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Identification of Inhibitors for Mycobacterial Protein Tyrosine Phosphatase B (MptpB) by Biology-Oriented Synthesis (BIOS)

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Abstract: Protein phosphatases have recently emerged as important targets for research in chemical biology and medicinal chemistry, and new classes of phosphatase inhibitors are in high demand. BIOS (biology-oriented synthesis) employs the criteria of relevance to nature and biological prevalidation for the design and synthesis of compound collections. In an application of the BIOS principle, an efficient solid-phase synthesis of highly substituted indolo[2,3-a]quinolizidines by using a vinylogous Mannich–Michael reaction in combination with phosgene- or acid-mediated ring closure was developed. Screening of this library for phosphatase inhibitors yielded a new inhibitor class for the *Mycobacterium tuberculosis* phosphatase MptpB.

Keywords: alkaloids · biology-oriented synthesis (BIOS) · enzyme inhibition · phosphatases · solid-phase synthesis

Introduction

Protein phosphatases are critically involved in numerous biological processes and play fundamental roles in cellular-signaling events.[1] As a consequence, small-molecule regulators of protein phosphatases have proven to be valuable tools in various studies of cell biology.[2] Moreover, selective small-molecule inhibition of protein phosphatases may result in a new approach for the treatment of various important diseases such as diabetes and cancer. Consequently, the development of such drug candidates is currently a major topic of research in medicinal chemistry. However, although research activities in this field have intensified substantially in recent years, new classes of phosphatase inhibitors are in high demand.[2] One of the most important criteria for compound collections for applications in chemical biology and research in medicinal chemistry is their relevance to nature.[3] The structural scaffolds of natural products encode evolutionary selected properties for binding to proteins and, therefore, represent biologically relevant and prevalidated fractions of chemical space.[4,5] Based on these arguments, BIOS (biology-oriented synthesis) employs the core structures of natural products as scaffolds for compound collections.[6] Such scaffolds can be identical with the core structure of a natural product in which different substituents are introduced at exactly the same positions as predetermined by nature. This approach led, for instance, to the discovery of new SHP-2 and VE-PTP inhibitors based on the furanodictine or cytisin scaffold.[6] In contrast to these "natural-

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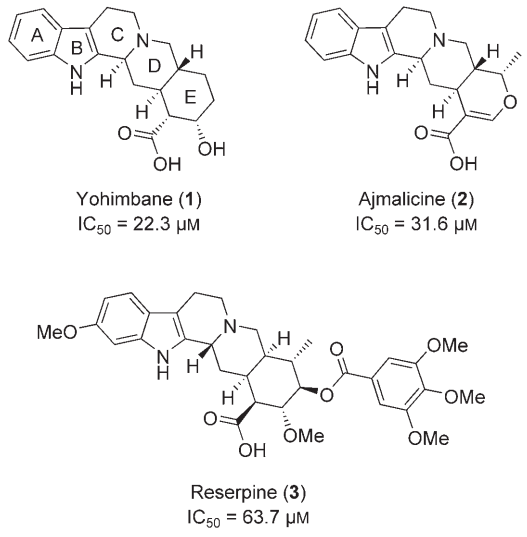
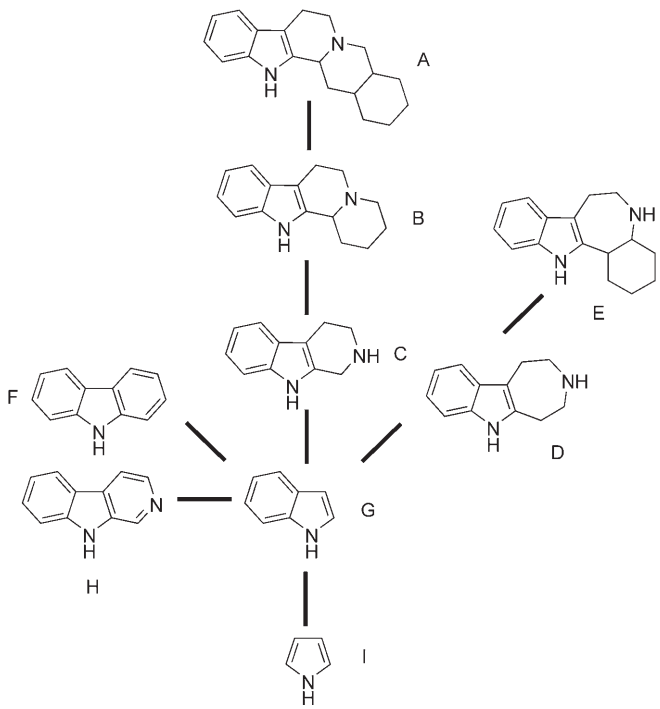
product-derived" scaffolds, unidentical but closely related structural frameworks of natural products may be used for library synthesis. In this "natural-product-inspired" approach, substituents are introduced not necessarily at the original substitution sites of the guiding natural product (NP). Also, the stereochemistry may be varied. Both strategies allow the creation of focused diversity around a biologically validated starting point in chemical space. BIOS builds on the diversity created by nature and in evolution and aims at local extension in areas of proven relevance. Therefore, it is to be expected that compound collections designed on the basis of NP structure will be enriched in biological activity. In the application of the BIOS concept for the development of phosphatase inhibitors, 354 chemically diverse natural products were screened for inhibition of the phosphatases PTP1B, Shp-2, VE-PTP, Cdc25A, and VHR, as well as MptpA and MptpB. PTP1B is considered a target for the development of new drugs against diabetes and metabolic syndromes.[7,8] Shp-2 is a tyrosine phosphatase which is a target for the development of new anticancer drugs.[9] VE-PTP dephosphorylates the Tie-2 receptor tyrosine kinase and enhances the adhesive function of endothelial VE-cadherin.[10] The phosphatase Cdc25A is involved in cell-cycle regulation and is, therefore, an anticancer target.[7] Finally, VHR influences signaling by dephosphorylation of ERK1/2 and Jun kinases.[11] Recently, the two protein phosphatases MptpA and MptpB of the human pathogen *Mycobacterium tuberculosis* were identified as potential targets for the treatment of tuberculosis infections.[7,12,13] *M. tuberculosis* secretes these two enzymes, thereby modulating the normal cell-signaling processes of the host by dephosphorylation of proteins involved in interferon–γ-signaling pathways. This process seems essential for bacterial survival in the macrophage cells of the host, which is further supported by recent investigations that found that the survival of bacteria lacking MptpB phosphatase activity was significantly decreased.[13]

Surprisingly, of the 354 isolated natural products screened in the phosphatase assay, three out of seven Yohimbane-type indole alkaloids displayed moderate to weak inhibitory activity for the dual-specificity phosphatase Cdc25A. Importantly, inhibition was influenced by the stereochemistry of the D–E ring linkage as well as the substitution pattern in the E ring (Scheme 1).

These results indicated that by appropriate structure variation, identification of more potent inhibitors may be possible. However, in view of the structural complexity of the pentacyclic Yohimbane alkaloids, which turns a library synthesis of these scaffolds into a tedious task, we consulted the SCONP principle (structural classification of natural products) for design guidance.[4] SCONP arranges natural products genealogically in a treelike structure, thereby relating structurally more complex scaffolds to structurally less complex ones under retention of biological activity. Following this design guidance, the basic scaffold of the Yohimbane alkaloids A was assigned to the indole branch of the SCONP tree (Scheme 2).[4] Brachiation along the line of prevalidation by nature then leads to tetracyclic indolo[2,3-a]quinolizidines B and, if further structural simplification is sought, via tetrahydro-β-carbolines C to indoles G.



Scheme 1. Inhibitors of the dual-specificity phosphatase Cdc25A identified through screening of 354 isolated natural products.



Scheme 2. Schematic representation of the indole branch of the SCONP tree and general structure of the indole-inspired compound collection **9**.

Natural products that contain the indolo[2,3-a]quinolizidine framework have been reported to display a wide range of biological activities. Examples include the antiplasmodial agent dihydrousambarensine (**4**),[14] the antiviral natural product hirsutine (**5**),[15] the antibacterial lercheine (**6**),[16] glabratine (**7**),[16] as well as the cytotoxic compound 10-hydroxyangustine (**8**)[17] (Scheme 3). These findings further va-

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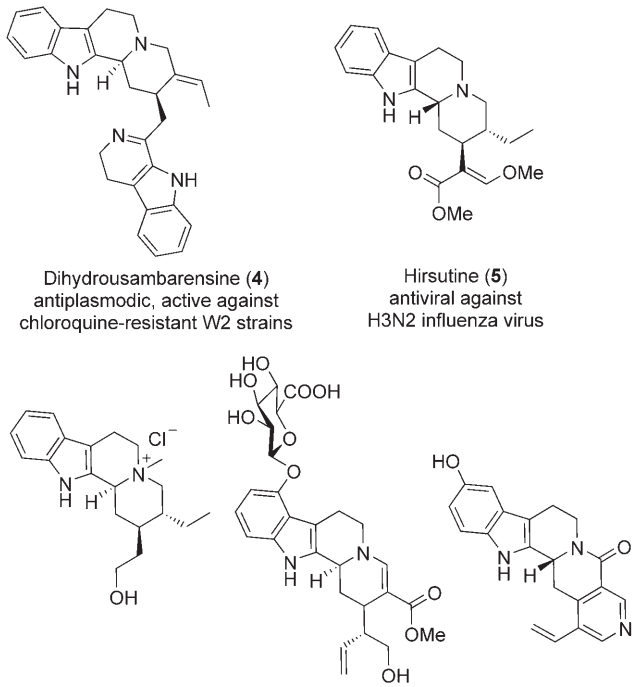


Scheme 3. Biologically active natural products with the indolo[2,3-a]-quinolizidine substructure.

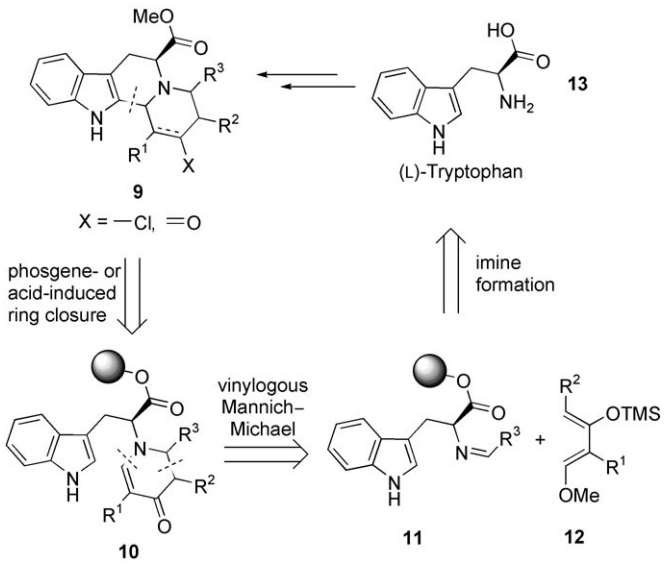
lidated our choice of the indolo[2,3-a]quinolizidine scaffold as a promising structural framework for the development of a natural-product-inspired compound collection.

Herein we describe in detail (for a preliminary account, see reference [6]) the development of two different approaches to the synthesis of a focused library of indolo[2,3-a]quinolizidines by a vinylogous Mannich–Michael reaction followed by a phosgene- or acid-induced ring closure as key steps, and their evaluation as phosphatase inhibitors.

Results and Discussion

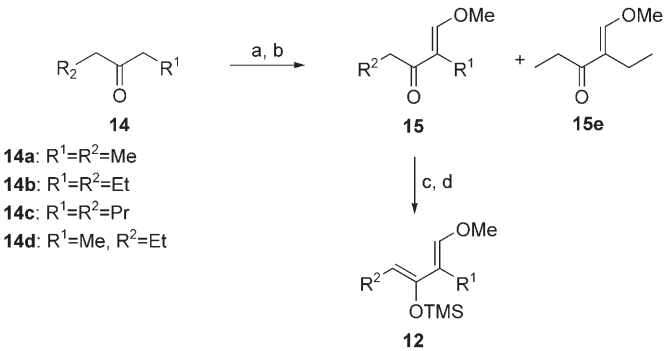
The indolo[2,3-a]quinolizidine framework **9** was retrosynthetically traced back to pyridone precursor **10** (Scheme 4). The carboxylate moiety was chosen for attachment to the solid support. Enaminone precursor **10** would be accessible by vinylogous Mannich–Michael reaction of imine **11** and various electron-rich silyloxydienes **12**.

Two different synthetic routes to indoloquinolizidines were followed, which differed mainly in the mode of ring closure. In the case of phosgene-mediated ring closure leading to tetracyclic vinyl chlorides, the Wang linker was chosen. Alternatively, tetracyclic ketones were synthesized by acid-mediated cyclization on the base-labile hydroxymethylene benzoic acid (HMBA) linker. Therefore, release from the Wang polymer would afford tetracyclic vinyl chlorides as free carboxylic acids, whereas cleavage from the HMBA resin would lead to methyl esters.



Scheme 4. Retrosynthetic analysis of indolo[2,3-a]quinolizidines **9**. TMS = trimethylsilyl.

Unsubstituted silyloxydienes are commercially available; however, disubstituted silyloxydiene building blocks **12** had to be prepared by a simple two-step procedure (Scheme 5).[18] Compounds **15** were synthesized by formylation of **14** in moderate to good yields. For larger R^1 and R^2 substituents, the yields of vinylogous ketones **15** increased significantly. For $R^1 = R^2 = Me$, a moderate yield of 60% was obtained for **15a**. However, changing R^1 and R^2 to propyl groups led to 84% yield for **15c**. In the case of the unsymmetrical ketone **15d** with $R^1 = Me$ and $R^2 = Et$, the corresponding regioisomer **15e** was also formed in 16% yield and was removed by distillation. Finally, silylation of ketones **15** led to the substituted silyloxydienes **12** in good to excellent yields (Scheme 5). In this reaction step, substitu-



Scheme 5. Synthesis of electron-rich silyloxydienes. a) HCOOMe, NaH, THF, 0°C, 1 h; b) Me_2SO_4, DMF, 0°C→RT, overnight, 60% for **15a**, 71% for **15b**, 84% for **15c**, 49% for **15d**, 16% for **15e** (over two steps); c) LDA, THF, −78°C, 1 h; d) TMSCl/TEA (3:1), −78°C→RT, overnight, 72% for **12a**, 98% for **12b**, 94% for **12c**, 76% for **12d** (over two steps). DMF = *N,N*-dimethylformamide, LDA = lithium diisopropylamide, TEA = triethylamine.

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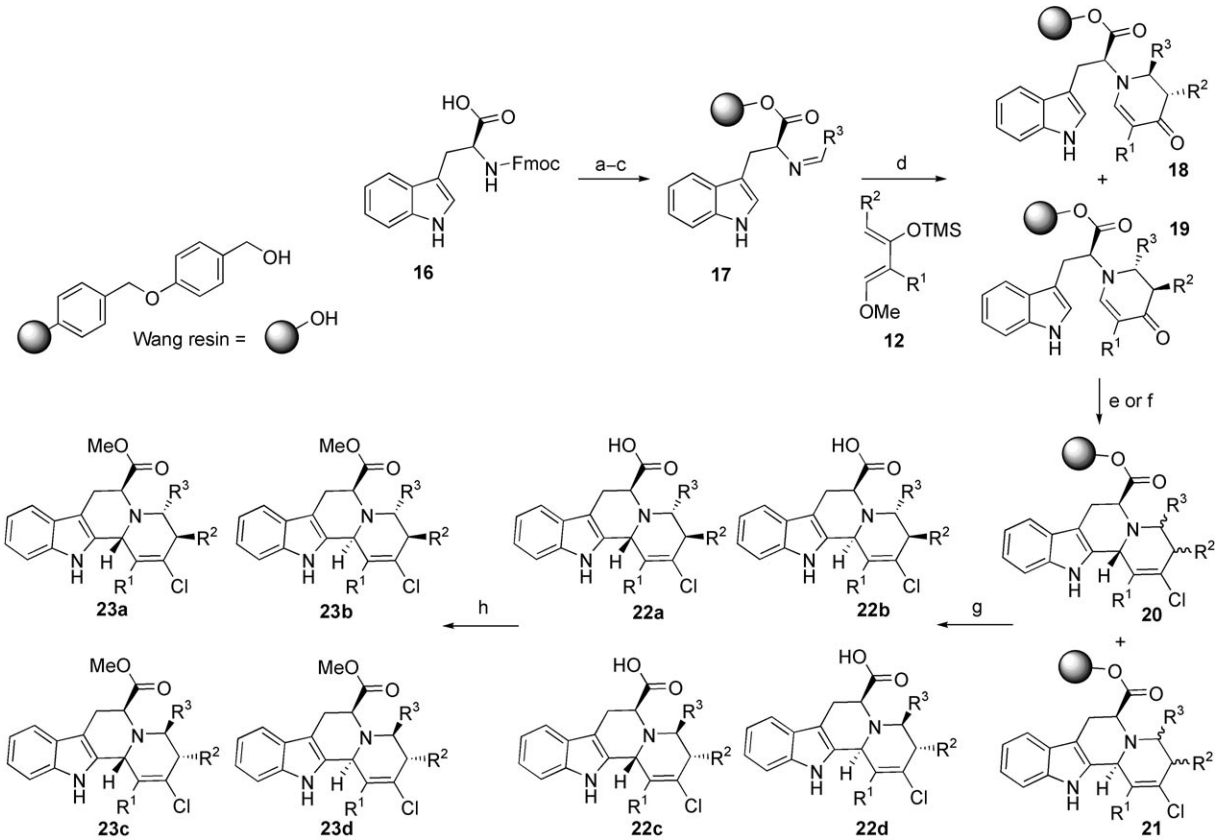
ents with larger R^1 and R^2 groups also led to improved yields. For $R^1 = R^2 = Me$, a yield of 72% was obtained, whereas replacement of R^1 and R^2 with ethyl or propyl groups yielded the silyloxydienes **12b** and **12c** in 94 and 98% yield, respectively.

The synthesis of the Yohimbane-inspired tetracyclic vinyl chlorides was performed as shown in Scheme 6. Towards this end, (L)-fluorenylmethoxycarbonyltryptophan (**16**) was loaded on polystyrene beads carrying a Wang linker (loading = 0.87 mmol g^{-1}) in the presence of pyridine and 2,6-dichlorobenzoyl chloride.[19] Cleavage of the Fmoc protecting group followed by reaction with various aldehydes R^3CHO led to the formation of tryptophan imines **17**.[20] These intermediates were then subjected to a Lewis acid mediated tandem Mannich–Michael reaction with various electron-rich silyloxydienes **12** to yield immobilized enaminones **18** and **19**,[21,22] with diastereomer ratios ranging from 65:35 to 90:10 and **19** as the major product.

Ring closure to the indolo[2,3-a]quinolizidine framework was carried out by treatment of enaminones **18** and **19** with phosgene and TMSCl, which resulted in the formation of solid-phase-bound vinyl chlorides **20** and **21**.[23] The diastereoselective induction follows the trends observed for analogous vinylogous Mannich–Michael and phosgene-induced ring-closure reactions in solution.[24]

Compounds **20** and **21** were then released from the solid support by addition of TFA to yield tetracyclic compounds **22**,[25] which were subsequently transformed to the methyl esters **23**.[26] The five- to six-step solid-phase reaction sequence was compatible with aromatic, heterocyclic, and aliphatic aldehydes as well as differently substituted electron-rich silyloxydienes **12**. Vinyl chlorides **22** and **23** were obtained in overall yields of 36–72%, thus indicating a high overall efficiency of the reaction sequence. With this synthetic methodology, 204 tetracyclic Yohimbane analogues were synthesized (for representative examples, see Table 1). The highest yields were obtained with aromatic aldehydes, whereas aliphatic aldehydes led to lower yields, possibly due to enamine tautomerization and side reactions in the imine-formation step (Table 1, compounds **23-6**, **23-10**, and **23-14**). The use of disubstituted silyloxydienes **12b–d** was well-tolerated for small R^1 and R^2 groups. In the case of $R^1 = R^2 =$ Me, Et or $R^1 = Me$, $R^2 = Et$, excellent yields were obtained (Table 1, compounds **22-1**, **23-3**, and **23-5**). For $R^1 = R^2 =$ propyl, yields were significantly lower, maybe as a result of steric hindrance in the vinylogous Mannich–Michael reac-



Scheme 6. Solid-phase synthesis of vinyl chlorides **22** and **23** by employing (L)-tryptophan. a) 2,6-Dichlorobenzoyl chloride (2 equiv), pyridine (3 equiv), Wang resin (0.30 equiv), DMF, RT, 31 h; b) 20% piperidine in DMF, RT, two times for 10 min; c) R^3CHO (5 equiv), trimethylorthoformiate/CH_2Cl_2 (1:1), RT, 12 h; d) dienes **12** (5 equiv), 1 M $ZnCl_2$ in THF (2 equiv), propionitrile, 0 °C→RT, 15 h; e) $COCl_2$, TMSCl, CH_2Cl_2, RT, 30 min; f) $COCl_2$, TMSCl, CH_2Cl_2, reflux, 8 h; g) TFA, H_2O, RT, 36–64% (overall yield of **22**); h) EDC·HCl (5 equiv), pyridine/MeOH/CH_2Cl_2 (1:1:1), RT, overnight, 36–72% (overall yield of **23**). EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, Fmoc = 9-fluorenylmethoxycarbonyl, TFA = trifluoroacetic acid.

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Table 1. Yields and selectivities recorded in the synthesis of selected tetracyclic vinyl chlorides **22** and **23**.

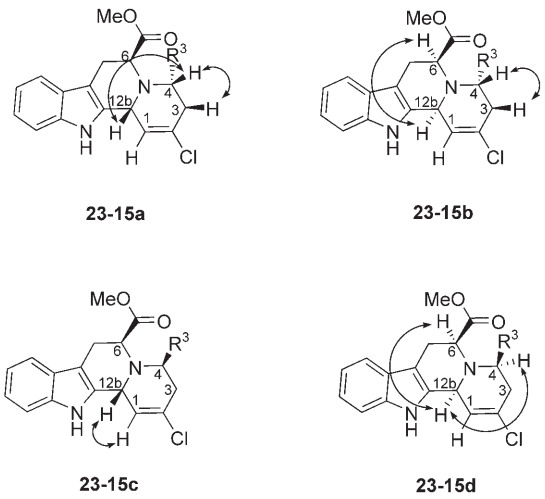
Compound	R^1, R^2	R^3	Yield[a] [%]	d.r.[b]	d.r.[c]
22-1[d]	Me, Me	phenyl	52	71:29	65:35
22-2	H, H	3,4-difluorophenyl	48	75:25	76:24
23-1	H, H	4-bromophenyl	65	73:27	75:25
23-2	H, H	3,4-difluorophenyl	46	75:25	76:24
23-3[d]	Me, Et	4-chlorophenyl	56	66:34	72:28
23-4	H, H	4-isopropylphenyl	71	72:28	66:34
23-5[d]	Et, Et	4-fluorophenyl	54	77:23	74:26
23-6	H, H	isopropyl	28	66:34	70:30
23-7[d]	Pr, Pr	4-chlorophenyl	25	72:28	68:32
23-8	H, H	3-furyl	57	86:14	71:29
23-9	H, H	3-methylphenyl	66	80:20	68:32
23-10	H, H	ethyl	36	69:31	67:33
23-11	H, H	4-hexyloxyphenyl	73	77:23	69:31
23-12	H, H	4-methylphenyl	65	72:28	68:32
23-13	H, H	4-methoxyphenyl	67	79:21	64:36
23-14	H, H	methyl	19	66:34	65:35
23-15	H, H	4-chlorophenyl	66	75:25	65:35

[a] Yield (all four diastereomers) over five or six steps including HPLC purification. For cyclization, phosgene and TMSCl in CH_2Cl_2 at room temperature for 30 min was used. [b] Diastereoselectivity of the vinylogous Mannich–Michael reaction. [c] Diastereoselectivity of the phosgene-induced cyclization. [d] For cyclization, phosgene and TMSCl in CH_2Cl_2 heated under reflux for 8 h was used.

tion or during the phosgene-induced cyclization (Table 1, compound **23-7**).

Furthermore, when disubstituted dienes **12b–d** were employed in the reaction sequence, the reaction had to be heated for 8 h at reflux to complete the cyclization. The diastereomer ratio in the cyclization step, which led to vinyl chlorides **20** and **21**, was approximately 2:1 in favor of **20**, and the corresponding tetracyclic indoloquinolizidines **22** and **23** were formed as mixtures of four isomers, which were readily separated by preparative HPLC on a C18 column. The diastereomer **22a**/**23a** was found as the main product after vinylogous Mannich–Michael reaction and phosgene-induced cyclization, followed by **22b**/**23b**, **22c**/**23c**, and finally **22d**/**23d** as the minor product.

The diastereomer ratios were determined gravimetrically after product isolation (Table 1). The configuration of vinyl chlorides **22** and **23** was determined by nuclear Overhauser effect (nOe) difference spectroscopy, by using the characteristic signal chemical shifts in their ^{1}H NMR spectra (Scheme 7). For instance, nOe measurements of the (4*S*,6*S*,12b*R*) diastereomer **23-15a** revealed a spatial proximity between 12b-H and 4-H, thus proving their equatorial orientation. The axial orientation of 12b-H of the (4*R*,6*S*,12b*S*) diastereomer **23-15b** was confirmed by an nOe enhancement between 12b-H and 6-H. For the (4*S*,6*S*,12b*S*) diastereomer **23-15c**, an nOe enhancement was observed between 12b-H and 1-H. Finally, the configuration of the (4*R*,6*S*,12b*S*) diastereomer **23-15d**, with its all-axial orientation, was demonstrated by an nOe enhancement of 12b-H, 6-H, and 4-H as a result of their spatial proximity. These results were further confirmed by comparison of the signals of 12b-H in the ^{1}H NMR spectra. Due to the Perlin effect, the signals of 12b-H of **23-15b** and **23-15d** were shifted upfield



Scheme 7. Observed nOe enhancements of the four model indoloquinolizidines **23-15a** to **23-15d**.

at 4.99 and 4.85 ppm, thus indicating that these protons adopt an axial orientation.

Therefore, the orientation of the carboxy group at the 6-position determines the diastereoselectivity in the vinylogous Mannich–Michael reaction, thus forcing the R^3 group into a *trans* configuration.

The polymer-bound tetracyclic vinyl chlorides **20**/**21** were further functionalized by means of N-acylation. To this end, resin **20**/**21** was stirred at −78 °C in a solution of LHMDS/HMPTA and treated with 10 equivalents of the corresponding acid chloride (Scheme 8).[26] Use of LHMDS as a base was essential, as dimethylaminopyridine (DMAP) led to complete isolation of the starting material, and NaH only provided **26-2** in a yield of 11 %, possibly due to the low solubility of the base. Release of the polymeric carrier led to modified indoloquinolizidines **25** in 30–65 % yield. Solution-phase methylation of **25** then resulted in N-acylated esters **26**, remarkably without cleaving the base-labile *N*-acyl group, in 19–56 % overall yield (for representative examples, see Table 2). Aliphatic R^4 groups usually resulted in lower yields (Table 2, compound **26-4**). With this methodology, a

Table 2. Selected N-acylated tetracyclic acids **25** and methyl esters **26**.

Compound	R^1	R^2, R^3	R^4	Yield[a] [%]	d.r.[b]	d.r.[c]
25-1	4-fluorophenyl	H, H	2-methylthio-3-pyridinecarbonyl	56	77:23	78:22
25-2	4-fluorophenyl	H, H	2-chlorobenzoyl	59	77:23	78:22
26-1	phenyl	H, H	4-nitrobenzoyl	46	65:35	67:33
26-2	phenyl	H, H	4-chlorobenzoyl	52	65:35	67:33
26-3	phenyl	H, H	3,5-difluorobenzoyl	43	65:35	67:33
26-4	phenyl	H, H	acetyl	19	65:35	67:33

[a] Yield (all four diastereomers) over six or seven steps including HPLC purification. [b] Diastereoselectivity of the vinylogous Mannich–Michael reaction. [c] Diastereoselectivity of the phosgene-induced cyclization.

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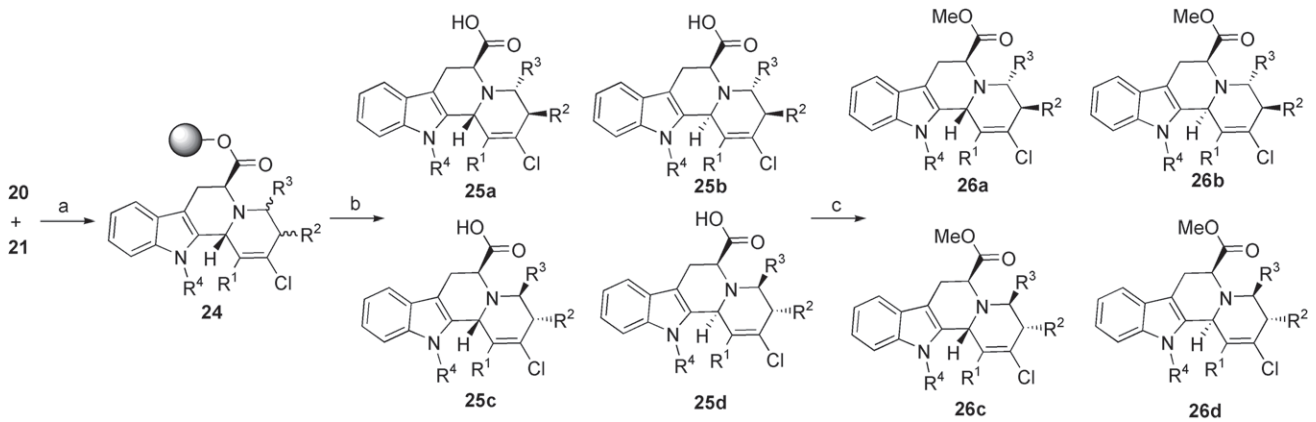
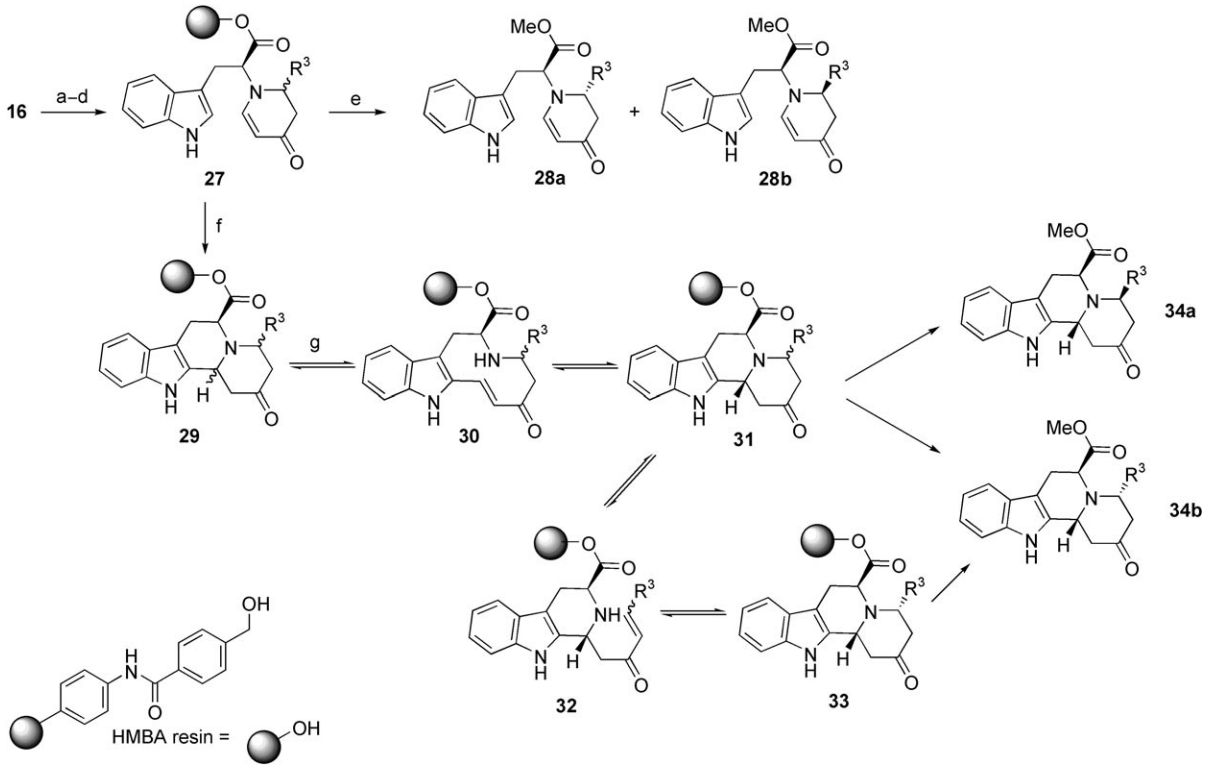


Scheme 8. Library expansion by N-acylation of tetracyclic vinyl chlorides. a) R^4X (X = halogen), LHMDS, HMPTA, −78 °C→RT, 12 h; b) TFA, H_2O, RT, 30–65 % (overall yield of **25**); c) EDC·HCl (5 equiv), pyridine/MeOH/CH_2Cl_2 (1:1:1), RT, overnight, 36–56 % (overall yield of **26**). HMPTA = hexamethylphosphorus triamide, LHMDS = lithium bis(trimethylsilyl)amide.

further 126 tetracyclic N-acylated indolo[2,3-a]quinolizidines were synthesized.

In summary, a combination of the reaction sequences displayed in Schemes 5–8 gave overall access to 360 tetracyclic vinyl chlorides that were at least 90 % pure.

In extension to this synthetic methodology, a synthesis of indolo[2,3-a]quinolizidines by an acid-mediated ring closure was also successfully applied (Scheme 9). To this end, Fmoc–(L)-tryptophan was loaded onto HMBA resin. Imine formation and tandem Mannich–Michael reaction led to polymer-bound enaminones **27**, which were then released from the polymeric carrier to determine the diastereoselectivity of the reaction.[27] Pyridones **28a** and **28b** were obtained in excellent yields with diastereomer ratios ranging from 56:44 to 68:32 with **28b** as the major product, as determined by ^{1}H NMR spectroscopy and a comparison of coupling constants (Scheme 9 and Table 3). The diastereomer ratio parallels the observations made for analogous vinylogous Mannich–Michael reactions in solution.[21]



Scheme 9. Synthesis of tetracyclic ketones **34a** and **34b** on HMBA resin. a) 2,6-Dichlorobenzoyl chloride (2 equiv), pyridine (3 equiv), HMBA resin (0.3 equiv), DMF, RT, 18 h; b) 20 % piperidine in DMF, RT, two times for 10 min; c) R^3CHO (5 equiv), trimethylorthoformiate/CH_2Cl_2 (1:1), RT, 12 h; d) dienes **12** (3 equiv), 1 M $ZnCl_2$ in THF (2 equiv), propionitrile, 0 °C→RT, 15 h; e) TEA/MeOH (1:9), 50 °C, 18 h; f) TFA, TMSCl, CH_2Cl_2 (0.5:1:3), RT, 30 min; g) 0.25 M NaOMe in MeOH, 1,4-dioxane (1:1), 50 °C, 18 h, 12–43 % (overall yield of **34**).

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Table 3. Yields and diastereoselectivities after vinylogous Mannich–Michael reaction and cleavage from solid support.

Compound	R^3	Yield[a] [%]	**28b**/**28a**
28-1	4-methoxyphenyl	59	66:34
28-2	4-chlorophenyl	65	63:37
28-3	4-nitrophenyl	48	68:32
28-4	2-chlorophenyl	60	64:36
28-5	4-carboxymethylphenyl	40	55:45
28-6	isobutyl	33	56:44

[a] Yield after four steps.

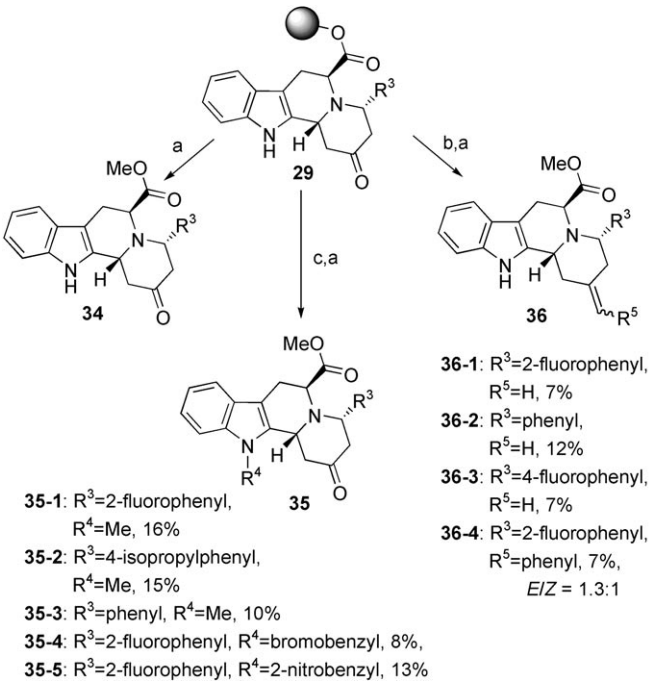
Acid-mediated ring closure to indolo[2,3-a]quinolizidines **29** was achieved by treatment of resin-bound enaminones **27** with TFA/TMSCl for 30 min.[21,22] By analogy to the phosgene-induced ring closure, a diastereomeric mixture should also be formed. In contrast to the synthesis of vinyl chlorides **22** and **23**, ketones **34** were isolated in most cases as single diastereomers after sodium methoxide induced cleavage from the resin,[28] possibly due to epimerization at the 12b- and 4-positions as a consequence of a retro-Michael reaction (Scheme 9 and Table 4, compounds **34-2**–**34-13**). In these cases, only the thermodynamically more stable *trans*-ketone **34b** was isolated. For aliphatic substituents at the 4-position, a diastereomeric mixture at the 4-position, probably due to lower stabilization of the intermediate **32**, was identified by ^{1}H NMR spectroscopy and GC–MS analysis (Table 4, compound **34-1**).

Table 4. Yields and diasteriomer ratios of selected ketones **34**.

Compound	R^3	Yield[a] [%]	**34b**/**34a**
34-1	ethyl	19	78:22
34-2	4-chlorophenyl	37	>99:1
34-3	4-fluorophenyl	30	>99:1
34-4	2-chlorophenyl	27	>99:1
34-5	4-trifluoromethylphenyl	43	>99:1
34-6	4-methylthiophenyl	18	>99:1
34-7	3-chloro-4-fluorophenyl	28	>99:1
34-8	3-trifluoromethoxyphenyl	36	>99:1
34-9	4-allyloxyphenyl	15	>99:1
34-10	4-methoxyphenyl	19	>99:1
34-11	3,4-dichlorophenyl	31	>99:1
34-12	3,4-difluorophenyl	37	>99:1
34-13	phenyl	27	>99:1

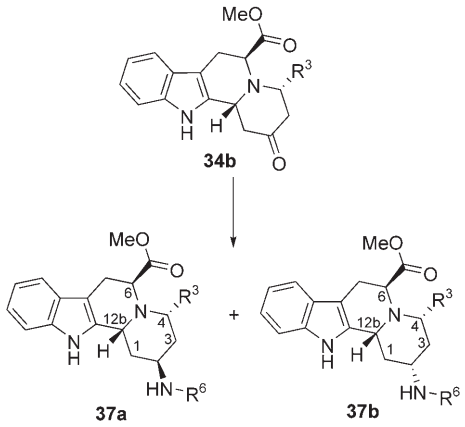
[a] Yield after five steps.

By analogy to resin-bound acylation of the tetracyclic vinyl chlorides, N-acylation and N-methylation or N-benzylation of resin-bound indolo[2,3-a]quinolizines **29** were carried out with BEMP as a base at room temperature (Scheme 10).[29] In contrast to N-acylated vinyl chlorides **25** and **26**, N-acylation of ketones **29** was unsuccessful and led only to the isolation of starting material, probably due to sodium methoxide induced cleavage of the acetyl group. However, N-methylated or N-benzylated compounds **35** were isolated in 13–16% yield over six steps and after HPLC purification. With the carbonyl group as a position for chemical functionalization, resin-bound ketones **29** were converted into alkenes **36** with commercially available phosphonium salts Ph_3PCH_2Br and $Ph_3PCH_2(Ph)Br$ in the presence of butyl lithium at −20 to 50°C in 7–12% yield over six steps and after HPLC purification (Scheme 10).[25] Substituted alkene **36-4** was obtained with a *trans*/*cis* diastereoselectivity of 1.3:1.



Scheme 10. Solid-phase modification of indoloquinolizidines **29** on HMBA resin. a) NaOMe, 0.25 M MeOH/1,4-dioxane (1:1), 50°C, 18 h; b) Ph_3PCHXR^5, *n*BuLi, THF, −20 to 50°C, 3 h; c) BEMP (5 equiv), R^4X (10 equiv), DMF, RT, 24 h. BEMP = 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine.

Further diversification of the library was achieved by reductive amination of ketones **34b** in solution (Scheme 11). The reaction that gave diastereomers **37a** and **37b** proceeded in high yields of 61–93% and was carried out as a one-



Scheme 11. Solution-phase reductive amination of ketones **34b**. Conditions: R^6NH_2, BH_3–pyridine complex, CH_2Cl_2, RT, 15 h, 61–93%.

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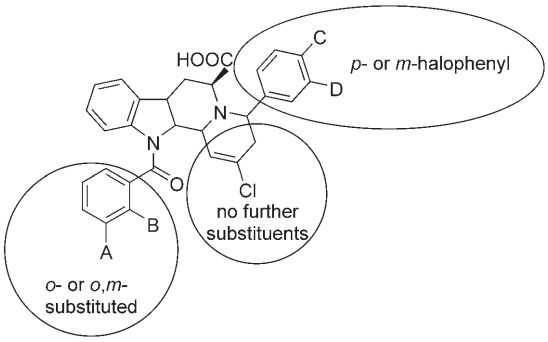
pot synthesis without prior isolation of the intermediate imine. To this end, a borane–pyridine complex was added to a mixture of the ketones **34b** and the respective amines (Scheme 11 and Table 5). The reaction yielded **37a** and **37b** in ratios of 3.6:1–1:1. The configuration of amines **37** was again assigned by ^{1}H NMR coupling constants and nOe experiments, thus identifying **37a** as the major diastereomer. Importantly, the diastereomers were readily separated by either column chromatography or preparative HPLC. The reaction sequence was compatible with a broad range of substituted ketones **34b** as well as different primary and secondary amines, thus leading to 273 secondary- and tertiary-amine derivatives of the indolo[2,3-a]quinolizidine system with more than 90% purity.

After the successful solid-phase synthesis of 702 indolo-[2,3-a]quinolizidines, a screening for phosphatase inhibition was initiated to prove our assumption that a joint application of the SCONP and BIOS principle to Yohimbane-type alkaloids can lead to simplified compounds with retained biochemical activity. Towards this end, all indolo[2,3-a]-quinolizidines were screened for inhibition of the phosphatases PTP1B, Shp-2, VE-PTP, MptpA, MptpB, Cdc25A, and VHR. The compound collection contained two weak inhibitors of Cdc25A (Table 6, entries 1 and 2; see also Supporting Information, Table 1) with an activity comparable to the guiding natural products. Thus, brachiation from the pentacyclic scaffold to a simplified tetracyclic ring system while retaining biochemical activity appears possible. Gratifyingly, investigation of the Yohimbane-inspired library also yielded potent inhibitors of the tyrosine phosphatase MptpB (Table 6 and Scheme 12). All compounds that displayed an IC_{50} of less than 10 μM were considered as hits.



Scheme 12. Structure–activity relationship (SAR) for MptpB inhibition by indolo[2,3-a]quinolizidines.

Analysis of the hits revealed that all inhibitors contained a vinyl chloride substructure in ring D, whereas all ketones, alkenes, and amines were inactive. Moreover, a free carboxylic acid and *ortho*-monosubstitution or *ortho*-/*meta*-disubstitution with *N*-acyl substituents at the indole nitrogen atom led to inhibitors that displayed the highest activities (Table 6, entries 3–8 and Supporting Information, Table 1).

Table 5. Yields and diastereoselectivities for secondary and tertiary amines **37**.

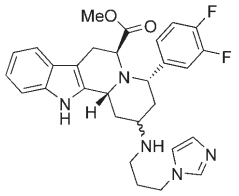
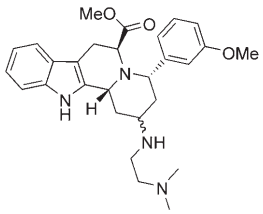
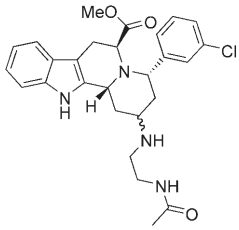
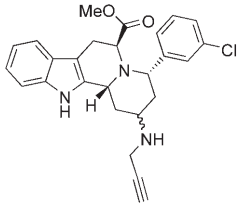
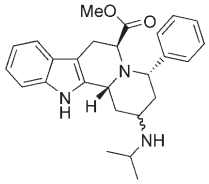
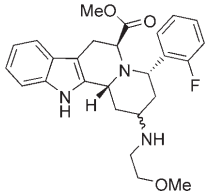
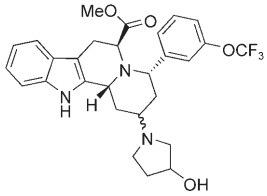
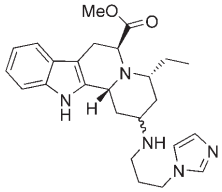
Compound	Structure	Yield [%]	**37a**/**37b**
37-1		73	11:9
37-2		68	3:2
37-3		57	2:1
37-4		62	1:1
37-5		66	3.6:1
37-6		63	1.3:1
37-7		48	1:1
37-8		41	1:1

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Table 6. Selected MptpB inhibitors identified from the screens.

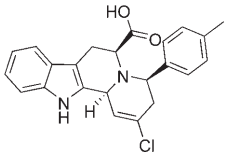
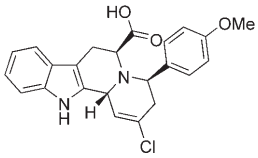
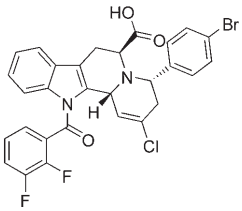
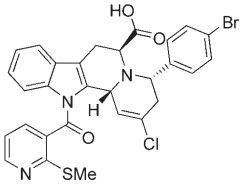
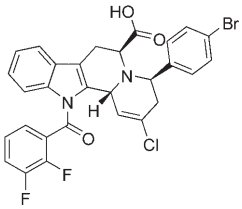
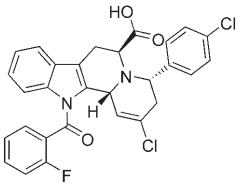
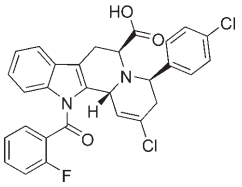
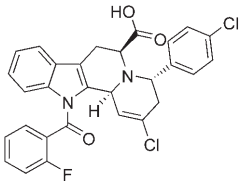
Entry	Compound	Structure	IC_{50}[a] [μM]					
			MptpB	Ptp1B	SHP-2	MptpA	VHR	Cdc25A
1	**22-3d**		92.5 ± 7.9	n.a.	n.a.	n.a.	n.a.	20.3 ± 11.7
2	**22-4c**		n.a.	n.a.	n.a.	n.a.	n.a.	30.8 ± 14.6
3	**25-3a**		1.13 ± 0.63	80.2 ± 7.3	81.2 ± 4.7	61.5 ± 6.2	78.2 ± 9.0	n.a.
4	**25-4a**		2.38 ± 1.17	n.a.	90.1 ± 15.7	n.a.	n.a.	51.0 ± 9.8
5	**25-3c**		3.42 ± 1.51	95.5 ± 2.5	n.a.	93.0 ± 8.5	n.a.	n.a.
6	**25-5a**		3.45 ± 1.66	n.a.	n.a.	n.a.	n.a.	n.a.
7	**25-5c**		8.20 ± 1.79	95.1 ± 6.1	n.a.	n.a.	n.a.	n.a.
8	**25-5b**		14.2 ± 6.3	n.a.	n.a.	n.a.	n.a.	n.a.

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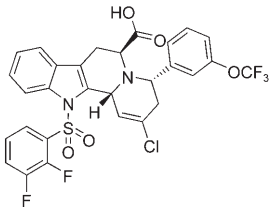
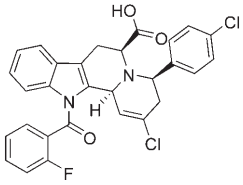
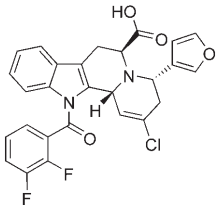
Table 6. (Continued)

Entry	Compound	Structure	IC_{50}[a] [μM]					
			MptpB	Ptp1B	SHP-2	MptpA	VHR	Cdc25A
9	**25-6a**		15.4 ± 4.0	82.8 ± 8.5	93.6 ± 10.4	n.a.	n.a.	n.a.
10	**25-5d**		33.7 ± 3.7	93.1 ± 3.6	n.a.	n.a.	n.a.	n.a.
11	**25-7a**		65.5 ± 6.2	n.a.	n.a.	n.a.	n.a.	n.a.

[a] All IC_{50} values were calculated from at least three independent determinations. n.a. = No inhibition observed at an inhibitor concentration of 100 μM.

Most of the active compounds were derived from *para*-halobenzaldehyde imines. Larger substituents or heterocyclic groups resulted in a decrease or even complete loss of activity (Table 6, entry 11).

In most cases, the major diastereomer with (12b*R*,4*S*,6*S*) configuration also displayed the best inhibitory activity. If the *para*-halophenyl substituent is oriented *syn* to the carboxy substituent, a twofold increase in IC_{50} was observed (Table 6, entries 3, 5 and 6, 7). Variation of the linkage at the C/D ring to a (12b*S*,4*S*,6*S*) configuration resulted in a slightly higher IC_{50} value (compare Table 6, entries 6 and 8). Furthermore, inhibition rates were even lower in the case of the (12b*S*,4*R*,6*S*) configuration, in which the *para*-halophenyl substituent is arranged *syn* to the carboxy group while the bridge proton is located *anti* to the carboxy group (compare Table 6, entries 8 and 10). The inhibitors were at least 20 times more selective for MptpB and did not inhibit VE-PTP. Furthermore, the compounds **25-5a** and **25-5b** did not inhibit any other phosphatase at an inhibitor concentration of 100 μM.

Conclusions

The joint application of BIOS and SCONP led to the discovery of structurally simplified inhibitors of the phosphatase Cdc25A. Furthermore, we have developed the first inhibitor class of the *M. tuberculosis* tyrosine phosphatase MptpB guided by the criteria of relevance to nature and biological prevalidation that form the basis of BIOS. Indolo[2,3-a]quinolizidines have not been described as phosphatase inhibitors before. Moreover, we have explored two efficient and versatile solid-phase synthesis routes to indolo[2,3-a]quinolizidines that allow the rapid synthesis of compounds with the basic framework of polycyclic alkaloids in high yields. Usually, all four diastereomers are obtained in parallel and can be readily separated into pure compounds by reverse-phase HPLC. The synthetic strategy allows the direct incorporation of various substituents at different positons of the heterocyclic skeleton by employing appropriate electron-rich silyloxydienes **12**, as well as different aldehydes and amines. Finally, the polymer-supported synthesis allows subsequent structural diversification of the natural-product-derived scaffold by alkylation or acylation as well as the Wittig reaction, thereby increasing the structural diversification of the indoloquinolizidine ring system. Screening of this library resulted in the identification of several potent small-molecule MptpB inhibitors, and an initial structure–activity relationship was determined. These inhibitors may find application in biological studies of the physiological role of MptpB by chemical-genomics approaches and could possibly serve as a new lead structure for the development of new drug candidates against tuberculosis.

Experimental Section

General

Unless otherwise noted, chemicals were obtained from Aldrich, Acros, or Fluka and were used without further purification. Wang resin

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(1.2 mmol g^{-1}, 1% divinyl benzene (DVB), 100–200 mesh) was purchased from Novabiochem, and HMBA resin (1.2 mmol g^{-1}, 1% DVB, 100–200 mesh) was purchased from Rapp-Polymere. NMR spectra were recorded on a Bruker DRX 400 or DRX 500 spectrometer with $CDCl_3$ as the solvent, unless otherwise noted. ^{1}H NMR spectra are reported in the following manner: chemical shifts relative to tetramethylsilane (0.00 ppm) or chloroform (7.33 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant, integration. ^{13}C NMR signals are reported in ppm relative to $CDCl_3$ (77.0 ppm). GC–MS (EI) analysis was performed on a Hewlett–Packard 5973 series mass spectrometer; column: H&W 19091σ-102 HP-5MS, capillary: 25.0 × 201 μm^2 × 0.33 μmm. HPLC–MS (ESI) analysis was performed on a Hewlett–Packard 110 series mass spectrometer connected to a Finnigan LCQ ESI mass spectrometer; column: VP125/21 Nucleodur C18 Gravity, 5μ (Machery-Nagel), gradient: H_2O/acetonitrile = 5:95–60:40 (*v*/*v*) in 29 min, flow: 10 mL min^{-1}. Specific optical rotation values were determined on a Perkin–Elmer Polarimeter 311. IR spectra were recorded on a JASCO Modell IR-700 spectrometer. Only significant diagnostic bands are reported, in cm^{-1}. Preparative HPLC was performed on an Agilent 1100 series chromatograph; column: VP130/21 Nucleodur C18, 5 μ, Machery-Nagel reverse phase. Accurate mass determinations were performed on a JEOL JMS-5X102A (FAB) high-resolution mass spectrometer. Dry tetrahydrofuran was distilled from sodium wire with a catalytic amount of benzophenone. Dry dichloromethane and dry pyridine were obtained by distillation over CaH_2.

Syntheses

General procedure for the formylation of **14**: Ketones **14** (0.50 mol) were dissolved under argon in dry THF (370 mL) and cooled to 0 °C, and NaH (37 g, 0.75 mol, 1.5 equiv, 60% suspension in mineral oil) was added. Subsequently, the suspension was warmed to 10 °C, and formic acid methyl ester (90.1 g, 1.5 mol, 3.0 equiv) was slowly added to the reaction mixture while the reaction mixture temperature was maintained between 10 and 20 °C. The reaction mixture was cooled to 0 °C and stirred at this temperature for 1 h. The solvent was removed under reduced pressure, and DMF (370 mL) was added to the remaining solid. The solution was cooled to 0 °C, and dimethyl sulfate (133.2 g, 1.00 mol, 2.0 equiv) was added slowly. The reaction solution was allowed to warm to room temperature overnight. Aqueous K_2CO_3 (1 M, 150 mL), methanol (300 mL), and cyclohexane (370 mL) were added. The aqueous phase was separated and extracted 10 times with cyclohexane (370 mL). The combined cyclohexane phases were dried over Na_2SO_4, the solvent was removed under reduced pressure, and the product was purified by distillation over a Vigreux column. In the case of the asymmetric ketone **15d**, an additional fractionation over a Fischer Spaltrohr column was performed for complete removal of the unwanted regioisomer **15e**.

15a: Analysis was in accordance to the reported values.[18]

15b: Colorless liquid, yield: 14.1 g, 90.3 mmol, 71%. B.p.: 94 °C (11 mbar); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17 (s, 1H), 3.84 (s, 3H), 2.47 (t, J = 7.5 Hz, 2H), 2.23 (q, J = 8.0 Hz, 2H), 1.65–1.60 (m, 2H), 0.93–0.90 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.9, 159.7, 136.2, 61.3, 44.2, 43.5, 37.5, 36.3, 14.8 ppm; HRMS (FAB): *m/z* calcd for $C_9H_{16}O_2$: 156.1150 $[M]^+$; found: 156.1136.

15c: Colorless liquid, yield: 21.4 g, 116.3 mmol, 84%. B.p.: 142 °C (1 mbar); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17 (s, 1H), 3.78 (s, 3H), 2.45 (t, J = 7.5 Hz, 2H), 2.15 (t, J = 6.0 Hz, 2H), 1.58–1.50 (m, 2H), 1.29–1.25 (m, 4H), 0.87–0.78 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.9, 159.7, 122.2, 61.3, 37.2, 30.5, 27.5, 25.1, 24.3, 21.9, 14.0 ppm; HRMS (FAB): *m/z* calcd for $C_{11}H_{20}O_2$: 184.1463 $[M]^+$; found: 184.1442.

15d: Colorless liquid, yield: 12.8 g, 90.1 mmol, 49%. B.p.: 72 °C (12 mbar); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (s, 1H), 3.74 (s, 3H), 2.46 (t, J = 7.4 Hz, 2H), 2.20 (t, J = 6.0 Hz, 2H), 1.37 (t, J = 7.4 Hz, 3H), 0.87 ppm (t, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.4, 160.0, 116.8, 58.6, 30.6, 11.9, 11.6, 8.9 ppm; HRMS (FAB) *m/z* calcd $C_8H_{14}O_2$: 142.0994 $[M]^+$; found: 142.0994.

12: Ketone **15** (0.14 mol) was added to a solution of LDA (0.150 mmol, 1.3 equiv) in THF at −78 °C, while the temperature was kept below −70 °C. The reaction solution was then stirred for 1 h at −78 °C, and TMSCl/TEA (3:1; 42 mL, 0.21 mol, 1.5 equiv TMSCl) was added through a dropping funnel while the temperature of the reaction mixture was carefully kept below −60 °C. After that, the solution was allowed to warm overnight to room temperature. Next, a saturated solution of NaCl (300 mL) and diethyl ether (200 mL) were added. The phases were separated, and the aqueous phase was extracted with diethyl ether (3 × 200 mL). The organic phases were combined and dried over Na_2SO_4, the solvent was removed under reduced pressure, and vacuum distillation over a Vigreux column followed for product purification.

12a: The reported values are in accordance with those reported in reference [18].

12b: Colorless liquid, yield: 20.2 g, 88.5 mmol, 98%. B.p.: 121 °C (13 mbar); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.26 (s, 1H), 4.69 (t, J = 7.3 Hz, 1H), 3.62 (s, 3H), 2.20 (t, J = 7.5 Hz, 2H), 2.10 (t, J = 6.0 Hz, 2H), 1.00–0.94 (m, 6H) 0.14 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.6, 121.0, 114.5, 61.3, 22.3, 20.8, 15.9, 14.8, 4.4, 1.9 ppm; HRMS (FAB): *m/z* calcd for $C_{12}H_{24}O_2Si$: 228.1546 $[M]^+$; found: 228.1569.

12c: Colorless liquid, yield: 19.4 g, 84.9 mmol, 94%. B.p.: 131 °C (1 mbar); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.30 (s, 1H), 4.69 (t, J = 11.4 Hz, 1H), 3.61 (s, 3H), 2.15 (t, J = 7.5 Hz, 2H), 2.03 (t, J = 6.0 Hz, 2H), 1.42–1.30 (m, 4H), 0.93–0.89 (m, 6H), 0.19 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.1, 119.4, 109.0, 102.4, 61.2, 29.6, 28.3, 23.2, 21.1, 15.6, 15.4, 2.2 ppm; HRMS (FAB): *m/z* calcd for $C_{14}H_{28}O_2Si$: 256.1889 $[M]^+$; found: 256.1873.

12d: Colorless liquid, yield: 12.1 g, 53.1 mmol, 76%. B.p.: 78 °C (12 mbar); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.21 (q, J = 5.7 Hz, 1H), 4.72 (q, J = 7.2 Hz, 1H), 3.61 (s, 3H), 2.10 (q, J = 6.0 Hz, 2H), 1.70 (d, J = 5.7 Hz, 3H), 1.08 (t, J = 6.0 Hz, 3H), 0.08 ppm (s, 9H); HRMS (FAB): *m/z* calcd for $C_{11}H_{22}O_2Si$: 214.1389 $[M]^+$; found: 214.1362.

Synthesis of **18** and **19** by vinylogous Mannich–Michael reaction: Wang resin (300 mg, loading = 1.2 mmol g^{-1}, 100–200 mesh) was swollen in DMF (2 mL) for 10 min, then **16** (494.2 mg, 1.20 mmol, 4 equiv), pyridine (285.4 mg, 3.58 mmol, 286 μL, 3.0 equiv), and 2,6-dichlorobenzoyl chloride (502.7 mg, 2.40 mmol, 424 μL, 2.0 equiv) were added, which resulted in a suspension that was shaken overnight at room temperature. The resin was washed three times with DMF, MeOH, and CH_2Cl_2. After the resin was dried under high vacuum, piperidine/DMF (20:80 *v*/*v*, 10 mL) was added to the resin (300 mg), and the mixture was shaken for 10 min. This step was repeated twice, followed by washing of the resin three times with DMF/CH_2Cl_2 (50:50 *v*/*v*) and once with CH_2Cl_2/trimethylorthoformiate (50:50 *v*/*v*). A solution of the corresponding aldehyde (1.08 mmol, 5 equiv with respect to resin-bound tryptophan) in CH_2Cl_2/trimethylorthoformiate (50:50 *v*/*v*, 8 mL) was added, and the mixture was shaken overnight at room temperature. Resin **17** was washed twice with CH_2Cl_2 and once with propionitrile. Next, resin **17** (300 mg) was shaken in propionitrile (2 mL) for 10 min followed by addition of $ZnCl_2$ (1 M, 1.8 mL, 0.42 mmol, 2.0 equiv) in THF. The resulting suspension was slowly agitated for 10 min at room temperature. The suspension was cooled to 0 °C, and **12** (1.83 mmol, 3.0 equiv) was added. The reaction mixture was allowed to warm overnight to room temperature. Resin **18**/**19** was filtered off, washed twice with CH_2Cl_2, HOAc (2%) in MeOH, and CH_2Cl_2 (20 mL each), and dried overnight in vacuo.

General procedure for phosgene-mediated cyclization of **18**/**19** and cleavage from Wang resin to yield **22**: Wang resin **18**/**19** (300 mg, loading = 0.87 mmol g)$^{-1}$ was added to a solution of phosgene (1.4 mL, 20% in toluene, 2.69 mmol, 12.8 equiv) and TMSCl (0.7 mL, 5.53 mmol, 37.6 equiv) in CH_2Cl_2. The resulting suspension was shaken at room temperature for 2 h. Resin **20**/**21** was filtered off, washed three times with CH_2Cl_2, MeOH, and CH_2Cl_2 (20 mL each), and dried for 1 h. For cleavage, Wang resin **20**/**21** or **24** (300 mg) was suspended in TFA/H_2O (9:1 *v*/*v*, 10 mL) and shaken overnight at room temperature. The resin was filtered off and washed twice with TFA (10 mL) and water (10 mL), and the solvent was removed under reduced pressure. The crude product was purified by preparative HPLC, and the individual diastereomers were isolated (conditions for all indoloquinolizidine derivatives: 0–30 min, 10→90% acetonitrile; 30–35 min, 90% acetonitrile; 35.1–36 min, 10% acetonitrile; detection wavelength = 254 nm, flow = 20 mL min^{-1}).

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22-1a: Major diastereomer, brown oil, yield: 21.2 mg, 0.052 mmol, 27%. $[\alpha]_D^{25}=-172$ ($c=0.71$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=1618\ cm^{-1}$; ^1H NMR (500 MHz, CD_3CN): $\delta=8.81$ (s, 1H), 7.42–7.42 (m, 3H), 7.19 (t, $J=7.8$ Hz, 1H), 7.07 (t, $J=7.8$ Hz, 1H), 6.99 (d, $J=8.1$ Hz, 2H), 6.69 (d, $J=8.1$ Hz, 2H), 4.61 (d, $J=6.7$ Hz, 1H), 4.21 (d, $J=10.5$ Hz, 1H), 4.05 (t, $J=7.8$ Hz, 1H), 3.31–3.01 (m, 2H); 2.20–2.18 (m, 1H), 1.93 (s, 3H), 1.75 ppm (d, $J=7.3$ Hz, 3H); ^{13}C NMR (125 MHz, CD_3CN): $\delta=172.3$, 155.8, 148.4, 137.3, 136.7, 130.4, 130.0, 128.9, 128.6, 127.2, 121.5, 119.2, 118.7, 115.6, 111.0, 106.4, 104.7, 70.5, 63.9, 50.9, 31.3, 18.5, 12.5, 11.8 ppm; HRMS (FAB): *m/z* calcd for $C_{24}H_{23}ClN_2O_2$: 406.1448 $[M]^+$; found: 406.1461.

22-2a: Major diastereomer, brown oil, yield: 19.4 mg, 0.047 mmol, 23%. $[\alpha]_D^{25}=-172$ ($c=0.71$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=1591\ cm^{-1}$; ^1H NMR (500 MHz, CD_3CN): $\delta=10.7$ (s, 1H), 7.79 (d, $J=8.0$ Hz, 1H), 7.22 (d, $J=8.0$ Hz, 1H), 7.11 (d, $J=8.0$ Hz, 1H), 7.00–6.92. (m, 2H), 6.63–6.59 (m, 2H), 4.93 (s, 1H), 4.67–4.63 (m, 1H), 3.98–3.96 (m, 1H), 3.05 (m, 1H), 2.45–2.29 ppm (m, 4H).

22-3d: Brown oil, yield: 7.9 mg, 0.013 mmol, 6%. $[\alpha]_D^{25}=-19.1$ ($c=1.0$ M, MeOH); ^1H NMR (500 MHz, CD_3CN): $\delta=8.18$ (s, 1H), 7.42 (d, $J=7.5$ Hz, 1H), 7.31–7.27 (m, 3H), 7.18–7.15 (m, 3H), 7.07 (t, $J=7.3$ Hz, 1H), 5.76 (s, 1H), 5.15–5.10 (m, 2H), 3.93 (d, $J=4.8$ Hz, 1H), 3.22–3.21 (m, 1H), 3.15 (d, $J=15.8$ Hz, 1H), 2.93–2.90 (m, 1H), 2.81 (d, $J=15.3$ Hz, 1H), 2.35 ppm (s, 3H); HRMS (FAB): *m/z* calcd for $C_{23}H_{21}ClN_2O_2$: 392.1362 $[M]^+$; found: 392.1366.

General procedure for the synthesis of **23** and **26**: After evaporation of the solvent, a solution of EDC·HCl (78.4 mg, 0.42 mmol, 5 equiv) in pyridine/MeOH/CH_2Cl_2 (1:1:1, 3 mL) was added to the crude mixture, which was subsequently stirred for 12 h. Water was added to the reaction mixture, which was extracted with CH_2Cl_2. The organic phase was evaporated to dryness, and the remaining residue was purified by RP-HPLC.

23-1a: Major diastereomer, brown oil, yield: 43.4 mg, 0.093 mmol, 36%. $[\alpha]_D^{25}=81$ ($c=1.0$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=1737\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.88$ (s, 1H), 7.45 (d, $J=8.0$ Hz, 2H), 7.35 (d, $J=8.0$ Hz, 1H), 7.26–7.19 (m, 3H), 7.10–7.07 (m, 1H), 7.02–6.97 (m, 1H), 5.64–5.60 (m, 1H), 4.94–4.90 (m, 1H), 4.89–4.85 (m, 1H), 3.68 (dd, $J=4.0$, 6.3 Hz, 1H), 3.48 (s, 3H), 3.04–3.03 (m, 2H), 2.76–2.75 ppm (m, 2H); HRMS (FAB): *m/z* calcd for $C_{23}H_{20}BrClN_2O_2$: 470.0397 $[M]^+$; found: 470.0438.

23-2a: Major diastereomer, brown oil, yield: 29.2 mg, 0.068 mmol, 26%. $[\alpha]_D^{25}=119$ ($c=1.0$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=1736\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta=8.61$ (s, 1H), 7.81 (s, 1H), 7.49 (d, $J=7.5$ Hz, 1H), 7.42 (d, $J=11.0$ Hz, 1H), 7.28–7.20 (m, 2H), 7.13–7.05 (m, 2H), 6.31 (s, 1H), 4.87 (d, $J=11.5$ Hz, 1H), 4.61–4.55 (m, 1H), 4.36–4.34 (m, 1H), 3.51 (s, 3H), 3.07–3.04 (m, 1H), 2.14–2.02 ppm (m, 3H); ^{13}C NMR (CD_3CN): $\delta=172.2$, 138.2, 137.1, 133.0, 129.0, 126.8, 126.7, 122.0, 119.6, 118.3, 117.6, 117.5, 117.4, 117.4, 117.3, 111.4, 105.4, 63.9, 56.1, 52.3, 51.7, 39.2, 24.6 ppm; HRMS (FAB): *m/z* calcd for $C_{23}H_{19}ClF_2N_2O_2$: 428.11031 $[M]^+$; found: 428.1137.

23-3a: Major diastereomer, brown oil, yield: 21.5 mg, 0.046 mmol, 18%. $[\alpha]_D^{25}=119$ ($c=1.0$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=1736\ cm^{-1}$; ^1H NMR (400 MHz, CD_3CN): $\delta=8.18$ (s, 1H), 7.42 (td, $J=1.0$, 8.0 Hz, 1H), 7.47–7.44 (m, 5H), 7.14 (dt, $J=1.0$, 7.4, Hz, 1H), 7.02 (dt, $J=1.0$, 7.4 Hz, 1H), 4.85 (d, $J=3.2$ Hz, 1H), 4.44 (d, $J=8.8$ Hz, 1H), 3.56–3.46 (m, 1H), 3.46 (s, 3H), 3.12 (dd, $J=2.0$, 8.4 Hz, 1H), 2.85–2.80 (m, 2H), 2.20–2.17 (m, 1H), 1.62–1.59 (m, 3H), 1.09 (t, $J=7.6$ Hz, 2H), 0.77 (t, $J=7.6$ Hz, 3H); HRMS (FAB): *m/z* calcd for $C_{23}H_{26}Cl_2N_2O_2$: 469.4028 $[M]^+$; found: 469.4042.

23-4a: Major diastereomer, brown oil, yield: 38.2 mg, 0.088 mmol, 34%. $[\alpha]_D^{25}=78$ ($c=0.4$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=1735\ cm^{-1}$; ^1H NMR (400 MHz, CD_3COCD_3): $\delta=9.19$ (s, 1H), 7.54 (d, $J=8.0$ Hz, 1H), 7.44 (d, $J=8.0$ Hz, 1H), 7.33 (d, $J=8.2$ Hz, 2H), 7.28 (d, $J=8.2$ Hz, 2H), 7.14 (t, $J=6.5$ Hz, 1H), 7.04 (t, $J=6.5$ Hz, 1H), 5.76 (s, 1H), 4.99 (d, $J=10.5$ Hz, 1H), 4.92 (s, 1H), 3.77 (d, $J=5.3$ Hz, 1H), 3.64 (s, 3H), 3.08 (d, $J=15.7$ Hz, 1H), 2.98–2.91 (m, 3H), 2.76–2.71 (m, 1H), 1.30 ppm (d, $J=7.0$ Hz, 6H); ^{13}C NMR (100 MHz, CD_3CN): $\delta=172.8$, 139.1, 137.8, 137.2, 134.4, 134.2, 129.8, 129.7, 127.9, 121.4, 119.0, 118.0, 111.2, 111.1, 105.3, 62.3, 55.8, 51.7, 50.9, 40.0, 24.9, 24.6, 20.6 ppm; HRMS (FAB): *m/z* calcd for $C_{26}H_{27}ClN_2O_2$: 434.1761 $[M]^+$; found: 434.1737.

23-5a: Major diastereomer, yellow oil, yield: 37.4 mg, 0.080 mmol, 30%. $[\alpha]_D^{25}=30$ ($c=1.0$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=1737\ cm^{-1}$; ^1H NMR (400 MHz, CD_3CN): $\delta=7.47$ (dd, $J=1.0$, 7.8 Hz, 1H), 7.45–7.38 (m, 5H), 7.05 (dt, $J=1.0$, 7.3 Hz, 1H), 7.02 (dt, $J=1.0$, 7.3 Hz, 1H), 4.86 (d, $J=3.3$ Hz, 1H), 4.39 (d, $J=10.4$ Hz, 1H), 3.72–3.69 (m, 1H), 3.61 (s, 3H), 3.04 (dd, $J=2.0$, 15.2 Hz, 1H), 3.00–2.97 (m, 1H), 2.44–2.42 (m, 1H), 2.42–2.30 (m, 1H), 2.36–2.33 (m, 1H), 1.67–1.60 (m, 2H), 1.02–0.97 ppm (m, 6H); HRMS (FAB): *m/z* calcd for $C_{27}H_{28}ClFN_2O_2$: 466.1837 $[M]^+$; found: 466.1842.

23-6a: Major diastereomer, brown oil, yield: 11.9 mg, 0.033 mmol, 15%. $[\alpha]_D^{25}=-112$ ($c=0.3$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=1734\ cm^{-1}$; ^1H NMR (400 MHz, CD_3CN): $\delta=7.51$ (d, $J=7.7$ Hz, 1H), 7.44 (d, $J=7.7$ Hz, 1H), 7.18 (t, $J=8.0$ Hz, 1H), 7.06 (d, $J=8.0$ Hz, 1H), 6.43 (d, $J=4.2$ Hz, 1H), 5.80 (s, 1H), 5.20 (dd, $J=2.5$, 5.5 Hz, 1H), 3.83 (s, 3H), 3.66–3.57 (m, 2H), 3.42 (dd, $J=4.0$, 15.4 Hz, 1H), 2.84–2.79 (m, 1H), 2.67 (dd, $J=4.8$, 18.5 Hz, 1H), 2.52–2.45 (m, 1H), 1.10 (d, $J=6.0$ Hz, 3H), 1.06 ppm (d, $J=6.0$ Hz, 3H); ^{13}C NMR (100 MHz, CD_3CN): $\delta=169.4$, 137.3, 130.5, 130.0, 126.1, 122.8, 121.0, 120.0, 118.0, 111.7, 105.0, 66.5, 56.0, 55.7, 52.7, 37.8, 27.8, 23.8, 19.3, 14.9 ppm; HRMS (FAB): *m/z* calcd for $C_{20}H_{23}ClN_2O_2$: 358.1448 $[M]^+$; found: 358.1453.

23-7a: Major diastereomer, brown oil, yield: 16.2 mg, 0.032 mmol, 12%. $[\alpha]_D^{25}=76$ ($c=1.0$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=1731\ cm^{-1}$; ^1H NMR (400 MHz, CD_3CN): $\delta=7.40$ (s, 1H), 7.38 (d, $J=8.0$ Hz, 1H), 7.33 (d, $J=8.0$ Hz, 1H), 7.14 (t, $J=7.3$ Hz, 1H), 7.00 (d, $J=8.5$ Hz, 2H), 6.98 (t, $J=7.3$ Hz, 1H), 6.84 (d, $J=8.5$ Hz, 2H), 4.39 (d, $J=4.0$ Hz, 1H), 4.09 (t, $J=7.0$ Hz, 1H), 3.59 (s, 3H), 3.44–3.39 (m, 1H), 3.39–3.37 (m, 1H), 2.14–2.09 (m, 6H), 2.06–2.03 (m, 1H), 1.56–1.53 (m, 1H), 1.45–1.42 (m, 1H), 0.98 (t, $J=7.5$ Hz, 3H), 0.84 ppm (t, $J=7.5$ Hz, 3H); ^{13}C NMR (100 MHz, CD_3CN): $\delta=171.6$, 144.1, 143.8, 142.9, 133.7, 131.4, 130.8, 129.1, 128.9, 127.8, 131.2, 136.0, 119.8, 112.3, 109.1, 59.2, 55.2, 51.8, 50.3, 44.5, 36.4, 31.8, 36.0, 21.1,14.6, 14.1 ppm; HRMS (FAB): *m/z* calcd for $C_{29}H_{32}Cl_2N_2O_2$: 510.1842 $[M]^+$; found: 510.1836.

23-8a: Major diastereomer, brown oil, yield: 34.7 mg, 0.078 mmol, 34%. $[\alpha]_D^{25}=152$ ($c=1.2$ M, CH_2Cl_2); IR (neat): $\tilde{\nu}_{max}=1739\ cm^{-1}$; ^1H NMR (500 MHz, CD_3CN): $\delta=9.42$ (s, 1H), 7.76 (s, 1H), 7.62 (s, 1H), 7.54 (d, $J=7.5$ Hz, 1H), 7.42 (d, $J=8.0$ Hz, 1H), 7.19 (t, $J=8.0$ Hz, 1H), 7.10 (t, $J=8.0$ Hz, 1H), 6.77 (s, 1H), 6.47 (d, $J=3.2$ Hz, 1H), 5.73 (s, 1H), 4.53 (dd, $J=4.5$, 14.7 Hz, 1H), 4.31 (d, $J=5.0$ Hz, 1H), 3.86 (s, 3H), 3.19 (d, $J=4.5$, 15.7 Hz, 1H), 3.17–3.12 (m, 2H), 2.65 ppm (d, $J=8.3$ Hz, 1H); ^{13}C NMR (125 MHz, CD_3CN): $\delta=170.2$, 145.4, 143.8, 137.1, 131.4, 128.8, 126.4, 122.7, 121.3, 120.6, 120.0, 118.6, 111.7, 109.7, 106.0, 56.7, 56.6, 55.5, 52.6, 39.7, 23.5 ppm; HRMS (FAB): *m/z* calcd for $C_{21}H_{19}ClN_2O_3$: 382.1084 $[M]^+$; found: 382.1070.

23-9a: Major diastereomer, yield: 38.0 mg, 0.093 mmol, 36%. $[\alpha]_D^{25}=105.6$ ($c=0.6$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=1738\ cm^{-1}$; ^1H NMR (400 MHz, CD_3CN): $\delta=9.18$ (s, 1H), 7.40 (d, $J=7.8$ Hz, 1H), 7.30 (d, $J=8.3$ Hz, 1H), 7.33 (t, $J=7.5$ Hz, 1H), 7.21 (s, 1H), 7.15–7.11 (m, 2H), 7.07 (dt, $J=1.2$, 7.5 Hz, 1H), 7.00 (dt, $J=1.2$, 7.5 Hz, 1H), 5.70 (s, 1H), 4.91 (d, $J=5.5$ Hz, 1H), 4.82 (s, 1H), 3.70 (d, $J=5.5$ Hz, 1H), 3.51 (s, 3H), 3.05 (d, $J=15.6$ Hz, 1H), 2.92–2.80 (m, 2H), 2.68–2.60 (m, 1H), 2.31 ppm (s, 3H); HRMS (FAB): *m/z* calcd for $C_{24}H_{23}ClN_2O_2$: 406.14481 $[M]^+$; found: 406.1442.

23-10a: Major diastereomer, yield: 14.9 mg, 0.043 mmol, 17%. $[\alpha]_D^{25}=77.5$ ($c=1.3$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=1739\ cm^{-1}$; ^1H NMR (500 MHz, CD_3CN): $\delta=7.45$ (d, $J=8.0$ Hz, 1H), 7.33 (d, $J=8.1$ Hz, 1H), 7.14 (t, $J=8.2$ Hz, 1H), 7.04 (t, $J=8.2$ Hz, 1H), 5.96 (s, 1H), 5.33 (d, $J=10.5$ Hz, 1H), 4.77 (d, $J=5.5$ Hz, 1H), 4.50 (br s, 1H), 3.64 (s, 3H), 3.45 (d, $J=16.5$ Hz, 1H), 3.33 (d, $J=4.3$ Hz, 1H), 3.14 (d, 16.5 Hz, 1H), 2.71–2.65 (m, 1H), 1.98–1.95 (m, 1H), 1.83–1.78 (m, 1H), 0.98 ppm (t, $J=9.8$ Hz, 3H); ^{13}C NMR (125 MHz, CD_3CN): $\delta=175.0$, 141.2, 137.8, 121.4, 120.3, 118.7, 117.3, 116.7, 115.8, 110.4, 104.7, 60.0, 54.4, 54.2, 51.3, 43.4, 36.8, 36.5, 7.9 ppm; HRMS (FAB): *m/z* calcd for $C_{19}H_{21}ClN_2O_2$: 344.1292 $[M]^+$; found: 344.1297.

23-11a: Major diastereomer, yield: 48.8 mg, 0.099 mmol, 38%. $[\alpha]_D^{25}=71.0$ ($c=1.0$ M, CH_2Cl_2); IR (neat): $\tilde{\nu}_{max}=1734\ cm^{-1}$; ^1H NMR (500 MHz, CD_3CN): $\delta=9.43$ (s, 1H), 7.45–7.38 (m, 4H), 7.17 (t, $J=8.0$ Hz, 1H), 7.07 (t, $J=8.0$ Hz, 1H), 6.99 (d, $J=8.8$ Hz, 2H), 6.41 (s, 1H), 5.71 (s, 1H), 4.95 (dd, $J=4.2$, 11.8 Hz, 1H), 4.02–3.99 (m, 3H), 3.58 (s, 3H),

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3.21–3.20 (m, 3H), 2.74 (dd, $J=2.0$, 15.0 Hz, 1H), 1.94–1.92 (m, 1H), 1.78–1.75 (m, 2H), 1.47–1.44 (m, 2H), 1.43–1.33 (m, 4H), 0.97 ppm (d, $J=7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CD_3CN): $\delta=182.1$, 172.0, 148.7, 143.3, 142.3, 138.1, 134.2, 133.0, 131.5, 130.1, 129.4, 129.2, 127.1, 123.4, 117.6, 80.0, 76.2, 68.0, 67.2, 64.0, 52.5, 43.2, 40.8, 44.3, 42.3, 42.3, 30.3 ppm; HRMS (FAB): *m/z* calcd for $C_{29}H_{33}ClN_2O_3$: 492.2180 $[M]^+$; found: 492.2170.

23-12a: Major diastereomer, brown oil, yield: 33.7 mg, 0.083 mmol, 31%. $[\alpha]_D^{25}=-19.1$ ($c=1.0$ M, MeOH); ^{1}H NMR (500 MHz, CD_3CN): $\delta=7.89$ (s, 1H), 7.49 (d, $J=7.5$ Hz, 1H), 7.29–7.20 (m, 4H), 7.15–7.11 (m, 2H), 7.09–7.05 (m, 1H), 4.94–2.92 (m, 1H), 4.91 (d, $J=3.1$ Hz, 1H), 3.77–3.75 (m, 1H), 3.76 (s, 3H), 3.22–3.18 (m, 2H), 2.98–2.95 (m, 1H), 2.92–2.88 (m, 1H), 2.79 (d, $J=15.3$, 1H), 2.35 ppm (s, 3H); ^{13}C NMR (125 MHz, CD_3CN): $\delta=195.8$, 138.0, 136.6, 132.0, 129.7, 128.1, 127.4, 127.0, 121.9, 118.2, 106.4, 64.1, 55.5, 51.5, 44.3, 27.3, 25.3, 21.3 ppm; HRMS (FAB): *m/z* calcd for $C_{24}H_{23}ClN_2O_2$: 406.1448 $[M]^+$; found: 406.1419.

23-13a: Major diastereomer, brown oil, yield: 36.8 mg, 0.071 mmol, 33%. $[\alpha]_D^{25}=76$ ($c=1.0$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=1741$ cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.89$ (s, 1H), 7.19 (d, $J=7.5$ Hz, 1H), 7.36–7.27 (m, 4H), 7.17–7.15 (m, 2H), 7.09–7.07 (m, 1H), 4.94–4.92 (m, 1H), 4.91 (d, $J=3.1$ Hz, 1H), 3.77–3.75 (m, 1H), 3.76 (s, 3H), 3.36–3.18 (m, 2H), 2.98–2.96 (m, 1H), 2.92–2.89 (m, 1H), 2.79 (d, $J=15.3$ Hz, 1H), 2.42 ppm (s, 3H); HRMS (FAB): *m/z* calcd for $C_{24}H_{23}ClN_2O_3$: 422.1397 $[M]^+$; found: 422.1414.

23-14a: Major diastereomer, yield: 5.8 mg, 0.018 mmol, 8%. $[\alpha]_D^{25}=-108.7$ ($c=1.0$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=1741$ cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN): $\delta=7.52$ (d, $J=8.0$ Hz, 1H), 7.36 (d, $J=8.0$ Hz, 1H), 7.17 (t, $J=8.2$ Hz, 1H), 7.07 (t, $J=8.2$ Hz, 1H), 6.41 (d, $J=4.3$ Hz, 1H), 5.83 (s, 1H), 5.05 (t, $J=5.0$ Hz, 1H), 3.97 (q, $J=4.5$ Hz, 1H), 3.69 (s, 3H), 3.56 (dd, $J=2.8$, 15.5 Hz, 1H), 3.40 (dd, $J=1.5$, 5.8 Hz, 1H), 2.78–2.74 (m, 2H), 1.44 ppm (d, $J=6.5$ Hz, 3H); HRMS (FAB): *m/z* calcd for $C_{18}H_{19}ClN_2O_2$: 330.1135 $[M]^+$; found: 330.1149.

23-15a: Major diastereomer, brown oil, yield: 36.8 mg, 0.069 mmol, 30%. $[\alpha]_D^{25}=33$ ($c=1.0$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=1738$ cm^{-1}; ^{1}H NMR (400 MHz, CD_3CN): $\delta=7.81$ (s, 1H), 7.42 (d, $J=8.0$ Hz, 1H), 7.43–7.30 (m, 3H), 7.31 (d, $J=7.6$ Hz, 2H), 7.08 (dt, $J=1.6$, 8.2 Hz, 1H), 6.99 (dt, $J=1.6$, 8.2 Hz, 1H), 6.52 (t, $J=2.4$ Hz, 1H), 5.21 (t, $J=1.6$ Hz, 1H), 4.55 (dd, $J=4.0$, 10.4 Hz, 1H), 3.81 (d, $J=5.2$ Hz, 1H), 3.64 (s, 3H), 3.15 (dt, $J=4.1$, 15.2 Hz, 1H), 2.92 (dd, $J=2.4$, 11.5 Hz, 1H), 2.86–2.81 (m, 1H), 2.61 ppm (dt, $J=1.8$, 12.1 Hz, 1H); ^{13}C NMR (100 MHz, CD_3CN): $\delta=172.0$, 144.9, 138.2, 134.1, 130.3, 130.0, 129.9, 129.6, 128.4, 128.1, 127.2, 126.7, 119.8, 112.3, 104.9, 63.0, 55.9, 54.0, 51.0, 43.5, 31.8, 20.7 ppm; HRMS (FAB): *m/z* calcd for $C_{23}H_{20}Cl_2N_2O_2$: 426.0902 $[M]^+$; found: 426.0936.

23-15b: Brown oil, yield: 16.0 mg, 0.044 mmol, 17%. $[\alpha]_D^{25}=-96$ ($c=1.0$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=1739$ cm^{-1}; ^{1}H NMR (400 MHz, CD_3COCD_3): $\delta=8.46$ (s, 1H), 7.43 (dt, $J=1.0$, 7.6 Hz, 1H), 7.43 (t, $J=1.0$ Hz, 1H), 7.37 (d, $J=6.4$ Hz, 2H), 7.21 (d, $J=6.4$ Hz, 2H), 7.10 (dt, $J=1.2$, 7.8 Hz, 1H), 7.02 (dt, $J=1.2$, 7.8 Hz, 1H), 5.73 (t, $J=5.8$ Hz, 1H), 4.99–4.96 (m, 1H), 4.89–4.86 (m, 1H), 3.76 (dd, $J=1.6$, 6.4 Hz, 1H), 3.52 (s, 3H), 3.14 (dt, $J=1.6$, 15.2 Hz, 1H), 3.07 (dt, $J=3.2$, 16.4 Hz, 1H), 2.95 (ddd, $J=2.4$, 6.2, 15.2 Hz, 1H), 2.72–2.66 ppm (m, 1H); ^{13}C NMR (100 MHz, CD_3COCD_3): $\delta=172.8$, 139.1, 137.8, 137.2, 134.4, 129.8, 128.4, 128.1, 127.9, 127.1, 121.4, 119.0, 118.0, 111.2, 105.3, 64.3, 55.8, 51.7, 50.9, 30.0, 20.6 ppm; HRMS (FAB): *m/z* calcd for $C_{23}H_{20}Cl_2N_2O_2$: 426.0902 $[M]^+$; found: 426.0911.

23-15c: Yellow oil, yield: 9.9 mg, 0.037 mmol, 11%. $[\alpha]_D^{25}=-42$ ($c=1.0$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=1737$ cm^{-1}; ^{1}H NMR (400 MHz, CD_3CN): $\delta=9.24$ (s, 1H), 7.47 (d, $J=7.6$ Hz, 2H), 7.38–7.33 (m, 2H), 7.31 (d, $J=8.0$ Hz, 2H), 7.13 (dt, $J=1.2$, 7.2 Hz, 1H), 7.07 (dt, $J=1.2$, 7.2 Hz, 1H), 6.43 (dd, $J=2.4$, 4.8 Hz, 1H), 5.11 (t, $J=2.0$ Hz, 1H), 3.96 (dd, $J=4.0$, 9.2 Hz, 1H), 3.87 (dd, $J=2.0$, 5.6 Hz, 1H), 3.61 (s, 3H), 3.15 (dt, $J=5.9$, 15.2 Hz, 1H), 2.92 (dd, $J=2.4$, 11.5 Hz, 1H), 2.86–2.81 (m, 1H), 2.61 ppm (dt, $J=1.8$, 12.1 Hz, 1H); HRMS (FAB): *m/z* calcd for $C_{23}H_{20}Cl_2N_2O_2$: 426.0902 $[M]^+$; found: 426.0894.

23-15d: Yellow oil, yield: 5.4 mg, 0.013 mmol, 6%. $[\alpha]_D^{25}=-130$ ($c=1.0$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=1740$ cm^{-1}; ^{1}H NMR (500 MHz, CD_3COCD_3): $\delta=9.15$ (s, 1H), 7.40 (d, $J=6.4$ Hz, 1H), 7.35 (d, $J=8.0$ Hz, 1H), 7.28 (d, $J=8.0$ Hz, 2H), 7.21 (d, $J=7.7$ Hz, 2H), 7.12 (t, $J=7.2$ Hz, 1H), 7.02 (t, $J=7.2$, 1H), 5.72 (t, $J=4.2$ Hz, 1H), 4.85 (d, $J=10.5$ Hz, 1H), 4.78 (d, $J=3.5$ Hz, 1H), 3.68 (dd, $J=1.3$, 6.3 Hz, 1H), 3.51 (s, 3H), 3.04 (d, $J=15.5$ Hz, 1H), 2.91–2.85 (m, 2H), 2.66–2.60 ppm (m, 1H); ^{13}C NMR (125 MHz, CD_3COCD_3): $\delta=174.4$, 140.2, 139.3, 138.1, 135.6, 130.9, 129.5, 129.4, 129.1, 128.1, 122.8, 120.5, 112.4, 106.6, 65.4, 56.9, 52.7, 52.3, 41.1, 26.0, 21.6 ppm; HRMS (FAB): *m/z* calcd for $C_{23}H_{20}Cl_2N_2O_2$: 426.0902 $[M]^+$; found: 426.0936.

General procedure for the synthesis of **25**: Wang resin **20/21** (700 mg) was washed with dry THF, filtered off, and resuspended in a solution of HMPA (0.7 mL, 717.0 mg, 4.13 mmol, 19 equiv), LHMDS (1 M in THF, 4 mL, 4.00 mmol, 19.0 equiv), and THF (10 mL) at −78 °C. The suspension was shaken at −78 °C for 1 h, followed by addition of acyl chloride (10 equiv). The mixture was allowed to warm to room temperature overnight. Resin **24** was filtered off, washed three times with CH_2Cl_2, MeOH, and DMF (20 mL each), and subjected to the cleavage procedure described above.

25-1a: Major diastereomer, yellow oil, yield: 112.2 mg, 0.205 mmol, 34%. $[\alpha]_D^{25}=42.2$ ($c=1.0$ M, MeOH); ^{1}H NMR (500 MHz, CD_3CN): $\delta=8.74$ (dd, $J=1.3$, 5.7 Hz, 1H), 7.96 (s, 1H), 7.51–7.46 (m, 3H), 7.31–7.28 (m, 1H), 7.24–7.23 (m, 1H), 7.22–7.17 (m, 2H), 7.11–7.08 (m, 2H), 6.66–6.64 (m, 1H), 5.47 (s, 1H), 4.68 (s, 1H), 3.84 (d, $J=5.0$ Hz, 1H), 3.12–3.06 (m, 3H), 2.92–2.89 (m, 1H), 2.48 ppm (s, 3H); LC–MS (ESI): $t_R=8.99$ min, $m/z=548.2$ $[M+H]^+$.

25-2a: Major diastereomer, yellow oil, yield: 115.0 mg, 0.215 mmol, 35%. $[\alpha]_D^{25}=42.2$ ($c=1.0$ M, MeOH); ^{1}H NMR (500 MHz, CD_3CN): $\delta=7.68$–7.53 (m, 7H), 7.42 (d, $J=7.8$ Hz, 1H), 7.21–7.03 (m, 3H), 6.99 (t, $J=7.5$ Hz, 1H), 6.23 (br s, 1H), 5.72 (br s, 1H), 4.83 (dd, $J=4.2$, 10.3 Hz, 1H), 3.99 (br s, 1H), 3.19–2.97 (m, 2H), 2.67 ppm (d, $J=16.7$ Hz, 2H).

25-3a: Major diastereomer, yellow oil, yield: 121.7 mg, 0.217 mmol, 37%. $[\alpha]_D^{25}=42.2$ ($c=1.0$ M, MeOH); ^{1}H NMR (500 MHz, CD_3CN): $\delta=7.61$ (dd, $J=10.1$, 18.9 Hz, 1H), 7.51 (d, $J=8.2$ Hz, 2H), 7.43 (d, $J=8.0$ Hz, 2H), 7.42 (d, $J=8.2$ Hz, 2H), 7.13 (t, $J=7.2$ Hz, 1H), 6.98 (t, $J=7.2$ Hz, 1H), 6.57 (d, $J=8.5$ Hz, 1H), 6.00 (s, 2H), 5.40 (s, 1H), 4.51 (dd, $J=4.2$, 10.7 Hz, 1H), 3.71 (d, $J=4.7$ Hz, 1H), 3.09 (d, $J=16.2$ Hz, 1H), 2.91–2.86 (m, 1H), 2.69–2.62 (m, 1H), 2.40 ppm (dt, $J=3.5$, 17.2 Hz, 1H); ^{13}C NMR (125 MHz, CD_3CN): $\delta=175.7$, 166.2, 143.2, 139.5, 137.4, 135.0, 134.2, 133.8, 132.4, 129.3, 128.6, 127.7, 127.6, 126.7, 124.7, 124.6, 124.5, 121.9, 121.8, 116.2, 65.9, 58.1, 57.6, 45.7, 28.4 ppm; HRMS (FAB): *m/z* calcd for $C_{29}H_{20}BrClF_2N_2O_3$: 596.0314 $[M]^+$; found: 596.0316.

25-3c: Yellow oil, yield: 65.3 mg, 0.064 mmol, 20%. $[\alpha]_D^{25}=-31.9$ ($c=1.2$ M, MeOH); ^{1}H NMR (500 MHz, CD_3CN): $\delta=7.58$–7.51 (m, 3H), 7.39 (d, $J=8.2$ Hz, 2H) 7.35–7.32 (m, 3H), 7.26 (t, $J=7.2$ Hz, 1H), 7.13 (t, $J=7.2$ Hz, 1H), 6.79 (d, $J=8.5$ Hz, 1H), 6.07 (s, 1H), 4.84 (s, 1H), 4.42 (s, 1H), 3.95 (t, $J=5.7$ Hz, 1H), 2.96–2.92 (m, 2H), 2.82 (d, $J=18.7$ Hz, 1H), 2.68 ppm (d, $J=18.2$ Hz, 1H); HRMS (FAB): *m/z* calcd for $C_{29}H_{20}BrClF_2N_2O_3$: 596.0314 $[M+H]^+$; found: 596.0318.

25-4a: Major diastereomer, brown oil, yield: 42.9 mg, 0.069 mmol, 30%. $[\alpha]_D^{25}=46.2$ ($c=1.3$ M, MeOH); ^{1}H NMR (500 MHz, CD_3CN): $\delta=8.74$ (dd, $J=1.3$, 5.7 Hz, 1H), 7.96 (s, 1H), 7.53–7.49 (m, 3H), 7.31–7.28 (m, 1H) 7.25–7.22 (m, 1H), 7.20–7.17 (m, 2H), 7.12–7.09 (m, 2H), 6.66 (br s, 1H), 5.47 (br s, 1H), 4.68 (br s, 1H), 3.84 (d, $J=5.0$ Hz, 1H), 3.12–3.05 (m, 3H), 2.93–2.90 (m, 1H), 2.61 (s, 3H), 2.13–2.10 ppm (m, 1H); HRMS (FAB): *m/z* calcd for $C_{29}H_{23}BrClN_3O_3S$: 563.0837 $[M+H]^+$; found: 563.0858.

25-5a: Major diastereomer, brown oil, yield: 39.0 mg, 0.073 mmol, 42%. $[\alpha]_D^{25}=31.2$ ($c=1.0$ M, MeOH); ^{1}H NMR (400 MHz, CD_3CN): $\delta=7.68$–7.53 (m, 7H), 7.42 (d, $J=7.8$ Hz, 1H), 7.21–7.03 (m, 3H), 6.99 (t, $J=7.5$ Hz, 1H), 6.37 (br s, 1H), 5.72 (br s, 1H), 4.83 (dd, $J=4.2$, 10.3 Hz, 1H), 3.99 (br s, 1H), 3.19–2.97 (m, 2H), 2.67 ppm (d, $J=16.7$ Hz, 2H); HRMS (FAB): *m/z* calcd for $C_{29}H_{21}Cl_2FN_2O_3$: 534.0913 $[M]^+$; found: 534.0919.

25-5b: Brown oil, yield: 17.1 mg, 0.031 mmol, 18%. $[\alpha]_D^{25}=31.2$ ($c=1.0$ M, MeOH); ^{1}H NMR (400 MHz, CD_3CN): $\delta=7.67$–7.44 (m, 7H), 7.11–7.30 (m, 4H) 7.04 (t, $J=7.2$ Hz, 1H), 5.73 (s, 1H), 5.16 (s, 2H), 3.76 (s, 1H), 3.11 (br s, 2H), 2.95 ppm (br s, 2H); HRMS (FAB): *m/z* calcd for $C_{29}H_{21}Cl_2FN_2O_3$: 534.0913 $[M]^+$; found: 534.0907.

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General procedure for the formation of **26**: The N-acylated acids **25** were subjected to ester formation as described above.

26-1a: Major diastereomer, yellow oil, yield: 64.7 mg, 0.122 mmol, 37%. $[\alpha]_D^{25}=-59$ ($c=0.1$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=1736\ cm^{-1}$; ^1H NMR (500 MHz, CD_3CN): $\delta=8.42$ (d, $J=9.0$ Hz, 2H), 8.00 (d, $J=9.0$ Hz, 2H), 7.50 (d, $J=7.7$ Hz, 2H), 7.43–7.42 (m, 2H), 7.28–7.16 (m, 4H), 7.08 (t, $J=7.5$ Hz, 1H), 6.74 (d, $J=8.5$ Hz, 1H), 5.69 (t, $J=2.2$ Hz, 1H), 4.91 (s, 1H), 3.71 (dd, $J=2.5$, 5.5 Hz, 1H), 3.63 (s, 3H), 3.12 (d, $J=16.2$ Hz, 2H), 2.74–2.63 (m, 1H), 2.64–2.59 ppm (m, 1H); ^{13}C NMR (125 MHz, CD_3CN): $\delta=173.8$, 169.1, 152.0, 142.0, 141.5, 137.9, 137.1, 137.4, 137.2, 136.7, 136.7, 136.6, 136.2, 130.8, 130.7, 130.1, 127.8, 120.3, 118.3, 115.3, 65.2, 82.3, 56.0, 54.4, 52.7, 40.9, 33.5 ppm; HRMS (FAB): *m/z* calcd for $C_{30}H_{24}ClN_3O_5$: 542.1404 $[M]^+$; found: 542.1444.

26-2a: Major diastereoisomer, yellow oil, yield: 73.0 mg, 0.138 mmol, 22%. $[\alpha]_D^{25}=-74$ ($c=0.1$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=1738\ cm^{-1}$; ^1H NMR (500 MHz, CD_3CN): $\delta=7.72$ (d, $J=8.4$ Hz, 1H), 7.45–7.39 (m, 4H), 7.42 (t, $J=7.8$ Hz, 1H), 7.36–7.21 (m, 7H), 6.03 (d, $J=5.6$ Hz, 1H), 5.74 (s, 1H), 5.54 (s, 1H), 4.13 (d, $J=5.0$ Hz, 1H), 3.70 (s, 3H), 3.42–3.38 (m, 1H), 3.21–3.15 (m, 1H), 3.11–3.06 ppm (m, 2H); HRMS (FAB): *m/z* calcd for $C_{30}H_{24}Cl_2N_2O_3$: 530.1164 $[M]^+$; found: 530.1178.

26-3a: Major diastereomer, yellow oil, yield: 60.7 mg, 0.114 mmol, 19%. $[\alpha]_D^{25}=-12$ ($c=0.1$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=1734\ cm^{-1}$; ^1H NMR (500 MHz, CD_3CN): $\delta=7.86$ (d, $J=6.5$ Hz, 1H), 7.49–7.44 (m, 3H), 7.39 (d, $J=6.5$ Hz, 1H), 7.31–7.20 (m, 5H), 7.16 (t, $J=7.6$ Hz, 1H), 6.72 (d, $J=8.5$ Hz, 1H), 6.01 (br s, 1H), 5.76 (d, $J=9.5$ Hz, 1H), 5.62 (s, 1H), 4.26 (d, $J=5.5$ Hz, 1H), 3.77 (s, 3H), 3.26 (d, $J=17.6$ Hz, 2H), 2.78–2.69 ppm (m, 2H); HRMS (FAB): *m/z* calcd for $C_{30}H_{23}ClF_2N_2O_3$: 532.1365 $[M]^+$; found: 532.1377.

26-4a: Major diastereomer, yellow oil, yield: 21.7 mg, 0.050 mmol, 8%. $[\alpha]_D^{25}=-83$ ($c=0.1$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=1731\ cm^{-1}$; ^1H NMR (500 MHz, CD_3CN): $\delta=7.72$ (d, $J=7.8$ Hz, 1H), 7.45–7.33 (m, 5H), 7.27–7.09 (m, 3H), 5.81–5.79 (m, 1H), 5.51 (d, $J=8.5$ Hz, 1H), 5.11 (dd, $J=6.6$, 8.0 Hz, 1H), 4.95 (s, 1H), 3.71 (s, 3H), 3.32–3.15 (m, 4H), 2.23 ppm (s, 3H); HRMS (FAB): *m/z* calcd for $C_{25}H_{23}ClN_2O_3$: 434.1397 $[M]^+$; found: 434.1404.

General procedure for the synthesis of **28/29**: HMBA resin (300 mg, loading = 1.2 mmol g^{-1}, 100–200 mesh) was swollen in DMF (2 mL) for 10 min, then **16** (494.2 mg, 1.20 mmol, 1 equiv), pyridine (285.4 mg, 3.58 mmol, 286 µL, 3.0 equiv), and 2,6-dichlorobenzoyl chloride (502.7 mg, 2.40 mmol, 424 µL, 2.0 equiv) were added. The resulting suspension was shaken at room temperature overnight. The resin was washed three times with DMF, MeOH, and CH_2Cl_2 and dried under high vacuum. The resin (300 mg) was shaken twice for 10 min with piperidine/DMF (20:80 *v/v*, 10 mL) and washed three times with DMF/CH_2Cl_2 and once with CH_2Cl_2/trimethylorthoformiate (50:50 *v/v*). A solution of the corresponding aldehyde (1.08 mmol, 5 equiv with respect to resin-bound tryptophan) and CH_2Cl_2/trimethylorthoformiate (50:50 *v/v*, 8 mL) was added, and the mixture was shaken overnight at room temperature. The resin was washed twice with CH_2Cl_2 and once with propionitrile. The resin (300 mg) was shaken in propionitrile (2 mL) for 10 min followed by addition of aqueous $ZnCl_2$ (1 M, 1.8 mL, 0.42 mmol, 2.0 equiv), and the resulting suspension was slowly agitated for 10 min at room temperature. The suspension was cooled to 0 °C, and **12** (1.83 mmol, 3.0 equiv) was added. The reaction mixture was allowed to warm overnight to room temperature. Resin **27** was filtered off, washed twice with CH_2Cl_2, HOAc (2%) in MeOH, and CH_2Cl_2 (20 mL each), and dried overnight in vacuo.

Cleavage of **27**: A suspension of **27** (100 mg) in TEA/MeOH (1:9, 3 mL) was heated at 50 °C overnight. The cleavage mixture was removed by filtration, and the resin was washed with MeOH (3×5 mL) and CH_2Cl_2 (3×5 mL). The cleavage mixture and washing solutions were combined and evaporated to dryness. The residue was redissolved in acetonitrile/methanol and purified by preparative RP-HPLC.

28-1a and **28-1b**: Mixture of diastereomers (65:35), yield: 10.1 mg, 0.030 mmol, 59%. IR (neat): $\tilde{\nu}_{max}=1591\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta=8.33$ (s, 1H), 7.46 (d, $J=7.8$ Hz, 1H), 7.38 (d, $J=8.8$ Hz, 1H), 7.20 (t, $J=7.2$ Hz, 1H), 7.10 (d, $J=8.0$ Hz, 1H), 7.01 (t, $J=7.7$ Hz, 1H), 6.97 (d, $J=1.7$ Hz, 1H), 6.72 (d, $J=7.7$ Hz, 1H,), 6.70 (d, $J=7.2$ Hz, 1H), 6.50 (d, 2H, $J=8.7$ Hz, 1H), 5.37 (d, $J=7.8$ Hz, 1H), 4.60 (dd, $J=5.8$, 12.9 Hz, 1H), 3.98 (dd, $J=6.0$, 9.3 Hz, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 3.42 (td, $J=5.3$, 14.5 Hz, 1H), 3.17–3.07 (m, 1H), 2.70–2.54 ppm (m, 2H); MS (70 eV): *m/z* (%) = 404 $[M]^+$ (10), 137 (100).

28-2a and **28-2b**: Mixture of diastereomers (63:37), yield: 10.5 mg, 0.033 mmol, 65%. IR (neat): $\tilde{\nu}_{max}=1591\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta=8.40$ (s, 1H), 7.42 (d, $J=8.0$ Hz, 1H), 7.40 (d, $J=7.4$ Hz, 1H), 7.36 (t, $J=7.7$ Hz, 1H), 7.15 (d, $J=7.5$ Hz, 1H), 7.03 (t, $J=7.6$ Hz, 1H), 6.97 (br s, 1H), 6.89 (d, $J=8.4$ Hz, 2H), 6.68 (d, $J=8.4$ Hz, 2H), 5.31 (d, $J=7.8$ Hz, 1H), 4.62 (dd, $J=4.8$, 10.6 Hz, 1H), 3.95 (dd, $J=5.5$, 9.9 Hz, 1H), 3.70 (s, 3H), 3.44–3.38 (m, 1H), 3.17–3.07 (m, 1H), 2.55 (d, $J=9.0$ Hz, 1H), 2.42 ppm (t, $J=7.8$ Hz, 1H); MS (70 eV): *m/z* (%) = 408 $[M]^+$ (5), 137 (100).

28-3a and **28-3b**: Mixture of diastereomers (68:32), yield: 9.5 mg, 0.037 mmol, 48%. IR (neat): $\tilde{\nu}_{max}=1591\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta=8.36$ (s, 1H), 7.64 (d, $J=8.5$ Hz, 2H), 7.45 (d, $J=8.0$ Hz, 1H), 7.39 (d, $J=8.2$ Hz, 1H), 7.19 (t, $J=7.2$ Hz, 1H), 7.12 (d, $J=8.0$ Hz, 1H), 7.01 (br s, 1H), 6.94 (t, $J=7.5$ Hz, 1H), 6.83 (d, $J=8.5$ Hz, 2H), 5.28 (d, $J=7.9$ Hz, 1H), 4.69 (dd, $J=6.4$, 10.3 Hz, 1H), 3.91 (dd, $J=4.6$, 10.7 Hz, 1H), 3.77 (s, 3H), 3.44 (dd, $J=4.6$, 15.1 Hz, 1H), 3.19 (dd, $J=10.8$, 15.1 Hz, 1H), 2.71 (dd, $J=6.3$, 16.5 Hz, 1H), 2.52 ppm (dd, $J=10.4$, 16.5 Hz, 1H); HRMS (FAB): *m/z* calcd for $C_{23}H_{21}N_3O_5$: 419.1481 $[M]^+$; found: 419.1463.

28-4a: Yield: 10.7 mg, 0.033 mmol, 38%. IR (neat): $\tilde{\nu}_{max}=1591\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta=8.28$ (s, 1H), 7.42 (d, $J=7.4$ Hz, 1H), 7.44 (d, $J=7.9$ Hz, 1H), 7.28 (d, $J=8.0$ Hz, 1H), 7.37 (d, $J=7.9$ Hz, 1H), 7.19 (t, $J=7.6$ Hz, 1H), 7.08 (t, $J=7.6$ Hz, 1H), 7.02 (t, $J=7.4$ Hz, 1H), 7.00 (br s, 1H), 6.77 (d, $J=7.7$ Hz, 1H), 6.71 (t, $J=7.4$ Hz, 1H), 5.27 (dd, $J=6.8$, 9.5 Hz, 1H), 5.20 (d, $J=7.8$ Hz, 1H), 3.97 (dd, $J=7.0$, 8.2 Hz, 1H), 3.62 (s, 3H), 3.45 (dd, $J=6.1$, 14.6 Hz, 1H), 3.21 (dd, $J=9.0$, 14.8 Hz, 1H), 2.71 (dd, $J=6.7$, 16.6 Hz, 1H), 2.57 ppm (dd, $J=10.0$, 16.4 Hz, 1H); MS (70 eV): *m/z* (%) = 408 $[M]^+$ (7), 137 (100).

28-4b: Yield: 7.8 mg, 0.019 mmol, 22%. IR (neat): $\tilde{\nu}_{max}=1591\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta=8.28$ (s, 1H), 7.54 (d, $J=7.9$ Hz, 1H), 7.48 (d, $J=7.9$ Hz, 1H), 7.44–7.39 (m, 2H), 7.36–7.28 (m, 1H), 7.21 (t, $J=7.5$ Hz, 1H), 7.18–7.10 (m, 3H), 6.98 (br s, 1H), 5.14 (d, 1H), 4.72 (dd, $J=5.2$, 7.4 Hz, 1H), 4.12 (dd, $J=5.9$, 9.2 Hz, 1H), 3.65 (s, 3H), 3.44 (dd, $J=5.8$, 14.7 Hz, 1H), 3.17 (dd, $J=9.4$, 14.6 Hz, 1H), 2.60 (dd, $J=8.0$, 16.5 Hz, 1H), 2.42 ppm (dd, $J=4.8$, 16.5 Hz, 1H); MS (70 eV): *m/z* (%) = 408 $[M]^+$ (6), 137 (100).

28-5a: Yield: 6.9 mg, 0.009 mmol, 22%. IR (neat): $\tilde{\nu}_{max}=1591\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta=8.15$ (s, 1H), 7.65 (d, 2H, $J=8.2$ Hz, 1H), 7.42 (d, $J=8.0$ Hz, 1H), 7.39 (d, $J=8.2$ Hz, 1H), 7.19 (t, $J=7.6$ Hz, 1H), 7.14 (d, $J=7.9$ Hz, 1H), 6.98 (t, $J=7.2$ Hz, 1H), 6.97 (br s, 1H), 6.90 (d, $J=8.2$ Hz, 2H), 5.30 (d, $J=8.0$ Hz, 1H), 4.68 (dd, $J=6.8$, 10.6 Hz, 1H), 3.93–3.89 (m, 1H), 3.91 (s, 3H), 3.68 (s, 3H), 3.42 (dd, $J=5.9$, 14.9 Hz, 1H), 3.16 (dd, $J=9.5$, 14.9 Hz, 1H), 2.61 ppm (dd, $J=5.6$, 8.6 Hz, 1H); MS (70 eV): *m/z* (%) = 432 $[M]^+$ (8), 137 (100).

28-5b: Yield: 3.6 mg, 0.008 mmol, 18%. IR (neat): $\tilde{\nu}_{max}=1591\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta=8.20$ (s, 1H), 7.87 (d, $J=8.3$ Hz, 2H), 7.51 (d, $J=7.9$ Hz, 1H), 7.43 (d, $J=8.2$ Hz, 1H), 7.44 (d, $J=8.0$ Hz, 1H), 7.33 (t, $J=7.5$ Hz, 1H), 7.10 (t, $J=7.5$ Hz, 1H), 6.99 (br s, 1H), 6.98 (d, $J=8.2$ Hz, 2H), 5.21 (d, $J=7.9$ Hz, 1H), 4.07 (dd, $J=5.0$, 10.3 Hz, 1H), 4.01 (t, $J=7.6$ Hz, 1H), 3.90 (s, 3H), 3.69 (s, 3H), 3.42 (dd, $J=5.0$, 14.7 Hz, 1H), 3.16 (dd, $J=10.4$, 14.7 Hz, 1H), 2.46 ppm (dd, $J=4.5$, 7.6 Hz, 2H); MS (70 eV): *m/z* (%) = 432 $[M]^+$ (10), 137 (100).

28-6a: Yield: 3.2 mg, 0.008 mmol, 18%. IR (neat): $\tilde{\nu}_{max}=1591\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta=8.17$ (s, 1H), 7.56 (d, $J=7.8$ Hz, 1H), 7.40 (d, $J=8.0$ Hz, 1H), 7.37 (d, $J=7.4$ Hz, 1H), 7.31 (t, $J=7.6$ Hz, 1H), 7.18 (t, $J=7.5$ Hz, 1H), 7.01 (br s, 1H), 5.16 (d, $J=7.3$ Hz, 1H), 4.21 (dd, $J=5.9$, 9.6 Hz, 1H), 3.80 (s, 3H), 3.56 (dd, $J=5.6$, 15.0 Hz, 1H), 3.44 (br s, 1H), 3.37 (dd, $J=9.8$, 15.0 Hz, 1H), 2.82 (d, $J=7.0$, 16.9 Hz, 1H), 2.30 (d, $J=16.8$ Hz, 1H), 1.40–1.42 (m, 1H), 1.33–1.28 (m, 1H), 0.95–0.87 (m, 1H), 0.61 (d, $J=6.5$ Hz, 3H), 0.58 ppm (d, $J=6.5$ Hz, 3H); MS (70 eV): *m/z* (%) = 424 $[M]^+$ (4), 100 (100).

28-6b: Yield: 2.7 mg, 0.007 mmol, 15%. IR (neat): $\tilde{\nu}_{max}=1591\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta=8.31$ (s, 1H), 7.59 (d, $J=8.1$ Hz, 1H), 7.42 (d, $J=8.1$ Hz, 1H), 7.42 (d, $J=7.5$ Hz, 1H), 7.31 (t, $J=7.5$ Hz, 1H),

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7.16 (t, $J=7.5$ Hz, 1H), 7.06 (br s, 1H), 5.15 (d, $J=7.2$ Hz, 1H), 4.17 (dd, $J=4.7$, 10.0 Hz, 1H), 3.83 (s, 3H), 3.54 (dd, $J=4.6$, 14.6 Hz, 1H), 3.15 (dd, $J=10.4$, 14.4 Hz, 1H), 2.98 (br s, 1H), 2.20 (d, $J=6.7$, 16.4 Hz, 1H), 2.08 (t, $J=17.2$ Hz, 1H), 1.69–1.63 (m, 1H), 1.44–1.38 (m, 1H), 1.21–1.15 (m, 1H), 1.82 (d, $J=6.5$ Hz, 1H), 0.67 ppm (d, 3H); MS (70 eV): m/z (%) = 424 $[M]^+$ (5), 137 (100).

General procedure for acid-mediated cyclization on HMBA support and base-mediated cleavage: Resin **27** (200 mg) was suspended in a solution of CH_2Cl_2/TMSCl/TFA (10 mL, 3:1:0.5), and the mixture was stirred at room temperature for 30 min. The resin was filtered, washed successively with CH_2Cl_2 (three times), methanol (three times), DMF (three times), and again with CH_2Cl_2 (three times), and dried in vacuo. Final cleavage of the product from the HMBA resin was achieved by addition of NaOMe (0.25 M) in methanol/dioxane (1:1) at 50 °C for 18 h. The remaining residues **34a** and **34b**, obtained after extraction with EtOAc and removal of the solvent under reduced pressure, was purified by RP-HPLC under the conditions indicated above.

34-1a and **34-1b**: Diastereomeric mixture (78:22), yield: 14.2 mg, 0.044 mmol, 19%. IR (neat): $\tilde{\nu}_{max}=3363$, 2820, 2800, 1735, 1716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=8.03$ (s, 1H), 7.50 (d, $J=7.6$ Hz, 1H), 7.16 (t, $J=7.4$ Hz, 1H), 7.11 (t, $J=7.4$ Hz, 1H), 4.70 (d, $J=11.8$ Hz, 1H), 4.36 (d, $J=5.2$ Hz, 1H), 3.58 (s, 3H), 3.45–3.39 (m, 1H), 3.30 (d, $J=15.4$ Hz, 1H), 3.18 (dd, $J=4.6$, 15.4 Hz, 1H), 2.82 (d, $J=14.3$ Hz, 1H), 2.59–2.38 (m, 3H), 1.72–1.61 (m, 2H), 0.96 ppm (d, $J=7.4$ Hz, 3H); MS (70 eV): m/z (%) = 333 $[M]^+$ (79), 337 (100), 169 (57).

34-2b: Yield: 8.3 mg, 0.020 mmol, 37%. $[\alpha]_D^{25}=56.1$ ($c=0.1$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=3348$, 2805, 1737, 1723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.78$ (s, 1H), 7.48 (d, $J=7.7$ Hz, 1H), 7.38 (d, $J=8.4$ Hz, 2H), 7.33 (d, $J=7.3$ Hz, 3H), 7.18 (t, $J=7.5$ Hz, 1H), 7.11 (t, $J=7.4$ Hz, 1H), 4.84 (d, $J=11.7$ Hz, 1H), 4.60 (dd, $J=4.0$, 10.6 Hz, 1H), 3.77 (d, $J=5.3$ Hz, 1H), 3.50 (s, 3H), 3.18 (d, $J=15.4$ Hz, 1H), 3.04 (ddd, $J=1.5$, 5.7, 15.1 Hz, 1H), 2.89 (d, $J=13.8$ Hz, 1H), 2.73–2.67 (m, 2H), 2.63 ppm (d, $J=13.9$ Hz, 1H); HRMS (FAB): m/z calcd for $C_{23}H_{21}O_3N_2Cl$: 408.1311 $[M]^+$; found: 408.1362.

34-3b: Yield: 15.3 mg, 0.039 mmol, 30%. $\tilde{\nu}_{max}=3370$, 2821, 2806, 1735, 1720 cm^{-1}; $[\alpha]_D^{25}=-14.9$ ($c=1.0$ M, CH_2Cl_2); ^1H NMR (500 MHz): $\delta=7.97$ (s, 1H), 7.48 (d, $J=7.7$ Hz, 1H), 7.39 (d, $J=6.8$ Hz, 1H), 7.43 (d, $J=6.9$ Hz, 1H), 7.33 (d, $J=8.1$ Hz, 1H), 7.18 (t, $J=7.5$ Hz, 1H), 7.12–7.08 (m, 3H), 4.84 (d, $J=11.9$ Hz, 1H), 4.60 (dd, $J=3.2$, 10.6 Hz, 1H), 3.78 (d, $J=5.9$ Hz, 1H), 3.50 (s, 3H), 3.18 (d, $J=15.2$ Hz, 1H), 3.04 (dd, $J=5.8$, 15.3 Hz, 1H), 2.91 (d, $J=13.1$ Hz, 1H), 2.75–2.67 (m, 2H), 2.63 ppm (d, $J=12.9$ Hz, 1H); ^{13}C NMR (125 MHz): $\delta=206.5$, 172.8, 143.9, 143.4, 130.9, 129.2, 129.1, 129.0, 128.3, 136.0, 119.6, 118.2, 116.2, 116.0, 111.0, 106.9, 64.6, 63.8, 56.2, 53.1, 51.4, 50.8, 47.7, 31.9 ppm; HRMS (FAB): m/z calcd for $C_{23}H_{21}FN_2O_3$: 392.1543 $[M]^+$; found: 392.1560.

34-4b: Yellow oil, yield: 9.4 mg, 0.037 mmol, 27%. $[\alpha]_D^{25}=-12.9$ ($c=0.1$ M, MeOH); ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.76$ (s, 1H), 7.62 (d, $J=5.1$ Hz, 1H), 7.48 (d, $J=7.8$ Hz, 1H), 7.40 (d, $J=8.0$ Hz, 1H), 7.42 (t, $J=6.9$ Hz, 1H), 7.33–7.31 (m, 1H), 7.18 (t, $J=7.5$ Hz, 1H), 7.11 (d, $J=7.4$ Hz, 1H), 5.19 (s, 1H), 5.01 (d, $J=11.3$ Hz, 1H), 3.85 (d, $J=5.5$ Hz, 1H), 3.55 (s, 3H), 3.18 (d, $J=15.3$ Hz, 1H), 3.11 (dd, $J=5.8$, 15.1 Hz, 1H), 2.91 (d, $J=14.2$ Hz, 1H), 2.80 (d, $J=12.6$ Hz, 1H), 2.71 ppm (t, $J=12.7$ Hz, 1H); HRMS (FAB): m/z calcd for $C_{23}H_{21}O_3N_2Cl$: 408.1241 $[M]^+$; found: 407.1189.

34-5b: Yellow oil, yield: 13.9 mg, 0.030 mmol, 43%. $[\alpha]_D^{25}=78.2$ ($c=0.1$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=3359$, 2821, 2802, 1736, 1724 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.80$ (s, 1H), 7.67 (d, $J=7.9$ Hz, 2H), 7.53 (d, $J=7.9$ Hz, 2H), 7.49 (d, $J=7.7$ Hz, 1H), 7.42 (d, $J=8.1$ Hz, 1H), 7.19 (t, $J=7.6$ Hz, 1H), 7.12 (t, $J=7.4$ Hz, 1H), 4.88 (d, $J=11.6$ Hz, 1H), 4.72 (dd, $J=4.2$, 10.0 Hz, 1H), 3.74 (d, $J=4.8$ Hz, 1H), 3.51 (s, 3H), 3.19 (d, $J=15.2$ Hz, 1H), 3.06 (dd, $J=5.9$, 15.3 Hz, 1H), 2.91 (d, $J=14.0$ Hz, 1H), 2.75–2.68 ppm (m, 3H); HRMS (FAB): m/z calcd for $C_{24}H_{21}O_3N_2F_3$: 442.1504 $[M]^+$; found: 442.1493.

34-6b: Yield: 6.9 mg, 0.016 mmol, 18%. $[\alpha]_D^{25}=29.0$ ($c=0.3$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=3365$, 2822, 2800, 1733, 1719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.74$ (s, 1H), 7.48 (d, $J=7.7$ Hz, 1H), 7.33 (d, $J=8.1$ Hz, 1H), 7.31 (d, $J=6.5$ Hz, 1H), 7.36 (d, $J=6.1$ Hz, 3H), 7.18 (t, $J=7.5$ Hz, 1H), 7.11 (t, $J=7.4$ Hz, 1H), 4.83 (d, $J=11.7$ Hz, 1H), 4.56 (dd, $J=3.6$, 11.0 Hz, 1H), 3.82 (dd, $J=1.2$, 5.9 Hz, 1H), 3.49 (s, 3H), 3.17 (d, $J=15.5$ Hz, 1H), 3.03 (ddd, $J=2.1$, 6.0, 15.3 Hz, 1H), 2.87 (d, $J=13.6$ Hz, 1H), 2.78–2.67 (m, 2H), 2.61 (d, $J=13.2$ Hz, 1H), 2.52 ppm (s, 3H); MS: $m/z=420$ $[M]^+$.

34-7b: Yield: 18.5 mg, 0.043 mmol, 28%. $[\alpha]_D^{25}=44.8$ ($c=0.1$ M, CH_2Cl_2); $\tilde{\nu}_{max}=3369$, 2820, 2804, 1737, 1716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.76$ (s, 1H), 7.49 (d, $J=7.6$ Hz, 1H), 7.43 (t, $J=7.8$ Hz, 1H), 7.42 (d, $J=8.0$ Hz, 1H), 7.37–7.17 (m, 2H), 7.14–7.10 (m, 1H), 4.85 (d, $J=12.5$ Hz, 1H), 4.62 (t, $J=7.3$ Hz, 1H), 3.77 (d, $J=4.6$ Hz, 1H), 3.51 (s, 3H), 3.20 (d, $J=15.3$ Hz, 1H), 3.05 (ddd, $J=2.1$, 6.2, 15.7 Hz, 1H), 2.89 (dd, $J=1.7$, 11.4 Hz, 1H), 2.71 (d, $J=12.5$ Hz, 1H), 2.66 ppm (d, 2H, $J=7.3$ Hz, 1H); MS (70 eV): m/z (%) = 433 $[M]^+$ (42), 169 (100); HRMS (FAB): m/z calcd for $C_{23}H_{20}O_3N_2ClF$: 426.1165 $[M]^+$; found: 426.1198.

34-8b: Yield: 20.6 mg, 0.044 mmol, 36%. $[\alpha]_D^{25}=-37.2$ ($c=2.5$ M, CH_2Cl_2); IR (neat): $\tilde{\nu}_{max}=3363$, 2827, 2800, 1735, 1714 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=8.15$ (s, 1H), 7.48 (d, $J=7.8$ Hz, 1H), 7.44 (t, $J=7.9$ Hz, 1H), 7.42 (d, $J=7.7$ Hz, 2H), 7.28 (s, 1H), 7.21 (d, $J=8.1$ Hz, 1H), 7.17 (t, $J=7.2$ Hz, 1H), 7.11 (t, $J=7.3$ Hz, 1H), 4.86 (d, $J=11.8$ Hz, 1H), 4.64 (dd, $J=4.7$, 9.9 Hz, 1H), 3.75 (d, $J=4.5$ Hz, 1H), 3.50 (s, 3H), 3.19 (d, $J=15.5$ Hz, 1H), 3.06 (ddd, $J=2.0$, 6.0, 15.4 Hz, 1H), 2.95 (d, $J=14.1$ Hz, 1H), 2.75–2.67 ppm (m, 3H); ^{13}C NMR (100 MHz): $\delta=206.4$, 172.7, 149.8, 143.6, 136.4, 132.8, 131.6, 130.6, 129.7, 129.0, 120.8, 120.0, 119.6, 119.5, 118.2, 111.0, 106.7, 63.9, 56.4, 53.0, 51.5, 50.4, 47.5, 42.8, 31.8 ppm; HRMS (FAB): m/z calcd for $C_{24}H_{21}O_4N_2F_3$: 459.1530 $[M+1]^+$; found: 459.1442.

34-9b: Yellow oil, yield: 8.8 mg, 0.020 mmol, 15%. $[\alpha]_D^{25}=-56.9$ ($c=0.2$ M, CH_2Cl_2); IR (neat): $\tilde{\nu}_{max}=3360$, 2821, 2803, 1736, 1716 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.71$ (s, 1H), 7.47 (d, $J=7.5$ Hz, 1H), 7.33 (d, $J=8.2$ Hz, 1H), 7.28 (d, $J=8.6$ Hz, 2H), 7.17 (t, $J=7.4$ Hz, 1H), 7.10 (t, $J=7.4$ Hz, 1H), 6.93 (d, $J=8.5$ Hz, 2H), 6.08 (dtd, $J=5.1$, 10.3, 15.5 Hz, 1H), 5.44 (d, $J=17.3$ Hz, 1H), 5.30 (d, $J=10.5$ Hz, 1H), 4.82 (d, $J=11.4$ Hz, 1H), 4.56 (d, $J=5.0$ Hz, 2H), 4.53 (dd, $J=2.8$, 10.9 Hz, 1H), 3.81 (d, $J=5.8$ Hz, 1H), 3.49 (s, 3H), 3.15 (d, $J=15.2$ Hz, 1H), 3.03 (dd, $J=5.4$, 15.2 Hz, 1H), 2.86 (d, $J=1.4$ Hz, 1H), 2.76 (dd, $J=1.1$, 12.3 Hz, 1H), 2.70 (t, $J=12.8$ Hz, 1H), 2.61 ppm (d, $J=1.5$ Hz, 1H); HRMS (FAB): m/z calcd for $C_{26}H_{26}N_2O_4$: 430.1893 $[M]^+$; found: 430.1877.

34-10b: Yellow oil, yield: 11.0 mg, 0.027 mmol, 19%. $[\alpha]_D^{25}=-14.8$ ($c=0.31$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=3368$, 2821, 2800, 1736, 1716 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.77$ (s, 1H), 7.48 (d, $J=7.8$ Hz, 1H), 7.42–7.36 (m, 2H), 7.18 (t, $J=7.5$ Hz, 1H), 7.11 (t, $J=7.4$ Hz, 1H), 6.97 (d, $J=7.6$ Hz, 1H), 6.93 (br s, 1H), 6.88 (dd, $J=2.2$, 8.0 Hz, 1H), 4.84 (d, $J=12.0$ Hz, 1H), 4.56 (dd, $J=3.7$, 10.9 Hz, 1H), 3.87 (dd, $J=1.3$, 5.8 Hz, 1H), 3.82 (s, 3H), 3.50 (s, 3H), 3.17 (dd, $J=5.1$, 15.4 Hz, 1H), 3.05 (ddd, $J=2.1$, 5.9, 15.4 Hz, 1H), 2.88 (dt, $J=2.2$, 13.5 Hz, 1H), 2.77 (dd, $J=11.1$, 14.0 Hz, 1H), 2.71 (t, $J=12.9$ Hz, 1H), 2.64 ppm (ddd, $J=2.3$, 3.5, 14.4 Hz, 1H); ^{13}C NMR (125 MHz, CD_3CN): $\delta=202.1$, 172.3, 160.1, 146.6, 143.9, 131.7, 130.5, 129.8, 129.4, 121.3, 120.5, 119.4, 112.9, 112.1, 111.0, 60.1, 56.4, 55.8, 54.6, 52.3, 51.0, 50.1, 18.4 ppm; HRMS (FAB): m/z calcd for $C_{24}H_{24}O_4N_2$: 403.1658 $[M]^+$; found: 403.1613.

34-11b: Brown oil, yield: 18.2 mg, 0.042 mmol, 31%. $[\alpha]_D^{25}=103.9$ ($c=0.1$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=3360$, 2826, 2800, 1735, 1717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.78$ (s, 1H), 7.49 (d, $J=9.5$ Hz, 1H), 7.42 (d, $J=8.0$ Hz, 1H), 7.31 (d, $J=8.4$ Hz, 1H), 7.19 (d, $J=7.5$ Hz, 1H), 7.12 (t, $J=7.4$ Hz, 1H), 4.85 (d, $J=11.9$ Hz, 1H), 4.61 (t, $J=7.3$ Hz, 1H), 3.77 (d, $J=5.7$ Hz, 1H), 3.52 (s, 3H), 3.20 (d, $J=15.4$ Hz, 1H), 3.06 (ddd, $J=2.0$, 5.9, 15.3 Hz, 1H), 2.90 (d, $J=14.1$ Hz, 1H), 2.71 (d, $J=12.4$ Hz, 1H), 2.66 ppm (d, $J=7.4$ Hz, 2H); HRMS (FAB): m/z calcd for $C_{23}H_{20}O_3N_2Cl_2$: 442.0851 $[M]^+$; found: 442.0810.

34-12b: Brown oil, yield: 17.1 mg, 0.042 mmol, 37%. IR (neat): $\tilde{\nu}_{max}=3365$, 2820, 2800, 1736, 1718 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.79$ (s, 1H), 7.49 (d, $J=7.7$ Hz, 1H), 7.42 (d, $J=8.0$ Hz, 1H), 7.31 (d, $J=9.1$ Hz, 1H), 7.19 (t, $J=7.7$ Hz, 2H), 7.12 (t, $J=7.0$ Hz, 2H), 4.85 (d, $J=11.9$ Hz, 1H), 4.61 (t, $J=7.1$ Hz, 1H), 3.77 (d, $J=5.5$ Hz, 1H), 3.51 (s, 3H), 3.20 (d, $J=15.3$ Hz, 1H), 3.06 (dd, $J=5.7$, 15.4 Hz, 1H), 2.89 (d, $J=1.9$ Hz, 1H), 2.71 (d, $J=12.7$ Hz, 1H), 2.66 ppm (d, $J=7.0$ Hz, 2H); HRMS (FAB): m/z calcd for $C_{23}H_{20}O_3N_2F_2$: 421.1520 $[M]^+$; found: 421.1509.

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34-13b: Brown oil, yield: 4.4 mg, 0.011 mmol, 27%. $[\alpha]_D^{25}=-11.8$ ($c=1.0$ M, CH_2Cl_2); IR (neat): $\tilde{\nu}_{max}=3363$, 2818, 2800, 1729, 1707 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.97$ (s, 1H), 7.48 (d, $J=7.7$ Hz, 1H), 7.40 (s, 4H), 7.43 (d, $J=6.1$ Hz, 1H), 7.42 (d, $J=8.1$ Hz, 1H), 7.18 (t, $J=7.5$ Hz, 1H), 7.11 (t, $J=7.3$ Hz, 1H), 4.85 (d, $J=11.8$ Hz, 1H), 4.60 (dd, $J=3.1$, 11.0 Hz, 1H), 3.83 (d, $J=5.0$ Hz, 1H), 3.50 (s, 3H), 3.17 (d, $J=15.3$ Hz, 1H), 3.05 (dd, $J=4.4$, 15.1 Hz, 1H), 2.91 (d, $J=1.7$ Hz, 1H), 2.78 (dd, $J=11.6$, 13.8 Hz, 1H), 2.71 (t, $J=13.0$ Hz, 1H), 2.65 (d, $J=14.1$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=206.7$, 172.9, 142.2, 143.4, 133.1, 131.2, 128.3, 127.5, 126.8, 121.9, 119.5, 118.2, 110.9, 107.0, 64.6, 56.3, 53.2, 51.3, 50.8, 47.7, 31.9 ppm; HRMS (FAB): *m/z* calcd for $C_{23}H_{23}O_3N_2$: 374.1630 $[M]^+$; found: 374.1639.

General procedure for alkylation of **29**: BEMP (0.1 mL, 0.73 mmol, 178.4 mg, 5 equiv) was added to a suspension of **29** (300 mg) in dry DMF (2 mL). After 30 min, the corresponding alkyl halide (1.31 mmol, 10 equiv) was added to the suspension. After overnight reaction at room temperature, the resin was filtered off and washed with MeOH (3× 5 mL), MeOH/H_2O (5 mL), MeOH (3×5 mL), DMF (3×5 mL), CH_2Cl_2 (3×5 mL), and MeOH (3×5 mL). The resin-bound *N*-alkyl-indolo[2,3-a]-quinolizidines were released with NaOMe according to the procedure described above. The residue was dissolved in acetonitrile/methanol and purified by preparative RP-HPLC under the conditions indicated above.

35-1: Brown oil, yield: 13.5 mg, 0.033 mmol, 16%. $[\alpha]_D^{25}=-5.2$ ($c=1.4$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=3363$, 2822, 2803, 1739, 1726 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.49$–7.46 (m, 2H), 7.42–7.33 (m, 1H), 7.28 (d, $J=8.2$ Hz, 1H), 7.37–7.17 (m, 2H), 7.12–7.07 (m, 2H), 5.01–4.96 (m, 2H), 3.81 (dd, $J=1.8$, 5.4 Hz, 1H), 3.69 (s, 3H), 3.48 (s, 3H), 3.18 (d, $J=14.9$ Hz, 1H), 3.14–3.08 (m, 2H), 2.88 (ddd, $J=1.1$, 5.2, 14.7 Hz, 1H), 2.81 (dd, $J=8.5$, 14.7 Hz, 1H), 2.64 ppm (dd, $J=11.8$, 15.0 Hz, 1H); HRMS (FAB): *m/z* calcd for $C_{24}H_{23}O_3N_2F$: 406.1605 $[M]^+$; found: 406.1614.

35-2: Yield: 10.2 mg, 0.023 mmol, 15%. $[\alpha]_D^{25}=-0.8$ ($c=0.62$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=3363$, 2813, 2801, 1739, 1716 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.47$ (d, $J=7.8$ Hz, 1H), 7.36–7.19 (m, 6H), 7.10 (t, $J=7.4$ Hz, 1H), 4.84 (d, $J=11.4$ Hz, 1H), 4.58 (dd, $J=5.1$, 9.3 Hz, 1H), 3.81 (dd, $J=1.9$, 5.4 Hz, 1H), 3.68 (s, 3H), 3.45 (s, 3H), 3.14 (d, $J=15.1$ Hz, 1H), 3.09–3.02 (m, 2H), 2.96–2.88 (m, 1H), 2.76–2.73 (m, 2H), 2.65 (dd, $J=11.9$,14.0 Hz, 1H), 1.28 (d, $J=6.9$ Hz, 3H), 1.27 ppm (d, $J=6.9$ Hz, 3H); HRMS (FAB): *m/z* calcd for $C_{27}H_{37}O_3N_2$: 437.3656 $[M]^+$; found: 437.3631; MS (70 eV): *m/z* (%) = 437 $[M]^+$ (38), 442 (33), 169 (100).

35-3: Yield: 10.8 mg, 0.028 mmol, 10%. $[\alpha]_D^{25}=-4.6$ ($c=0.73$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=3356$, 2822, 2800, 1736, 1718 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.46$ (d, $J=7.7$ Hz, 1H), 7.40–7.42 (m, 6H), 7.21 (t, $J=7.5$ Hz, 1H), 7.10 (t, $J=7.4$ Hz, 1H), 4.89 (d, $J=11.5$ Hz, 1H), 4.63 (dd, $J=4.9$, 9.3 Hz, 1H), 3.79 (dd, $J=1.7$, 4.9 Hz, 1H), 3.68 (s, 3H), 3.45 (s, 3H), 3.16–3.07 (m, 1H), 2.83–2.68 ppm (m, 3H); MS (70 eV): *m/z* (%) = 388 $[M]^+$ (40), 336 (42), 183 (100).

35-4: Brown oil, yield: 5.9 mg, 0.011 mmol, 8%. $[\alpha]_D^{25}=17.1$ ($c=0.28$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=3369$, 2820, 2800, 1735, 1719 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.53$–7.51 (m, 1H), 7.39 (d, $J=8.5$ Hz, 2H), 7.43–7.30 (m, 1H), 7.36 (d, $J=8.6$ Hz, 1H), 7.15–7.05 (m, 4H), 6.80 (d, $J=8.5$ Hz, 2H), 5.28 (d, $J=17.4$ Hz, 1H), 5.19 (d, $J=17.4$ Hz, 1H), 5.02 (dd, $J=5.0$, 8.6 Hz, 1H), 4.97 (br s, 1H), 3.89 (d, $J=4.3$ Hz, 1H), 3.49 (s, 3H), 3.42–3.28 (m, 1H), 3.36 (d, $J=15.3$ Hz, 1H), 2.96 (br s, 2H), 2.85 (br s, 1H), 2.81 ppm (dd, $J=4.8$, 14.8 Hz, 1H); HRMS (FAB): *m/z* calcd for $C_{30}H_{26}BrFN_2O_3$: 560.1111 $[M]^+$; found: 560.1112.

35-5: Yield: 10.6 mg, 0.025 mmol, 13%. $[\alpha]_D^{25}=+0.9$ ($c=1.0$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=3369$, 2828, 2799, 1739, 1716 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta=8.30$ (dd, $J=1.5$, 7.9 Hz, 1H); 7.56–7.54 (m, 1H), 7.53–7.51 (m, 1H), 7.47–7.39 (m, 2H), 7.42–7.37 (m, 1H), 7.19 (t, $J=7.5$ Hz, 1H), 7.15–7.13 (m, 2H), 7.11–7.06 (m, 1H), 6.97–6.95 (m, 1H), 6.44 (d, $J=7.7$ Hz, 1H), 5.76 (d, $J=19.1$ Hz, 1H), 5.64 (d, $J=19.1$ Hz, 1H), 5.02 (d, $J=11.4$ Hz, 1H), 4.98 (t, $J=6.7$ Hz, 1H), 3.86 (dd, $J=2.4$, 4.4 Hz, 1H), 3.53 (s, 3H), 3.31 (br s, 2H), 2.89 (dd, $J=5.6$, 14.9 Hz, 1H), 2.82–2.76 (m, 1H), 2.71 (dd, $J=2.5$, 15.7 Hz, 1H), 2.65–2.59 ppm (m, 1H).

General procedure for Wittig reaction with **29**: A solution of *n*BuLi in hexane (2.5 M, 2.08 mmol, 0.5 mL, 8.0 equiv) was added to a suspension of the corresponding phosphonium salt (1.51 mmol, 10 equiv) in dry THF (5 mL) at −20°C. After 15 min, **29** (370 mg, 0.33 mmol) was added to the mixture. The temperature was warmed from −20 to 50°C. After 3 h at 50°C, the reaction was quenched with MeOH (1 mL). The resin was filtered off and washed with MeOH, MeOH/H_2O (1:1 *v*/*v*), MeOH, DMF, CH_2Cl_2, and MeOH. The resin-bound alkene-indolo[2,3-a]quinolizidine was cleaved by NaOMe according to the procedure described above. The residue was dissolved in acetonitrile/methanol and purified by preparative RP-HPLC under the conditions indicated above.

36-1: Brown oil, yield: 6.8 mg, 0.017 mmol, 7%. $[\alpha]_D^{25}=-11.2$ ($c=0.11$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=3078$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.80$ (s, 1H), 7.55–7.52 (m, 1H), 7.44 (d, $J=6.7$ Hz, 1H), 7.33–7.28 (m, 2H), 7.36–7.18 (m, 1H), 7.14 (t, $J=7.6$ Hz, 1H), 7.09–7.05 (m, 2H), 4.89 (br s, 1H), 4.83 (br s, 1H), 4.63 (br s, 1H), 4.48 (br s, 1H), 3.80 (br s, 1H), 3.53 (s, 3H), 3.11 (d, $J=14.7$ Hz, 1H), 3.04 (br s, 1H), 2.77 (br s, 1H), 2.46–2.39 ppm (m, 3H); HRMS (FAB): *m/z* calcd for $C_{24}H_{23}O_2N_2F$: 390.1744 $[M]^+$; found: 390.1777.

36-2: Yield: 12.1 mg, 0.030 mmol, 12%. $[\alpha]_D^{25}=-2.8$ ($c=0.42$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=3065$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.84$ (s, 1H), 7.70–7.65 (m, 1H), 7.55–7.37 (m, 6H), 7.14 (t, $J=7.5$ Hz, 1H), 7.08 (t, $J=7.3$ Hz, 1H), 4.86 (br s, 1H), 4.80 (br s, 1H), 4.45 (d, $J=11.2$ Hz, 1H), 4.37 (dd, $J=3.7$, 9.9 Hz, 1H), 3.76 (d, $J=5.3$ Hz, 1H), 3.49 (s, 3H), 3.09 (d, $J=15.3$ Hz, 1H), 2.98 (dd, $J=5.7$, 14.8 Hz, 1H,), 2.76 (d, 2H, $J=12.0$ Hz, 1H), 2.49–2.42 ppm (m, 3H); MS (70 eV): *m/z* (%) = 372 $[M]^+$ (66), 313 (92), 169 (100); HRMS (FAB): *m/z* calcd for $C_{24}H_{23}O_2N_2$: 372.1838 $[M]^+$; found: 372.1831.

36-3: Yield: 7.9 mg, 0.020 mmol, 7%. $[\alpha]_D^{25}=8.1$ ($c=0.52$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=3099$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.76$ (s, 1H), 7.46 (d, $J=7.7$ Hz, 1H), 7.44–7.31 (m, 3H), 7.15 (t, $J=7.4$ Hz, 1H), 7.10–7.04 (m, 3H), 4.88 (br s, 1H), 4.81 (br s, 1H,), 4.43 (d, $J=10.7$ Hz, 1H), 4.37 (t, $J=7.2$ Hz, 1H), 3.71 (d, $J=5.3$ Hz, 1H), 3.49 (s, 3H,), 3.10 (d, $J=15.3$ Hz, 1H), 2.97 (ddd, $J=2.1$, 6.0, 15.3 Hz, 1H), 2.75 (dd, $J=2.4$, 12.8 Hz, 1H), 2.42–2.42 ppm (m, 3H); MS (70 eV): *m/z* (%) = 391 $[M]^+$ (100), 331 (97), 169 (100); HRMS (FAB): *m/z* calcd for $C_{24}H_{23}O_2N_2F$: 391.1836 $[M]^+$; found: 390.1777.

36-4: Major diastereomer: Yield: 4.4 mg, 0.008 mmol, 4%. $[\alpha]_D^{25}=-15.1$ ($c=0.38$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=3079$ cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.72$ (s, 1H), 7.58 (br s, 1H), 7.45–7.42 (m, 3H), 7.31–7.28 (m, 5H), 7.30–7.19 (m, 1H), 7.14–7.06 (m, 3H), 6.44 (br s, 1H), 4.77 (br s, 1H), 4.51 (br s, 1H), 3.82 (br s, 1H), 3.53 (s, 3H), 3.30 (br s, 1H), 3.13 (br s, 2H), 2.66 (br s, 1H), 2.60 (br s, 1H), 2.42 ppm (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=171.6$, 160.8, 144.8, 143.2, 142.7, 142.0, 137.0, 131.9, 131.8, 130.0, 128.9, 126.5, 120.9, 119.9, 115.1, 112.1, 109.0, 100.4, 58.0, 56.1, 51.7, 50.1, 40.9, 43.7, 19.0 ppm; HRMS (FAB): *m/z* calcd for $C_{30}H_{27}O_2N_2F$: 466.2057 $[M]^+$; found: 466.2065. Minor diastereomer: Brown oil, yield: 2.2 mg, 0.005 mmol, 3%. $[\alpha]_D^{25}=-4.0$ ($c=0.76$ M, MeOH); $\tilde{\nu}_{max}=3088$ cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.86$ (s, 1H), 7.47–7.42 (m, 1H), 7.38–7.33 (m, 1H), 7.30–7.36 (m, 4H), 7.36–7.19 (m, 4H), 7.15 (t, $J=7.5$ Hz, 1H), 7.07–7.03 (m, 2H), 6.50 (br s, 1H), 4.63 (br s, 2H), 3.80 (br s, 1H), 3.54 (s, 3H), 3.11 (br s, 2H), 3.02 (d, $J=14.1$ Hz, 1H), 2.83 (br s, 1H), 2.60 (br s, 1H), 2.42 ppm (br s, 1H); ^{13}C NMR (130 MHz, $CDCl_3$): $\delta=172.3$, 161.0, 145.1, 143.9, 142.3, 142.1, 137.9, 128.9, 128.0, 127.3, 133.4, 131.8, 131.0, 121.9, 120.4, 119.3, 115.1, 111.3, 107.5, 102.3, 58.3, 56.4, 53.1, 51.6, 45.7, 43.0, 19.4 ppm; HRMS (FAB): *m/z* calcd for $C_{30}H_{27}O_2N_2F$: 466.2057 $[M]^+$; found: 466.2043.

General procedure for reductive amination of **34b**: The corresponding amine (0.87 mmol, 1.0 equiv) was added to a solution of **34b** (0.87 mmol) in CH_2Cl_2 (10 mL). After 15 min, borane–pyridine complex (0.7 mL, 0.87 mmol, 1.0 equiv) was added to the suspension. The reaction was quenched with water (10 mL) after 15 h at room temperature and extracted twice with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and evaporated. The residue was purified by RP-HPLC under the conditions indicated above.

37-1a: Yield: 57.1 mg, 0.110 mmol, 34%. $[\alpha]_D^{25}=-18.2$ ($c=0.9$ M, MeOH); IR (neat): $\tilde{\nu}_{max}=1588$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=10.7$ (s, 1H), 7.60 (s, 1H), 7.42–7.33 (m, 3H), 7.36 (d, $J=8.1$ Hz, 1H), 7.16 (br s, 1H), 7.02 (t, $J=7.6$ Hz, 1H), 6.88 (t, $J=7.8$ Hz, 1H), 6.88 (s, 1H), 4.36 (d, $J=11.1$ Hz, 1H), 4.18 (d, $J=10.1$ Hz, 1H), 4.04 (t, $J=7.1$ Hz, 2H), 3.58 (d, $J=7.1$ Hz, 1H), 3.55 (s, 3H), 2.97 (d, $J=15.2$ Hz, 1H), 2.81 (dd, $J=4.6$,

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12.4 Hz, 1H), 2.55–2.52 (m, 3H), 2.51–2.49 (m, 1H), 1.98 (d, J=10.9 Hz, 1H), 1.85–1.83 (m, 2H), 1.33 (dd, J=11.5, 11.7 Hz, 1H), 1.19 ppm (dd, J=11.5, 11.7 Hz, 1H); HPLC–MS (ESI): t_R=6.65 min, m/z=520.4 $[M+H]^+$.

37-1b: Yield: 49.6 mg, 0.095 mmol, 29%. $[\alpha]_D^{25}=-117.1$ (c=0.7 M, MeOH); IR (neat): $\tilde{\nu}_{max}$=1599 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=10.7 (s, 1H), 7.67 (s, 1H), 7.42–7.33 (m, 3H), 7.36 (d, J=8.1 Hz, 1H), 7.36 (br s, 1H), 7.01 (t, J=7.6 Hz, 1H), 6.92 (m, 2H), 4.78 (d, J=11.1 Hz, 1H), 4.52 (t, J=7.1 Hz, 1H), 4.16–4.11 (m, 2H), 3.53 (d, J=5.1 Hz, 1H), 3.52 (s, 3H), 2.99 (s, 1H), 2.94 (d, J=15.2 Hz, 1H), 2.81 (dd, J=4.6, 12.4 Hz, 1H), 2.68–2.66 (m, 1H), 2.55–2.52 (m, 1H), 1.96–1.94 (m, 3H), 1.74 (d, J=5.1 Hz, 1H), 1.65 (br s, 1H), 1.54 ppm (t, J=10.6 Hz, 1H); HPLC–MS (ESI): t_R=6.38 min, m/z=520.4 $[M+H]^+$.

37-2a: Yield: 43.4 mg, 0.091 mmol, 27%. $[\alpha]_D^{25}=+28.9$ (c=0.3 M, MeOH); IR (neat): $\tilde{\nu}_{max}$=1599 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=10.8 (s, 1H), 7.33–7.33 (m, 3H), 7.02 (t, J=7.6 Hz, 1H), 6.93–6.84 (m, 4H), 4.77 (d, J=11.4 Hz, 1H), 4.43 (d, J=8.6 Hz, 1H), 3.75 (s, 3H), 3.58 (d, J=5.1 Hz, 1H), 3.45 (s, 3H), 3.44 (br s, 1H), 3.02 (s, 1H), 2.93–2.89 (m, 1H), 2.85–2.80 (dd, J=6.5, 8.1 Hz, 1H), 2.68–2.62 (m, 1H), 2.50–2.39 (m, 2H), 2.13 (s, 3H), 1.79–1.72 (m, 1H), 1.56 ppm (t, J=3.5 Hz, 1H); HPLC–MS (ESI): t_R=6.91 min, m/z=477.5 $[M+H]^+$.

37-2b: Yield: 62.2 mg, 0.130 mmol, 41%. $[\alpha]_D^{25}=+48.1$ (c=0.2 M, MeOH); IR (neat): $\tilde{\nu}_{max}$=1609 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.42–7.27 (m, 3H), 7.02 (t, J=7.6 Hz, 1H), 6.93–6.85 (m, 4H), 4.44 (d, J=11.4 Hz, 1H), 4.11 (d, J=8.6 Hz, 1H), 3.75 (s, 3H), 3.62 (d, J=5.1 Hz, 1H), 3.46 (s, 3H), 3.38 (br s, 1H), 3.00 (d, J=15.4 Hz, 1H), 2.93–2.89 (m, 1H), 2.85–2.62 (m, 4H), 2.36 (t, J=6.1 Hz, 1H), 2.07 (s, 3H), 1.96 (d, J=11.1 Hz, 1H), 1.42 (t, J=3.5 Hz, 1H), 1.16 ppm (t, J=3.5 Hz, 1H); HPLC–MS (ESI): t_R=6.77 min, m/z=477.5 $[M+H]^+$.

37-3a: Yield: 44.6 mg, 0.090 mmol, 38%. $[\alpha]_D^{25}=-38.2$ (c=0.1 M, MeOH); IR (neat): $\tilde{\nu}_{max}$=1611 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=10.8 (s, 1H), 7.89–7.86 (m, 1H), 7.42–7.33 (m, 4H), 7.01 (t, J=7.6 Hz, 1H), 6.94 (t, J=7.6 Hz, 1H), 4.75 (d, J=11.1 Hz, 1H), 4.47 (d, J=13.5 Hz, 1H), 3.53 (d, J=5.1 Hz, 1H), 3.47 (s, 3H), 3.33 (s, 2H), 3.42–3.17 (m, 2H), 3.03 (br s, 1H), 2.90 (d, J=15.2 Hz, 1H), 2.85–2.76 (m, 1H), 2.69–2.63 (m, 1H), 2.44 (d, J=12.6 Hz, 1H), 1.84 (s, 3H), 1.84–1.72 (m, 4H), 1.53 ppm (t, J=2.5 Hz, 1H); HPLC–MS (ESI): t_R=6.48 min, m/z=495.5 $[M+H]^+$.

37-3b: Yield: 20.8 mg, 0.042 mmol, 19%. $[\alpha]_D^{25}=45.9$ (c=0.2 M, MeOH); IR (neat): $\tilde{\nu}_{max}$=1601 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=10.8 (s, 1H), 7.82–7.80 (m, 1H), 7.42–7.27 (m, 4H), 7.01 (t, J=7.6 Hz, 1H), 6.93 (t, J=7.6 Hz, 1H), 4.31 (d, J=11.1 Hz, 1H), 4.18 (d, J=13.5 Hz, 1H), 3.57 (d, J=5.1 Hz, 1H), 3.47 (s, 3H), 3.44 (br s, 1H), 3.33 (d, J=6.1 Hz, 2H), 2.97 (d, J=15.2 Hz, 1H), 2.85–2.76 (m, 1H), 2.69–2.60 (m, 2H), 1.95 (d, J=10.6 Hz, 1H), 1.79 (s, 3H), 1.44 (dd, J=11.5, 11.7, 1H), 1.16 ppm (dd, J=11.5, 11.7 Hz, 1H); HPLC–MS (ESI): t_R=6.25 min, m/z=495.5 $[M+H]^+$.

37-4a: Yield: 44.8 mg, 0.105 mmol, 32%. $[\alpha]_D^{25}=-87.2$ (c=0.4 M, MeOH); IR (neat): $\tilde{\nu}_{max}$=1599 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=10.7 (s, 1H), 7.38–7.27 (m, 7H), 7.01 (t, J=7.1 Hz, 1H), 6.92 (t, J=7.1 Hz, 1H), 4.78 (d, J=11.6 Hz, 1H), 4.49 (d, J=9.6 Hz, 1H), 3.56–3.53 (m, 3H), 3.56 (s, 3H), 3.43 (s, 1H), 2.91 (d, J=15.2 Hz, 1H), 2.83 (dd, J=4.6, 12.4 Hz, 1H), 2.46 (d, J=11.9 Hz, 1H), 1.86 (t, J=11.2 Hz, 1H), 1.73 (d, J=11.6 Hz, 1H), 1.52 ppm (t, J=10.1 Hz, 1H); HRMS (FAB): m/z calcd for $C_{26}H_{27}N_3O_2$: 413.2103 $[M]^+$; found: 413.2119.

37-4b: Yield: 42.3 mg, 0.099 mmol, 30%. $[\alpha]_D^{25}=-99.3$ (c=0.2 M, MeOH); IR (neat): $\tilde{\nu}_{max}$=1597 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=10.8 (s, 1H), 7.38–7.36 (m, 7H), 7.02 (t, J=8.1 Hz, 1H), 6.95 (t, J=8.1 Hz, 1H), 4.44 (d, J=11.6 Hz, 1H), 4.16 (d, J=10.6 Hz, 1H), 3.58 (d, J=5.1 Hz, 1H), 3.46 (s, 3H), 3.42 (s, 1H), 3.38 (s, 3H), 3.11 (s, 1H), 2.98–2.91 (m, 2H), 2.83–2.80 (m, 1H), 1.95 (d, J=11.6 Hz, 1H), 1.42 (dd, J=11.5, 11.7 Hz, 1H), 1.12 ppm (dd, J=11.5, 11.7 Hz, 1H); HRMS (FAB): m/z calcd for $C_{26}H_{27}N_3O_2$: 413.2103 $[M]^+$; found: 413.2089.

37-5a: Yield: 49.9 mg, 0.117 mmol, 52%. $[\alpha]_D^{25}=+114.2$ (c=0.11 M, MeOH); IR (neat): $\tilde{\nu}_{max}$=1577 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=10.8 (s, 1H), 7.38–7.27 (m, 7H), 7.02 (t, J=7.1 Hz, 1H), 6.94 (t, J=7.1 Hz, 1H), 4.44 (d, J=11.6 Hz, 1H), 4.15 (d, J=10.6 Hz, 1H), 3.58 (d, J=5.1, 1H), 3.45 (s, 3H), 3.01–2.94 (m, 2H), 2.85–2.78 (m, 2H), 2.69 (d, J=10.6 Hz, 1H), 1.93 (d, J=10.6 Hz, 1H), 1.44 (dd, J=11.5, 11.7 Hz, 1H), 1.18 (dd, J=11.5, 11.7 Hz, 1H), 0.99 ppm (d, J=6.1 Hz, 6H); HPLC–MS (ESI): t_R=7.39 min, m/z=418 $[M+H]^+$.

37-5b: Yield: 13.9 mg, 0.0325 mmol, 14%. $[\alpha]_D^{25}=-45.9$ (c=0.11 M, MeOH); IR (neat): $\tilde{\nu}_{max}$=1595 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=10.8 (s, 1H), 7.38–7.33 (m, 7H), 7.00 (t, J=7.1 Hz, 1H), 6.92 (t, J=7.1 Hz, 1H), 4.77 (d, J=11.6 Hz, 1H), 4.47 (d, J=10.6 Hz, 1H), 3.56 (d, J=5.1, 1H), 3.46 (s, 3H), 3.04 (s, 1H), 3.05–2.99 (m, 1H), 2.88 (d, J=15.2 Hz, 1H), 2.83–2.79 (m, 1H), 2.45 (d, J=11.6 Hz, 1H), 1.82 (t, J=3.0, 5.4 Hz, 1H), 1.69 (d, J=11.6 Hz, 1H), 1.54 (dd, J=3.0, 5.4 Hz, 1H), 1.11–1.08 ppm (m, 6H); HPLC–MS (ESI): t_R=7.23 min, m/z=418 $[M+H]^+$.

37-6a: Yield: 41.1 mg, 0.096 mmol, 19%. $[\alpha]_D^{25}=-99.1$ (c=0.21 M, MeOH). Minor diastereomer: Yield: 31.3 mg, 0.079 mmol, 27%. IR (neat): $\tilde{\nu}_{max}$=1592 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=7.94 (br s, 1H), 7.52 (dd, J=6.7, 7.1 Hz, 1H), 7.44 (d, J=7.4 Hz, 1H), 7.31 (d, J=7.4 Hz, 1H), 7.30 (t, 1H) (the coupling constant could not be determined because of overlap with the solvent signal), 7.16 (t, J=7.1 Hz, 1H), 7.13 (t, J=7.4 Hz, 1H), 7.07 (t, J=7.4 Hz, 1H), 7.05 (d, J=7.5 Hz, 1H), 4.97 (dd, J=4.1, 9.9 Hz, 1H), 4.90 (br d, J=11.5 Hz, 1H), 3.74 (br d, J=5.0 Hz, 1H), 3.63–3.60 (m, 2H), 3.52 (s, 3H), 3.42 (s, 3H), 3.20 (br s, 1H), 3.08 (dd, J=5.0, 15.3 Hz, 1H), 3.00 (br d, J=15.3 Hz, 1H), 2.97 (dt, J=4.7, 12.2 Hz, 1H), 2.90 (dt, J=4.7, 12.2 Hz, 1H), 2.42 (br d, J=12.7 Hz, 1H), 1.97–1.94 (m, 1H), 1.89 ppm (ddd, J=3.3, 11.5, 12.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=173.0, 160.8, 138.1, 144.2, 136.1, 128.9, 128.8, 128.3, 127.8, 121.4, 119.3, 118.1, 116.1, 110.1, 106.8, 71.9, 58.9, 56.9, 51.9, 51.3, 51.1, 48.1, 47.0, 38.8, 38.4, 31.9 ppm; HRMS (FAB): m/z calcd for $C_{26}H_{30}FN_3O_3$: 451.2271 $[M]^+$; found: 451.2259.

37-6b: Yield: 40.7 mg, 0.103 mmol, 44%. $[\alpha]_D^{25}=-71.2$ (c=0.31 M, MeOH); IR (neat): $\tilde{\nu}_{max}$=1593 cm^{-1}; ^{1}H NMR (CD_3SOCD_3, 500 MHz): δ=7.45 (dd, J=6.8, 7.5, Hz, 1H), 7.38 (d, J=8.0 Hz, 1H), 7.37 (d, J=8.0 Hz, 1H), 7.18 (t, J=7.5 Hz, 1H), 7.09 (t, J=7.5 Hz, 1H), 7.06 (t, J=8.0 Hz, 1H), 7.00 (t, J=8.0 Hz, 1H), 6.99–6.96 (m, 1H), 4.90 (dd, J=4.0, 9.9 Hz, 1H), 4.83 (br d, J=12.4 Hz, 1H), 3.68 (br d, J=5.5 Hz, 1H), 3.13 (br s, 1H), 3.55–3.52 (m, 2H), 3.46 (s, 3H), 3.42 (s, 3H), 3.01 (br d, J=15.2 Hz, 1H), 2.94 (dd, J=5.5, 15.2 Hz, 1H), 2.89 (ddd, J=5.4, 5.4, 11.6 Hz, 1H), 2.84 (ddd, J=5.4, 5.4, 11.6 Hz, 1H), 2.62 (br d, J=12.4 Hz, 1H), 1.83 (ddd, J=3.3, 12.4, 12.4 Hz, 1H), 1.90–1.88 ppm (m, 2H); ^{13}C NMR (CD_3SOCD_3, 125 MHz): δ=173.4, 161.1, 138.6, 144.5, 137.5, 136.2, 136.0, 127.6, 130.0, 121.6, 119.7, 118.3, 116.1, 111.1, 107.7, 72.1, 59.2, 56.5, 52.1, 51.5, 51.4, 47.1, 48.4, 39.0, 38.7, 30.3 ppm; HRMS (FAB): m/z calcd for $C_{26}H_{30}FN_3O_3$: 451.2271 $[M]^+$; found: 451.2268.

37-7a: Yield: 62.2 mg, 0.138 mmol, 48%. $[\alpha]_D^{25}=-27.2$ (c=0.1 M, MeOH); IR (neat): $\tilde{\nu}_{max}$=1590 cm^{-1}; ^{1}H NMR (500 MHz, CD_3SOCD_3): δ=10.6 (s, 1H), 7.33 (s, 1H), 7.17–7.12 (m, 4H), 7.07 (d, J=8.1 Hz, 1H), 6.84 (t, J=7.1 Hz, 1H), 6.74 (t, J=7.1 Hz, 1H), 4.49 (s, 1H), 4.12 (d, J=11.1 Hz, 1H), 4.03 (d, J=11.6 Hz, 1H), 3.97 (br s, 1H), 3.30 (d, J=5.9 Hz, 1H), 3.33 (s, 3H), 2.75 (d, J=15.2 Hz, 1H), 2.64 (d, J=2.6 Hz, 1H), 2.55 (d, J=9.6 Hz, 1H), 2.46 (d, J=7.5 Hz, 1H), 2.42–2.36 (m, 3H), 2.20–2.17 (m, 1H), 1.76–1.73 (m, 2H), 1.42–1.30 (m, 2H), 1.08 ppm (dd, J=5.6, 11.1 Hz, 1H); ^{13}C NMR (125 MHz, CD_3SOCD_3): δ=172.3, 147.5, 142.8, 138.1, 144.2, 133.5, 121.4, 121.1, 120.6, 118.4, 117.5, 111.0, 104.5, 69.0, 62.6, 60.6, 59.9, 55.7, 52.5, 51.1, 49.4, 42.1, 42.5, 38.3, 42.1, 31.1 ppm; HRMS (FAB): m/z calcd for $C_{28}H_{30}F_3N_3O_4$: 529.2188 $[M]^+$; found: 529.2164.

37-8a: Yield: 20.1 mg, 0.044 mmol, 21%. $[\alpha]_D^{25}=+87.2$ (c=0.1 M, MeOH); IR (neat): $\tilde{\nu}_{max}$=1600 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=10.7 (s, 1H), 7.51 (s, 1H), 7.38 (d, J=7.6 Hz, 1H), 7.37 (d, J=8.0 Hz, 1H), 7.02 (t, J=7.1 Hz, 1H), 6.94 (t, J=7.1 Hz, 1H), 4.39 (d, J=5.1 Hz, 1H), 4.11 (d, J=11.2 Hz, 1H), 3.56 (d, J=9.8 Hz, 1H), 3.49 (s, 3H), 3.06 (d, J=8.1 Hz, 1H), 2.94–2.78 (m, 5H), 2.66–2.58 (m, 4H), 2.00 (d, J=10.9 Hz, 1H), 1.66 (br s, 1H), 1.55 (t, J=10.6 Hz, 1H), 1.36 (br s, 1H), 0.84–0.79 (m, 4H), 0.94 ppm (d, J=5.9 Hz, 1H); HPLC–MS (ESI): t_R=6.42 min, m/z=422 $[M+H]^+$.

37-8b: Yield: 20.3 mg, 0.045 mmol, 20%. $[\alpha]_D^{25}=-100.8$ (c=0.11 M, MeOH); IR (neat): $\tilde{\nu}_{max}$=1599 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=10.7 (s, 1H), 7.51 (s, 1H), 7.44 (d, J=7.6 Hz, 1H), 7.31 (d, J=8.0 Hz, 1H), 7.01 (t, J=7.1 Hz, 1H), 6.99 (t, J=7.1 Hz, 1H), 6.78 (s, 1H), 4.18

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(d, $J=5.6$ Hz, 1H), 4.10 (d, $J=11.1$ Hz, 1H), 3.50 (s, 3H), 3.06 (d, $J=15.1$ Hz, 1H), 3.00–2.78 (m, 4H), 2.66–2.50 (m, 4H), 1.84 (d, $J=12.1$ Hz, 1H), 1.62–1.57 (m, 2H), 1.08 (dd, $J=11.5$, 11.7 Hz, 1H), 0.95 (dd, $J=11.5$, 11.7 Hz, 1H), 0.86 ppm (t, $J=7.1$ Hz, 3H); HPLC–MS (ESI): $t_R=6.19$ min, $m/z=422$ $[M+H]^+$.

Protein Phosphatase Assays

All enzyme assays were performed on an automated system consisting of a Zymark SciClone ALH 500 workstation in conjunction with a Twister II and a Bio-Tek Power Wave 420 reader. The reaction volume was 10 µL. The reaction was started by the addition of *p*-nitrophenyl phosphate (0.5 M stock solution, 5 µL) to 5 µL of a solution containing the respective enzymes that had been preincubated for 10–15 min with different concentrations from a twofold-dilution series of inhibitors. The reaction velocity was determined from the slope of the absorbance change at 405 nm and related to control values in the absence of the inhibitor. IC_{50} values were calculated from linear extrapolations of reaction velocity as a function of the logarithm of the concentration.

All buffered solutions contained DTE (1,4-dithio-D,L-threitol added on the day of the experiment from 100 mM stock; 2 mM) and the detergent NP-40 (0.030% *v*/*v*). The buffers consisted of Tris (tris(hydroxymethyl)-aminomethane; 50 mM), NaCl (50 mM), and EDTA (ethylenediamine tetraacetic acid; 0.1 mM) in the case of Cdc25A, HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; 30 mM), NaCl (50 mM), and EDTA (2.5 mM) in the case of PTP1b, MptpA and MptpB, and MOPS (3-(*N*-morpholino)propanesulfonic acid; 30 mM) and EDTA (5 mM) in the case of VHR. The concentrations for the enzyme reaction were 50 mM in the case of Cdc25A and 1 mM for all other phosphatases. All determinations were performed as quadruplets from identical manual dilutions (1:10 in buffer from 10 mM stock solutions in dimethyl sulfoxide).

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[1] T. Hunter, *Cell* **2000**, *100*, 113–127.
[2] a) K. Hinterding, D. Alonso-Díaz, H. Waldmann, *Angew. Chem.* **1998**, *110*, 716–780; *Angew. Chem. Int. Ed.* **1998**, *37*, 688–749; b) L. Bialy, H. Waldmann, *Angew. Chem.* **2005**, *117*, 3880–3906; *Angew. Chem. Int. Ed.* **2005**, *44*, 3814–3839.
[3] M. A. Koch, L.-O. Wittenberg, S. Basu, D. A. Jeyaraj, E. Gourzoulidou, K. Reinecke, A. Odermatt, H. Waldmann, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 16721–16726.
[4] M. A. Koch, A. Schuffenhauer, M. Scheck, S. Wetzel, M. Casaulta, A. Odermatt, P. Ertl, H. Waldmann, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 17272–17277.
[5] a) M. A. Koch, H. Waldmann, *Drug Discovery Today* **2005**, *10*, 471–483; b) R. Breinbauer, I. Vetter, H. Waldmann, *Angew. Chem.* **2002**, *114*, 3002–3015; *Angew. Chem. Int. Ed.* **2002**, *41*, 2879–2890.
[6] a) A. Nören-Müller, I. Reis-Corrêa, Jr., H. Prinz, C. Rosenbaum, K. Saxena, H. Schwalbe, D. Vestweber, G. Cagna, S. Schunk, O. Schwarz, H. Schiewe, H. Waldmann, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 10606–10611; for further examples of the synthesis of NP-derived and -inspired compound collections and BIOS, see: b) D. Brohm, S. Metzger, A. Bhargava, O. Müller, F. Lieb, H. Waldmann, *Angew. Chem.* **2002**, *114*, 319–323; *Angew. Chem. Int. Ed.* **2002**, *41*, 307–311; c) D. Brohm, N. Philippe, S. Metzger, A. Bhargava, O. Müller, F. Lieb, H. Waldmann, *J. Am. Chem. Soc.* **2002**, *124*, 13171–13178; d) O. Barun, S. Sommer, H. Waldmann, *Angew. Chem.* **2004**, *116*, 3258–3261; *Angew. Chem. Int. Ed.* **2004**, *43*, 3195–3199; e) S. Sommer, H. Waldmann, *Chem. Commun.* **2005**, 5684–5686; f) B. Meseguer, D. Alonso-Díaz, N. Griebenow, T. Herget, H. Waldmann, *Angew. Chem.* **1999**, *111*, 3083–3087; *Angew. Chem. Int. Ed.* **1999**, *38*, 2902–2906; g) M. A. Sanz, T. Voigt, H. Waldmann, *Adv. Synth. Catal.* **2006**, *348*, 1511–1515; h) A. B. Garcia, T. Leßmann, J. D. Umarye, V. Mamane, S. Sommer, H. Waldmann, *Chem. Commun.* **2006**, 3868–3870; i) J. D. Umarye, T. Leßmann, A. B. Garcia, V. Mamane, S. Sommer, H. Waldmann, *Chem. Eur. J.* **2007**, *13*, 3305–3319; j) T. Leßmann, M. G. Leuenberger, S. Menninger, M. Lopez-Canet, O. Müller, S. Hümmer, J. Bormann, K. Korn, E. Fava, M. Zerial, T. U. Mayer, H. Waldmann, *Chem. Biol.* **2007**, *14*, 443–451; k) V. Mamane, A. B. Garcia, J. D. Umarye, T. Leßmann, S. Sommer, H. Waldmann, *Tetrahedron* **2007**, *63*, 5754–5767.
[7] A. Koul, T. Herget, B. Klebl, A. Ullrich, *Nat. Rev. Microbiol.* **2004**, *2*, 189–202.
[8] T. O. Johnson, J. Ermolieff, M. R. Jirousek, *Nat. Rev. Drug Discovery* **2002**, *1*, 696–709.
[9] A. Östman, C. Hellberg, F. D. Böhmer, *Nat. Rev. Cancer* **2006**, *6*, 307–320.
[10] R. Nawroth, G. Poell, A. Ranft, S. Kloep, U. Samulowitz, G. Fachinger, M. Golding, D. T. Shima, U. Deutsch, D. Vestweber, *EMBO J.* **2002**, *21*, 4885–4895.
[11] D. J. Anderson, S. P. Arneric, *Eur. J. Pharmacol.* **1994**, *253*, 261–267.
[12] A. Koul, A. Choidas, M. Treder, A. K. Tyagi, K. Drlica, Y. Singh, A. Ullrich, *J. Bacteriol.* **2000**, *182*, 5425–5432.
[13] a) D. Butler, *Nature* **2000**, *406*, 670–672; b) R. Singh, V. Rao, H. Shakila, R. Gupta, A. Khera, N. Dhar, A. Singh, A. Koul, Y. Singh, M. Naseema, R. P. Narayanan, C. N. Paramasivan, V. D. Ramanathan, A. K. Tyagi, *Mol. Microbiol.* **2003**, *50*, 751–762.
[14] M. Frederich, M. Tits, L. Angenot, *Chem. Nat. Prod.* **2003**, *39*, 513–519.
[15] H. Takayama, Y. Iimura, M. Kitajima, N. Aimi, K. Konno, H. Inoue, M. Fujiwara, T. Mizuta, T. Yokota, S. Shigeta, K. Tokuhisa, Y. Hanasaki, K. Katsuura, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 3145–3148.
[16] D. Arbain, N. H. Lajis, D. P. Putra, M. V. Sargent, B. W. Skelton, A. H. White, *J. Chem. Soc. Perkin Trans. 1* **1992**, 3039–3042.
[17] J. E. Saxton, *Nat. Prod. Rep.* **1993**, *10*, 349–395.
[18] C. Gaul, J. T. Njardarson, D. Shan, D. C. Dorn, K.-D. Wu, W. P. Tong, X.-Y. Huang, M. A. S. Moore, S. J. Danishefsky, *J. Am. Chem. Soc.* **2004**, *126*, 11326–11337.
[19] P. Sieber, *Tetrahedron Lett.* **1987**, *28*, 6147–6150.
[20] H. Wang, A. Ganesan, *Org. Lett.* **1999**, *1*, 1647–1649.
[21] H. Waldmann, M. Braun, M. Dräger, *Angew. Chem.* **1990**, *102*, 1445–1447; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1468–1471.
[22] H. Waldmann, M. Braun, *J. Org. Chem.* **1992**, *57*, 4444–4451.
[23] R. Lock, H. Waldmann, *Chem. Eur. J.* **1997**, *3*, 143–151.
[24] Y. Wang, S. R. Wilson, *Tetrahedron Lett.* **1997**, *38*, 4021–4024.
[25] K. Tanaka, K. Nakanishi, N. Berova, *J. Am. Chem. Soc.* **2003**, *125*, 10802–10803.
[26] A. Deiters, K. Chen, C. T. Eary, S. F. Martin, *J. Am. Chem. Soc.* **2003**, *125*, 4541–4550.
[27] G. J. Kuster, H. W. Scheren, *Tetrahedron Lett.* **1998**, *39*, 3613–3616.
[28] Y. Sheng, K. T. Chapman, *Tetrahedron Lett.* **1997**, *38*, 1497–1500.
[29] U. Schöllkopf, I. Hoppe, *Angew. Chem.* **1975**, *87*, 814–815; *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 765.
[30] A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff, R. D. Shah, *J. Org. Chem.* **1996**, *61*, 3849–3862.
[31] U. Heinelt, S. Herok, H. Matter, P. Wildgoose, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 227–230.

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