yellow solid. M.p. 136–139°. $[\alpha]_D^{20} = -172.4$ ($c = 1.02$, $CHCl_3$). IR (neat): 3052*w*, 2970*w*, 2933*w*, 1775*w*, 1702*s*, 1699*s*, 1683*m*, 1568*w*, 1511*w*, 1456*w*, 1431*m*, 1398*m*, 1359*m*, 1347*m*, 1317*m*, 1259*w*, 1217*w*, 1174*m*, 1126*m*, 1105*m*, 1073*m*, 1038*m*, 981*m*, 942*m*, 932*m*, 893*m*, 880*m*, 864*m*, 818*m*, 747*m*, 722*m*, 707*m*, 699*m*, 633*m*, 623*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.85–2.08 (*m*, 1 H); 2.41 (*ddd*, ^3J(H,F) = 30.3, J = 14.4, 6.1, 1 H); 2.98–3.22 (*m*, 2 H); 3.56 (*d*, J = 8.3, 1 H); 3.59 (*dd*, J = 8.3, 8.3, 1 H); 4.13–4.21 (*m*, 2 H); 4.54 (*s*, 2 H); 5.20–5.44 (*m*, 1 H); 7.25–7.28 (*m*, 6 H); 7.43–7.49 (*m*, 2 H); 7.71–7.74 (*m*, 3 H); 7.80–7.83 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 37.4 (*d*, ^2J(C,F) = 22.4); 42.6; 48.1; 50.6; 59.4 (*d*, ^2J(C,F) = 26.1); 66.0; 71.1; 94.8 (*d*, ^1J(C,F) = 175.5); 125.9; 126.0; 126.2; 126.8; 127.8; 127.9; 128.1; 128.6; 128.9; 133.3; 133.3; 134.7; 135.6; 174.6; 177.4 (one arom. signal missing due to overlap). HR-MALDI-MS: 415.1815 ($[M+H]^+$, $C_{26}H_{24}FN_2O_2^+$; calc. 415.1816). Anal. calc. for $C_{26}H_{23}FN_2O_2$ (414.48): C 75.34, H 5.59, N 6.76; found: C 75.18, H 5.62, N 6.66.

*(−)-Methyl (1S,2R,3S,6S,7aR)-6-Fluorohexahydro-3-(naphthalen-2-yl)-2-{[(phenylmethyl)amino]-carbonyl}-1*H-*pyrrolizine-1-carboxylate* ((−)-**37b**). *General Procedure H* with (−)-*endo*-**36b** (2.60 g, 6.27 mmol, 1 equiv.), 0.05M NaOH in THF/H_2O 2:1 (251 ml), MeOH (150 ml), and $SOCl_2$ (2.28 ml, 31.4 mmol, 5 equiv.). The crude product was taken up in sat. aq. $NaHCO_3$ soln. (350 ml) and CH_2Cl_2 (320 ml). The layers were separated. The aq. phase was extracted with CH_2Cl_2 (2×300 ml). The comb. org. phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a solid, which was purified by CC (SiO_2; AcOEt/hexane 7:3) to give (−)-**37b** (1.95 g, 70%). Beige solid. M.p. 190–193°. $[\alpha]_D^{20} = -89.8$ ($c = 1.10$, $CHCl_3$). IR (neat): 3053*w*, 2970*w*, 2933*w*, 2867*w*, 1775*w*, 1699*s*, 1602*w*, 1569*w*, 1511*w*, 1456*w*, 1431*m*, 1398*m*, 1348*m*, 1317*m*, 1260*w*, 1217*w*, 1174*m*, 1143*w*, 1125*m*, 1106*m*, 1072*m*, 1038*m*, 982*m*, 963*w*, 941*m*, 909*w*, 894*m*, 864*m*, 818*m*, 747*m*, 722*m*, 707*m*, 699*m*, 660*w*, 633*m*, 623*m*. ^{1}H-NMR (300 MHz $CDCl_3$): 1.65–1.90 (*m*, 2 H); 2.56–2.83 (*m*, 2 H); 3.16 (*dd*, J = 7.7, 7.7, 1 H); 3.53 (*dd*, ^3J(H,F) = 22.7, J = 13.1, 1 H); 3.72 (*s*, 3 H); 3.91 (*dd*, J = 14.9, 5.3, 1 H); 4.10 (*dd*, J = 14.9, 5.7, 1 H); 4.38 (*d*, J = 5.4, 1 H); 4.69–4.77 (*m*, 1 H); 5.44 (*ddd*, ^2J(H,F) = 52.2, J = 3.6, 3.6, 1 H); 5.98–6.01 (*m*, 1 H); 6.54–6.57 (*m*, 2 H); 6.87 (*dd*, J = 7.4, 7.4, 2 H); 7.03 (*dd*, J = 7.4, 7.4, 1 H); 7.39–7.42 (*m*, 1 H); 7.48–7.53 (*m*, 2 H); 7.74–7.84 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 39.9 (*d*, ^2J(C,F) = 20.6); 43.4; 52.2; 52.9; 58.7; 60.1 (*d*, ^2J(C,F) = 21.8); 64.5; 72.9; 97.7 (*d*, ^1J(C,F) = 176.7); 124.9; 125.7; 126.0; 126.3;

126.9; 127.3; 127.7; 128.0; 128.1; 128.4; 133.0; 133.4; 137.5; 169.0; 171.3 (one arom. signal missing due to overlap). HR-MALDI-MS: 447.2086 ($[M+H]^+$, $C_{27}H_{28}FN_2O_3^+$; calc. 447.2079). Anal. calc. for $C_{27}H_{27}FN_2O_3$ (446.52): C 72.63, H 6.09, N 6.27; found: 72.51, H 5.97, N 6.19.

*(−)-(1*S*,2*R*,3*S*,6*S*,7a*R*)-6-Fluorohexahydro-1-(hydroxymethyl)-3-(naphthalen-2-yl)-*N*-(phenylmethyl)-1*H*-pyrrolizine-2-carboxamide* ((−)-**38b**). *General Procedure I* with (−)-**37b** (1.84 g, 4.1 mmol, 1 equiv.), 20 wt.-% DIBAL-H in toluene (10.2 ml, 12.4 mmol, 3 equiv.), and THF (65 ml) afforded, after purification by CC (SiO_2; Et_2O/MeOH/Et_3N 96 : 3 : :1), (−)-**38b** (1.00 g, 58%). White solid. M.p. 95–100°. $[\alpha]_D^{20} = -67.2$ ($c = 1.00$, $CHCl_3$). IR (neat): 3309*w*, 3054*w*, 2972*w*, 2919*w*, 1648*s*, 1600*w*, 1537*m*, 1468*w*, 1452*w*, 1419*w*, 1398*w*, 1357*w*, 1321*w*, 1237*w*, 1136*w*, 1057*w*, 1020*s*, 960*w*, 946*w*, 898*w*, 859*m*, 817*m*, 799*m*, 761*w*, 742*m*, 720*m*, 694*m*, 675*m*, 631*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.76 (*ddd*, ^3J(H,F) = 14.1, J = 10.5, 3.6, 1 H); 1.90 (*ddd*, ^3J(H,F) = 14.1, J = 10.5, 3.6, 1 H); 2.40–2.87 (*m*, 4 H); 3.12–3.18 (*m*, 1 H); 3.61–3.84 (*m*, 3 H); 3.99 (*dd*, J = 15.2, 4.7, 1 H); 4.36–4.45 (*m*, 2 H); 5.46 (br. *d*, ^2J(H,F) = 52.5, 1 H); 6.55 (*d*, J = 7.5, 2 H); 6.79 (*dd*, J = 7.5, 7.5, 2 H); 6.97 (*d*, J = 7.5, 1 H); 7.36 (*dd*, J = 8.4, 1.5, 1 H); 7.44–7.53 (*m*, 2 H); 7.60–7.85 (*m*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 39.3 (*d*, ^2J(C,F) = 20.6); 43.1; 51.3; 58.5; 60.5 (*d*, ^2J(C,F) = 21.8); 62.6; 65.2; 71.4; 98.2 (*d*, ^1J(C,F) = 175.3); 124.6; 124.9; 125.8; 126.2; 126.7; 126.9; 127.5; 127.8; 128.0; 128.5; 132.5; 133.2; 136.0; 137.2; 170.8. HR-MALDI-MS: 419.2121 ($[M+H]^+$, $C_{26}H_{28}FN_2O_2^+$; calc. 419.2129). Anal. calc. for $C_{26}H_{27}N_2O_2F$ (418.51): C 74.62, H 6.50, N 6.69; found: C 74.56, H 6.72, N 6.71.

*(−)-((1*S*,2*R*,3*S*,6*S*,7a*R*)-6-Fluorohexahydro-3-(naphthalen-2-yl)-2-{[(phenylmethyl)amino]carbonyl}-1*H*-pyrrolizin-1-yl)methyl Bis(phenylmethyl) Phosphate* ((−)-**39b**). *General Procedure J* with (−)-**38b** (419 mg, 1.0 mmol, 1.0 equiv.), 0.45M 1*H*-tetrazole in MeCN (6.7 ml, 3.0 mmol, 3.0 equiv.), dibenzyl-*N*,*N*-diisopropylphosphoramidite (0.5 ml, 1.5 mmol, 1.5 equiv.), MeCN (10 ml), and 70% pure *m*CPBA (591 mg, 2.4 mmol, 2.4 equiv.) yielded, after purification by CC (SiO_2; AcOEt/hexane/Et_3N 50 : 50 : 1), (−)-**39b** (400 mg, 59%). White solid. M.p. 129–131°. $[\alpha]_D^{20} = -25.5$ ($c = 1.06$, $CHCl_3$). IR (neat): 3279*w*, 3057*w*, 2886*w*, 1665*w*, 1642*m*, 1602*w*, 1552*w*, 1509*w*, 1452*w*, 1423*w*, 1383*w*, 1359*w*, 1325*w*, 1278*m*, 1251*m*, 1213*w*, 1178*w*, 1133*w*, 1013*s* (br.), 881*m*, 867*m*, 833*m*, 809*m*, 793*w*, 761*w*, 724*m*, 693*m*, 645*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.50–1.69 (*m*, 2 H); 2.25–2.38 (*m*, 1 H); 2.50–2.69 (*m*, 2 H); 3.39–3.55 (*m*, 2 H); 3.76–3.91 (*m*, 2 H); 4.08–4.29 (*m*, 3 H); 4.93–4.98 (*m*, 4 H); 5.29 (br. *d*, ^2J(H,F) = 54.0, 1 H); 6.41 (*d*, J = 7.5, 2 H); 6.66 (*dd*, J = 7.5, 7.5, 2 H); 6.85 (*dd*, J = 7.5, 7.5, 1 H); 6.97–7.04 (*m*, 1 H); 7.16 (*s*, 1 H); 7.21–7.27 (*m*, 10 H); 7.33–7.43 (*m*, 2 H); 7.56–7.72 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 39.7 (*d*, ^2J(C,F) = 20.6); 43.1; 48.2; 58.0; 60.3 (*d*, ^2J(C,F) = 20.6); 67.1; 67.8; 69.4 (*d*, ^2J(C,P) = 5.5); 71.9; 98.1 (*d*, ^1J(C,F) = 174.2); 124.7; 125.2; 125.8; 126.2; 126.7; 127.0; 127.4; 127.5; 127.8; 128.0; 128.4; 128.5; 132.6; 133.2; 135.6; 135.7; 137.4; 168.9 (one arom. signal missing due to overlap). HR-MALDI-MS: 679.2721 ($[M+H]^+$, $C_{40}H_{41}FN_2O_5P^+$; calc. 679.2732).

*(+)-((1*S*,2*R*,3*S*,6*S*,7a*R*)-6-Fluorohexahydro-3-(naphthalen-2-yl)-2-{[(phenylmethyl)amino]carbonyl}-1*H*-pyrrolizin-1-yl)methyl Dihydrogen Phosphate* ((+)-**33b**). *General Procedure K* with (−)-**39b** (125 mg, 0.18 mmol, 1 equiv.), cat. Pd/C (13 mg), and MeOH (5 ml) yielded (+)-**33b** (88 mg, 98%). White solid. M.p. 142–147° (dec.). $[\alpha]_D^{20} = +31.8$ ($c = 1.00$, MeOH). IR (neat): 3245*w* (br.), 3058*w*, 2956*w*, 2145*w*, 1644*s*, 1556*m*, 1454*m*, 1427*m*, 1354*m*, 1238*m*, 1172*m*, 1073*m*, 1035*s*, 917*m*, 853*m*, 822*m*, 743*m*, 695*m*. ^{1}H-NMR (300 MHz, CD_3OD): 2.22–2.48 (*m*, 2 H); 2.81–2.97 (*m*, 1 H); 3.07–3.20 (*m*, 1 H); 3.39–3.58 (*m*, 1 H); 3.80–3.93 (*m*, 2 H); 3.98–4.06 (*m*, 2 H); 4.47 (*d*, J = 15.3, 1 H); 4.73–4.88 (*m*, 1 H); 5.20 (*d*, J = 4.5, 1 H); 5.59 (br. *d*, ^2J(H,F) = 51.0, 1 H); 6.51 (*d*, J = 7.8, 2 H); 6.67 (*dd*, J = 7.8, 7.8, 2 H); 6.90 (*dd*, J = 7.8, 7.8, 1 H); 7.50–7.63 (*m*, 3 H); 7.86–7.95 (*m*, 3 H); 8.02 (*s*, 1 H). ^{13}C-NMR (75 MHz, CD_3OD): 40.0 (*d*, ^2J(C,F) = 20.9); 40.5; 43.6; 57.5; 60.6 (*d*, ^2J(C,F) = 23.3); 64.8; 72.8; 75.5; 97.8 (*d*, ^1J(C,F) = 178.2); 125.8; 127.6; 127.8; 128.0; 128.1; 128.2; 128.9; 129.1; 129.4; 130.2; 134.6; 135.0; 139.0; 170.9 (one arom. signal missing due to overlap). HR-MS (MALDI): 499.1784 ($[M+H]^+$, $C_{26}H_{29}FN_2O_5P^+$; calc. 499.1793).

*(−)-(3a*R*,4*S*,7*R*,8a*R*,8b*S*)-Hexahydro-7-methoxy-4-(naphthalen-2-yl)-2-(phenylmethyl)pyrrolo[3,4-a]pyrrolizine-1,3(2*H*,4*H*)-dione* ((−)-**36c**). To a soln. of (−)-**35** (2.35 g, 5.70 mmol, 1.00 equiv.) in THF (65 ml), 60% NaH in mineral oil (400 mg, 9.67 mmol, 1.75 equiv.) was added. The mixture was stirred at 20° for 45 min. [15]crown-5 (1.9 ml, 10.30 mmol, 1.8 equiv.) was added, and the suspension was stirred at 20° for 1 h. MeI (390 ml, 6.27 mmol, 1.10 equiv.) was added. The mixture was stirred at 20° for 3 h and then poured into sat. aq. NH_4Cl soln. (85 ml). The mixture was extracted with AcOEt (3 × 100 ml). The comb.

org. phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by CC (SiO_2; hexane/AcOEt 6:4 → 1:1) to afford (−)-**36c** (1.52 g, 63%). White solid. M.p. 139–141°. $[\alpha]_D^{20} = -201.7$ ($c = 1.00$, $CHCl_3$). IR (neat): 3049*w*, 2928*w*, 2893*w*, 2821*w*, 1772*w*, 1690*s*, 1606*w*, 1512*w*, 1496*w*, 1455*w*, 1426*m*, 1400*m*, 1362*m*, 1340*m*, 1302*w*, 1283*w*, 1254*w*, 1237*w*, 1201*w*, 1165*m*, 1156*m*, 1127*w*, 1109*w*, 1081*s*, 1042*m*, 1018*w*, 1002*w*, 994*w*, 979*w*, 967*w*, 938*w*, 929*m*, 920*w*, 888*w*, 970*w*, 836*w*, 818*s*, 750*m*, 732*m*, 695*m*, 656*m*, 646*m*, 635*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.82–1.91 (*m*, 1 H); 2.58 (*ddd*, $J = 14.5, 7.5, 7.5$, 1 H); 2.86–2.99 (*m*, 2 H); 3.23 (*s*, 3 H); 3.37–3.39 (*m*, 1 H); 3.66 (*dd*, $J = 8.7, 8.7$, 1 H); 3.88–3.94 (*m*, 1 H); 4.03–4.10 (*m*, 1 H); 4.52 (*AB*, $J = 4.1$, 2 H); 4.79 (*d*, $J = 8.7$, 1 H); 7.26–7.29 (*m*, 5 H); 7.30 (*dd*, $J = 8.4, 1.6$, 1 H); 7.44 (*ddd*, $J = 9.7, 3.4, 3.4$, 2 H); 7.70–7.75 (*m*, 3 H); 7.78–7.83 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 38.2; 42.6; 49.6; 50.5; 56.5; 57.4; 67.0; 69.3; 84.2; 125.6; 125.7; 126.4; 126.8; 127.5; 127.7; 128.0; 128.4; 128.8; 133.1; 133.2; 135.3; 135.6; 175.0; 177.8 (one arom. signal missing due to overlap). HR-MALDI-MS: 449.1829 ($[M+Na]^+$, $C_{27}H_{26}N_2NaO_3^+$; calc. 449.1836). Anal. calc. for $C_{27}H_{26}N_2O_3$ (426.51): C 76.03, H 6.14, N 6.57; found: C 76.11, H 6.04, N 6.57.

*(−)-Methyl (1S,2R,3S,6R,7aR)-Hexahydro-6-methoxy-3-(naphthalen-2-yl)-2-{[(phenylmethyl)amino]carbonyl}-1*H*-pyrrolizine-1-carboxylate* ((−)-**37c**). *General Procedure H* with (−)-*endo*-**36c** (1.63 g, 3.81 mmol, 1 equiv.), 0.05M NaOH in THF/H_2O 2:1 (150 ml), MeOH (40 ml), and $SOCl_2$ (1.38 ml, 19.05 mmol, 5 equiv.). The crude product was taken up in sat. aq. $NaHCO_3$ soln. (100 ml) and CH_2Cl_2 (100 ml). The layers were separated. The aq. phase was extracted with CH_2Cl_2 (2 × 100 ml). The comb. org. phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a solid, which was purified by CC (SiO_2; AcOEt/hexane 7:3) to yield (−)-**37c** (1.65 g, 94%). White solid. M.p. 166–168°. $[\alpha]_D^{20} = -97.5$ ($c = 1.00$, $CHCl_3$). IR (neat): 3378*w*, 3056*w*, 2951*w*, 2887*w*, 2823*w*, 1723*s*, 1656*m*, 1602*w*, 1521*m*, 1496*w*, 1456*w*, 1427*m*, 1405*w*, 1371*w*, 1355*w*, 1306*w*, 1284*w*, 1266*w*, 1222*m*, 1207*m*, 1168*w*, 1125*w*, 1114*m*, 1101*m*, 1083*s*, 1039*m*, 1016*m*, 991*w*, 983*w*, 969*w*, 900*w*, 853*w*, 821*m*, 808*m*, 776*w*, 737*s*, 693*s*, 651*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.06–2.14 (*m*, 1 H); 2.22 (*ddd*, $J = 13.9, 8.4, 5.0$, 1 H); 2.93–3.08 (*m*, 2 H); 3.28 (*s*, 3 H); 3.40 (*dd*, $J = 9.0, 6.5$, 1 H); 3.54–3.58 (*m*, 1 H); 3.73 (*s*, 3 H); 3.91 (*dd*, $J = 14.6, 5.6$, 1 H); 3.98–4.05 (*m*, 1 H); 4.06 (*dd*, $J = 14.6, 5.6$, 1 H); 4.45–4.50 (*m*, 1 H); 4.80 (*d*, $J = 5.3$, 1 H); 5.78–5.82 (*m*, 1 H); 6.51 (*d*, $J = 7.5$, 1 H); 6.85 (*dd*, $J = 7.5, 7.5$, 2 H); 7.01 (*dd*, $J = 7.5, 7.5$, 2 H); 7.41–7.52 (*m*, 3 H); 7.74–7.88 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 37.4; 43.4; 52.1; 53.5; 56.4; 56.7; 57.2; 64.5; 72.7; 84.3; 125.2; 125.6; 125.7; 126.1; 126.8; 127.3; 127.6; 127.9; 128.0; 128.2; 132.9; 133.4; 137.5; 169.4; 171.8 (one arom. signal missing due to overlap). HR-ESI-MS: 459.2270 ($[M+H]^+$, $C_{28}H_{31}N_2O_4^+$; calc. 459.2278). Anal. calc. for $C_{28}H_{30}N_2O_4$ (458.56): C 73.34, H 6.59, N 6.11; found: C 73.11, H 6.76, N 5.93.

*(−)-(1S,2R,3S,6R,7aR)-Hexahydro-1-(hydroxymethyl)-6-methoxy-3-(naphthalen-2-yl)-*N*-(phenylmethyl)-1*H*-pyrrolizine-2-carboxamide* ((−)-**38c**). *General Procedure I* with (−)-**37c** (4.30 g, 9.38 mmol, 1 equiv.), 20 wt.-% DIBAL-H in toluene (23.2 ml, 28.1 mmol, 3 equiv.), and THF (140 ml) afforded, after purification by CC (SiO_2; Et_2O/MeOH/Et_3N 95:5:1), (−)-**38c** (1.80 g, 45%). White solid. M.p. 162–163°. $[\alpha]_D^{20} = -86.7$ ($c = 1.00$, $CHCl_3$). IR (neat): 3329*m*, 3060*w*, 2933*w*, 2890*w*, 2819*w*, 1640*m*, 1600*w*, 1533*m*, 1507*w*, 1495*w*, 1482*w*, 1451*m*, 1428*w*, 1417*w*, 1383*w*, 1354*w*, 1306*w*, 1270*m*, 1238*m*, 1188*w*, 1163*w*, 1121*w*, 1098*s*, 1075*s*, 1023*s*, 995*m*, 955*w*, 941*w*, 905*w*, 894*w*, 865*w*, 832*w*, 818*m*, 776*w*, 750*m*, 738*m*, 730*s*, 713*m*, 693*s*, 677*m*, 644*m*, 628*m*, 618*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.04–2.08 (*m*, 2 H); 2.84–2.95 (*m*, 1 H); 3.02–3.21 (*m*, 2 H); 3.26 (*s*, 3 H); 3.44–3.55 (*m*, 1 H); 3.55–3.65 (*m*, 1 H); 3.71 (*dd*, $J = 5.6, 5.6$, 1 H); 3.77 (*dd*, $J = 11.8, 5.6$, 1 H); 3.99 (*dd*, $J = 14.9, 4.7$, 1 H); 3.99–4.05 (*m*, 1 H); 4.31 (*dd*, $J = 14.9, 6.8$, 1 H); 4.81 (*d*, $J = 5.0$, 1 H); 6.52 (*d*, $J = 7.5$, 2 H); 6.79 (*dd*, $J = 7.5, 7.5$, 2 H); 6.98 (*d*, $J = 7.5, 7.5$, 1 H); 7.32–7.42 (*m*, 1 H); 7.37–7.40 (*m*, 1 H); 7.45–7.51 (*m*, 2 H); 7.69–7.85 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 36.6; 43.2; 51.9; 56.1; 56.8; 57.4; 62.9; 65.1; 70.8; 84.4; 125.1; 125.1; 125.9; 126.4; 127.0; 127.2; 127.9; 128.1; 128.3; 128.7; 132.7; 133.6; 137.7; 171.7 (one arom. signal missing due to overlap). HR-MALDI-MS: 431.2322 ($[M+H]^+$, $C_{27}H_{31}N_2O_3^+$; calc. 431.2329). Anal. calc. for $C_{27}H_{30}N_2O_3$ (430.55): C 75.32, H 7.02, N 6.51; found: C 75.26, H 7.03, N 6.47.

*(−)-[(1S,2R,3S,6R,7aR)-Hexahydro-6-methoxy-3-(naphthalen-2-yl)-2-{[(phenylmethyl)amino]carbonyl}-1*H*-pyrrolizin-1-yl]methyl Bis(phenylmethyl) Phosphate* ((−)-**39c**). *General Procedure J* with (−)-**38c** (861 mg, 2.0 mmol, 1.0 equiv.), 0.45M 1*H*-tetrazole in MeCN (13.34 ml, 6.0 mmol, 3.0 equiv.), dibenzyl-*N*,*N*-diisopropylphosphoramidite (0.99 ml, 3.0 mmol, 1.5 equiv.), MeCN (10 ml), and 70% pure *m*CPBA (1.18 g, 4.8 mmol, 2.4 equiv.) afforded, after purification by CC (SiO_2; AcOEt/Et_3N 100:1),

(−)-**39c** (965 mg, 70%). White solid. M.p. 100–101°. $[\alpha]_D^{20} = -40.4$ ($c = 1.00$, $CHCl_3$). IR (neat): 3255*w*, 3062*w*, 2897*w*, 1662*w*, 1636*w*, 1542*w*, 1496*w*, 1454*m*, 1363*w*, 1264*m*, 1216*w*, 1174*w*, 1130*w*, 1103*m*, 1084*m*, 993*s*, 969*s*, 917*m*, 865*m*, 836*m*, 812*m*, 727*s*, 694*s*, 639*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.02–2.14 (*m*, 2 H); 2.77–2.87 (*m*, 1 H); 2.94–2.98 (*m*, 1 H); 3.05–3.12 (*m*, 1 H); 3.24 (*s*, 3 H); 3.34–3.38 (*m*, 1 H); 3.68–3.78 (*m*, 1 H); 3.93 (*dd*, $J = 14.9$, 5.3, 1 H); 3.97–4.09 (*m*, 2 H); 4.10 (*dd*, $J = 14.9$, 6.2, 1 H); 4.34 (*ddd*, $J = 10.3$, 6.5, 6.5, 1 H); 4.75 (*d*, $J = 5.0$, 1 H); 5.05–5.10 (*m*, 4 H); 6.46–6.49 (*m*, 2 H); 6.74–6.79 (*m*, 3 H); 6.94–6.99 (*m*, 1 H); 7.33–7.39 (*m*, 11 H); 7.44–7.51 (*m*, 2 H); 7.71–7.84 (*m*, 4 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 37.1; 43.0; 48.7 (*d*, ^2J(C,P) = 7.4); 56.0; 56.6; 57.0; 66.5; 67.9 (*d*, ^2J(C,P) = 5.9); 69.3; 71.4; 84.3; 125.1; 125.2; 125.6; 126.1; 126.8; 127.2; 127.6; 128.0; 128.0; 128.2; 128.5; 128.5; 128.6; 128.6; 132.7; 133.4; 135.9; 137.7; 169.6. HR-MALDI-MS: 691.2921 ($[M+H]^+$, $C_{41}H_{44}N_2O_6P^+$; calc. 691.2932). Anal. calc. for $C_{41}H_{43}N_2O_6P$ (690.77): C 71.29, H 6.27, N 4.06; found: C 71.04, H 6.22, N 4.06.

*(+)-[(1*S*,2*R*,3*S*,6*R*,7a*R*)-Hexahydro-6-methoxy-3-(naphthalen-2-yl)-2-{[(phenylmethyl)amino]carbonyl}-1*H*-pyrrolizin-1-yl]methyl Dihydrogen Phosphate* ((+)-**33c**). *General Procedure K* with (−)-**39c** (345 mg, 0.5 mmol, 1 equiv.), cat. Pd/C (35 mg), MeOH (15 ml) yielded (+)-**33c** (247 mg, 97%). White solid. M.p. 171–172° (dec.). $[\alpha]_D^{20} = +24.1$ ($c = 1.00$, MeOH). IR (neat): 3339*w*, 3059*w*, 2927*m*, 2866*w*, 1651*s*, 1601*w*, 1520*m*, 1495*m*, 1456*m*, 1441*m*, 1406*w*, 1354*w*, 1315*w*, 1231*m*, 1202*m*, 1179*m*, 1146*m*, 1121*m*, 1081*m*, 1050*m*, 1018*s*, 970*m*, 908*m*, 800*m*, 737*s*, 696*s*, 628*m*. ^{1}H-NMR (300 MHz, CD_3OD): 2.37 (*ddd*, $J = 14.6$, 9.7, 4.7, 1 H); 2.57–2.62 (*m*, 1 H); 3.17–3.27 (*m*, 1 H); 3.42 (*s*, 3 H); 3.46–3.49 (*m*, 2 H); 3.71 (*dd*, $J = 5.6$, 5.6, 1 H); 3.84 (*d*, $J = 14.9$, 1 H); 3.99–4.04 (*m*, 2 H); 4.28–4.32 (*m*, 1 H); 4.44 (*d*, $J = 14.9$, 1 H); 4.62–4.68 (*m*, 1 H); 5.32 (*d*, $J = 5.6$, 1 H); 6.50–6.52 (*m*, 2 H); 6.65–6.71 (*m*, 2 H); 6.88–6.93 (*m*, 1 H); 7.50–7.63 (*m*, 3 H); 7.85–7.98 (*m*, 4 H). ^{13}C-NMR (75 MHz, CD_3OD): 35.5; 43.2; 55.0; 56.9; 57.4; 64.5; 64.5; 71.9; 75.3; 83.5; 125.3; 126.9; 127.2; 127.4; 127.5; 127.6; 128.4; 128.6; 128.9; 129.6; 134.1; 134.4; 138.5; 170.5 (one arom. signal missing due to overlap). HR-MALDI-MS: 511.1984 ($[M+H]^+$, $C_{27}H_{32}N_2O_6P^+$; calc. 511.1993).

*(±)-(3a*RS*,4*SR*,9a*RS*,9b*SR*)-Octahydro-4-(naphthalen-2-yl)-2-(phenylmethyl)-1*H*-pyrrolo[3,4-*a*]-indolizine-1,3(2*H*)-dione* ((±)-*endo*-**41**) *and (±)-(3a*RS*,4*RS*,9a*SR*,9b*SR*)-Octahydro-4-(naphthalen-2-yl)-2-(phenylmethyl)-1*H*-pyrrolo[3,4-*a*]indolizine-1,3(2*H*)-dione* ((±)-*exo*-**42**). *General Procedure G* with **23** (5.62 g, 30.0 mmol, 1.00 equiv.), DL-pipecolinic acid ((±)-**40**; 4.07 g, 31.5 mmol, 1.05 equiv.), **25** (4.92 g, 31.5 mmol, 1.05 equiv.), and MeCN (50 ml) yielded, after purification by CC (SiO_2; hexane/AcOEt 8:2), (±)-*endo*-**41** (2.06 g, 17%) and (±)-*exo*-**42** (3.89 g, 32%).

Data of (±)-endo-**41**. White solid. M.p. 193–195°. IR (neat): 2929*w*, 2892*w*, 2820*w*, 1764*w*, 1693*s*, 1599*w*, 1506*w*, 1498*w*, 1460*w*, 1432*m*, 1398*m*, 1348*m*, 1335*m*, 1313*m*, 1283*w*, 1241*w*, 1175*m*, 1121*m*, 1092*w*, 1021*w*, 944*w*, 921*w*, 888*w*, 844*m*, 824*m*, 772*w*, 763*m*, 749*m*, 716*w*, 697*s*, 667*m*, 653*m*, 635*m*, 621*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.06–1.12 (*m*, 1 H); 1.49–1.60 (*m*, 4 H); 1.86–1.92 (*m*, 1 H); 2.66–2.82 (*m*, 2 H); 2.96 (*d*, $J = 7.8$, 1 H); 3.51 (*dd*, $J = 9.0$, 7.8, 1 H); 3.82–3.86 (*m*, 1 H); 4.53 (*s*, 2 H); 4.75 (*d*, $J = 9.0$, 1 H); 7.07–7.12 (*m*, 1 H); 7.28–7.32 (*m*, 5 H); 7.41–7.46 (*m*, 2 H); 7.58–7.68 (*m*, 3 H); 7.77–7.80 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 18.1; 24.6; 25.8; 42.6; 44.9; 49.5; 50.8; 62.0; 63.4; 125.6; 125.7; 127.2; 127.7; 127.7; 127.8; 127.9; 128.4; 129.0; 133.1; 133.1; 134.8; 135.7; 175.6; 178.5 (one arom. signal missing due to overlap). HR-MALDI-MS: 411.2059 ($[M+H]^+$, $C_{27}H_{27}N_2O_2^+$; calc. 411.2067). Anal. calc. for $C_{27}H_{26}N_2O_2$ (410.51): C 79.00, H 6.38, N 6.82; found: C 78.73, H 6.53, N 6.78.

Data of (±)-exo-**42**. White solid. M.p. 165–166°. IR (neat): 2930*w*, 2892*w*, 2820*w*, 1764*w*, 1690*s*, 1599*w*, 1506*w*, 1498*w*, 1460*w*, 1432*m*, 1398*m*, 1378*w*, 1348*m*, 1335*m*, 1283*w*, 1248*w*, 1241*w*, 1175*m*, 1141*w*, 1120*w*, 1074*m*, 1021*w*, 967*w*, 944*w*, 907*w*, 824*m*, 773*w*, 750*m*, 716*w*, 698*s*, 653*w*, 635*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.87–1.13 (*m*, 2 H); 1.24–1.44 (*m*, 2 H); 1.62–1.70 (*m*, 2 H); 1.89–1.98 (*m*, 1 H); 2.88–2.94 (*m*, 2 H); 3.52 (*d*, $J = 7.8$, 1 H); 3.58 (*dd*, $J = 7.8$, 7.8, 1 H); 4.75 (*s*, 2 H); 4.76–4.79 (*m*, 1 H); 7.23–7.36 (*m*, 6 H); 7.39–7.42 (*m*, 3 H); 7.82–7.87 (*m*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 24.2; 24.9; 28.5; 42.6; 48.5; 48.6; 50.2; 59.6; 69.1; 126.1; 126.3; 126.6; 127.1; 127.6; 127.6; 127.8; 127.9; 128.0; 128.5; 132.7; 132.8; 134.1; 135.6; 176.4; 178.5. HR-MALDI-MS: 411.2061 ($[M+H]^+$, $C_{27}H_{27}N_2O_2^+$; calc. 411.2067). Anal. calc. for $C_{27}H_{26}N_2O_2$ (410.51): C 79.00, H 6.38, N 6.82; found: C 79.01, H 6.48, N 6.84.

*(±)-Methyl (1*RS*,2*SR*,3*RS*,8a*SR*)-Octahydro-3-(naphthalen-2-yl)-2-{[(phenylmethyl)amino]carbonyl}indolizine-1-carboxylate* ((±)-**44**). *General Procedure H* with (±)-*endo*-**41** (1.42 g, 3.45 mmol, 1 equiv.), 0.05M NaOH in THF/H_2O 2:1 (140 ml); MeOH (40 ml), and $SOCl_2$ (1.25 ml, 17.26 mmol, 5

equiv.). The crude product was taken up in sat. aq. $NaHCO_3$ soln. (100 ml) and CH_2Cl_2 (100 ml). The layers were separated. The aq. phase was extracted with CH_2Cl_2 (2×100 ml). The comb. org. phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a solid, which was purified by CC (SiO_2; AcOEt) to yield (±)-**44** (830 mg, 54%). Pale yellow solid. M.p. 150–152°. IR (neat): 3292*w*, 3045*w*, 2924*w*, 2847*w*, 1723*s*, 1643*s*, 1609*w*, 1588*w*, 1558*m*, 1508*w*, 1497*w*, 1453*w*, 1436*w*, 1426*w*, 1352*w*, 1317*w*, 1306*w*, 1279*w*, 1236*m*, 1214*s*, 1179*m*, 1169*m*, 1147*w*, 1124*w*, 1087*w*, 1052*w*, 1044*w*, 1026*m*, 909*w*, 897*w*, 886*w*, 819*m*, 746*m*, 721*s*, 694*s*, 651*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.34–1.45 (*m*, 4 H); 1.73–1.80 (*m*, 1 H); 1.93–1.98 (*m*, 1 H); 2.62 (*ddd*, *J* = 12.8, 9.3, 4.0, 1 H); 2.74–2.83 (*m*, 1 H); 3.01 (*dd*, *J* = 9.3, 6.5, 1 H); 3.58 (*dd*, *J* = 9.3, 7.2, 1 H); 3.65 (*s*, 3 H); 3.88–3.94 (*m*, 1 H); 3.95 (*d*, *J* = 5.3, 2 H); 4.72 (*d*, *J* = 7.2, 1 H); 5.97 (*dd*, *J* = 5.3, 5.3, 1 H); 6.67–6.70 (*m*, 2 H); 6.95–7.00 (*m*, 2 H); 7.07–7.12 (*m*, 1 H); 7.42–7.51 (*m*, 3 H); 7.70–7.85 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 22.1; 23.6; 30.2; 43.6; 46.3; 52.0; 52.4; 53.4; 59.5; 67.5; 125.9; 126.0; 126.5; 127.0; 127.6; 127.6; 127.8; 127.8; 128.2; 133.0; 133.1; 134.7; 137.6; 169.8; 172.4 (one arom. signal missing due to overlap). HR-MALDI-MS: 443.2321 ($[M+Na]^+$, $C_{28}H_{30}N_2NaO_3^+$; calc. 443.2329).

*(±)-(1*RS*,2*SR*,3*RS*,8a*SR*)-Octahydro-1-(hydroxymethyl)-3-(naphthalen-2-yl)*-N-*(phenylmethyl)indolizine-2-carboxamide* ((±)-**43**). *General Procedure I* with (±)-**44** (780 mg, 1.76 mmol, 1.0 equiv.), 20 wt.-% DIBAL-H in toluene (3.63 ml, 4.41 mmol, 2.5 equiv.), THF (25 ml) afforded, after purification by CC (SiO_2; AcOEt/MeOH 85:15), (±)-**43** (233 mg, 32%). White solid. M.p. 172–174°. IR (neat): 3346*w*, 2926*m*, 2866*w*, 1652*s*, 1634*w*, 1600*w*, 1519*m*, 1495*w*, 1455*m*, 1441*m*, 1404*w*, 1353*w*, 1315*w*, 1294*w*, 1242*w*, 1178*m*, 1131*w*, 1121*m*, 1081*w*, 1050*m*, 1018*s*, 969*w*, 952*w*, 891*w*, 843*m*, 799*m*, 739*s*, 696*s*, 641*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.36–1.60 (*m*, 4 H); 1.72–1.84 (*m*, 3 H); 2.42–2.51 (*m*, 1 H); 2.72–2.89 (*m*, 2 H); 3.19–3.25 (*m*, 1 H); 3.57–3.62 (*m*, 1 H); 3.77 (*dd*, *J* = 11.8, 4.4, 1 H); 3.82 (*dd*, *J* = 11.8, 7.1, 1 H); 3.97 (*dd*, *J* = 14.6, 5.3, 1 H); 4.13 (*dd*, *J* = 14.6, 5.9, 1 H); 4.66 (*d*, *J* = 7.5, 1 H); 6.71 (*d*, *J* = 7.2, 2 H); 6.97 (*dd*, *J* = 7.2, 7.2, 2 H); 7.07–7.12 (*m*, 1 H); 7.18–7.23 (*m*, 1 H); 7.38 (*dd*, *J* = 8.4, 1.6, 1 H); 7.44–7.51 (*m*, 2 H); 7.64–7.83 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.3; 22.7; 28.4; 43.7; 46.1; 50.1; 53.6; 61.1; 63.0; 67.0; 126.2; 126.4; 126.5; 127.1; 127.3; 127.7; 127.9; 128.2; 128.2; 128.6; 133.1; 133.4; 135.2; 137.7; 171.7. HR-MALDI-MS: 415.2372 ($[M+H]^+$, $C_{27}H_{31}N_2O_2^+$; calc. 415.2380).

*(±)-(3a*RS*,4*SR*,6*RS*,6a*SR*)-Tetrahydro-4-(naphthalen-2-yl)-2,6-bis(phenylmethyl)pyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione* ((±)-*endo*-**46a**). *General Procedure G* with **23** (5.62 g, 30.0 mmol, 1.00 equiv.), L-*phenylalanine* ((−)-**45a**; 5.20 g, 31.5 mmol, 1.05 equiv.), **25** (4.92 g, 31.5 mmol, 1.05 equiv.), and MeCN (60 ml) yielded (±)-**46a** (4.02 g, 30%) after purification by CC (SiO_2; hexane/AcOEt 7:3). Only the (±)-*endo*-**46a** was isolated in pure form.

*Data of (±)-*endo-**46a**. White solid. M.p. 146–147°. IR (neat): 3314*w*, 3052*w*, 3026*w*, 2939*w*, 2855*w*, 1768*w*, 1690*s*, 1602*w*, 1512*w*, 1494*m*, 1453*m*, 1431*m*, 1390*m*, 1352*m*, 1337*m*, 1306*m*, 1234*w*, 1169*m*, 1126*w*, 1099*m*, 1081*m*, 1031*w*, 1012*m*, 991*w*, 927*m*, 888*w*, 864*m*, 814*m*, 799*m*, 756*s*, 707*s*, 692*s*, 649*m*, 635*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.98 (br. *s*, 1 H); 2.88–3.01 (*m*, 2 H); 3.20 (*d*, *J* = 7.5, 1 H); 3.53–3.58 (*m*, 1 H); 4.19 (*dd*, *J* = 9.3, 5.9, 1 H); 4.51 (*s*, 2 H); 4.98 (*d*, *J* = 8.7, 1 H); 7.21–7.35 (*m*, 11 H); 7.40–7.46 (*m*, 2 H); 7.62–7.69 (*m*, 3 H); 7.77–7.80 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 39.5; 42.7; 49.1; 51.1; 61.4; 61.7; 125.9; 125.9; 126.0; 126.1; 127.1; 127.9; 127.9; 128.0; 128.2; 128.7; 129.1; 129.2; 133.3; 133.3; 135.5; 135.9; 138.0; 175.3; 178.4 (one arom. signal missing due to overlap). HR-MALDI-MS: 447.2061 ($[M+Na]^+$, $C_{30}H_{26}N_2NaO_2^+$; calc. 447.2067).

*(±)-Methyl (2*RS*,3*SR*,4*RS*,5*SR*)-Tetrahydro-5-(naphthalen-2-yl)-2-(phenylmethyl)-4-{[(phenylmethyl)amino]carbonyl}pyrrole-3-carboxylate* ((±)-**47a**). *General Procedure H* with (±)-*endo*-**46a** (1.33 g, 2.98 mmol, 1 equiv.), 0.05M NaOH in THF/H_2O 2:1 (120 ml); MeOH (40 ml), and $SOCl_2$ (1.08 ml, 14.89 mmol, 5 equiv.). The crude product was taken up in sat. aq. $NaHCO_3$ soln. (100 ml), H_2O (100 ml), and CH_2Cl_2/i-PrOH 3:1 (200 ml). The layers were separated. The aq. phase was extracted with CH_2Cl_2/i-PrOH (3×100 ml). The comb. org. phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a solid, which was purified by CC (SiO_2; hexane/AcOEt 1:1) to afford (±)-**47a** (263 mg, 18%). White solid. M.p. 129–131°. IR (neat): 3297*w*, 3027*w*, 2944*w*, 1729*m*, 1634*m*, 1525*m*, 1495*m*, 1453*m*, 1433*m*, 1357*w*, 1225*m*, 1198*m*, 1125*w*, 1080*w*, 1017*w*, 893*w*, 857*m*, 817*m*, 737*s*, 696*s*, 643*m*, 611*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.89 (*dd*, *J* = 13.7, 8.4, 1 H); 3.14 (*dd*, *J* = 13.7, 4.7, 1 H); 3.21 (*dd*, *J* = 7.2, 7.2, 1 H); 3.43 (*dd*, *J* = 7.2, 5.2, 1 H); 3.65 (*s*, 3 H); 3.92 (*dd*, *J* = 14.9, 5.6, 1 H); 4.04 (*dd*, *J* = 14.9, 5.6, 1 H); 4.68 (*d*, *J* = 5.2, 1 H); 6.02–6.06 (*m*, 1 H); 6.52 (*d*, *J* = 7.2, 2 H); 6.81–6.99 (*m*, 2 H);

7.01–7.04 (*m*, 1 H); 7.22–7.34 (*m*, 6 H); 7.44–7.52 (*m*, 2 H); 7.70–7.75 (*m*, 3 H); 7.80–7.84 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 43.0; 43.2; 52.0; 53.7; 55.4; 59.6; 63.8; 124.5; 124.8; 125.8; 126.2; 126.4; 126.8; 127.2; 127.5; 127.9; 128.0; 128.1; 128.4; 129.4; 132.7; 133.2; 135.6; 137.5; 138.7; 169.8; 171.7. HR-MALDI-MS: 479.2322 ($[M+H]^+$, $C_{31}H_{31}N_2O_3^+$; calc. 479.2329). Anal. calc. for $C_{31}H_{30}N_2O_3$ (478.59): C 77.80, H 6.32, N 5.85; found: C 77.66, H 6.13, N 5.78.

*(±)-(2*RS*,3*SR*,4*RS*,5*SR*)-Tetrahydro-4-(hydroxymethyl)-2-(naphthalen-2-yl)-*N*,5-bis(phenylmethyl)-pyrrole-3-carboxamide* ((±)-**48a**). *General Procedure I* with (±)-**47a** (242 mg, 0.51 mmol, 1.0 equiv.), 20 wt.-% DIBAL-H in toluene (1.25 ml, 1.52 mmol, 3.0 equiv.), and THF (10 ml) afforded, after purification by CC (SiO_2; hexane/AcOEt/25% aq. NH_3 2:8:0.1), (±)-**48a** (68 mg, 30%). White solid. M.p. 143–146°. IR (neat): 3275*w*, 3060*w*, 2906*w*, 1639*m*, 1603*w*, 1538*m*, 1495*m*, 1453*m*, 1355*w*, 1232*w*, 1126*w*, 1072*m*, 1041*m*, 1029*m*, 961*w*, 924*w*, 893*w*, 859*w*, 816*m*, 738*s*, 695*s*, 693*s*, 625*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.73–2.83 (*m*, 2 H); 2.89 (*dd*, *J* = 13.4, 8.1, 1 H); 3.02 (*dd*, *J* = 13.4, 5.6, 1 H); 3.31–3.38 (*m*, 1 H); 3.45–3.59 (*m*, 2 H); 3.64 (*dd*, *J* = 7.3, 4.8, 1 H); 3.95 (*dd*, *J* = 14.9, 4.7, 1 H); 4.34 (*dd*, *J* = 14.9, 7.0, 1 H); 4.83 (*d*, *J* = 4.4, 1 H); 6.47 (*d*, *J* = 7.5, 2 H); 6.71–6.77 (*m*, 2 H); 6.93–6.98 (*m*, 1 H); 7.24–7.40 (*m*, 6 H); 7.44–7.52 (*m*, 2 H); 7.64–7.68 (*m*, 1 H); 7.76–7.85 (*m*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 43.0; 43.2; 51.9; 53.8; 58.9; 61.0; 62.9; 124.2; 124.3; 125.8; 126.2; 126.7; 126.8; 127.0; 127.6; 127.8; 128.0; 128.4; 128.9; 128.9; 132.4; 133.2; 136.6; 137.4; 138.1; 171.6. HR-MALDI-MS: 451.2374 ($[M+H]^+$, $C_{30}H_{31}N_2O_2^+$; calc. 451.2380).

*(±)-(3a*RS*,4*SR*,6*RS*,6a*SR*)-Tetrahydro-4-(1-methylethyl)-6-(naphthalen-2-yl)-2-(phenylmethyl)pyrrolo[3,4-c]pyrrole-1,3(2*H*,3a*H*)-dione* ((±)-*endo*-**46b**). *General Procedure G* with **23** (5.62 g, 30.0 mmol, 1.00 equiv.), L-valine ((+)-**45b**) (3.69 g, 31.5 mmol, 1.05 equiv.), **25** (4.92 g, 31.5 mmol, 1.05 equiv.), and MeCN (60 ml) afforded (±)-**46b** (3.29 g, 28%) after purification by CC (SiO_2; CH_2Cl_2/Et_2O 97:3). Only the (±)-*endo*-**46b** was isolated in pure form. White solid. M.p. 135–137°. IR (neat): 3350*w*, 3336*w*, 3031*w*, 2955*w*, 2892*w*, 2870*w*, 1772*w*, 1690*s*, 1603*w*, 1586*w*, 1512*w*, 1496*w*, 1455*w*, 1424*m*, 1398*m*, 1358*w*, 1338*m*, 1312*m*, 1266*w*, 1237*w*, 1211*w*, 1175*m*, 1151*w*, 1124*w*, 1079*w*, 1048*w*, 1028*w*, 1002*w*, 979*w*, 931*w*, 860*m*, 817*m*, 771*w*, 744*m*, 723*m*, 701*m*, 684*w*, 657*m*, 651*m*, 617*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.99 (*d*, *J* = 6.7, 3 H); 1.09 (*d*, *J* = 6.7, 3 H); 1.78–1.90 (*m*, 1 H); 2.16 (br. *s*, 1 H); 3.21 (*d*, *J* = 7.8, 1 H); 3.42–3.47 (*m*, 2 H); 4.50 (*s*, 3 H); 4.78 (*d*, *J* = 8.7, 1 H); 7.23–7.29 (*m*, 7 H); 7.41–7.46 (*m*, 2 H); 7.66–7.70 (*m*, 2 H); 7.78–7.81 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 19.2; 20.0; 29.8; 42.6; 49.6; 49.8; 62.1; 67.2; 125.5; 125.6; 125.7; 125.8; 127.6; 127.7; 128.0; 128.4; 128.7; 128.8; 133.0; 133.1; 135.7; 135.8; 175.3; 178.6. HR-MALDI-MS: 399.2061 ($[M+H]^+$, $C_{26}H_{27}N_2O_2^+$; calc. 399.2067).

*(±)-Methyl (2*RS*,3*SR*,4*RS*,5*SR*)-Tetrahydro-2-(1-methylethyl)-5-(naphthalen-2-yl)-4-{[(phenylmethyl)amino]carbonyl}pyrrole-3-carboxylate* ((±)-**47b**). *General Procedure H* with *endo*-(±)-**46b** (3.19 g, 8 mmol, 1 equiv.), 0.05M NaOH in THF/H_2O 2:1 (320 ml), MeOH (200 ml), and $SOCl_2$ (2.91 ml, 40 mmol, 5 equiv.). The crude product was taken up in sat. aq. $NaHCO_3$ soln. (350 ml), H_2O (75 ml), and CH_2Cl_2/i-PrOH 3:1 (400 ml). The layers were separated. The aq. phase was extracted with CH_2Cl_2/i-PrOH 3:1 (2×400 ml). The comb. org. phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a solid, which was purified by CC (SiO_2; CH_2Cl_2/MeOH/Et_3N 95:5:1) to give (±)-**47b** (380 mg, 11%). White solid. M.p. 152–154°. IR (neat): 3292*m*, 3057*w*, 2954*w*, 2867*w*, 1726*s*, 1626*s*, 1603*w*, 1559*m*, 1548*w*, 1454*m*, 1432*m*, 1399*w*, 1384*m*, 1262*m*, 1230*m*, 1128*m*, 1082*m*, 1014*m*, 967*w*, 953*w*, 906*w*, 890*w*, 853*m*, 819*m*, 805*m*, 780*w*, 740*s*, 722*s*, 693*s*, 643*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.03 (*d*, *J* = 6.7, 3 H); 1.06 (*d*, *J* = 6.7, 3 H); 1.85 (*quint*, *J* = 6.7, 1 H); 2.67 (br. *s*, 1 H); 3.24 (*dd*, *J* = 7.2, 7.2, 1 H); 3.48 (*dd*, *J* = 7.2, 5.0, 1 H); 3.68 (*s*, 3 H); 3.86 (*dd*, *J* = 7.2, 7.2, 1 H); 3.95 (*dd*, *J* = 14.9, 5.6, 1 H); 4.09 (*dd*, *J* = 14.9, 5.6, 1 H); 4.66 (*d*, *J* = 5.0, 1 H); 6.24 (*dd*, *J* = 5.6, 5.6, 1 H); 6.54–6.57 (*m*, 2 H); 6.57–6.88 (*m*, 2 H); 7.00–7.05 (*m*, 1 H); 7.35 (*dd*, *J* = 8.7, 1.8, 1 H); 7.42–7.52 (*m*, 2 H); 7.75–7.84 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 18.9; 19.6; 33.4; 43.0; 51.8; 55.9; 64.0; 64.4; 124.5; 124.7; 125.8; 126.2; 126.8; 127.2; 127.6; 127.9; 128.0; 128.1; 132.7; 133.3; 135.6; 137.6; 170.0; 172.3. HR-MALDI-MS: 431.2328 ($[M+H]^+$, $C_{27}H_{31}N_2O_3^+$; calc. 431.2329). Anal. calc. for $C_{27}H_{30}N_2O_3$ (430.55): C 75.23, H 7.02, N 6.51; found: C 75.27, H 6.85, N 6.28.

*(±)-(2*RS*,3*SR*,4*RS*,5*SR*)-Tetrahydro-4-(hydroxymethyl)-5-(1-methylethyl)-2-(naphthalen-2-yl)-N-(phenylmethyl)pyrrole-3-carboxamide* ((±)-**48b**). *General Procedure I* with (±)-**47b** (329 mg, 0.76 mmol, 1.0 equiv.), 20 wt.-% DIBAL-H in toluene (1.89 ml, 2.29 mmol, 3.0 equiv.), and THF (8 ml) afforded (±)-**48b** (105 mg, 34%) after purification by CC (SiO_2; Et_2O/MeOH/Et_3N 98:1:1). White solid. M.p.

130–132°. IR (neat): 3319*w*, 3059*w*, 2955*w*, 2919*w*, 1700*w*, 1637*s*, 1604*w*, 1545*m*, 1496*w*, 1455*m*, 1419*w*, 1386*w*, 1357*w*, 1272*w*, 1250*w*, 1227*m*, 1157*w*, 1126*w*, 1077*m*, 1029*m*, 962*w*, 899*m*, 851*m*, 817*s*, 779*w*, 735*s*, 721*s*, 698*s*, 641*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.05 (*d*, *J* = 6.5, 6 H); 1.80–1.91 (*m*, 1 H); 2.28 (br. *s*, 1 H); 2.74–2.85 (*m*, 2 H); 3.24–3.33 (*m*, 1 H); 3.55–3.66 (*m*, 2 H); 3.73–3.82 (*m*, 1 H); 4.00 (*dd*, *J* = 14.9, 4.7, 1 H); 4.36 (*dd*, *J* = 14.9, 6.9, 1 H); 4.73 (*d*, *J* = 4.4, 1 H); 6.51 (*d*, *J* = 7.5, 2 H); 6.74–6.80 (*m*, 2 H); 6.97 (*dd*, *J* = 7.5, 1 H); 7.35–7.39 (*m*, 1 H); 7.45–7.53 (*m*, 2 H); 7.70–7.86 (*m*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 19.5; 19.8; 33.3; 43.0; 49.4; 53.9; 61.6; 63.3; 63.8; 124.1; 124.3; 125.7; 126.2; 126.7; 127.0; 127.6; 127.8; 128.0; 128.4; 132.4; 133.2; 136.9; 137.5; 172.0. HR-MALDI-MS: 403.2373 ($[M+H]^+$, $C_{26}H_{31}N_2O_2^+$; calc. 403.2380). Anal. calc. for $C_{26}H_{30}N_2O_2$ (402.54): C 77.58, H 7.51, N 6.96; found: C 77.46, H 7.54, N 6.85.

PPIase Assay. PPIase Activity and inhibition assays were performed using a *Hewlett-Packard 8453A* UV/VIS spectrophotometer. 10 nM Pin1 was incubated in 35 mM HEPES buffer, pH 7.8, in the presence or absence of inhibitors. The enzyme activity of hPin1 towards the substrate Suc-Ala-Glu-Pro-Phe-pNA was measured using the protease free PPIase assay according to *Janowski et al.* [30][49][50]. A 30 mM stock soln. of the substrate in 0.5M LiCl/TFE (anh.) was prepared fresh before the measurement (60-μM final substrate concentration). Prior to every measurement, all components except substrate were incubated for 300 s at 10° under vigorous stirring. The measurement was started upon substrate addition and the *cis*/*trans* isomerization kinetic of the substrate was followed at 330 nm.

The limit for measuring K_i values in this PPIase assay is primarily given by the solubility of the respective inhibitor. K_i can be reliably determined when *ca.* 80% inhibition is reached, which is roughly the case at inhibitor concentrations, ten times greater than the inhibition constant. The function used to fit K_i values to measured first-order rate constants is:

$$k_{enz} = (k_{cat}/K_M\,[E])\;(1/(1+[I]/K_i))$$

where k_{enz} is the measured first-order rate constant for the enzyme-catalyzed *cis*/*trans* isomerization, k_{cat}/K_M is the specific activity of the enzyme towards the substrate used, [E] is the enzyme concentration, [I] the concentration of the inhibitor, and K_i the inhibition constant.

^{15}N,^{1}H-HSQC-NMR Spectroscopy. Full length wild-type PIN1 was cloned into pGEX1T vector and expressed as a GST-fusion protein in soluble form in *E. coli* strain BL21 grown in minimal medium containing ^{15}N-labeled amino acids. Cells were lysed using *Frech* press and resuspended in PBS buffer, 1% *Triton X-100*, 10% glycerol. The supernatant was centrifuged and applied to a *GSH*-sepharose column equilibrated in PBS. Bound protein was cleaved on-column using thrombin, eluted in PBS buffer, and analyzed using *Coomassie*-stained SDS-PAGE. Fractions containing Pin1 were pooled, concentrated, and applied to *S200* column, equilibrated in 20 mM phosphate buffer, pH 6.6, with 100 mM Na_2SO_4, 5 mM EDTA, and 1 mM DTT. The peak fractions containing Pin1 were supplemented with D_2O, concentrated, and used for NMR experiments.

The samples contained 0.2 mM U-^{15}N-labeled PIN1 protein in 20 mM phosphate buffer pH 6.6 with 100 mM Na_2SO_4, 5 mM EDTA, 1 mM DTT, and 5% D_2O. Spectra were acquired at 298 K on a *Bruker DRX700* spectrometer equipped with a triple resonance (^{1}H, ^{13}C, ^{15}N) inverse probe head with a *z*-gradient. A tenfold molar excess of the test compound dissolved in 10 ml $(CD_3)_2SO$ was added to the protein sample.

^{15}N,^{1}H-HSQC spectra of the Pin1 protein were acquired either from the free protein with a $(CD_3)_2SO$ control or in the presence of inhibitors (−)-**1a**, (−)-**1b**, or (+)-**22a**.

The spectra were processed with the XWinNMR software package and further evaluated using the program SPARKY [51]. NMR Resonance assignment according to *Jacobs et al.* [31a] was applied on the spectrum of the free protein, and the spectra after addition of the test compound were overlaid. Further evaluation was made by classifying the residues into signals with no, weak, and strong effect on the peak position, and mapping the chemical-shift perturbation onto the crystal structure of Pin1 (PDB code 1PIN) [23]. The residues are colored in *Figs. 4* and *7* according to the following scheme: *red*: signals disappear or shift far apart to other spectral region, *yellow*: shifts stronger than the linewidth.

*X-Ray Crystal Structure of (+)-***12**. Crystal data at 173(2) K for $C_{17}H_{27}NO_4$ (M_r 309.40), orthorhombic, space group $P2_12_12_1$ (No. 19), $D_c = 1.197$ g cm^{-3}, $Z = 4$, $a = 5.9157(3)$ Å, $b = 14.0249(8)$ Å,

$c = 20.6938(13)$ Å, $V = 1716.90(13)$ Å^3. *Bruker-Nonius Kappa-CCD* diffractometer, MoK_α radiation, $\lambda = 0.7107$ Å, $\mu = 0.084$ mm^{-1}. Crystal dimensions *ca.* $0.20 \times 0.12 \times 0.04$ mm. The structure was solved by direct methods (SIR97) [52] and refined by full-matrix least-squares analysis (SHELXL-97) [53], using an isotropic extinction correction. All non-H-atoms were refined anisotropically, H-atoms isotropically, whereby H-positions are based on stereochemical considerations. Final $R(F) = 0.061$, w$R(F2) = 0.140$ for 227 parameters and 2294 reflections with $I > 2\sigma(I)$ and $1.97 < \theta < 25.00°$ (corresponding R values based on all 2926 reflections are 0.087 and 0.175 resp.). CCDC-622545.

*X-Ray Crystal Structure of (−)-***35**. Crystal data at 223(2) K for $C_{26}H_{24}N_2O_3$ (M_r 412.47), orthorhombic, space group $P2_12_12_1$ (No. 19), $D_x = 1.341$ g cm^{-3}, $Z = 4$, $a = 10.7576(2)$ Å, $b = 11.9045(3)$ Å, $c = 15.9498(4)$ Å, $V = 2042.59(8)$ Å^3. *Bruker-Nonius Kappa-CCD* diffractometer, MoK_α radiation, $\lambda = 0.7107$ Å, $\mu = 0.088$ mm^{-1}. Linear crystal dimensions *ca.* $0.35 \times 0.31 \times 0.30$ mm. Numbers of measured and unique reflections are 4594 and 2628, resp. ($R_{int} = 0.019$). The structure was solved by direct methods (SIR97) [52] and refined by full-matrix least-squares analysis (SHELXL-97) [53], using an isotropic extinction correction. All non-H-atoms were refined anisotropically, H-atoms isotropically, whereby H-positions are based on stereochemical considerations. $R(F) = 0.049$, w$R(F2) = 0.125$ for 300 parameters and 2325 reflections with $I > 2\sigma(I)$ and $3.07 < \theta < 27.49°$ (corresponding R values based on all 2628 reflections are 0.055 and 0.129 resp.). CCDC-600420.

X-Ray Crystal Structure of **38c**. Crystal data at 223(2) K for $C_{27}H_{30}N_2O_3$ (M_r 430.53), monoclinic, space group $C2$ (No. 5), $D_x = 1.285$ g cm^{-3}, $Z = 4$, $a = 18.4825(3)$ Å, $b = 5.0671(1)$ Å, $c = 25.2401(6)$ Å, $\beta = 109.645(1)°$, $V = 2226.21(8)$ Å^3. *Bruker-Nonius Kappa-CCD* diffractometer, MoK_α radiation, $\lambda = 0.7107$ Å, $\mu = 0.084$ mm^{-1}. Linear crystal dimensions *ca.* $0.25 \times 0.23 \times 0.15$ mm. Numbers of measured and unique reflections are 3960 and 2428, resp. ($R_{int} = 0.024$). The structure was solved by direct methods (SIR97) [52] and refined by full-matrix least-squares analysis (SHELXL-97) [53], using an isotropic extinction correction. Naphthalenyl and phenyl groups are disordered over two orientations; only one orientation is shown in *Fig. 6, b*. All non-H-atoms were refined anisotropically, H-atoms isotropically, whereby H-positions are based on stereochemical considerations. Final $R(F) = 0.044$, w$R(F2) = 0.107$ for 381 parameters, 1 restraint, and 2138 reflections with $I > 2\sigma(I)$ and $3.33° < \theta < 26.01°$ (corresponding R values based on all 2428 reflections are 0.052 and 0.113 resp.). CCDC-600421.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre*. Copies of the data can be obtained, free of charge, on application to the *CCDC*, 12 Union Road, Cambridge CB2 1EZ UK (fax:+44(1223) 336 033; e-mail: deposit@ccdc.cam.ac.uk).

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