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Pyrrolo[3,2-*e*][1,4]diazepin-2-one Synthesis: A Head-to-Head Comparison of Soluble versus Insoluble Supports

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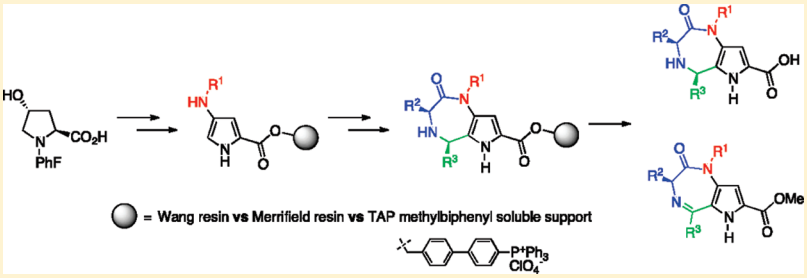
Supporting Information

ABSTRACT:



Aryldiazepin-2-ones are known as "privileged structures", because they bind to multiple receptor types with high affinity. Toward the development of a novel class of aryldiazepin-2-one scaffolds, the synthesis of pyrrolo[3,2-*e*][1,4]diazepin-2-ones on a support was explored starting from *N*-(PhF)-4-hydroxyproline and featuring an acid-catalyzed Pictet−Spengler reaction to form the diazepine ring. Three supports [Wang resin, tetraarylphosphonium (TAP) soluble support, and Merrifield resin] were examined in the synthesis of the heterocycle and exhibited different advantages and disadvantages. Wang resin proved effective for exploratory optimization of the synthesis by identification of intermediates after resin cleavage under mild conditions; however, the acidic conditions of the Pictet−Spengler reaction caused premature loss of resin-bound material. Direct monitoring of reactions by TLC, RP-HPLC-MS, and in certain cases NMR spectroscopy was possible with the TAP support, which facilitated purification of intermediates by precipitation; however, incomplete precipitation of material led to overall yields lower than those from solid-phase approaches on resin. Merrifield resin proved stable to the conditions for the synthesis of the pyrrolo[3,2-*e*][1,4]diazepin-2-one targets and would be amenable to "split-and-mix" chemistry; however, relatively harsh conditions were necessary for final product cleavage. Perspective for the application of different solid-phase approaches in heterocycle library synthesis was thus obtained by demonstration of the respective utility of the three supports for preparation of pyrrolo[3,2-*e*][1,4]diazepin-2-one.

INTRODUCTION

Aryldiazepin-2-ones, such as [1,4]benzodiazepin-2-ones, are considered as "privileged structures",[1] because of their affinity for multiple receptor targets. Their ability to bind protein receptors and elicit interesting biological activity may be due to their potential to mimic peptide turn secondary structures.[2] The aryldiazepin-2-one scaffold[3] achieved popularity first in the 1960s as a component of GABA receptor antagonists (i.e., diazepam (Valium))[3d,e] for treating CNS-related conditions. The platform was later shown to interact with various hormone receptors[1b,4] and has been used in enzyme inhibitors[5] as well as in inhibitors of protein−DNA interactions.[6]

Pyrrolodiazepin-2-ones have been reported less often in the literature; however, they similarly display remarkable biological activities. For example, the DNA-binding pyrrolo[2,1-*c*][1,4]benzodiazepine natural product, anthramycin (**2**, Figure 1), is an antitumor antibiotic.[7] Pyrrolodiazepin-2-ones **3** and **4** are, respectively, inhibitors of angiotensin converting enzyme (ACE)[8] and HIV reverse transcriptase (HIV-RT).[9] In addition, pyrrolodiazepin-2-one scaffolds **5** and **6** have been reported in the patent literature to exhibit, respectively, antimuscarinic[10] and GABA antagonist properties.[11]

Their notable activities and opportunity for novel structural diversity have made the development of methods for constructing and functionalizing pyrrolodiazepinone scaffolds a promising subject for medicinal chemistry research. Recent examples have key steps featuring the use of the multicomponent Ugi-type condensation,[12] phenyliodine(III)bis-(trifluoroacetate)-mediated intramolecular *N*-acylnitrenium ion reaction,[13] and cyclization via Schmidt thermolysis of acylazides.[14] In addition, the intramolecular Paal−Knorr reaction has provided pyrrolo[1,2-*d*][1,4]diazepin-4-ones **7** (Figure 1).[2b]

A solution-phase synthesis of the pyrrolo[3,2-*e*][1,4]diazepin-2-one scaffold **13** was recently achieved starting from (2*S*,4*R*)-4-hydroxproline (Scheme 1).[15] The key for introducing structural diversity in this approach was the synthesis of 4-*N*-substituted-aminopyrrole-2-carboxylates **10** upon treatment

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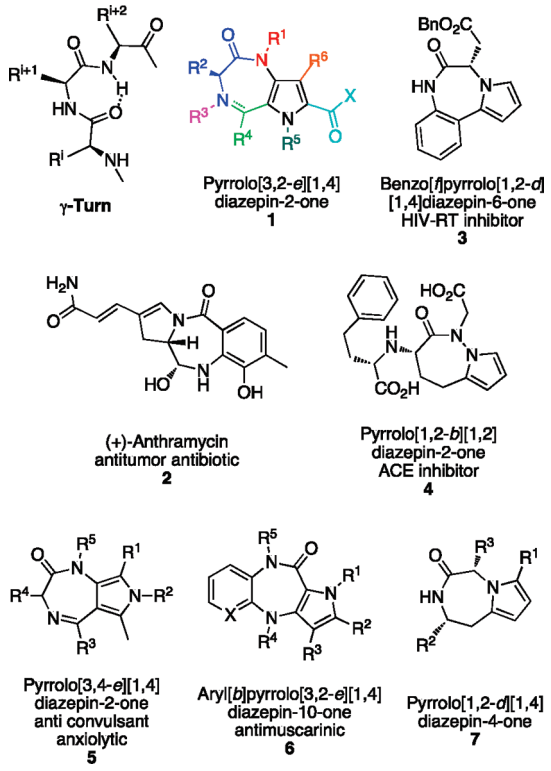
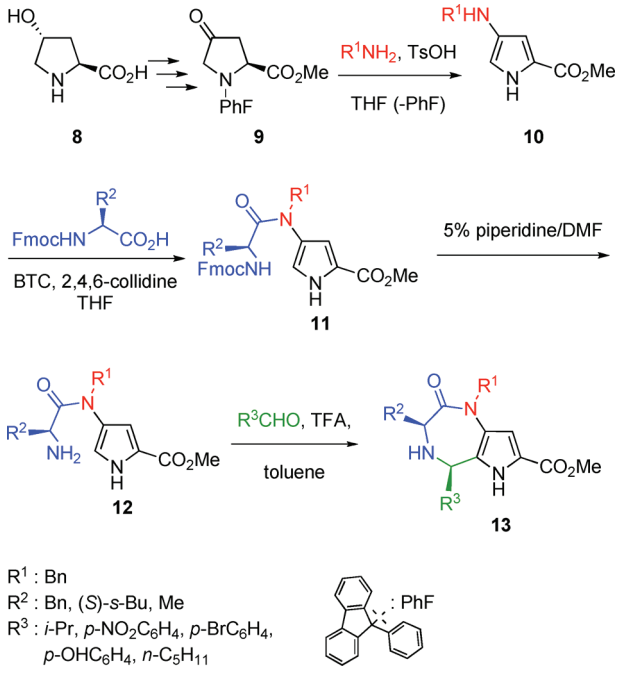


Figure 1. Representative pyrrolodiazepinones.

Scheme 1. Solution-Phase Synthesis of Pyrrolo[3,2-*e*]-[1,4]diazepin-2-ones.[15]



of methyl (*S*)-4-oxo-1-(9-phenyl-9*H*-fluoren-9-yl)prolinate **9** with different primary amines in the presence of catalytic *p*-TsOH, which caused pyrrole formation and concomitant loss of the 9-phenyl-9*H*-fluorene (PhF-H) group.[16,17] Compounds **11** were obtained by 4-aminoacylation with various Fmoc-amino acids

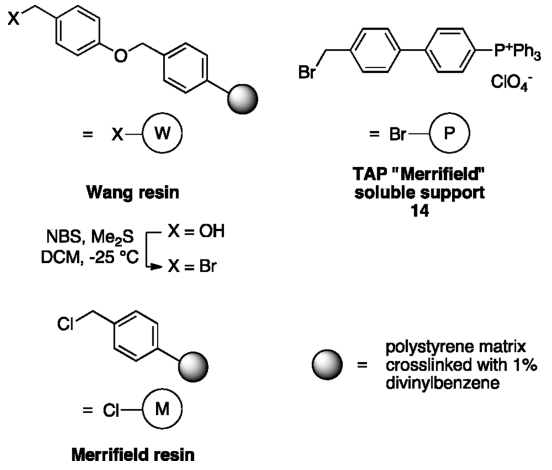


Figure 2. Supports used for the synthesis of pyrrolo[3,2-*e*]-[1,4]diazepin-2-one.

and deprotection with piperidine. Ring closure was accomplished by Pictet–Spengler condensation with aldehydes, giving the pyrrolo[3,2-*e*][1,4]diazepin-2-ones with a cis relative stereochemistry for the major compounds. The stereoselective outcome of the reaction favored an endo attack of the *E* iminium ion in a transition state having the amino acid side chain in an equatorial orientation. Aromatic aldehydes, especially those bearing electron-withdrawing groups, gave generally better yields than aliphatic aldehydes.

In addition to offering a modular approach for making the bicyclic ring system, crystals of pyrrolo[3,2-*e*][1,4]diazepin-2-one **13** (Scheme 1, R^1 = Bn, R^2 = (*S*)-*s*-Bu, R^3 = Ph) were isolated and subjected to X-ray analysis, which demonstrated that the dihedral angles of the diazepinone α-amino acid residue ($\phi = 71°$, $\psi = -93°$) compared favorably with those of an ideal reverse γ-turn ($\phi = 60°$ to $70°$, $\psi = -70°$ to $-85°$).[15]

Considering the importance of γ-turn conformations for the biological activity of various peptides, such as enkephalin,[18] angiotensin,[19] bradykinin,[20] vasopressin,[21] substance P,[22] somatostatin,[23] and oxytocin,[24] we are developing a diversity-oriented methodology for modular construction of pyrrolo[3,2-*e*]-[1,4]diazepin-2-one libraries. Herein is reported the examination of three different supports to provide the desired scaffold without purification of intermediates by chromatography.

Wang resin (Figure 2) was tried because of previous success in the solid-phase synthesis of 3-aminopyrrole-2,5-dicarboxylate analogues;[25] however, its labile nature under acidic conditions meant cleavage of product in the Pictet–Spengler cyclization, inhibiting further modification of the pyrrolo[3,2-*e*][1,4]diazepin-2-one scaffold on the support. Merrifield resin was effective for synthesizing the pyrrolo[3,2-*e*][1,4]diazepin-2-one scaffold without resin cleavage, offering an opportunity for further modification of the heterocycle; however, resin cleavage necessitated relatively harsh conditions. The (4′-(bromomethyl)-[1,1′-biphenyl]-4-yl)triphenylphosphonium salt **14**[26] (Figure 2), a soluble variant of Merrifield resin, was chosen as a solubility control group (SCG) for its advantages in the preparation of small molecules and peptides,[26,27] because reactions can be performed under homogeneous conditions in polar solvent systems prior to purification by precipitation from solvents of low polarity. Precipitation of the tetraarylphosphonium (TAP) substrates from Et_2O has been shown to be counterion dependent

($Br^- < ClO_4^- < PF_6^-$);[27b] thus, the inexpensive perchlorate salt was chosen for our study. In contrast to resins, which required cleavage prior to reaction analysis, substrates were examined directly on the TAP support by TLC, RP-HPLC-MS, and NMR spectroscopy. The head-to-head comparison of these three supports in the context of the synthesis of pyrrolo[3,2-*e*]-[1,4]diazepin-2-one has revealed their strengths and limitations and is guiding efforts toward the development of an effective method for diversity-oriented library synthesis.

RESULTS

4-Aminopyrrole-2-carboxylate Synthesis. In the synthesis of pyrrolo[3,2-*e*][1,4]diazepin-2-one, the initial unit of diversity was added in the synthesis of the 4-aminopyrrole-2-carboxylate. In previous syntheses of aminopyrrole on solid support, an ester linkage to the Wang resin was used to prepare 4-aminopyrrole-2-carboxylates with tertiary 4-amino groups,[25] and a cysteinamine linker to the Merrifield resin was used to attach the aminopyrrole to the resin as a secondary amine, which was employed in the synthesis of pyrrolopyrimidines.[28] In both cases, a 4-oxo-*N*-(PhF)proline-2-carboxylate served as precursor in the amino-pyrrole forming reaction, which has proven applicable using a wide variety of primary and secondary amines in solution.[17] In light of this precedent, benzylamine was the only example employed to form 4-aminopyrrole-2-carboxylate in the comparative study.

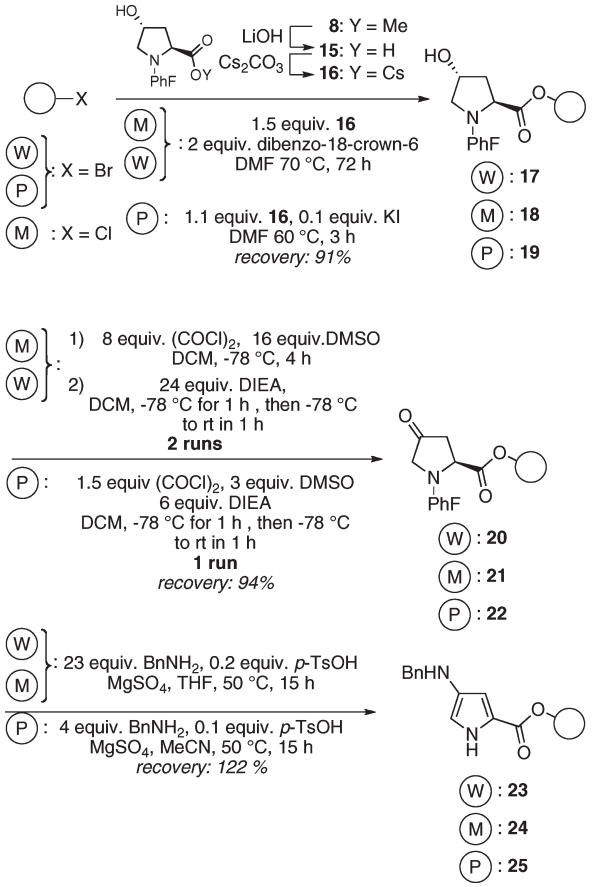
To link (2*S*,4*R*)-4-hydroxy-*N*-(PhF)proline (**15**) to the support, the corresponding cesium salt **16** was prepared and reacted with the Wang bromide resin [4-(bromomethyl)phenoxymethyl polystyrene, prepared from Wang resin, Figure 2] according to previously published procedures, and loading was ascertained as previously described (Scheme 2).[25,29] Merrifield resin and its soluble TAP variant **14** were employed as obtained from the manufacturer.

To avoid experimental bias during comparisons of the solid supports, Wang and Merrifield resins were placed in IRORI MacroKans and reacted simultaneously together in the same pot, using magnetic stirring to agitate the Kans without crushing the resin. Cesium salt **16** (150 mol %) was reacted with Wang bromide and Merrifield resins in the presence of dibenzo-18-crown-6 in DMF at 70 °C for 48 h.[30] Anchoring efficiency was estimated to be quantitative based on the increase of the resin mass. Moreover, IR spectroscopy indicated disappearance of the C−Br band at 592 cm^{-1} and appearance of bands at 3448 and 1737 cm^{-1} for the OH and C═O stretches of resin-bound (2*S*,4*R*)-4-hydroxy-*N*-(PhF)proline **17**.

Soluble support **14** was reacted with cesium salt **16** (110 mol %) in the presence of catalytic potassium iodide in DMF at 60 °C for 3 h, which gave quantitative conversion to the TAP-bound 4-hydroxy-*N*-(PhF)proline **19** as indicated by TLC (R_f = 0.51, 7.5% MeOH in DCM).[31] After reactions on the TAP support, workup was completed by a saturated aqueous $LiClO_4$ wash to ensure the presence of the counteranion. Partial purification of TAP-supported material was achieved by dissolving in a minimum volume of CH_2Cl_2 and precipitation using a 5-fold volume of Et_2O. For characterization purposes, analytical samples of TAP-supported intermediates were purified by radial chromatography (see Supporting Information).[32]

4-Oxo-*N*-(PhF)prolines **20** and **21** were obtained, respectively, from oxidation of resin-bound alcohols **17** and **18** using oxalyl chloride and DMSO at −78 °C for 4 h, followed by

Scheme 2. Supported Synthesis of 4-Aminopyrrole-2-carboxylates



treatment with DIEA. In both cases, the oxidation was performed twice for complete conversion to ketone, which was ascertained by the appearance of a second carbonyl band at 1758 cm^{-1} and disappearance of the OH band around 3440−3460 cm^{-1} in the IR spectra of resins **20** and **21**. On TAP support, complete oxidation of alcohol **19** was achieved using similar conditions and less reagent in a single reaction as comfirmed by RP-HPLC-MS. Ketone **22** exhibited low stability and was best employed immediately in the following step.

Resin-bound 4-aminopyrroles **23** and **24** were, respectively, prepared by treatment of ketones **20** and **21** with an excess of benzylamine (2300 mol %), in the presence of catalytic *p*-TsOH (0.1 equiv) in dry THF. In individual cases, 4-benzylaminopyrrole loading was evaluated by the amount of PhF-H recovered after filtration of the resin, washings, evaporation of the filtrate, and column chromatography (2% Et_2O/hexanes). 4-Aminopyrrole-2-carboxylate could not be detected by RP-LCMS after resin cleavage with acid (TFA/DCM 1/1) or methoxide (0.44 M $NaOCH_3$ in THF/MeOH). After *N*-acylation, 4-amidopyrroles (see below, Table 1) could however be detected by RP-HPLC-MS analysis after cleavage with sodium methoxide, which caused concomitant Fmoc removal. Accordingly, the PhF group was observed to be retained on 10 to 30% of pyrrole, because of premature aromatization before PhF-H extrusion.[17] This side reaction was presumed to be due to residual oxygen and avoided by degassing the resin suspended in THF using freeze−thaw cycles of exposure to high vacuum followed by flushing argon and

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Table 1. Aminoacylation of 4-Benzylaminopyrrole 23

		purity after cleavage	
entry	acylating acid	**30** (t_R; $[M + H]^+$)	**31** (t_R; $[M + H]^+$)[b]
a	Fmoc-Phe-OH	82% (18.4; 364.2)[a]	85% (16.6; 378.2)[b]
b	Fmoc-Leu-OH	81% (17.2; 330.2)[a]	93% (15.1; 344.2)[a]
c	Fmoc-Asp(OMe)-OH	76% (16.0; 346.2)[a]	ND[d]
d	Fmoc-His(Trt)-OH	90% (11.9; 354.2)[a]	75% (21.2; 610.2)[b]
e	Fmoc-Ser(OtBu)-OH	87% (11.4; 304.2)[b,c]	83% (16.4; 374.2)[b]
f	Fmoc-Lys(Boc)-OH	82% (12.5; 345.2)[a]	91% (17.6; 459.2)[b]
g	Fmoc-Cys(Trt)-OH	84% (12.8; 320.0)[b,c]	60% (21.2; 576.2)[b]
h	Fmoc-Met-OH	68% (16.7; 348.2)[a]	69% (14.9; 362.2)[b]
i	Fmoc-Glu(OtBu)-OH	74% (12.9; 346.2)[a]	ND
j	Fmoc-Pro-OH	65% (15.8; 314.2)[a]	52% (13.7; 328.2)[b]
k	Fmoc-Orn(Boc)-OH	ND	82% (15.1; 445.2)[b]
l	Fmoc-Aib-OH	**32** (11.7; 259.1)[a]	**33** (16.2; 273.2)[a]
m	*p*-NO_2PhCO_2H	82% (21.9; 366.2)[b]	37% (23.1; 380.0)[b]

[a] Determined by RP-HPLC-MS [C18 column 150 mm × 4.6 mm, 5 μm, 5−90% MeOH in H_2O in 20 min and then 90% MeOH for 15 min, 0.1% FA, UV: λ = 254 nm, retention time (t_R) expressed in min.]. [b] Determined by RP-HPLC-MS (C18 column 150 mm × 4.6 mm, 5 μm, 5−80% MeOH in H_2O in 20 min and then 90% MeOH for 15 min, 0.1% FA, UV: λ = 254 nm). [c] Several conformers were detected. [d] ND: not detected.

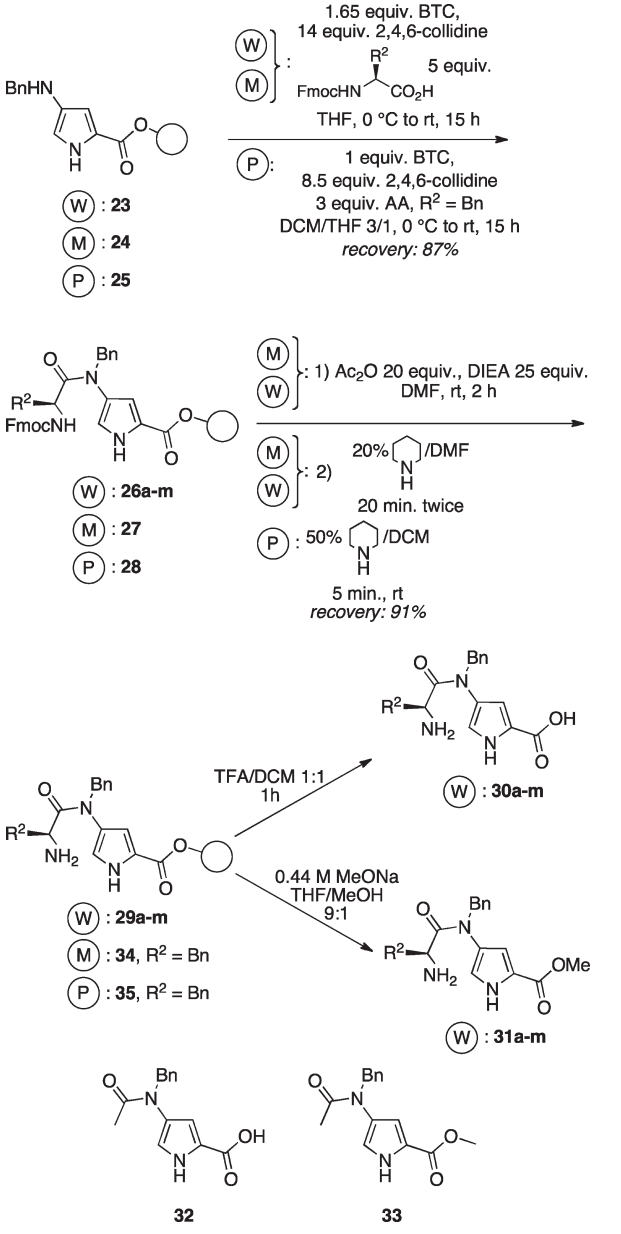
addition of predried $MgSO_4$ (2-fold the weight of dry resin), benzylamine, and *p*-TsOH, followed by further degassing by argon bubbling for 30 min before heating the reaction at 50 °C for 15 h. Under these optimized conditions, complete conversion to 4-benzylaminopyrroles **23** and **24** was achieved as indicated by the quantitative amounts of PhFH recovered, as well as by RP-HPLC-MS analysis of 4-amidopyrrole **26a** after resin cleavage with sodium methoxide.

4-Benzylaminopyrrole **25** was prepared on the TAP support in acetonitrile instead of THF, because of limited solubility in the latter. Quantitative conversion of TAP-supported ketone **22** to aminopyrrole **25** was indicated by RP-HPLC-MS analysis in the same amount of time (15 h) as on resin using less *N*-benzylamine (400 mol %).

Aminoacylation. The scope of *N*-(Fmoc)amino acids which could be employed in the acylation of 2-aminopyrroles was examined on Wang resin **23** on 0.03 mmol scale using 12 *N*-(Fmoc)amino acids (listed in Table 1) and *p*-nitrobenzoic acid (500 mol %, Scheme 3). Triphosgene (BTC) was employed as coupling agent in the presence of 2,4,6-collidine in dry THF for 15 h. Efficiency of coupling was ascertained on two resin aliquots, which were first both treated with excess acetyl chloride and DIEA in DMF for 2 h, followed by 20% piperidine in DMF to, respectively, cap excess aminopyrrole and remove the Fmoc group. Subsequently, the resins were, respectively, cleaved with TFA/DCM 1:1 for 1 h to give the corresponding acids, or with 0.44 M $NaOCH_3$ in 9:1 THF/MeOH for 3 h to furnish the ester counterparts. Cleaved material was analyzed by RP-HPLC-MS without isolation on a 0.01 mmol scale. Although tertiary amide isomers complicated certain chromatographic analyses, the detection of residual aminopyrrole **23** was facilitated by conversion to the corresponding acetamide.

Except for *N*-(Fmoc)amino isobutyramide **26l**, for which only the cleaved capped starting material **32** and **33** were detected, all desired amides **26** were produced, with complete consumption

Scheme 3. Supported Aminoacylation of 4-Aminopyrrole-2-carboxylates



of the aminopyrrole starting material. The steric bulk of *N*-(Fmoc)Aib was presumed to inhibit coupling, which also failed using its symmetric anhydride prepared with DIC. Purities were generally higher after the acidic cleavages, which failed only to detect the His and Orn analogues **26d** and **26k** that were observed after the methoxide cleavage. The latter, however, was unable to detect the dicarboxylate Asp and Glu analogues **26c** and **26i**.

Phenylalanine was deemed the amino acid of choice for comparative analyses with the other supports, because of its effective coupling as determined by both cleavage methods and utility in subsequent Pictet−Spengler chemistry as described below. On the Merrifield resin, the BTC-mediated coupling of Fmoc-Phe (500 mol %) gave amide **34** in 85% purity, as determined by the methoxide cleavage analysis. On the TAP support, a DCM/THF 8:2 mixture enhanced solubility in

coupling of Fmoc-Phe (300 mol %) with BTC and 2,4,6-collidine to give amide **35**. Subsequent Fmoc removal was performed, respectively, with 20% piperidine in DMF twice for 20 min, and with 50% piperidine in DCM once for 10 min on the resin-bound and TAP-supported Fmoc-Phe substrates.

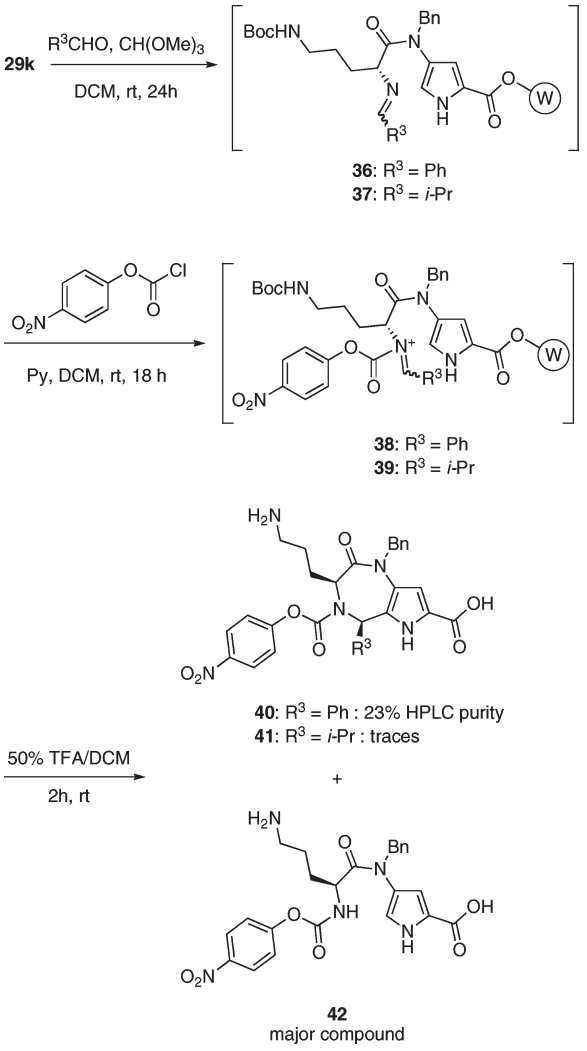
Pictet−Spengler Reaction and Pyrrolo[3,2-*e*][1,4]diazepin-2-one Cleavage. The conditions for the Pictet−Spengler cyclization were initially examined on Wang resin, because parallel chemistry could be conveniently performed and assessed using this support as demonstrated in the amino acylation study above. Conjecturing that the use of strong Brønsted acids might cause premature cleavage of substrate, milder protocols were first explored using $B(OMe)_3$,[33] $Yb(OTf)_3$,[34] LiCl in DCM/hexafluoropropanol,[35] and iodine;[36] however, all had no effect and left the starting material unchanged. A Pictet−Spengler protocol was attempted using an *N*-acyliminium ion (Scheme 4),[37] which have previously enhanced such iminium-mediated Mannich-type reactions.[38] On 0.01 mmol scale, ornithine derivative **29k** was arbitrarily chosen as substrate and reacted, respectively, with benzaldehyde and isobutyraldehyde in the presence of methyl orthoformate, as water scavenger, in dry DCM to give imines **36** and **37**, which were treated with *p*-nitrophenyl chloroformate in pyridine to induce Pictet−Spengler cyclization by way of the respective *N*-acyliminiums **38** and **39**. After 18 h at room temperature, resin cleavage with 50% TFA in DCM and RP-HPLC-MS analysis revealed diazepinones **40** and **41** as minor components contaminated with carbamate **42** as major product.

Previous success, in the solution-phase synthesis of pyrrolo[3,2-*e*][1,4]diazepin-2-ones using trifluoroacetic acid as catalyst in the Pictet−Spengler cyclization, compelled study of protic acid conditions on resin. Optimization was performed on Leu amide **29b** on 0.01 mmol scale using isobutyraldehyde (1000 mol %) as a challenging substrate, by varying the solvent (2 mL), temperature, mode of heating, and TFA concentration (Scheme 5).

Reaction efficiency was evaluated after resin cleavage with 50% TFA in DCM and RP-HPLC-MS analysis, without product isolation. The conditions were optimized to produce the highest amount of the postulated major stereoisomer (3*S*,5*R*)-**44b** and minimum side products and starting material (Table 2). Unsaturated diazepinone side-product **45** was soon recognized as an inherent product in the synthesis of pyrrolo[3,2-*e*]-[1,4]diazepin-2-one, which is presumed to be formed by a mechanism as that described for the formation of similar unsaturated carbolines[39] and could not be avoided by careful degassing using freeze−thaw cycles under vacuum. Moreover, pyrrolo[3,2-*e*][1,4]diazepin-2-ones (3*S*,5*R*)-**44b** and (3*S*,5*S*)-**44b** were observed to convert to their unsaturated counterpart **45b** upon standing over time.

Treating Wang resin **29b** with 1% TFA in DCM and TFE/DCM 1:1 at rt for 24 h led, respectively, to 10% and 15% conversion to (3*S*,5*R*)-**44b** (Table 2).[40] Heating **29b** with 1% TFA in DCM and TFE/DCM 1:1 at 70 °C in a sealed tube for 24 h increased conversion to 29%, albeit with formation of almost equal amounts of dehydro analogue **45b** and some (3*S*,5*S*)-diastereoisomer. Microwave heating at 70 °C in a sealed reactor in a 4:1 DCM/TFE mixture reduced the reaction time to 2 h, minimized formation of **45b**, and improved conversion to (3*S*,5*R*)-**44b** to 73%. Microwave heating at lower temperature (60 °C) decreased the rate of cyclization, and higher temperature (80 °C) promoted formation of (3*S*,5*S*)-**44b** and **45b**. More polar solvents such as THF or $CHCl_3$ increased the amount of **45b** and caused formation of unidentified impurities. Toluene gave similar results as DCM/TFE 4:1. Benzene gave the best results with 83% conversion to (3*S*,5*S*)-**44b** with minimal amounts of (3*S*,5*S*)-**44b** and **45b** (6% and 8%). Further attempts to reduce the amount of TFA in benzene caused a drop in the

Scheme 4. *N*-Acyliminium Pictet−Spengler Reaction on Compound 29k



Scheme 5. Pictet−Spengler Cyclization of Pyrrole 29b

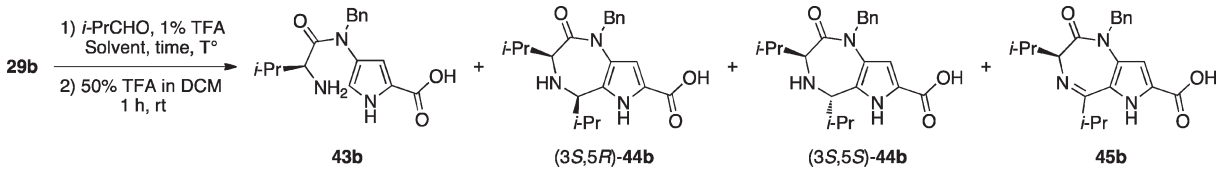


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Table 2. Optimization of the Pictet−Spengler Cyclization on Compound 29b

entry	TFA, %	*T*	*t*, h	solvent	**43b**,[a] %	(3*S*,5*R*)-**44b**,[a] %	(3*S*,5*R*)-**44b**,[a] %	**45b**,[a] %
1	1	RT	24	DCM	90	10	ND[b]	ND
2	1	RT	24	DCM/TFE 1/1	85	15	ND	ND
3	1	70 °C	24	DCM/TFE 1/1	42	29	5	24
4	1	60 °C microwave	2	DCM/TFE 4/1	67	23	3	7
5	1	70 °C microwave	2	DCM/TFE 4/1	17	73	3	7
6	1	80 °C microwave	2	DCM/TFE 4/1	11	65	9	15
7	1	70 °C microwave	2	$CHCl_3$	8[c]	55	4	18
9	1	70 °C microwave	2	THF	13[c]	9	ND	61
9	1	70 °C microwave	2	toluene	17	74	4	5
10	1	70 °C microwave	2	benzene	3	83	6	8
11	0.1	70 °C microwave	2	benzene	23	45	6	26

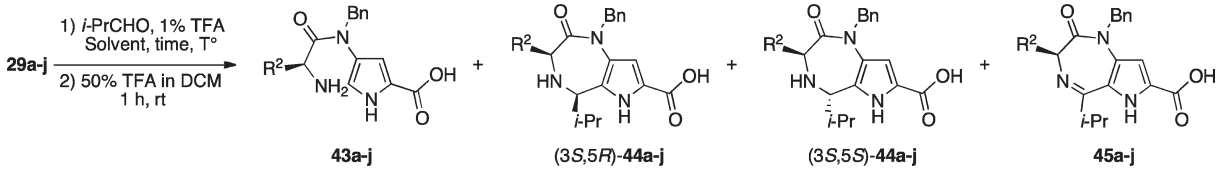
[a] Determined by RP-HPLC-MS (C18 column 150 mm × 4.6 mm, 5 μm, 0−90% MeOH in H_2O in 20 min and then 90% MeOH for 15 min, 0.1% FA, UV: λ = 254 nm). [b] ND: not detected. [c] In these cases, unknown impurities (15−20%) were also detected.

Table 3. Pictet−Spengler Cyclization with Diverse Amino Acid-Derived Amidopyrroles 29

entry	R^2	**43**,[a] % (t_R; $[M + H]^+$)	(3*S*,5*R*)-**44**,[a] % (t_R; $[M + H]^+$)	(3*S*,5*S*)-**44**,[a] % (t_R; $[M + H]^+$)	**45**,[a] % (t_R; $[M + H]^+$)
a	Bn	27 (12.2; 364.0)	73 (15.1; 418.2)	ND[b]	ND
b	*i*-Pr	12 (17.3; 330.2)	72 (20.8; 384.4)	5 (19.8; 384.4)	11 (22.6; 382.3)
c	$(CH_2)_2CO_2CH_3$	9 (10.7; 346.2)	63 (14.7; 400.2)	8 (13.4; 400.2)	20 (15.9; 398.3)
d[c]	4-CH_2-1*H*-imidazole	17 (8.8; 354.2)	54 (11.8; 408.3)	29 (11.7; 408.3)	ND
e	CH_2OH	29 (10.7; 304.1)	38 (12.8; 358.2)	8 (12.2; 358.2)	25 (13.3; 356.1)
f	$(CH_2)_4NH_2$	76 (9.0; 345.2)	24 (10.5; 399.2)	ND	ND
g[c]	CH_2SH	ND	ND	ND	ND
h[d]	$(CH_2)_2SCH_3$	ND[e]	ND	ND	ND
i[c]	$(CH_2)_3CO_2H$	ND	ND	ND	ND
j[c]	pyrrolidine (from Pro)	78 (11.1; 314.2)	ND	ND	ND

[a] Determined by RP-HPLC-MS (C18 column 150 mm × 4.6 mm, 5 μm, 0−90% MeOH in H_2O in 20 min and then 90% MeOH for 15 min, 0.1% FA, UV: λ = 254 nm). [b] ND: not detected. [c] In these cases, unknown impurities were also detected. [d] In this case, two isomers with very close retention time were observed. [e] **43h**, **44h**, and **45h** products bearing one extra oxygen atom were detected.

Scheme 6. One-Pot Pictet−Spengler Cyclization of Pyrroles 29a−j



formation of (3*S*,5*S*)-**44b** and increased the proportion of **45b** (entry 11, Table 2).

With optimized Pictet−Spengler conditions in hand, we employed a "one-pot" procedure: isobutyraldehyde was reacted with resins **29a−j** (0.01 mmol scale) packed in IRORI MicroKans, and substrates were cleaved separately using 50% TFA in DCM containing 1% of triethylsilane as scavenger and analyzed by RP-HPLC-MS, without isolation (Table 3, Scheme 6).

Substrates bearing simpler alkyl R^2 groups (i.e., *i*-Pr and Bn) gave better conversion than their heteroalkyl counterparts. Supported *N*-(γ-methyl aspartyl)-, *N*-(histidyl)-, and *N*-(serinyl)amidopyrroles **29c−e** gave the corresponding (3*S*,5*S*)-pyrrolodiazepinone **44** in reasonable proportions. In the case of **29d**, RP-HPLC-MS analysis indicated peaks with retention times and molecular ions that suggested a side product from Pictet−Spengler reaction with the imidazole ring. *N*-(Lysyl)amidopyrrole **29f** furnished the corresponding cyclized product (3*S*,5*R*)-**44f**, albeit in low conversion (24%) with considerable product derived from residual starting material. No desired products were detected from reactions of *N*-(cysteinyl), *N*-(methioninyl), *N*-(glutamyl), and *N*-(prolyl)amidopyrroles **29g−j**; however, analysis of the cleaved product from reaction of Met analogue **29h** indicated molecular ions for product plus 16 and 32 mass units, suggesting sulfur oxidation under the conditions of the Pictet−Spengler reaction.

The synthesis of phenylalanine-derived amidopyrrole **29a** was repeated on larger scale using 300 mg of starting Wang bromide resin (0.66 mmol) employing IRORI MacroKans in parallel reactions with its Merrifield resin counterpart **34** (0.37 mmol, 420 mg of resin) in the same pot. For the Pictet−Spengler reaction, resins **29a** and **34** were separately transferred into three IRORI MiniKans (100 mg of resin capacity), which could be fit

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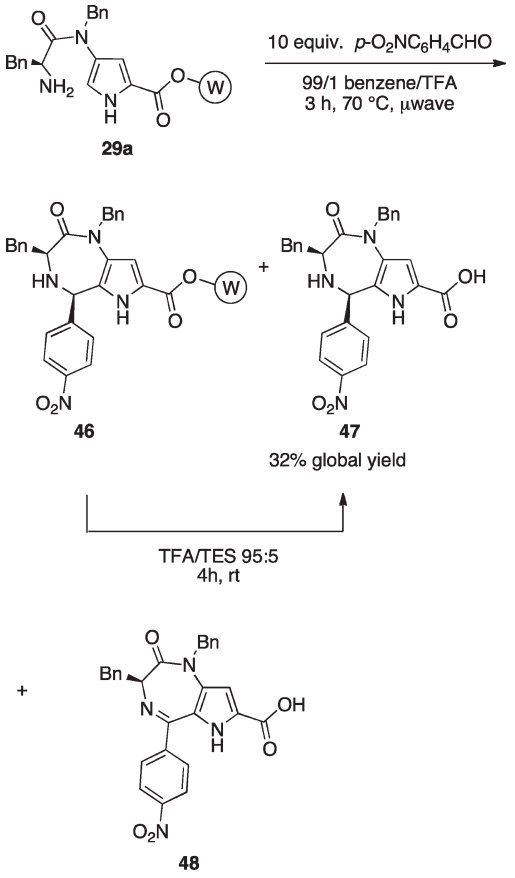
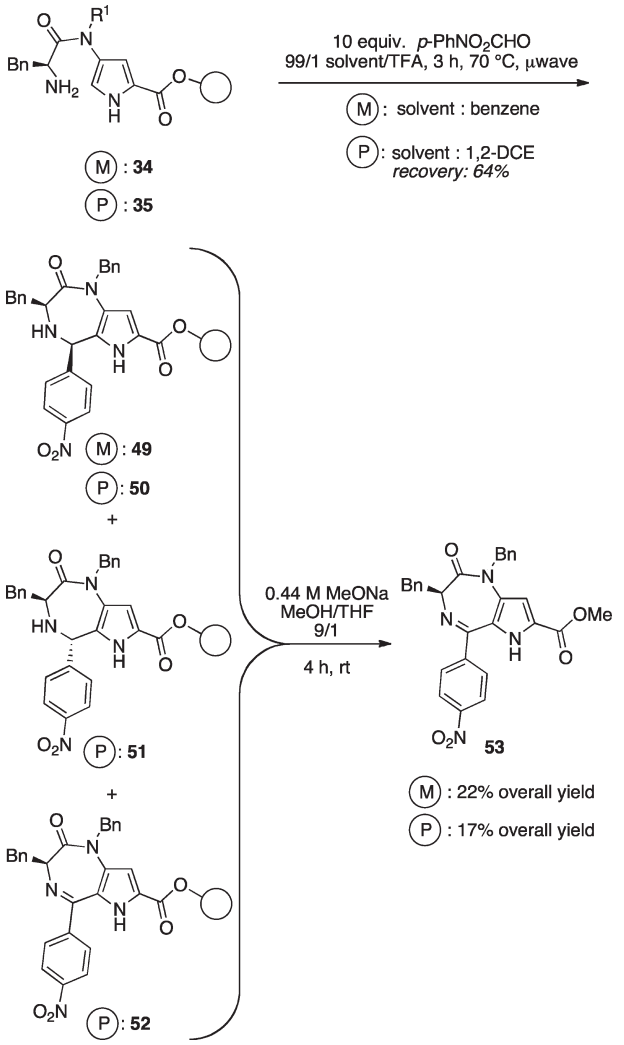
Scheme 7. Large-Scale Pictet–Spengler Cyclization on Wang Resin



Scheme 8. Pictet–Spengler Cyclization on Merrifield Resin and TAP Soluble Support



into the 20 mL Biotage microwave vessel and, respectively, reacted with *p*-nitrobenzaldehyde, which had given better yields of diazepinone in the solution-phase synthesis,[15] using optimized conditions (1% TFA in benzene, 1000 mol % aldehyde, 70 °C) for an extended 3 h reaction time to complete conversion (Schemes 7 and 8).

In the case of Wang resin, after the microwave reaction, the resin and liquid phase were filtered, the resin was washed, and the filtrate and washings were evaporated. The resin was cleaved using TFA/DCM 1:1 containing 1% of triethylsilane, filtered, and washed, and the filtrate and washings were similarly evaporated. Residues from evaporation of the filtrate after Pictet–Spengler reaction and cleavage were separately purified by flash column chromatography[41] (AcOEt/MeOH/MeCN/H_2O 70:10:10:10 as eluent) to yield inseparable 30:70 mixtures of hexahydropyrrolodiazepinone **47** and tetrahydropyrrolodiazepinone **48** in 29% (from the Pictet–Spengler cyclization) and 3% yields (from resin cleavage). The premature cleavage of around 90% of the Pictet–Spengler cyclization product suggested that substrate may have been cleaved and reacted both in the solid and solution phases during the reaction; moreover, it disqualified the use of Wang resin for further modification of the pyrrolo-[3,2-*e*][1,4]diazepin-2-one scaffold on support. On the contrary, a similar analysis of the residue from the liquid phase of the Pictet–Spengler reaction on Merrifield resin **34** by RP-HPLC-MS revealed the presence of residual *p*-nitrobenzaldehyde without cleaved starting material and only trace amounts of product **48** (less than 1% of the UV signal at λ = 280 nm).

Pyrrolo[3,2-*e*][1,4]diazepin-2-one **47** was prone to oxidation even when stored under argon at −10 °C which led to a 1:1 mixture of **47** and unsaturated analogue **48** after a few hours. Compared with the isopropyl analogue **44b**, the presence of the electron-withdrawing nitrophenyl group may account for the low stability of **47**, because of the increased acidic character of the 5-position proton of the diazepinone ring. Analytical samples were purified by reverse phase preparative HPLC, yielding pure **48** and a 9/1 **47**:**48** mixture after freeze-drying.

Attempts to cleave pyrrolo[3,2-*e*][1,4]diazepin-2-one from 10 mg aliquots of Merrifield resin using TFA under microwave heating (TFA/TES/H_2O 95:2.5:2.5, 2 mL at 50 °C for 30 min)[42] gave only enough material for RP-HPLC-MS analysis, which indicated **48** to be 35% pure, contaminated with other degradation products, with neither a trace of its diastereoisomer nor dehydro counterpart **48** nor starting material (Scheme 9).

On the TAP support, the Pictet–Spengler reaction was performed using 1% TFA in 1,2-dichloroethane, instead of benzene, to ensure solubility of amidopyrrole **35** during microwave irradiation at 70 °C for 3 h (Scheme 8). Analysis by RP-HPLC-MS, after precipitation, indicated no cleavage products in the decanted reaction solution and that the TAP-supported

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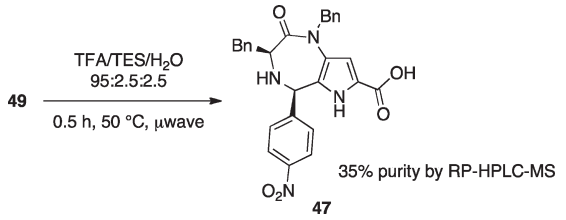
Scheme 9. Microwave-Assisted TFA Cleavage of Compound 49



material consisted of 92% (3*S*,5*R*)-**50**, 2% (3*S*,5*S*)-**51**, and 6% dehydrogenated product **52** without any starting material **35**.

Cleavage of pyrrolo[3,2-*e*][1,4]diazepin-2-one from both Merrifield resin and the TAP support was effectively accomplished using 0.44 M $NaOCH_3$ in 9:1 THF/MeOH for, respectively, 4 and 1 h. Treating the Merrifield resin substrate with methoxide for longer reaction times resulted in significant amounts of degradation. Cleavage provided only tetrahydro diazepinone methyl ester **53** in, respectively, 22% and 17% overall yields from the Merrifield and TAP supports, after preparative RP-HPLC.

DISCUSSION AND CONCLUSIONS

All three supports served to provide pyrrolo[3,2-*e*][1,4]diazepin-2-one products. None proved, however, to be ideal for the most significant criteria of (1) effective monitoring of reaction mixtures, (2) balancing between stability for broad applications and facile cleavage, (3) capacity to minimize the use of excess reagents for obtaining high yield, and (4) utility in split-and-mix[43] experiments. Nevertheless, each support had benefits. For example, the solid supports, Wang and Merrifield resins were particularly useful for parallel experiments, because the cross-linked polymers could be conveniently split into independent reactors, which could be employed together in exploratory chemistry in the same pot, before separate cleavages and analyses. The labile nature of Wang resin under both the acid and methoxide cleavage conditions facilitated subsequent analysis by LCMS. The stability of Merrifield resin offers the potential for further modification of the pyrrolo[3,2-*e*][1,4]diazepin-2-one scaffold after the Pictet−Spengler cyclization. The soluble TAP support offered the practical advantage of employing homogeneous conditions, which resulted in the use of less reagents for driving reactions to completion and quicker reaction times; moreover, chemistry on the soluble TAP support could be conveniently monitored by TLC (using $MeOH/CH_2Cl_2$ eluents) and RP-HPLC-MS, in addition to, in certain cases, NMR spectroscopy. Although the chemistry on both the solid and soluble supports was similar, in some cases, solvents were changed to comply with the solubility requirements of the TAP-supported compounds.

The recovery of the TAP support by precipitation showed variable efficiency (based on theoretical mass) during the course of the synthesis, which amounted to a 43% overall recovery of supported material after six steps. Attempts to enhance recovery by additional precipitation of material from filtrates often caused the coprecipitatation of unwanted impurities. For example, after the preparation of aminopyrrole **25**, precipitation gave a 122% mass recovery due to coprecipitation of impurities, which were not eliminated by additional precipitation. In general, preciptitation performances were contingent on the molecular weight of the supported substrates, with those of lower mass having less solubility in diethyl ether, leading to higher recovery. The monitoring of TAP-supported substrates during reactions was facilitated by RP-HPLC-MS, because of the relatively high UV absorbance and ion detection of the tetrarylphosphonium group; however, impurities not linked to the TAP support were better detected by ^1H NMR spectroscopy. A single purification by silica gel column chromatography of the final pyrrolo[3,2-*e*][1,4]-diazepin-2-one was performed after seven steps to isolate pure final ester **53** in 22% overall yield. Although the TAP support was not deemed convenient for "split-and-mix" methodology, the potential for performing synthesis in solution and for examining reactions directly on the support made this method useful for preparing a specific pyrrolo[3,2-*e*][1,4]diazepin-2-one target.

The solid support Wang and Merrifield resins and the soluble tetraarylphosphonium support exhibited complementary utilities in the synthesis of pyrrolo[3,2-*e*][1,4]diazepin-2-one. With respect to overall yield, the Wang resin provided pyrrolodiazepinone in a 32% combined yield for **47** and **48**, albeit product was prematurely cleaved under the acidic conditions used for the Pictet−Spengler cyclization. The overall yields for Merrifield resin and the TAP soluble support **14** were somewhat lower, likely because of the need for vigorous conditions in the final cleavage of the former and incomplete mass recoveries after precipitation of the latter support; however, both were resistant to the acidic conditions of the Pictet−Spengler reaction and could in principle be used for further modification of the scaffold on the support. Considering the applicability of the former for split-and-mix chemistry in IRORI Kans, an investigation is currently underway for the construction of pyrrolo[3,2-*e*]-[1,4]diazepin-2-ones using Merrifield resin and alternative cleavage methods, which will be reported in due course.

EXPERIMENTAL SECTION

General. Wang resin SS (75−100 mesh, 1.2 mmol/g) and Merrifield resin SS (70−90 mesh, 1.3 mmol/g) were purchased from Advanced Chemtech (Louisville, KY). Wang bromide resin was prepared from Wang resin according to the literature method.[29] TAP soluble support (bromomethylphenyltriphenylphosphonium) was obtained from Soluphase Inc. (Montreal, Quebec, Canada). IRORI MacroKans and MiniKans were from Nexus Biosystems, Inc. (Poway, CA). (2*S*,4*R*)-4-Hydroxy-*N*-1-(PhF)proline was prepared from (2*S*,4*R*)-4-hydroxy-*N*-1-(PhF)proline methyl ester according to refs 25 and 16. Fmoc-Orn(Boc) and Fmoc-Asp(OMe) were synthesized according to known procedures.[44] Anhydrous THF, MeCN, DCM, MeOH, and DMF were obtained from a commercial drying and filtrating system; DMSO was dried over activated 4 Å molecular sieves 24 h prior to use and stored in a tightly sealed bottle under an argon atmosphere.[45] Reactions requiring anhydrous conditions were performed under an atmosphere of dry argon; glassware was flame-dried immediately prior to use and allowed to cool under argon atmosphere. Liquid reagents, solutions, and solvents were added via syringe through rubber septa. Flash column chromatography[41] was performed using SiliaFlashF60 silica (Silicycle, Quebec City). Glass-backed plates precoated with silica gel (SiliaPlate TLC Extra Hard Layer 60 Angstrom F-254, Silicycle, Quebec City) were used for thin layer chromatography (TLC) and were visualized by UV fluorescence or staining with a ninhydrin or a phosphomolybdic acid solution in EtOH prior to heating. Purification by radial chromatography[32] was performed using 2 mm sorbent layers. Sorbent consists in a 2.5/1 mix of silica gel (TLC standard grade, 2−25 μm, pore size 60 Å with fluorescent indicator)/calcium sulfate

hemihydrate. Plates were prepared according to ref 32, and elution flow varied between 6 and 8 mL/min. ^{1}H NMR and ^{13}C NMR spectra were recorded on 300, 400, and 500 MHz spectrometers with chemical shift values in ppm relative to residual chloroform (δ_H 7.26 and δ_C 77.2), acetone (δ_H 2.05 and δ_C 29.84), or DMSO (δ_H 2.50 and δ_C 39.52) as standards. Coupling constant J values are given in hertz, with splitting described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Specific rotation, $[\alpha]_D$ values are given in units $10^{-1}\cdot$deg$\cdot$cm$^2\cdot$g^{-1}. Microwave-assisted reactions were performed in a Biotage Initiator microwave apparatus (Biotage AB, Uppsala, Sweden) in glass Biotage reaction vessels containing a magnetic stir bar and sealed with a septum cap. Analytical RP-HPLC analyses were performed on a C18 column 50 mm × 4.6 mm, 5 μm (column A) or on a C18 column 150 mm × 4.6 mm, 5 μm (column B) with a flow rate of 0.5 mL/min using a linear gradient of MeOH (0.1% formic acid (FA)) in water (0.1% FA). Retention times (t_R) from analytical RP-HPLC are reported in minutes. Indicated compounds were purified with a C18 column 250 mm × 21 mm, 5 μm (column C), using a specified linear gradient of MeOH or MeCN (0.1% FA) in water (0.1% FA), with a flow rate of 10.6 mL/min.

Resin Swelling in IRORI Kans. Under a stream of argon, resins in Kans and a stir bar were placed in a flame-dried round-bottom flask, which was exposed to three cycles of vacuum (20 mmHg) followed by argon, prior to addition of the specified amount of the appropriate dry solvent. The flask was purged with argon and sealed using a rubber septum, and the resin was allowed to swell for 30 min under inert atmosphere.

Resin Washing in IRORI Kans. The Kans were placed together in a glass bottle equipped with a stir bar and treated with solvent. The bottle was sealed with a screw cap and shaken by hand for 10 s. The Kans were next magnetically stirred for 5 min. The solvent was decanted through a perforated screw cap, and then the bottle was shaken vigorously by hand, head down, for 10 s. This operation was repeated for as many times and solvents as specified. At the end of the process, residual solvent in the Kans was removed by centrifugation or by subjecting the head of each Kan to vacuum for 1 min using a water aspirator.

(2*S*,4*R*)-4-Hydroxy-*N*-(PhF)proline Wang and Merrifield Resins (17, 18). In a 200 mL round-bottom flask, a solution of *N*-(PhF)hydroxyproline **15** (1.65 g, 4.44 mmol, 200 mol %, prepared according to ref 25) in MeOH (9 mL) was treated with 1 mL of water, titrated with 20% Cs_2CO_3 to pH 7 (about 2.5 mL), evaporated to dryness, twice suspended in toluene, and evaporated. The residue was ground into a powder by scraping the wall of the flask with a spatula. The round-bottom flask was charged with two IRORI MacroKans containing Wang bromide resin[29] (0.30 g × 2, 1.1 mmol/g, 0.66 mmol) and four IRORI MacroKans containing Merrifield resin (0.30 g, × 4, 1.3 mmol/g, 1.56 mmol). The resins were swollen, and cesium salt **16** was dissolved in DMF (100 mL). After treatment with dibenzo-18-crown-6 (1.2 g, 3.33 mmol, 1.5 equiv), the flask was purged with argon,[46] and the reaction mixture was heated to 70 °C with an oil bath and agitated gently with magnetic stirring for 48 h. The Kans containing resins were transferred together into a 250 mL bottle and washed sequentially with 100 mL volumes of DCM, MeOH, H_2O, DCM, MeOH, H_2O, MeOH (3×), and DCM (3×). The beige resins in the Kans were dried in vacuo and usually stored in desiccators under vacuum or under argon in the refrigerator. Anchoring efficiency of respective resins was evaluated by measuring their mass increase after the reaction. Excess (2*S*,4*R*)-4-hydroxy-*N*-(PhF)proline was recovered as previously described.[25] **17**: IR (KBr, cm^{-1}): 3448 (OH), 1737 (C═O). The mass increase after reaction was 216 mg and corresponded to a loading of 0.80 mmol/g (98% conversion). **18**: IR (KBr, cm^{-1}): 3457 (OH), 1732 (C═O). The mass increase after reaction was 501 mg and corresponded to a loading of 0.88 mmol/g (96% conversion).

(2*S*)-4-Oxo-*N*-(PhF)proline Wang and Merrifield resins (20, 21). To a 100 mL round-bottom flask, under argon atmosphere, was added $(COCl)_2$ (2.20 mL, 25.80 mmol, 12 equiv) dropwise to a solution of DMSO (3.70 mL, 51.60 mmol, 24 equiv) in DCM (50 mL) at −78 °C, and the mixture was stirred for 30 min. Into a 200 mL round-bottom flask containing, respectively, IRORI MacroKans possessing (2*S*,4*R*)-4-hydroxy-*N*-(PhF)proline Wang (**17**, 0,406 g × 2, 0.80 mmol/g, 0.65 mmol) and Merrifield (**18**, 0.425 g × 4, 0.88 mmol/g, 1.50 mmol) resins swollen in dry DCM (50 mL) at −78 °C, the DMSO mixture was transferred by a double-tipped needle, and the Kans were agitated gently with magnetic stirring for 4 h at −78 °C. The resins became a light green color, which turned progressively to light brown within 1 h. After 4 h, the resins at −78 °C were treated dropwise with DIEA (13.50 mL, 77.40 mmol, 36 equiv) over 1 h, after which time the resins appeared dark brown. The suspension containing the Kans was allowed to warm to room temperature over 1 h and filtered. The Kans were transferred into a 250 mL bottle and washed sequentially with 100 mL volumes of DCM (×2), MeOH (×2), DCM (×2), MeOH (×2), and DCM (×2) as described above. The resins in Kans were dried in vacuo, and the reaction was repeated a second time to ensure complete alcohol oxidation as ascertained by the disappearance of the hydroxyl absorption around 3440−3460 cm^{-1} in the IR spectrum. The beige resin was usually stored in desiccators under vacuum or under argon in the refrigerator. **20**: IR (KBr, cm^{-1}): 1732 and 1758 (C═O). **21**: IR (KBr, cm^{-1}): 1732 and 1758 (C═O).

4-Benzylamino-1*H*-pyrrole-2-carboxylate Wang Resin (23). In a 100 mL round-bottom flask, two IRORI MacroKans containing (2*S*)-4-oxo-*N*-(PhF)proline Wang resin **20** (0.405 g × 2, 0.80 mmol/g, 0.65 mmol) were swollen in THF (40 mL). The mixture was degassed by three freeze−thaw cycles, covered with a blanket of argon, and treated with anhydrous $MgSO_4$ (0.8 g, dried overnight at 100 °C prior to use), followed by *p*-TsOH$\cdot H_2O$ (25 mg, 0.13 mmol, 0.2 equiv) and benzylamine (1.60 mL, 14.95 mmol, 23 equiv). The mixture was purged with argon bubbles for 30 min and stirred for 18 h at 50 °C in an oil bath under an argon atmosphere. The Kans containing the green resin were transferred to a bottle and washed sequentially with 50 mL volumes of THF, DCM, MeOH, H_2O, DCM, MeOH, H_2O, MeOH (×2), and DCM (×3). The light green resin (total weight: 697 mg) was usually stored in desiccators under vacuum or under argon in the refrigerator. The filtrate from the reaction mixture and all washings was combined and evaporated in vacuo to a residue, which was partitioned between water (20 mL) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with 10% HCl (2 × 30 mL), satd $NaHCO_3$ (30 mL), and brine (30 mL), dried over sodium sulfate, filtered, and evaporated to a residue, which was purified by column chromatography (2% Et_2O/hexanes). Combination of the collected fractions and evaporation of the volatiles yield 130 mg of 9,9-phenylfluorene (0.54 mmol, PhF-H, mp 146 °C, lit.[25] mp 148 °C) corresponding to a 0.77 mmol/g loading of aminopyrrole on Wang resin.

4-Benzylamino-1*H*-pyrrole-2-carboxylate Merrifield Resin (24). 4-Benzylamino-1*H*-pyrrole-2-carboxylate Merrifield resin **24** was synthesized as described above for 4-benzylamino-1*H*-pyrrole-2-carboxylate Wang resin **23** from **21** (0.425 g × 4, 0.88 mmol/g, 1.50 mmol) using 4 IRORI MacroKans, 80 mL of THF, 3.77 mL of benzylamine (34.5 mmol, 23 equiv), 57 mg of *p*-TsOH$\cdot H_2O$ (0.3 mmol, 0.2 equiv) and 1.2 g of dry $MgSO_4$. After reaction, the Kans containing brownish green resin (total weight: 1.467 g) were usually stored in desiccators under vacuum or under argon in the refrigerator. Purification of the residue from resin filtration and washings as described above yielded 359 mg (1.48 mmol) of PhF-H, indicative of an aminopyrrole loading on Merrifield resin of 1.01 mmol/g.

4-[*N*-(9-Fluorenylmethoxycarbonyl)-L-phenylalaninyl]benzylamino-1*H*-pyrrole-2-carboxylate Wang and Merrifield Resins (26a, 27). In a 100 mL round-bottom flask under argon atmosphere, Fmoc-Phe (3.971 g, 10.25 mmol, 5 equiv) was mixed with

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bis(trichloromethyl) carbonate (0.912 g, 3.38 mmol, 1.65 equiv) in THF (50 mL) at 0 °C and treated dropwise with 2,4,6-collidine (3.8 mL, 28.70 mmol, 14 equiv) over 5 min. The white suspension was stirred for 10 min at 0 °C and transferred by syringe to a 200 mL round-bottom flask containing IRORI MacroKans filled, respectively, with 4-benzylamino-1*H*-pyrrole-2-carboxylate Wang (**23**, 0.348 g × 2, 0.77 mmol/g, 0.54 mmol) and Merrifield (**24**, 0.368 g × 4, 1.01 mmol/g, 1.48 mmol) resins swollen in THF (50 mL) at 0 °C. The mixture was allowed to warm to room temperature with stirring for 15 h. The Kans containing resin were transferred to a bottle and washed with 100 mL volumes of DMF (×3), MeOH (×3), and DCM (×3) as described above. The dark green resins (Wang: 0.899 g; Merrifield: 2.005 g) were usually stored in desiccators under vacuum or under argon in the refrigerator. Aliquots (15 mg) of each resin were removed from the Kans, partitioned into two 2 mL plastic filtration tubes equipped with polyethylene frits, swollen, respectively, in DMF for 20 min, treated twice with a 20% solution of piperidine in DMF for 20 min, and filtered. The resins were washed successively with agitation for 1 min and filtered from DMF (3 × 1 mL), MeOH (3 × 1 mL), and DCM (3 × 1 mL). A positive Kaiser test[47] indicated qualitatively the presence of free amine. The resins were, respectively, treated with acetic anhydride (37 μL, 0.39 mmol, 20 equiv) and DIEA (85 μL, 0.49 mmol, 25 equiv) in DMF (1 mL) for 2 h, washed as described above. Afterward, a negative Kaiser test indicated quantitative acylation. In the case of 4-[*N*-(9-fluorenylmethoxycarbonyl)-L-phenylalaninyl]benzylamino-1*H*-pyrrole-2-carboxylate Wang resin **26a**, the acylated material was cleaved from the resin using 50% TFA in DCM (1 mL) for 1 h and the filtrate was evaporated to dryness to a residue, which was subjected to RP-LCMS analysis (column A, 0−80% MeOH in H_2O for 10 min then 90% MeOH for 5 min, 0.1% FA, UV: λ = 280 nm, t_R 8.76), which indicated >90% purity, with no sign of acetylated starting material. In the case of 4-[*N*-(9-fluorenylmethoxycarbonyl)-L-phenylalaninyl]benzylamino-1*H*-pyrrole-2-carboxylate Merrifield resin **27**, cleavage was performed using a 0.44 M MeONa solution in THF/MeOH (9:1, 1 mL)[48] for 2 h. The sequence of filtration, washing of the resin with EtOAc, and partitioning of the filtrate between EtOAc and saturated aqueous NH_4Cl solution gave an organic layer, which was filtered through a Pasteur pipet containing a 5 mm layer of Na_2SO_4 and evaporated to dryness. Analysis of the residue by RP-LCMS (column B, 0−80% MeOH over H_2O in 20 min and then 90% MeOH for 15 min, 0.1% FA, UV: λ = 280 nm, t_R 26.34) demonstrated >82% purity, with no sign of acetylated starting material.

4-(L-Phenylalaninyl)benzylamino-1*H*-pyrrole-2-carboxylate Wang and Merrifield Resins (29a, 34). In a 250 mL bottle, 4-[*N*-(9-fluorenylmethoxycarbonyl)-L-phenylalaninyl]benzylamino-1*H*-pyrrole-2-carboxylate Wang (**26a**, 0.442 g × 2, 0.60 mmol/g, 0.53 mmol) and Merrifield (**27**, 0.497 g × 4, 0.74 mmol/g, 1.47 mmol) resins in IRORI MacroKans were swollen in DMF (100 mL) for 0.5 h, filtered, and exposed to a freshly prepared 20% piperidine in DMF solution (100 mL) with gentle magnetic stirring for 20 min. The reaction mixture was decanted, and the resin Kans were retreated with the piperidine in DMF solution as performed previously. The resins in Kans were washed with 100 mL volumes of DMF (×3), MeOH (×3), and DCM (×3) as described above. A positive Kaiser test[47] indicated qualitatively the presence of free amines. The resins (**29a**: 0.754 g, light brownish orange, **34**: 1.682 g, light brownish green) were usually stored in desiccators under vacuum or under argon in the refrigerator.

(*S*)-1,3-Dibenzyl-5-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrrolo[3,2-*e*][1,4]diazepine-7-carboxylic Acid (46). The contents from one MacroKan containing 4-(L-phenylalaninyl)benzylamino-1*H*-pyrrole-2-carboxylate Wang resin (**29a**, 0.377 g, 0.69 mmol/g, 0.26 mmol) were split into three IRORI MiniKans, which were treated with benzene (15 mL) and placed into a 20 mL Biotage microwave vessel.[49] The vessel was sealed with a conventional rubber septum and placed under argon atmosphere. After being swollen for 20 min, the resin was treated with *p*-nitrobenzaldehyde (0.390 g, 2.58 mmol, 10 equiv), followed by TFA (150 μL), and stirred with heating under microwave irradiation at 75 °C for 3.5 h. The MiniKans containing resin were transferred to a bottle and sequentially washed with 50 mL volumes of THF (×3), MeOH (×3), and DCM (×3) as described above. The filtrates were evaporated to dryness, and the residue (450 mg) was purified by flash silica gel column chromatography using EtOAc/MeOH/MeCN/H_2O (70:10:10:10) as eluent to yield two different fractions, the first one consisting of an inseparable 30/70 mixture of hexahydropyrrolodiazepinone **47** and tetrahydropyrrolodiazepinone **48** (33 mg), and the second one (4 mg) consisting in a 8/92 mixture of **47** and **48** (29% global yield). The resin in the Kans was treated with TFA/TES (95:5, 6 mL) for 4 h, filtered, and washed with 50 mL volumes of THF (×3), MeOH (×3), and DCM (×3) as described above. The filtrate and washings were combined and evaporated to a residue (9 mg), which was purified by chromatography using AcOEt/MeOH/MeCN/H_2O (70:10:10:10) as eluent. Evaporation of the collected fractions gave the same yellow oil consisting of an inseparable 30/70 mixture of hexahydro pyrrolodiazepinone **47** (4 mg, 3% global yield). Pure **48** (2 mg) was obtained by preparative HPLC (column C, 60−90% MeOH in H_2O over 30 min.): $[\alpha]^{21}_D$ = −47.5 (c = 0.75); ^{1}H NMR (CD_3OD, 300 MHz) δ 3.55 (dd, J = 8.0, 13.6 Hz, 1H), 3.68 (dd, J = 6.0, 13.8 Hz, 1H), 4.08 (dd, J = 8.0, 6.0 Hz, 1H), 5.01 (d, J = 15.4 Hz, 1H), 5.31 (d, J = 15.4 Hz, 1H), 6.69 (s, 1H), 7.09 (dd, J = 2.1, 3.5 Hz, 2H), 7.19 (m, H, 4H), 7.30 (t, J = 7.3 Hz, 2H), 7.37 (d, J = 7.2 Hz, 2H), 7.62 (d, J = 8.7 Hz, 2H), 8.23 (d, J = 8.7 Hz, 2H), 8.50 (s, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 38.7 (CH_2), 49.5 (CH_2), 67.0 (CH), 102.7 (CH), 120.2 (C), 123.1 (3CH), 126.0 (C), 126.7 (2CH), 126.9 (CH), 128.0 (2CH), 128.3 (2CH), 129.9 (2CH), 130.1 (2CH), 133.5 (C), 137.6 (C), 139.9 (C), 143.5 (C),148.7 (C), 158.9 (C=O + C=N), 165.5 (C=O); HRMS calcd for $C_{28}H_{23}N_4O_5$ $[M + H]^+$: 495.1665, found: 495.1663; IR υ_{max}/cm^{-1} (NaCl): 3424 (N-H), 3154 (OH), 3057, 3036, 2942 (C−H), 1674 (C=O acid), 1655 (C=O amide), 1603 (C=C_{arom}), 1553 (C=C_{arom}), 1520 (Ar-NO_2), 1494 (C=C_{arom}), 1453 (C=C_{arom}), 1434 (C=C_{arom}), 1346 (C−H), 1314 (C−O), 1116.

(*S*)-Methyl 1,3-Dibenzyl-5-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrrolo[3,2-*e*][1,4]diazepine-7-carboxylate from Merrifield Resin (53). In IRORI Kans, the Pictet−Spengler reaction was performed on 4-(L-phenylalaninyl)benzylamino-1*H*-pyrrole-2-carboxylate Merrifield resin **34** using microwave heating as described above for Wang resin **29a**. Resin **34** (0.420 g, 0.88 mmol/g, 0.37 mmol) from one MacroKan was split into three IRORI MiniKans, swollen in benzene (15 mL), treated with *p*-nitrobenzaldehyde (0.559 g, 3.70 mmol, 10 equiv) and TFA (150 μL), and heated with microwave irradiation. The resin in MiniKans was sequentially washed with 50 mL volumes of THF (×3), MeOH (×3), and DCM (×3) as described above. Evaporation of the combined washing solutions gave a trace amount of (3*S*,5*R*)-1,3-dibenzyl-5-(4-nitrophenyl)-2-oxo-1,2,3,4,5,6-hexahydropyrrolo[3,2-*e*]-[1,4]diazepine-7-carboxylic acid **48** as analyzed by RP-HPLC analysis (column A, 10−90% MeOH in H_2O for 20 min then 90% MeOH for 15 min, 0.1% FA, UV: λ = 280 nm, t_R 24.34, accounting for less than 1% of the UV signal) along with *p*-nitrobenzaldehyde. An aliquot of resin **49** (10 mg) was suspended in TFA/TES/H_2O (95:2.5:2.5, 2 mL) and treated under microwave-assisted cleavage conditions[42a] at 50 °C for 30 min in a V-shaped 2 mL Biotage vessel with a triangular stir bar. Filtration of the resin and evaporation of the filtrate gave a residue, which was analyzed by RP-HPLC (column A, 0−80% MeOH in H_2O over 10 min then 90% MeOH for 5 min, 0.1% FA, UV: λ = 280 nm) and found to contain (3*S*,5*R*)-1,3-dibenzyl-5-(4-nitrophenyl)-2-oxo-1,2,3,4,5,6-hexahydropyrrolo[3,2-*e*][1,4]diazepine-7-carboxylic acid **48** of 35% purity (UV signal at λ = 280 nm, t_R 11.08) with no trace of starting 4-(L-phenylalaninyl)benzylamino-1*H*-pyrrole-2-carboxylic acid (t_R 7.05). Product cleavage was performed in a 60 mL filtration tube with

a polyethylene frit, by shaking the remaining resin suspended in a 0.44 M MeONa solution in THF/MeOH (9:1, 30 mL) at room temperature for 4 h. The resin was filtered and washed with EtOAc (3 × 30 mL). The filtrate and washings were combined and washed with saturated aqueous NH_4Cl (50 mL). The aqueous phase was extracted with EtOAc (2 × 20 mL), and the combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and evaporated to dryness. Purification of the residue was performed by flash chromatography on a silica gel column (15 to 20% gradient of EtOAc in hexanes) to yield (*S*)-methyl 1,3-dibenzyl-5-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrrolo-[3,2-*e*][1,4]diazepine-7-carboxylate **53** as a yellow oil (42 mg, 0.084 mmol, 22%). $[\alpha]^{21}_D = -46.4$ ($c = 0.33$,); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.68 (dd, $J = 8.0$, 13.5 Hz, 1H), 3.75 (dd, $J = 5.7$, 13.5 Hz, 1H), 3.82 (s, 3H), 4.08 (dd, $J = 8.0$, 5.7 Hz, 1H), 4.96 (d, $J = 15.4$ Hz, 1H), 5.28 (d, $J = 15.4$ Hz, 1H), 6.74 (d, $J = 2.4$ Hz, 1H), 7.08 (dd, $J = 2.2$, 3.5 Hz, 2H), 7.23 (m, 4H), 7.34 (t, $J = 7.2$ Hz, 2H), 7.4 (d, $J = 7.2$ Hz, 2H), 7.62 (d, $J = 8.8$ Hz, 2H), 8.23 (d, $J = 8.8$ Hz, 2H), 8.92 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 38.7 (CH_2), 50.4 (CH_2), 52.5 (CH_3), 67.4 (CH), 106.2 (CH), 122.9 (C), 124.0 (2CH), 124.9 (C), 126.5 (CH), 127.1 (2 CH), 127.6 (CH), 128.4 (2CH), 128.8 (2CH), 130.0 (2CH), 130.1 (2CH), 134.4 (C), 136.6 (C), 139.2 (C), 142.6 (C),149.3 (C),158.5 (C═O),160.8 (C═N),165.6 (C═O); HRMS calcd for $C_{29}H_{25}N_4O_5$ $[M + H]^+$: 509.1819, found: 509.1822; IR υ_{max}/cm^{-1} (NaCl): 3423 (N−H), 3064, 3030, 2954, 2929 (C−H), 1718 (C═O ester), 1674 (C═O amide), 1582 (C═C_{arom}), 1556 (C═C_{arom}), 1521 (arom-NO_2), 1494 (C═C_{arom}), 1453 (C═C_{arom}), 1434 (C═C_{arom}), 1347 (C−H_{methyl}), 1307, 1270 (C−O), 1224 (C−O), 1163, 1107, 1008.

(2*S*,4*R*)-4-Hydroxy-*N*-(PhF)proline TAP (19). In a 100 mL round-bottom flask, a solution of *N*-(PhF)hydroxyproline **15** (2 g, 5.39 mmol, 1 equiv, prepared according to reference[25]) in MeOH (10 mL) was treated with 1 mL of water, titrated with 20% Cs_2CO_3 to pH 7 (about 3 mL), evaporated to dryness, and twice suspended in toluene and evaporated. The residue was ground into a powder by scraping the wall of the flask with a spatula. The round-bottom flask was charged with (4′-(bromomethyl)-[1,1′-biphenyl]-4-yl)triphenylphosphonium perchlorate **14** (TAP-Br, 2.95 g, 4.85 mmol, 0.9 equiv), DMF (50 mL), and potassium iodide (90 mg, 0.54 mmol, 10 mol %). The flask was purged with argon,[47] and the reaction mixture was heated to 60 °C with an oil bath and agitated with magnetic stirring for 3 h at which point TLC showed no remaining TAP-Br starting material (R_f = 0.64). The volatiles were removed by purging with air while stirring for 3 h, and the residue was dissolved in DCM (50 mL). The solution was washed with aqueous saturated $NaHCO_3$ (2 × 30 mL), water (30 mL), aqueous saturated $LiClO_4$ (2 × 30 mL), and water (2 × 30 mL), dried (Na_2SO_4), and evaporated to a residue which was redissolved in DCM (10 mL) and precipitated in ice-cold Et_2O (50 mL). The white solid was filtered off, washed with ice-cold Et_2O (2 × 20 mL), and dried in vacuo to give a white powder, which was stored under argon in the refrigerator (3.09 g, 91% recovery). An analytical sample (90 mg) was purified by radial chromatography (gradient: 0 to 5% MeOH in DCM). After evaporation, the residue was redissolved in DCM (2 mL) and precipitated in ice-cold Et_2O (10 mL). The white solid was filtered off, washed with ice-cold Et_2O (2 × 5 mL), dried in vacuo to give **19** as a white powder (82 mg). R_f = 0.51 (7.5% MeOH in DCM); $[\alpha]^{21}_D = -13.5$ ($c = 0.9$,); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.80 (m, 2H), 1.99 (dt, $J = 12.5$, 5.5 Hz, 1H), 2.92 (dd, $J = 5.4$, 9.7 Hz, 1H), 3.37 (dd, $J = 4.7$, 9.1 Hz, 1H), 3.59 (dd, $J = 5.4$, 9.7 Hz, 1H), 4.55 (dt, $J = 5.8$, 11.6 Hz, 1H), 4.61 (d, $J = 12.9$ Hz, 1H), 4.81 (d, $J = 12.9$ Hz, 1H), 7.12 (td, $J = 1.1$, 7.5 Hz, 1H), 7.22 (m, 4H), 7.29 (m, 2H), 7.32 (dd, $J = 1.1$, 7.5 Hz, 1H), 7.36 (dt, $J = 7.5$, 0.7 Hz, 1H), 7.42 (td, $J = 1.1$, 7.5 Hz, 1H), 7.56 (m, 3H), 7.61−7.75 (m, 12H), 7.75−7.81 (m, 6H), 7.89 (ttd, $J = 1.2$, 2.0, 6.8 Hz, 3H), 7.97 (ddt, $J = 1.9$, 3.2, 8.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): two conformers are observed, signals given by the second conformer are signaled with an asterisk (*), δ 39.9 (s, 1CH_2), 56.7 (s, 1CH_2), 59.5 (s, 1CH), 65.5 (s, 1CH_2), 70.1 (s, 1CH), 76.2 (s, 1C), 115.6 (d, $J = 91.5$ Hz, 1C), 117.7 (d, $J = 89.5$ Hz, 3C), 119.9 (s, 2CH), 120.2 (s, 2CH*), 126.7 (s, 2CH), 127.2 (s, 1CH*), 127.37 (s, 2CH), 127.41 (s, 2CH), 127.67 (s, 2CH*), 127.75 (s, 2CH*), 128.4 (s, 2CH),128.6 (s, 2CH), 128.7 (s, 4CH), 128.8 (s, 2CH*), 129.1 (s, 2CH), 129.3 (s, 2CH*), 130.8 (d, $J = 12.9$ Hz, 6CH), 134.5 (d, $J = 10.3$ Hz, 6CH), 135.1 (d, $J = 10.7$ Hz, 2CH), 135.8 (d, $J = 3.0$ Hz, 3CH), 137.1 (s, 1C), 137.9 (d, $J = 1.5$ Hz, 1C), 140.0 (s, 1C), 141.4 (s, 2C), 142.8 (s, 2C*), 146.1 (s, 2C), 147.5 (s, 2C*), 147.86 (s, 1C), 147.9 (s, 1C*), 175.4 (s, C═O); HRMS calcd for $C_{55}H_{45}NO_3P$ $[M]^+$: 798.3140, found: 798.3131; IR υ_{max}/cm^{-1} (NaCl): 3494 (N-H), 3072, 3020, 2927 (C−H), 1736 (C═O ester), 1596 (C═C_{arom}), 1486 (C═C_{arom}), 1439 (C═C_{arom}), 1272 (C−O), 1216 (C−O), 1150 (arom), 1094 (arom).

4-Benzylamino-1*H*-pyrrole-2-carboxylate TAP (25). A stirred solution of oxalyl chloride (0.42 mL, 5.01 mmol, 1.5 equiv) in DCM (6 mL) at −78 °C was treated with dry DMSO (0.47 mL, 6.68 mmol, 2 equiv) in DCM (6 mL). After being stirred for 20 min, a solution of **19** (3.0 g, 3.34 mmol, 1 equiv) in DCM (18 mL) was added dropwise to the mixture, which was stirred for 4 h at −78 °C, treated with DIEA (3.5 mL, 20.04 mmol, 6 equiv) over 20 min, stirred at −78 °C for 1 h, and allowed to warm to room temperature for 1 h. The mixture was treated with KH_2PO_4 1 M (60 mL). The layers were separated, and the aqueous phase was extracted with DCM (2 × 30 mL). The organic layers were combined, washed with water (90 mL), aqueous saturated $LiClO_4$ (2 × 90 mL), and water (2 × 90 mL), dried (Na_2SO_4), and evaporated to a residue, which was redissolved in DCM (10 mL) and precipitated in ice-cold Et_2O (50 mL). The white solid was filtered off, washed with ice-cold Et_2O (2 × 20 mL), and dried in vacuo to give **22** as a white powder (2.81 g, 94% recovery). Ketone **22** was directly used in the next step. A stirred solution of **22** (2.81 g, 3.53 mmol, 1 equiv) in dry MeCN (80 mL) was degassed by three freeze−thaw cycles. The mixture was treated with $MgSO_4$ (dried overnight prior use, 3 g). The vessel was purged with argon, the mixture was treated with benzylamine (1.5 mL, 14.12 mmol, 4 equiv) and *p*-TsOH (95 mg, 0.35 mmol, 10 mol %), and degassed with bubbling of argon for 30 min. The reaction mixture was warmed to 50 °C, stirred overnight at this temperature, and evaporated to a residue, which was partitioned between DCM (60 mL) and water (60 mL). The layers were separated. The aqueous layer was extracted with DCM (2 × 30 mL). The organic layers were combined, washed with aqueous saturated $NaHCO_3$ (2 × 60 mL), water (90 mL), aqueous saturated $LiClO_4$ (2 × 90 mL), and water (2 × 90 mL), dried (Na_2SO_4), and evaporated to a residue, which was redissolved in DCM (10 mL) and precipitated in ice-cold Et_2O (50 mL). The white solid was filtered off, washed with ice-cold Et_2O (2 × 20 mL), dried in vacuo to a white powder, and stored under argon in the refrigerator (3.20 g, 122% recovery). An analytical sample (100 mg) was purified by radial preparative chromatography (gradient: 0 to 5% MeOH in DCM). After evaporation of the collected fractions, the residue was redissolved in DCM (2 mL) and precipitated in ice-cold Et_2O (10 mL). The white solid was filtered off, washed with ice-cold Et_2O (2 × 5 mL), and dried in vacuo to give **25** as a white powder (74 mg). R_f: 0.46 (7.5% MeOH in DCM); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.14 (s, 2H), 5.27 (s, 2H), 6.45 (t, $J = 1.9$ Hz, 1H), 6.51 (t, $J = 1.9$ Hz, 1H), 7.23 (t, $J = 7.0$ Hz, 1H), 7.29−7.37 (m, 4H), 7.50 (d, $J = 8.2$ Hz, 2H), 7.60−7.72 (m, 10H), 7.77 (td, $J = 3.6$, 7.8 Hz, 6H), 7.88 (dt, $J = 1.9$, 7.8 Hz, 3H), 7.93 (dd, $J = 3.1$, 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.3 (s, 1CH_2), 65.9 (s, 1CH_2), 105.4 (s, 1C), 110.0 (s, 1C), 116.4 (d, $J = 91.6$ Hz, 1C), 118.4 (d, $J = 88.9$ Hz, 1C), 121.0 (s, 1C), 127.9 (s, 1C), 128.49 (s, 2CH), 128.51 (s, 2CH), 129.3 (s, 2CH), 129.6 (s, 2CH), 129.9 (d, $J = 13.3$ Hz, 2CH), 131.6 (d, $J = 12.8$ Hz, 6CH), 135.2 (d, $J = 12.8$ Hz, 6CH), 135.2 (d, $J = 10.7$ Hz, 2CH), 136.6 (d, $J = 2.9$ Hz, 3CH), 137.9 (s, 1C), 138.4 (s, 1C), 138.7 (d, $J = 1.5$ Hz, 1C),140.6 (s, 1C), 148.6 (d, $J = 3.1$ Hz, 1C), 161.4 (C═O); HRMS calcd for $C_{43}H_{36}N_2O_2P$ $[M]^+$: 643.2517, found: 643.2509; IR υ_{max}/cm^{-1} (NaCl): 3447 (N-H), 3065, 3021, 2925,

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2855 (C−H), 1698 (C═O ester), 1596 (C═C_{arom}), 1483 (C═C_{arom}), 1439 (C−P), 1393 (C−N), 1094 (arom), 998 (C−P).

(*S*)-Methyl 1,3-dibenzyl-5-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrrolo[3,2-*e*][1,4]diazepine-7-carboxylate from TAP Support (53). A solution of *N*-(Fmoc)-Phe (4.9 g, 12.52 mmol, 3 equiv) and bis(trichloromethyl) carbonate (BTC, 1.1 g, 4.18 mmol, 1 equiv) in 1.7:1 DCM/THF (72 mL) at 0 °C was treated slowly with 2,4,6-collidine (4.7 mL, 35.51 mmol, 8.5 equiv), yielding a white suspension. After 1−3 min, a solution of aminopyrrole **25** in DCM (45 mL) was added to the mixture containing the freshly formed acid chloride. The reaction mixture was stirred for 15 h under argon atmosphere and treated with 1 N HCl (100 mL). The organic layer was separated and washed with saturated aqueous $NaHCO_3$ (2 × 90 mL), water (90 mL), aqueous saturated $LiClO_4$ (2 × 90 mL), and water (2 × 90 mL), dried (Na_2SO_4), and evaporated to a residue, which was redissolved in DCM (10 mL) and precipitated in ice-cold Et_2O (50 mL). The white solid was filtered off, washed with ice-cold Et_2O (2 × 10 mL), and dried in vacuo to give **28** as a beige powder which was stored under argon in the refrigerator [3.7 g, 87% recovery, R_f: 0.45 (5% MeOH in DCM), HRMS: calcd for $C_{67}H_{55}N_3O_5P$ $[M]^+$: 1012.3874, found: 1012.3894]. Acylaminopyrrole **28** (0.7 g, 0.63 mmol, 1 equiv) was dissolved in DCM (5 mL), treated with piperidine (5 mL), stirred for 10 min, and added dropwise to a stirring mixture of Et_2O and hexane 1/1 (100 mL). The precipitate was collected by filtration, washed with ice-cold Et_2O (2 × 10 mL), and dried in vacuo. The beige solid **35** (499 mg, 89% recovery) was dissolved in dichloroethane (20 mL), transferred to a 20 mL Biotage microwave vessel, treated with trifluoroacetic acid (0.2 mL) and 4-nitrobenzaldehyde (1.2 g, 6.29 mmol, 10 equiv), sealed, and heated at 70 °C under microwave for 3 h. The vessel was cooled to room temperature and treated with aqueous saturated $NaHCO_3$ (20 mL). The phases were separated, and the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic layers were washed with aqueous saturated $LiClO_4$ (2 × 50 mL) and water (50 mL), dried (Na_2SO_4), and evaporated to a residue, which was redissolved in DCM (10 mL) and precipitated in ice-cold Et_2O (50 mL). The white solid was filtered off, washed with ice-cold Et_2O (2 × 10 mL), and dried in vacuo to give **51** as a yellow powder [0.41 g, 64% recovery, R_f: 0.43 (5% MeOH in DCM), HRMS: calcd for $C_{59}H_{48}N_4O_5P$ $[M]^+$: 923.3357, found: 923.3374]. Pyrrolodiazepinone **51** was dissolved in a 0.44 M MeONa solution in THF/MeOH (9:1, 25 mL) at room temperature under argon, and the solution was stirred for 1 h and then quenched with saturated aqueous NH_4Cl (50 mL). The aqueous phase was extracted with EtOAc (2 × 50 mL), and the combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), and evaporated to a residue which was purified by flash chromatography on a silica gel column (15 to 20% gradient of EtOAc in hexanes) to yield (*S*)-methyl 1,3-dibenzyl-5-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrrolo[3,2-*e*][1,4]diazepine-7-carboxylate **53** as a yellow oil (13 mg, 39% yield, 17% overall yield). All the characterization data were identical to those of compound **53** obtained from Merrifield resin.

■ ASSOCIATED CONTENT

Supporting Information. ^1H and ^{13}C NMR spectra of isolated compounds (**48**, **53**, **19**, and **25**), RP-HPLC-MS traces for aminoacylation and Pictet−Spengler cyclization compounds prepared on Wang resin. This material is available free of charge via the Internet at http://pubs.acs.org.

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(48) Preparation of 0.44 M MeONa solution in THF/MeOH (9:1): a 100 mL stock solution was prepared by diluting 10 mL of a 25 wt % MeONa solution in MeOH in 90 mL of dry THF. The solution was kept in a tightly sealed dry glass bottle under argon and was stable for several weeks. The solution was used with a dry syringe under a flow of argon.

(49) Contrary to MacroKans, MiniKans are small enough to be introduced into a 20 mL Biotage microwave reactor. Resin is kept in the Kans to avoid grinding by the stir bar.