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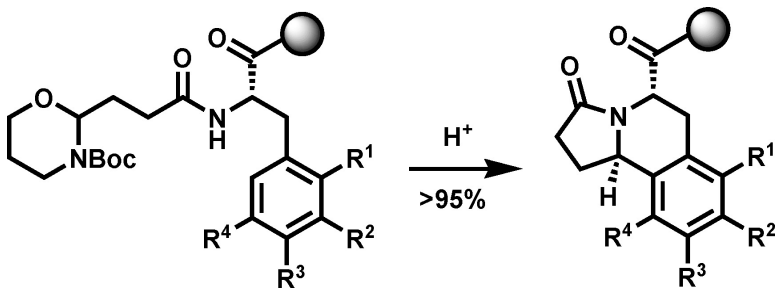

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Solid-Phase Synthesis of Pyrroloisoquinolines via the Intramolecular *N*-Acyliminium Pictet−Spengler Reaction

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In the present investigation, solid-phase routes toward 1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3-ones via the intramolecular *N*-acyliminium Pictet−Spengler reaction are established. Peptide aldehydes generated from their parent *N*-Boc 1,3-oxazines by acidic reaction conditions undergo intramolecular condensation reactions with the amide *N* of a solid-supported peptide backbone, thus forming a 1:1 epimeric mixture of a cyclic 5-hydroxylactam, which in turn is in equilibrium with the corresponding intermediate *N*-acyliminium ion. Provided appropriate acidic reaction conditions, a second ring may be appended via Pictet−Spengler cyclization from the aromatic ring of a neighboring phenylalanine derivative in the peptide sequence. The aromatic substitution pattern of the nucleophilic benzene ring of the phenylalanine derivative and the nature of the acidic reaction media are critically important for the course of the reaction, and both Lewis and Brønsted acids may be employed to effect the cyclization process. This intramolecular reaction is under strict control of stereoselectivity, and only a single stereoisomer is detected in the crude products. A range of mono-, di-, and trisubstituted phenylalanines with diverse sets of electron-donating and electron-withdrawing substituents, pyrene, and naphthalenes have successfully been brought within the scope of the reaction, thus providing a unique scaffold for combinatorial library synthesis.

Introduction

In the search for new drugs, solid-phase combinatorial synthesis of peptide isosteres and peptidomimetics has received considerable attention, among both academic and industrial research groups.[1] The present state of solid-phase peptide synthesis has been developed to high levels of efficiency, thus enabling the high-throughput generation and screening of peptide libraries. However, leads obtained from traditional combinatorial libraries and compound collections composed of hydrophilic peptide oligomers typically display poor pharmacokinetic properties. Solid-phase synthesis of molecular entities following the more general guidelines for druglike molecules, such as Lipinski's rule of five,[2] has accordingly emerged as an area of intense research. Toward this end, novel routes to privileged heterocyclic structures and substructures in a combinatorial library format continue to be one of the most important goals for solid-phase synthesis.[3−5]

In efforts aimed at developing new, efficient, solid-phase routes to constrained peptidomimetic ring systems, which preferably incorporate privileged core structures, such as the pharmacologically important tetrahydro-β-carbolines (THBCs) and tetrahydroisoquinolines (THIQs), we have previously developed an intramolecular version[6] of the *N*-acyliminium Pictet−Spengler reaction.[7−9] The methodology allows the generation of indolizinoindoles **1**, which are known to be potent and selective CCK_1 receptor antagonists.[10] The analogous benzothienoindolizine **2**, thienoindolizine **3**−**4**, and furaindolizine **5** scaffolds were also

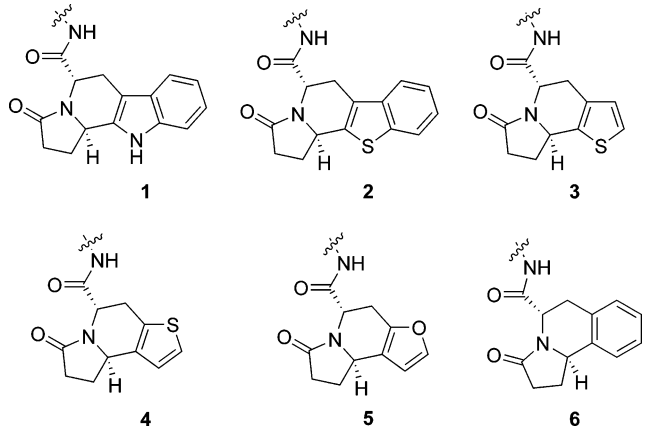

Figure 1. Constrained Peptidomimetic Scaffolds Accessible via the Intramolecular *N*-Acyliminium Pictet−Spengler Reaction.

obtained in excellent yields and diastereoselectivities (both typically above 95%), whereas the extension to produce pyrroloisoquinolines **6** without electron-donating substituents on the aromatic ring remained unsuccessful (Figure 1).

The latter was illustrated by the incorporation of a phenylalanine residue between the masked aldehyde moiety and the peptide backbone **7** (Scheme 1), which upon acid treatment with 10% TFA (aq) quantitatively releases the aldehyde **8**, which underwent immediate cyclization to the corresponding 5-hydroxylactam **9**. Despite well-established intermediacy of the *N*-acyliminium ion **10**, no traces of the Pictet−Spengler cyclized product **11** were detected in these initial studies. Evidently, whereas analogous *N*-acyliminium ions are attacked by reactive aromatic heterocycles, such as indoles and thiophenes, the unsubstituted phenyl group was

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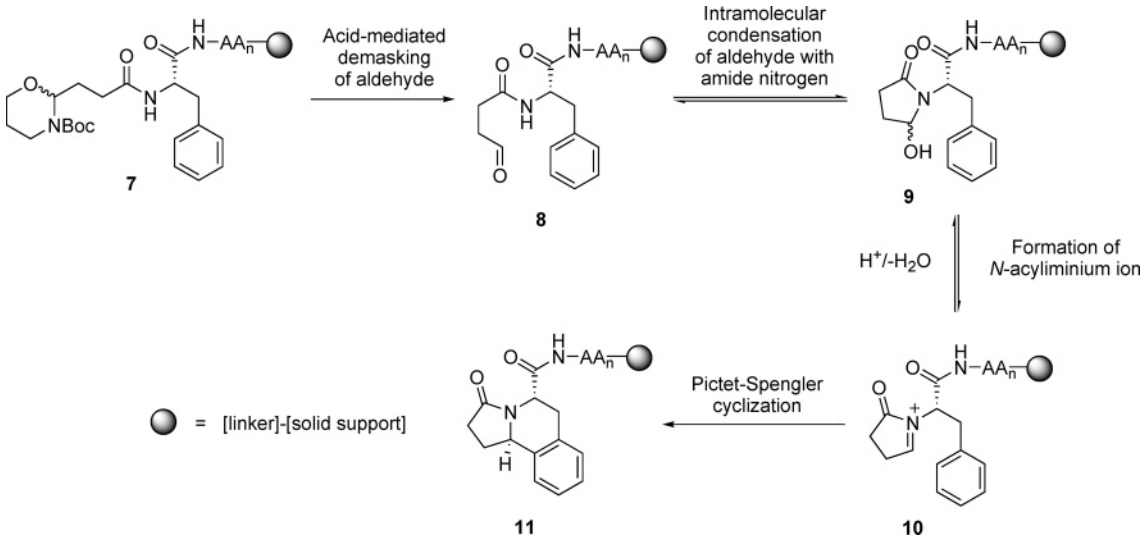
Scheme 1. Solid-Phase Intramolecular *N*-Acyliminium Pictet−Spengler Reaction for the Synthesis of Pyrroloisoquinolines

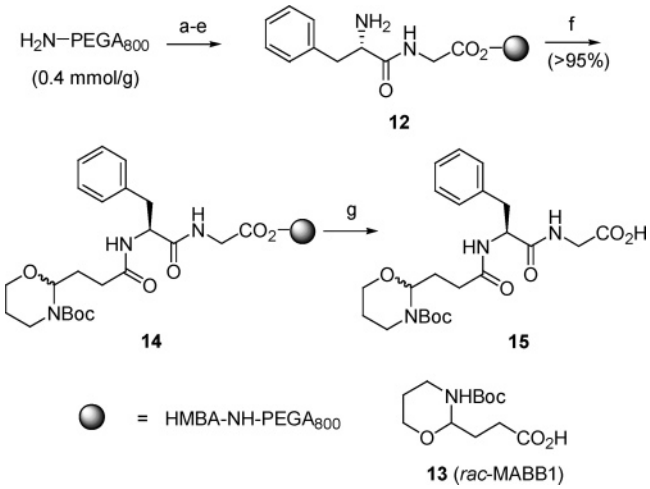


not sufficiently reactive for Pictet−Spengler cyclization to occur under such reaction conditions.

However, the original work of Pictet and Spengler demonstrated the feasibility of phenylethylamine, phenylalanine, and tyrosine to be condensed with formaldehyde under acidic reaction conditions (concentrated HCl, reflux) to produce an *N*-alkyliminium ion capable of reacting with the phenyl moiety to form a 1,2,3,4-tetrahydroisoquinoline ring system.[11] In contrast to the most commonly adapted solid-phase version of the Pictet−Spengler reaction,[12] where aldehydes in solution are condensed with solid-supported tryptophan or tryptamine residues in acidic reaction media to produce tetrahydro-β-carbolines via *N*-alkyliminium intermediates, surprisingly few applications have been reported for the analogous solid-phase synthesis of tetrahydroisoquinolines. The reported routes employ electron-rich aromatic moieties as solid-supported *C*-nucleophiles, such as (3,4-dimethoxyphenyl)ethylamine and (3,4-dimethoxyphenyl)-alanine derivatives, to access this ring system under basic[13,14] and acidic reaction conditions.[6,15] In addition, Lewis acid-mediated Pictet−Spengler cyclizations[16] have been carried out on solid support, most impressively to afford the two tetrahydroisoquinoline rings of structural analogues of the natural product (−)-saframycin A.[17] An alternative approach on solid support utilizes the Bischler−Napieralski reaction to generate tetrahydroisoquinolines, but this method generally relies on much harsher reaction conditions ($POCl_3$, elevated temperatures).[18,19]

There are several reports for the synthesis of pyrroloisoquinolines in solution via acid-catalyzed cyclization of phenyl moieties to cyclic *N*-acyliminium ions.[20] To the best of our knowledge, no reports have dealt with the Pictet−Spengler reaction of solid-supported phenylalanine derivatives lacking electron-donating substituents on the aromatic ring, or even containing electron-withdrawing substituents, presumably because such transformations are expected to require harsh reaction conditions or even be impossible via traditional *N*-alkyliminium chemistry. Accordingly, it was considered worthwhile to extend the intramolecular *N*-acyliminium Pictet−Spengler reaction to the solid-phase synthesis of tetrahydroisoquinoline derivatives. The intramolecular nature

Scheme 2. Solid-Phase Synthesis of the Masked Aldehyde Precursor for the Intramolecular *N*-Acyliminium Pictet−Spengler Reaction Precursor[a]



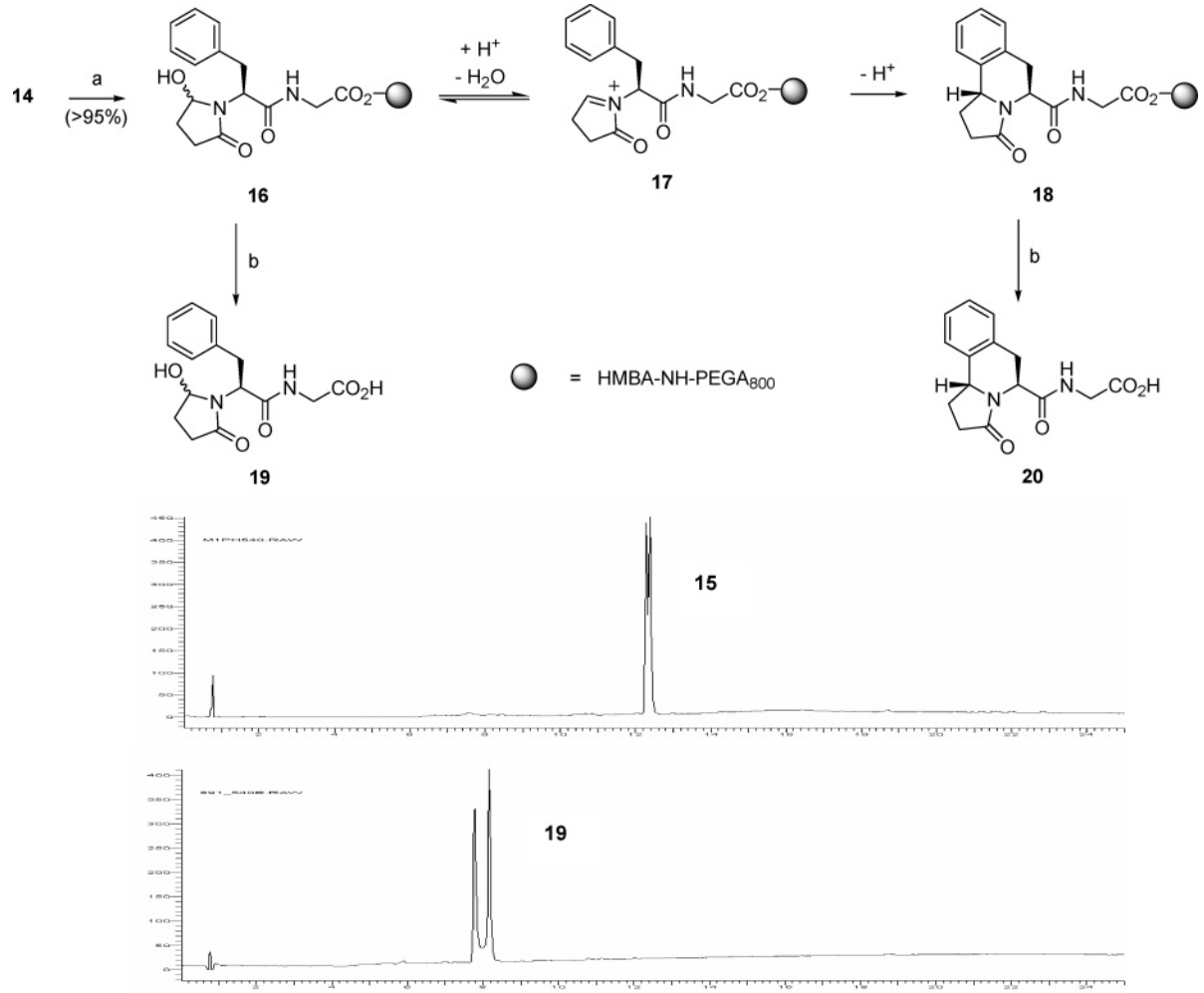
[a] Reagents and conditions: (a) HMBA, TBTU, NEM, DMF, 3 h; (b) Fmoc-Gly-OH, MSNT, MeIm, CH_2Cl_2; (c) 20% piperidine (DMF); (d) Fmoc-Phe-OH, TBTU, NEM, DMF; (e) 20% piperidine (DMF); (f) **13**, TBTU, NEM, DMF; (g) 0.1 M NaOH (aq).

of this reaction and the high reactivity of the intermediate *N*-acyliminium ions were expected to facilitate product formation under reaction conditions mild enough to ensure resin integrity and prevent premature cleavage of product from the resin, thereby enabling the Pictet−Spengler cyclization of a range of substituted phenylalanine derivatives. These pharmacophores constitute important structural motifs of numerous drugs and biologically active molecules and are, in addition, readily available (e.g., as their Fmoc-protected building blocks) in large numbers from commercial suppliers, thereby rendering the methodology a most relevant and convenient platform for the generation of combinatorial libraries based on privileged core structures.

Results and Discussion

The Pictet−Spengler reaction substrates of the present investigation were made according to standard Fmoc amino acid coupling protocols for solid-phase peptide synthesis. For the purpose of utilizing acidic reaction conditions, which are

Scheme 3. Solid-Phase Synthesis of 5-Hydroxylactam and Generation *N*-Acyliminium Ion[a]



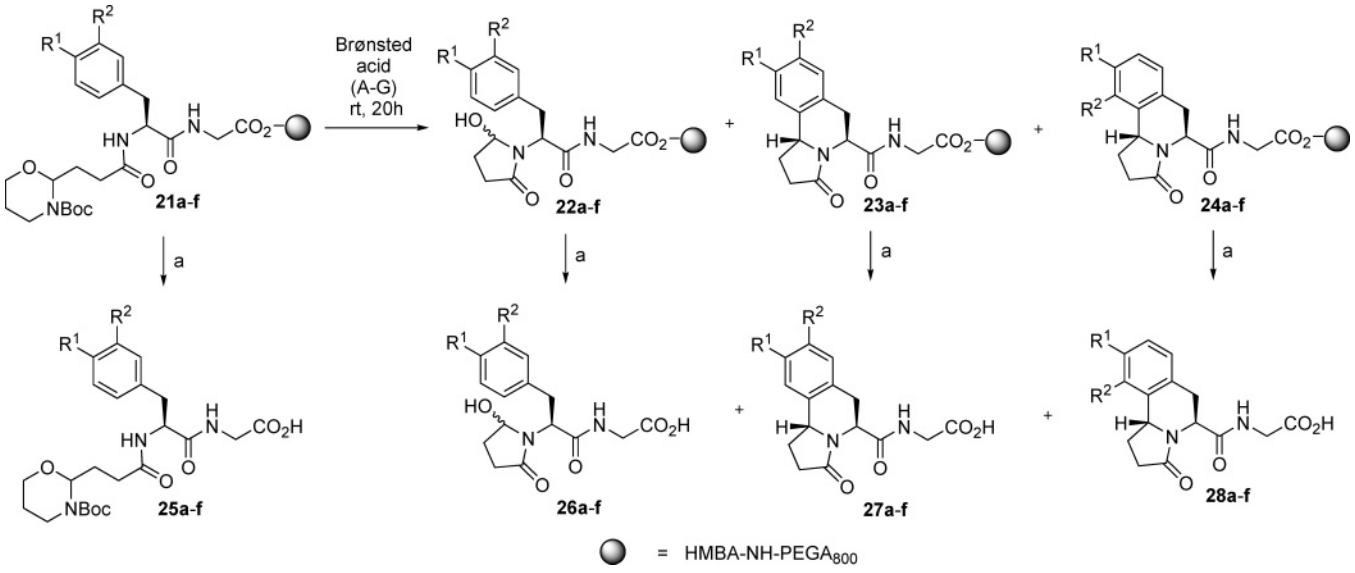
[a] Reagents and conditions: (a) 10% TFA (aq), 24 h; (b) 0.1 M NaOH (aq). Crude analytical RP-HPLCs of masked aldehyde **15** and 5-hydroxylactam **19** cleaved off the solid support by treatment with 0.1 M NaOH (aq).

normally required for Pictet−Spengler reactions, the base labile hydroxymethylbenzoic acid (HMBA) linker was attached to the amino-functionalized PEGA resin[21] by the TBTU-activation procedure.[22] The hydroxy handle of the linker was esterified by treatment with MSNT-activated Fmoc-Gly-OH,[23] thus attaching the first amino acid residue (glycine) and providing a convenient cleavage site for quantitative release from the solid support via basic hydrolysis under mild conditions. Subsequent cycles of Fmoc deprotection and TBTU-mediated couplings to incorporate Fmoc-Phe-OH and racemic masked aldehyde building block **13**[24] and afforded the Pictet−Spengler reaction substrate **14** in the expected 1:1 diastereomeric ratio (purity >95%).

Treatment of **14** with 10% TFA (aq) according to previously described conditions for the intramolecular *N*-acyliminium Pictet−Spengler reaction gave none of the desired product **18**.[6] Within minutes, the *N*-Boc 1,3-oxazinane moiety of **14** is cleanly converted into the corresponding aldehyde, which quantitatively reacts with the amide nitrogen of the peptide backbone to form a cyclic five-membered 5-hydroxylactam **16** (Scheme 3). As indicated by analytical RP-HPLC chromatograms of 5-hydroxylactam **19**, the solid-supported 5-hydroxylactam **16** was cleanly formed as a ∼1:1 epimeric mixture. Each epimer was carefully fractionated by analytical HPLC. However, upon immediate reinjection, the same 1:1 epimeric ratio appeared in each fraction, which indicates a rapid equilibration either via ring-opening or via the intermediate *N*-acyliminium ion in the eluent (0.1% TFA in water/acetonitrile mixture).

Accordingly, when proper substitution patterns of hydroxy and methoxy groups (activating groups) are introduced on the benzene ring of phenylalanine, the intramolecular *N*-acyliminium Pictet−Spengler reaction proceeds readily under mild acidic aqueous reaction conditions. When treating the dimethoxy derivative **21a** (R^1 = OMe, R^2 = OMe) with 10% TFA (aq), the reaction sequence proceeds smoothly to afford pyrroloisoquinoline **23a** in excellent purity (>95%, Table 1, entry 1), resulting from attack of the para position of the R^2 methoxy group. In general, when R^2 is OMe (**21a**, **21c**) or OH (**21e**), 10% TFA (aq) is sufficient for clean conversion into the Pictet−Spengler products, whereas substrates **21b** and **21d** (both with R^2 = H) are not sufficiently activated for attack from either C2 or C5 of the benzene ring (Table 1, entries 2 and 9). Bearing in mind the ortho/para-directing properties of hydroxy and alkoxy functionalities, the results are readily understood by reference to the general rules of electrophilic aromatic substitution. Notably, whereas the reaction proceeds in a quantitative fashion, the regioselec-

Table 1. Brønsted Acidic Aqueous and Nonaqueous Reaction Conditions for Solid-Phase Intramolecular *N*-Acyliminium Pictet−Spengler Reactions of Electron-Rich Phenylalanine Derivatives[a]



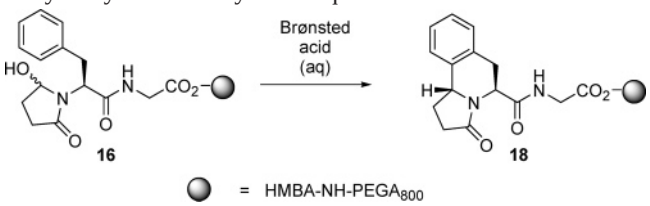
entry	masked aldehyde[a]	reaction conditions[b]	R^1	R^2	ratio of **22**:**23**:**24**[c]	HPLC purity of **22** + **23** + **24** (%)
1	**21a**	A	OMe	OMe	0:100:0	>95
2	**21b**	A	OMe	H	100:0:0	>95
3	**21c**	A	H	OMe	0:82:18	>95
4	**21c**	B	H	OMe	0:63:37	73
5	**21c**	C	H	OMe	0:58:42	76
6	**21c**	D	H	OMe	0:85:15	69
7	**21c**	E	H	OMe	0:85:15	40[d]
8	**21c**	F	H	OMe	0:63:37	87
9	**21c**	G	H	OMe	0:93:7	57
10	**21d**	A	OH	H	100:0:0	>95
11	**21e**	A	H	OH	0:65:35	>95
12	**21e**	B	H	OH	0:64:36	83
13	**21e**	C	H	OH	0:64:36	89
14	**21e**	D	H	OH	0:75:25	76
15	**21e**	E	H	OH	0:67:33	38[d]
16	**21e**	F	H	OH	0:66:34	93
17	**21e**	G	H	OH	0:55:45	94
18	**21f**	A	OH	OH	n.d.	0[e]

[a] 0.1 M NaOH (aq). The masked aldehydes **21a**−**f** were prepared via procedures similar to those of **14** in Scheme 2. [b] Reaction conditions: A, 10% TFA (aq); B, 10% TFA (CH_2Cl_2); C, 50% TFA (CH_2Cl_2); D, 10% H_2SO_4 (CH_3CO_2H); E, 10% TFA (DMF); F, 10% TFA (heptane); G, 10% TFA (dioxane). [c] The **22**:**23**:**24** ratio and product purity were determined by analytical RP-HPLC of the crude mixture of **26**, **27**, and **28** cleaved off the solid support with 0.1 M NaOH (aq). [d] The low product purity is mainly due to unconverted material of **21**. [e] None of the Pictet−Spengler product was detected due to decomposition under these reaction conditions.

tivity is not complete for **21c** and **21e** (Table 1, entries 3 and 11). Products **24c** and **24e** result from attack of the ortho position of R^2, although generally in lower amounts than regioisomers **23c** and **23e** resulting from attack of the para position of R^2. Similar trends in regioselectivity have been made for related solution-phase cyclizations to *N*-acyliminium ions.[25] The dependence of the regioselectivity on the solvent was briefly examined by exposing **21c** and **21e** to various acidic reaction conditions (Table 1, entries 4−9 and 12−17). Here, the regioselectivity of the methoxy derivative **21c** was found to be highly dependent on the solvent, as illustrated by the change in product ratio of **23c**/**24c** by changing from CH_2Cl_2 (∼2:1, Table 1, entry 4) to dioxane (∼13:1, Table 1, entry 9). It is also noteworthy that HPLC purities above 95% could only be obtained when aqueous reaction media were employed (Table 1, reaction conditions A), which points to the importance of water for a clean demasking of the aldehyde (see also Table 3). The masked aldehyde substrate derived from 3,4-dihydroxyphenylalanine (L-DOPA) was also prepared (**21f**, with R^1 = OH and R^2 = OH), but treatment with 10% TFA resulted in a complex product mixture according to RP-HPLC (many peaks), and none of the Pictet−Spengler product was found by inspection of ^{1}H NMR and MS data of crude **26f**−**28f**.

A range of Brønsted acidic reaction conditions were examined for the Pictet−Spengler cyclization of 5-hydroxylactam **16** (Table 2). In previous studies, we demonstrated how aqueous TFA and HCl were superior to aqueous solutions of, for example, CH_3COOH, HCOOH, CSA, and TCA, to mediate the intramolecular *N*-acyliminium Pictet−Spengler reaction of electron-rich aromatic heterocycles.[6] Starting with 10% TFA (aq), no conversion of **16** to **18** was observed during 72 h (Table 2, entry 1). Heating the reaction to higher temperatures (Table 2, entries 2 and 3) provided

Table 2. Brønsted Acidic Aqueous Reaction Conditions for Solid-Phase *N*-Acyliminium Pictet−Spengler Cyclization of 5-Hydroxylactam to Pyrroloisoquinoline



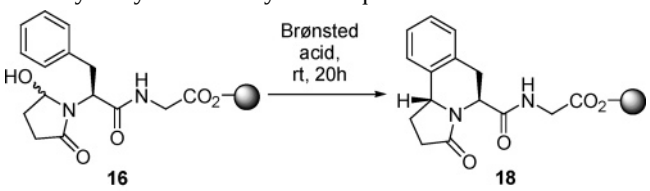
entry	reaction conditions	HPLC purity of **18**[a]
1	10% TFA, rt, 72 h	no conversion
2	10% TFA, 75 °C, 48 h	no conversion[b]
3	10% TFA, 100 °C, 24 h	linker cleaved
4	50% TFA, rt, 24 h	trace
5	50% TFA, 100 °C, 24 h	resin decomposed[c]
6	95% TFA, rt, 24 h	>95%
7	10% HCl, rt, 72 h	no conversion
8	10% HCl, 75 °C, 48 h	no conversion[b]
9	10% HCl, 100 °C, 24 h	linker cleaved
10	20% HCl, rt, 24 h	linker cleaved
11	20% HCl, 100 °C, 24 h	resin decomposed[c]
12	1% H_2SO_4, rt, 24 h	no conversion
13	10% H_2SO_4, rt, 24 h	no conversion[d]
14	50% H_2SO_4, rt, 24 h	>50%[b]

[a] Purity, conversion and decomposition were indicated by RP-HPLC of the crude reaction mixture of **19** and **20** cleaved off the solid support with 0.1 M NaOH (aq). [b] Loading reduced (<5% of original loading). [c] Decomposition of the resin was apparent by complete dissolution in the acidic reaction medium during the reaction period. [d] Loading reduced (<25% of original loading).

none of the desired product **18**. Instead, the product was cleaved from the linker by acidic hydrolysis of the ester bond. Increasing the acidity to 50% TFA (aq) provided traces of the Pictet−Spengler cyclized product **18** (Table 2, entry 4), but heating to reflux under these conditions resulted in resin decomposition (Table 2, entry 5). However, the Pictet−Spengler cyclization proceeded smoothly at 95% TFA (aq) (Table 2, entry 6) to afford pyrroloisoquinoline **18** in high purity. With aqueous HCl, it was not possible to adjust the reaction conditions to allow Pictet−Spengler cyclization without hydrolyzing the linker or decomposing the resin (Table 2, entries 7−11). Similar results were obtained with H_2SO_4. At lower acidity, the 5-hydroxylactam **16** remains unconverted (Table 2, entries 12−13), whereas increased acidity provides the Pictet−Spengler product **18**, albeit in low isolated yield due to cleavage of the linker (Table 2, entry 14).

As indicated in Scheme 3, the shift of the equilibrium toward the *N*-acyliminium ion **17** should depend on both the acidity and water content of the reaction medium. Bearing in mind the problems of acidic hydrolysis of the linker in aqueous media of the acidity required to effect Pictet−Spengler cyclization of **16** (Table 2), it was natural to also test the reaction in nonaqueous solvent systems. Only minor traces of Pictet−Spengler cyclization product appeared after treatment of **16** with CH_3COOH for 20 h (Table 3, entry 1), whereas the presence of 1−50% H_2SO_4 in CH_3COOH[26] (Table 3, entries 2−4) provided the Pictet−Spengler product **18** in excellent purity and diastereoselectivity (both above 95%) in less than 4 h, notably with retained loading, since hydrolysis is suppressed when using CH_3COOH as solvent instead of water. Evidently, the product **18** was also cleanly

Table 3. Brønsted Acidic Nonaqueous Reaction Conditions for Solid-Phase *N*-Acyliminium Pictet−Spengler Cyclization of 5-Hydroxylactam to Pyrroloisoquinoline

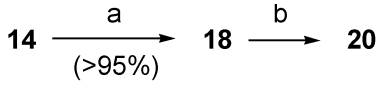


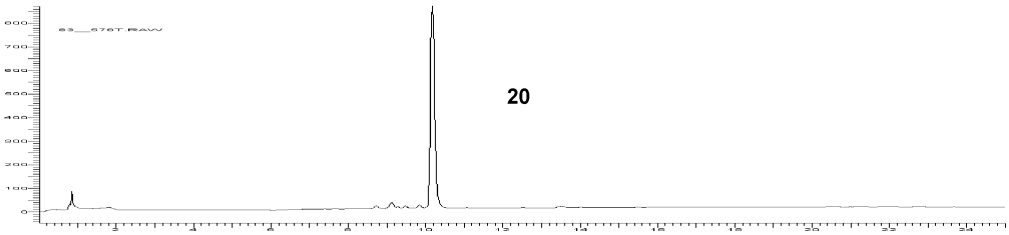
entry	reaction conditions	HPLC purity of **18**[a]
1	CH_3CO_2H	<2[b]
2	CH_3CO_2H/H_2SO_4 (99:1)	94
3	CH_3CO_2H/H_2SO_4 (9:1)	>95[c] (80[d])
4	CH_3CO_2H/H_2SO_4 (1:1)	>95[c] (76[d])
5	H_2SO_4 (conc)	resin decomposed[e]
6	TFA/CH_2Cl_2 (1:99)	60[b]
7	TFA/CH_2Cl_2 (1:9)	>95 (76[d])
8	TFA/CH_2Cl_2 (1:1)	>95 (88[d])
9	TFA	>95[c] (88[d])
10	TFA/$CHCl_3$ (1:9)	>95 (93[d])
11	TFA/CH_3CN (1:9)	56
12	TFA/THF (1:9)	53[b]
13	TFA/toluene (1:9)	>95[c]
14	TFA/DMF (1:9)	70[b] (17[d])
15	TFA/DMSO (1:9)	43[b]
16	TFA/heptane (1:9)	>95[c] (92[d])
17	TFA/ether (1:9)	52[b]
18	TFA/ethyl acetate (1:9)	58[b]
19	TFA/acetone (1:9)	44[b]

[a] Purity was indicated by RP-HPLC of the crude reaction mixture of **19** and **20** cleaved off the solid support with 0.1 M NaOH (aq). [b] The (low) product purity is mainly due to unconverted material of **16**. [c] The reaction was complete in less than 4 h. [d] Crude purity of **18** when masked aldehyde **14** was treated with same acidic reaction conditions for 20 h. In 10% TFA (DMF), only 25% conversion of **14** was obtained during 20 h. [e] Decomposition of the resin was apparent by complete dissolution in the acidic reaction medium during the reaction period; however, after 4 h, the product had cleanly been formed (>95%), but the loading of the partially decomposed resin was estimated as <25% due to acidic hydrolysis of the linker.

formed when **16** was treated with concentrated H_2SO_4 (Table 3, entry 5), but the resin gradually decomposed, in addition to cleavage of the linker during 20 h. Less harsh, mixtures of TFA/CH_2Cl_2 (in ratios ranging from 100:0 to 1:9) proved to be highly useful for mediating the reaction, generally affording the product in excellent yield during 20 h (Table 3, entries 7−9), although generally slower than mixtures of H_2SO_4 and CH_3COOH. By screening organic solvents containing 10% TFA (Table 3, entries 10−20), a range of solvents in addition to CH_2Cl_2 were found to be compatible with the reaction, most efficiently chloroform, toluene, and hexane. The possibility of carrying out a one-pot aldehyde-demasking, amide backbone condensation and Pictet−Spengler cyclization was also investigated by subjecting masked aldehyde **14** to selected nonaqueous acidic reaction conditions (the obtained purity in these experiments is noted in the parentheses of Table 3, entries 3−4, 7−10, 14, 16, and 20). In these experiments, purities of pyrroloisoquinoline **18** exceeding 95% could generally not be obtained directly from masked aldehyde **14**. This indicates the necessity of acidic aqueous reaction conditions for the clean formation of 5-hydroxylactam **16** before changing to acidic nonaqueous

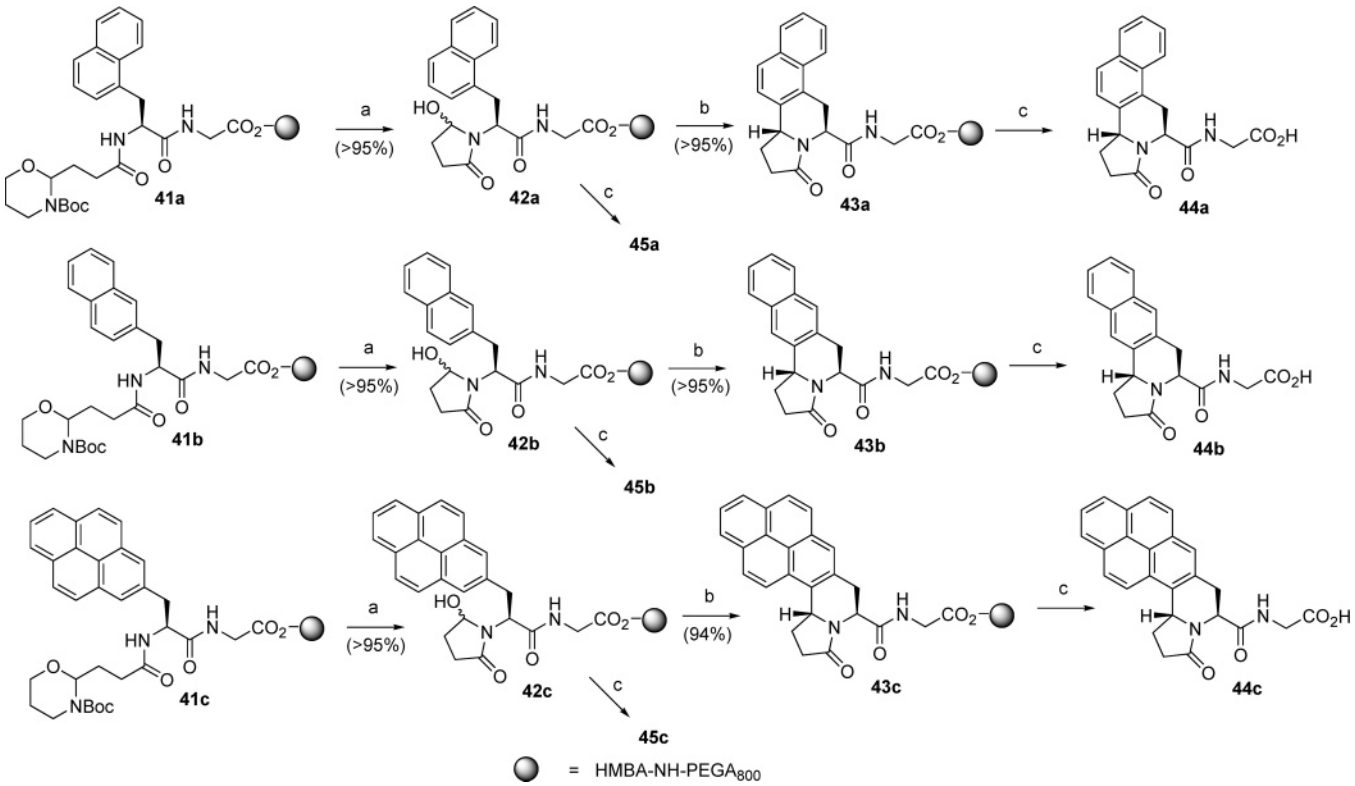
Scheme 4. Solid-Phase Intramolecular *N*-Acyliminium Pictet−Spengler Reaction of Masked Aldehyde Derivative[a]





[a] Reagents and conditions: (a) 95% TFA (aq); (b) 0.1 M NaOH (aq). Crude analytical RP-HPLC of Pictet−Spengler-cyclized product **20** cleaved off the solid support by treatment with 0.1 M NaOH (aq).

Scheme 5. Solid-Phase Intramolecular *N*-Acyliminium Pictet−Spengler Reactions of Fused Aromatic Rings[a]

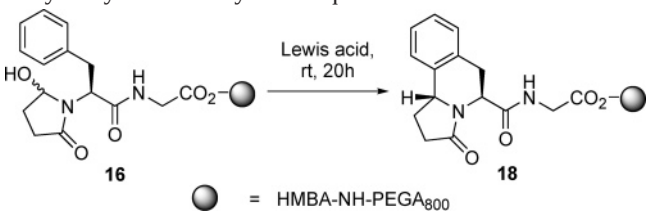


[a] Reagents and conditions: (a) 95% TFA (aq), 20 h; (b) TFA/CH_2Cl_2 (1:1), 20 h; (c) 0.1 M NaOH (aq).

reaction conditions for efficient Pictet−Spengler cyclization into the desired product **18**. However, since 95% TFA (aq) was used for the clean conversion of 5-hydroxylactam **16** to pyrroloisoquinoline **18** (Table 2, entry 6), it was envisioned that these reaction conditions could also be applied for a clean aldehyde umasking/amide backbone condensation. Gratifyingly, the desired transformation (**14** → **18**) proceeded cleanly to afford **18** in excellent purity (>95%, as shown by the analytical RP-HPLC chromatogram of the crude product in Scheme 4).

Lewis acids have found broad utility for the cyclization of aromatic rings to cyclic and acyclic *N*-acyliminium ions in solution-phase synthesis,[20] as exemplified in the generation of pyrroloisoquinolines, where $TiCl_4$, $BF_3{\cdot}Et_2O$, TMSOTf, and $SnCl_4$ have been successfully employed.[27−31] Pictet−Spengler reactions have been carried out using Lewis acids as activators of nitrones,[32−35] *N*-acyliminium ions,[36,37] and imines in combination with microwave irradiation.[16] However, the application of Lewis acids for solid-phase Pictet−Spengler type reactions has, to the best of our knowledge, not been reported, and it was therefore considered worth testing a selection of common Lewis acids for transforming 5-hydroxylactam **16** into pyrroloisoquinoline **18** (Table 4). Indeed, the desired transformation could readily be effected with stock solutions of 0.1 M $SnCl_4$, $TiBr_4$, and $BF_3{\cdot}Et_2O$ (Table 4, entries 1, 3−4) in amounts of dichloromethane sufficient for covering the resin. At lower concentration, that is, 0.01 M, incomplete conversion was generally observed. When shifting to lanthanides, no conversion was seen in polar and nonpolar solvents (Table 4, entries 6−8), even at 0.5 M Lewis acid. Since *N*,*O*-acetals are prone to cleavage with Lewis acids, the conversion of masked aldehyde **14** into pyrroloisoquinoline **18** should also be within the scope of this methodology. Although the direct exposure of **14** to 0.5

Table 4. Lewis Acidic Nonaqueous Reaction Conditions for Solid-Phase *N*-Acyliminium Pictet−Spengler Cyclization of 5-Hydroxylactam to Pyrroloisoquinoline



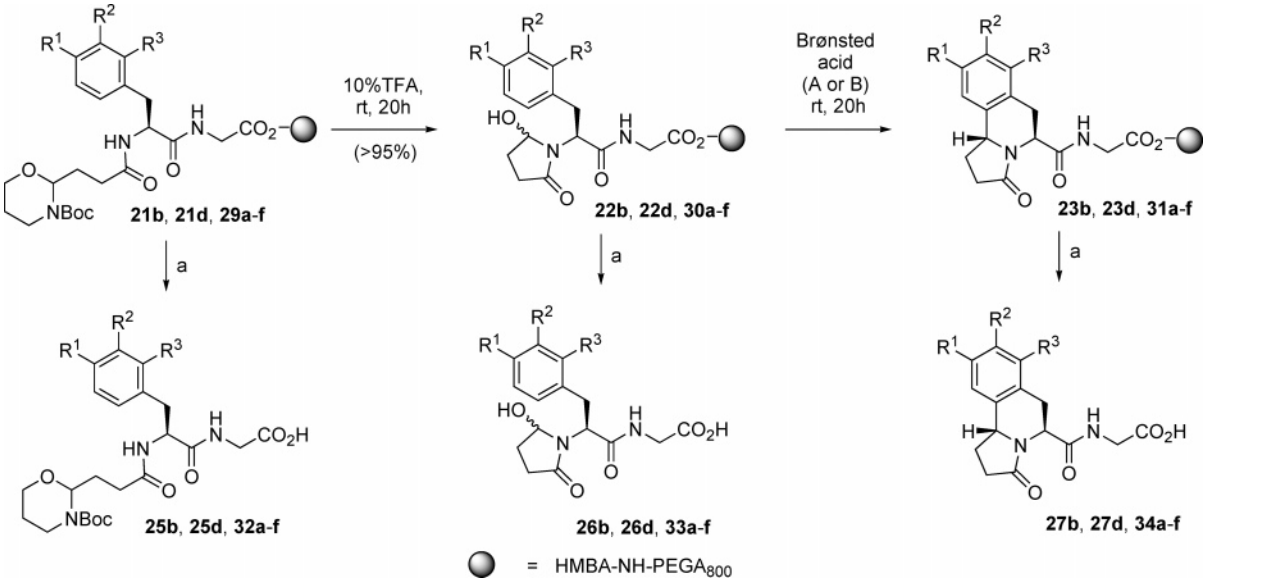
entry	Lewis acid[a]	HPLC purity of **18** (%)[b]
1	0.1 M $SnCl_4$	87
2	0.1 M $TiCl_4$	23
3	0.1 M $TiBr_4$	79
4	0.1 M $BF_3{\cdot}Et_2O$	89
5	0.1 M $AlCl_3$[c]	0[e]
6	0.1 M $Sc(OTf)_3$[d]	no conversion of **16**
7	0.1 M $Yb(OTf)_3$[d]	no conversion of **16**
8	0.1 M $Y(OTf)_3$[d]	no conversion of **16**

[a] All reactions were performed for 20 h in CH_2Cl_2 unless otherwise indicated. Each reaction was followed by extensive washing with CH_2Cl_2. [b] Purity was indicated by RP-HPLC of the crude reaction mixture of **20** cleaved off the solid support with 0.1 M NaOH (aq). [c] The reaction was carried out in CH_2Cl_2/THF (4:1). [d] At this concentration, the lanthanide is partly suspended in the reaction solvent. The lanthanide-catalyzed reactions were also tested at 0.1 M concentrations in DMF and THF as solvents, but no significant conversions were detected in these experiments. [e] When exposing **16** to 0.01−0.5 M $AlCl_3$ in CH_2Cl_2/THF (4:1), none of **18** was formed at complete substrate conversion.

M Lewis acids in dichloromethane resulted in the formation of **18**, product purities were generally much lower than those depicted in Table 4.

Encouraged by the findings in Table 3 that several Brønsted acidic reaction conditions could be used to effect clean and quantitative cyclization of the unsubstituted phenyl moiety of phenylalanine to the *N*-acyliminium ion, it was decided to further investigate the functional group tolerance and substitution pattern of the aromatic ring. Initially, a series of solid-supported masked aldehyde substrates incorporating phenylalanine derivatives **29a**−**f** devoid of electron-withdrawing substituents were made via coupling procedures analogous to those depicted in Scheme 2, and treatment with 10% TFA (aq) gave the 5-hydroxylactams as 1:1 epimeric mixtures in excellent purity (>95% for all 5-hydroxylactams of Table 5). Rewardingly, all methyl- and phenyl-substituted 5-hydroxylactams **30a**−**d** gave quantitative formation of the desired Pictet−Spengler products **31a**−**d** (Table 5, entries 1−4), as opposed to the 3-hydroxyphenyl and 3-methoxyphenyl-derived masked aldehyde substrates (**21e** and **21c**, respectively), in which regioisomeric Pictet−Spengler products form, the 3-methylphenyl-derived 5-hydroxylactam **30b** only gave rise to the regioisomer resulting from attack para to the substituent (methyl) group. The tyrosine-derived 5-hydroxylactams **22b** and **22d** (Table 5, entries 7−8) performed equally well in the reaction (Table 5, entries 7−8),

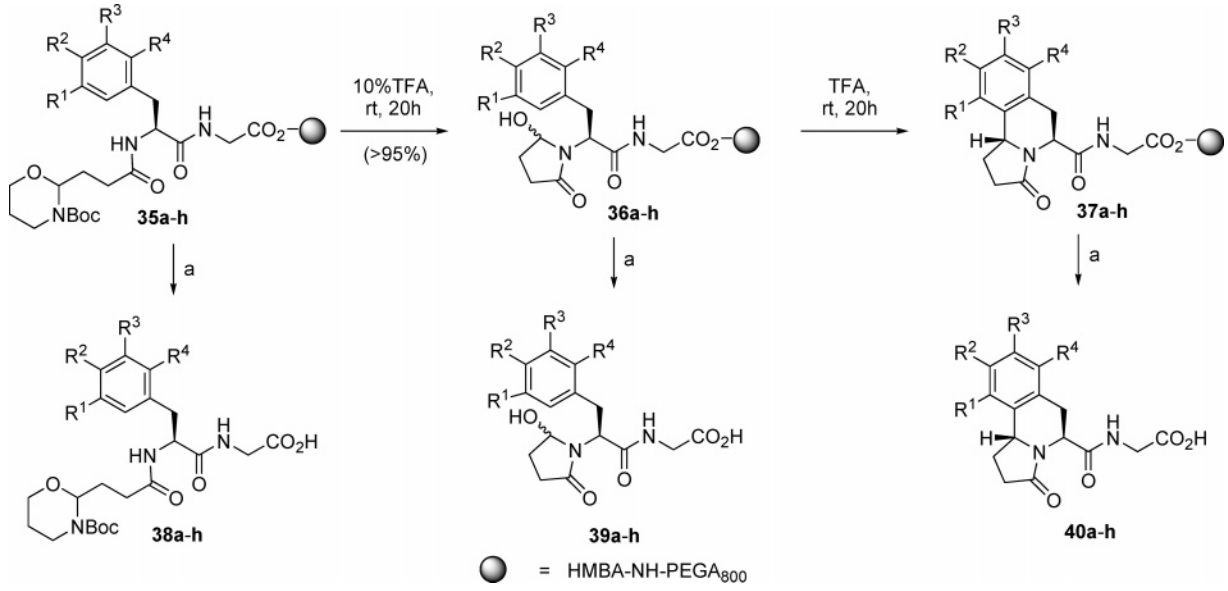
Table 5. Brønsted Acidic Nonaqueous Solid-Phase Intramolecular *N*-Acyliminium Pictet−Spengler Reactions of Phenylalanine Derivatives



entry	masked aldehyde	reaction conditions[a]	R^1	R^2	R^3	HPLC purity of **31** or **23** (%)[b]
1	**29a**	A or B	Me	H	H	>95
2	**29b**	A or B	H	Me	H	>95
3	**29c**	A or B	H	H	Me	>95
4	**29d**	A or B	Ph	H	H	>95
5	**29e**	A or B	N_3	H	H	0[c]
6	**29f**	A or B	NH_2	H	H	0[c]
7	**21d**	A or B	OH	H	H	>95
8	**21b**	A or B	OMe	H	H	>95

[a] 0.1 M NaOH (aq). Reaction conditions: A, 50% TFA (CH_2Cl_2); B, 10% H_2SO_4 (CH_3CO_2H). [b] The product purity of **31** was determined by analytical RP-HPLC of the crude mixture of **34** cleaved off the solid support with 0.1 M NaOH (aq). [c] 5-Hydroxylactams **30e** and **30f** decomposed under reaction conditions A or B.

Table 6. Brønsted Acidic Nonaqueous Solid-Phase Intramolecular *N*-Acyliminium Pictet−Spengler Reactions of Phenylalanine Derivatives **2**



entry	masked aldehyde	R^1	R^2	R^3	R^4	HPLC purity of **37** (%)[a]
1	**35a**	H	H	H	F	60[b]
2	**35b**	H	H	H	Br	68[b]
3	**35c**	H	Br	H	H	>95
4	**35d**	H	I	H	H	>95
5	**35e**	H	Cl	H	H	>95
6	**35f**	H	H	Cl	H	>95
7	**35g**	H	Cl	Cl	H	92
8	**35h**	Br	OH	Br	H	>95

[a] 0.1 M NaOH (aq). The product purity of **37a**−**h** was determined by analytical RP-HPLC of the crude mixture of **40a**−**h** cleaved off the solid support with 0.1 M NaOH (aq). [b] The reaction was carried out for 72 h. The noted purity reflects the conversion of the 5-hydroxylactam at this time. The crude mixture was separated by preparative RP-HPLC to afford amounts of material sufficient for NMR analysis.

whereas the shelf-stable 4-azidophenyl and 4-aminophenyl-derived 5-hydroxylactams (**30e**−**f**) completely decomposed when subjected to reaction conditions A or B (Table 5, entries 5−6).

The utility of the reaction would be greatly broadened if substrates with electron-withdrawing substituents on the aromatic ring participate in the reaction. Such substituents are highly desired in terms of scaffold diversity and may provide a convenient handle for further synthetic transformations, for example, metal-catalyzed cross-coupling reactions of halogen-substituted aromatics on solid support. The substrates would be expected to exhibit significantly lower reaction rates than those in Table 5. To investigate the effect of introducing a halogen on the phenyl ring, a series of substrates were made via procedures similar to those depicted in Scheme 2. As expected, treatment with 10% TFA (aq) gave the 5-hydroxylactams **36a**−**h** as 1:1 epimeric mixtures in excellent purity (>95% for all 5-hydroxylactams of Table 6). Furthermore, treatment of the 5-hydroxylactams **36a**−**h** with TFA for 20 h mediated a clean formation of Pictet−Spengler products **37c**−**h** (Table 6, entries 3−8). As expected, the 2-fluoro and 2-bromophenyl derivatives **36a**−**b** were less reactive, giving only 60 and 68% conversion into the desired Pictet−Spengler products **37a**−**b** when treated with TFA for 72 h (Table 6, entries 1−2). In further experiments, phenylalanine derivatives with more electron-withdrawing substituents, for example, nitro-, cyano-, and trifluoromethyl groups, were also attempted in the reaction. However, products resulting from cyclization of such deactivated rings were generally unstable and resisted proper characterization.

In addition to miscellaneously substituted phenyl moieties, fused aromatic rings systems should also be within the scope of the reaction, although literature reports on cyclizations of fused aromatic ring systems to *N*-acyliminium ions are scarce.[38,39] To test the idea, 1-naphthylalanine, 2-naphthylalanine, and 1-pyrenylalanine residues were incorporated between the masked aldehyde and glycine moieties via coupling procedures analogous to those depicted in Scheme 2. Following the methodology above, masked aldehyde substrates **41a**−**c** were treated with 10% TFA (aq) to afford the 5-hydroxylactams **42a**−**c**, and upon switching to nonaqueous reaction conditions in (TFA/CH_2Cl_2 (1:1)), the Pictet−Spengler cyclization was smoothly mediated, affording the products **43a**−**c** in excellent purity (>94%).

Conclusion

In summary, the scope of the solid-phase intramolecular *N*-acyliminium Pictet−Spengler reaction has been expanded. Whereas initial work focused on the utility of electron-rich

aromatic heterocycles, the present study demonstrates how a diverse range of phenylalanine derivatives smoothly participate in this process. Following a straightforward solid-phase approach, the reaction substrates are all readily available via standard peptide synthesis protocols, and the range of possible products may draw upon the large pool of aromatic amino acids available. Treatment of masked aldehyde substrates with aqueous TFA liberates the aldehyde, which is immediately condensed with the nitrogen amide backbone to form a cyclic 5-hydroxylactam. The latter species is in equilibrium with the corresponding *N*-acyliminium ion, and provided the presence of a neighboring, properly substituted, electron-rich phenylalanine residue, a subsequent quantitative Pictet−Spengler cyclization is mediated. The scope of the process is greatly expanded when changing from aqueous to nonaqueous reaction conditions. Formation of 5-hydroxylactams proceeds most cleanly with aqueous TFA, whereas subsequent Pictet−Spengler cyclization of phenyl rings devoid of electron-donating substituents only occurs in acidic organic solvents, such as 50% TFA in dichloromethane. A range of substitution patterns and substituents are tolerated on the aromatic ring, comprising hydroxy, chloro, bromo, fluoro, aryl, alkoxy, and alkyl moieties in the 2-, 3-, and 4-positions. The reaction was equally efficient for fused aromatic rings, such as pyrene and naphthalenes, incorporated in the peptide backbone as the aryl alanine derivatives.

The reaction provides a smooth and easy access to a range of pharmacologically interesting pyrroloisoquinolines. The constrained core structures built into peptide sequences seem ideally suited for combinatorial library synthesis, where key points of diversity may be provided by the nature and substituents of the aromatic ring undergoing the Pictet−Spengler cyclization, the amide backbone, and optional substituents on the applied masked aldehyde building blocks. The synthetic work was carried out on PEGA resins, which are highly useful for assays involving on-bead screening for biological activity and single bead analysis, for example, in one-bead two-compound assays.[40] Although the PEGA resin displayed some instability under harsh, aqueous acidic reaction conditions, presumably caused by hydrolysis of PEGA amide-bonds, it remained intact using the nonaqueous acidic reaction conditions generally used for Pictet−Spengler cyclization in this investigation. Combinatorial libraries based on the intramolecular *N*-acyliminium Pictet−Spengler reaction are currently being explored in on-bead screening for agonistic activity at G-protein coupled receptors, and the results will be reported in due course.

Experimental Section

Solid-Phase Synthesis. Attachment of the 4-hydroxymethylbenzoic acid (HMBA) linker to the amino-functionalized $PEGA_{800}$ (poly(ethylene glycol) dimethyl acrylamide, 0.3 mmol/g) resin was carried out by premixing 4-hydroxymethylbenzoic acid (HMBA, 3.0 equiv), *N*-ethyl morpholine (NEM, 4.0 equiv), and *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU, 2.88 equiv) for 5 min in DMF.[22] The resulting solution was added to the resin preswelled in DMF and allowed to react for 2 h, followed by washing with DMF (×6), and CH_2Cl_2 (×6). Coupling of the first amino acid (Gly) to the HMBA-derivatized resin was accomplished by treating the freshly lyophilized resin with a mixture of the Fmoc-Gly-OH (3.0 equiv), 1-methylimidazole (MeIm, 5.0 equiv), and 1-(mesitylene-2-sulfonyl)-3-nitro-1,2,4-triazole (MSNT, 3.0 equiv) in CH_2Cl_2.[23] The MSNT-mediated coupling was repeated once. Peptide synthesis and attachment of masked aldehyde building blocks to the amino-functionalized resin were subsequently accomplished following standard amino acid coupling procedures (Fmoc-AA-OH or *rac*-MABB1 (**13**), TBTU, NEM, DMF), as described above for the attachment of the HMBA linker. The usual washing protocol followed each coupling and deprotection step. Completion of the reaction was monitored using the Kaiser test. Fmoc-deprotection was accomplished with 20% piperidine in DMF, first for 2 min and then for 18 min, followed by washing with DMF (×6). Resin loading was determined by Fmoc cleavage and measurement of the optical density at 290 μm. Loadings were then calculated from a calibration curve. HRMS (ESI) analysis were generally performed on collected analytical RP-HPLC fractions.

General Procedure for Solid-Phase Synthesis of 5-Hydroxylactams. The solid-supported masked aldehyde substrate was swelled in 10% TFA (aq) and allowed to react for 2 h before being washed with water (×6), DMF (×6), and CH_2Cl_2 (×6). The resin was lyophilized overnight prior to cleavage of the reaction product from the solid support with amounts of 0.1 M NaOH (aq), sufficient to cover the resin, then it was neutralized with equimolar amounts of 0.1 M HCl (aq) and diluted with acetonitrile prior to RP-HPLC ananlysis.

Analytical Data for 5-Hydroxylactams. 5-Hydroxylactam from *rac*-MABB1-Phe-Gly-OH (15). Purity: >95%; R_t = 8.20, 8.52 min; MS (ESI) calcd for $C_{15}H_{18}N_2O_5Na$ $[M + Na]^+$ 329.1, found 329.1.

5-Hydroxylactam from *rac*-MABB1-(4-OMe)Phe-Gly-OH (25b). Purity: >95%; R_t = 8.01, 8.55 min; MS (ESI) calcd for $C_{16}H_{20}N_2O_6Na$ $[M + Na]^+$ 359.1, found 359.1.

5-Hydroxylactam from *rac*-MABB1-Tyr-Gly-OH (25d). Purity: >95%; R_t = 5.79, 6.57 min; MS (ESI) calcd for $C_{15}H_{18}N_2O_6Na$ $[M + Na]^+$ 345.1, found 345.1.

5-Hydroxylactam from *rac*-MABB1-(4-Me)Phe-Gly-OH (32a). Purity: >95%; R_t = 9.15, 9.55 min; MS (ESI) calcd for $C_{16}H_{20}N_2O_5Na$ $[M + Na]^+$ 343.1, found 343.1.

5-Hydroxylactam from *rac*-MABB1-(3-Me)Phe-Gly-OH (32b). Purity: >95%; R_t = 10.74, 11.05 min; MS (ESI) calcd for $C_{16}H_{20}N_2O_5Na$ $[M + Na]^+$ 343.1, found 343.1.

5-Hydroxylactam from *rac*-MABB1-(2-Me)Phe-Gly-OH (32c). Purity: >95%; R_t = 10.50, 10.80 min; MS (ESI) calcd for $C_{16}H_{20}N_2O_5Na$ $[M + Na]^+$ 343.1, found 343.1.

5-Hydroxylactam from *rac*-MABB1-(4-Ph)Phe-Gly-OH (32d). Purity: >95%; R_t = 12.20, 12.48 min; MS (ESI) calcd for $C_{21}H_{22}N_2O_5Na$ $[M + Na]^+$ 405.1, found 405.1.

5-Hydroxylactam from *rac*-MABB1-(4-azido)Phe-Gly-OH (32e). Purity: >95%; R_t = 9.56, 9.89 min; MS (ESI) calcd for $C_{15}H_{17}N_5O_5Na$ $[M + Na]^+$ 327.1, found 327.0.

5-Hydroxylactam from *rac*-MABB1-(4-amino)Phe-Gly-OH (32f). Purity: >95%; R_t = 12.12, 12.49 min; MS (ESI) calcd for $C_{15}H_{19}N_3O_5Na$ $[M + Na]^+$ 344.1, found 344.0.

5-Hydroxylactam from *rac*-MABB1-(2-F)Phe-Gly-OH (39a). Purity: >95%; R_t = 9.68, 9.99 min; MS (ESI) calcd for $C_{15}H_{17}FN_2O_5Na$ $[M + Na]^+$ 347.1, found 347.1.

5-Hydroxylactam from *rac*-MABB1-(2-Br)Phe-Gly-OH (39b). Purity: >95%; R_t = 10.92, 11.09 min; MS (ESI) calcd for $C_{15}H_{17}N_3O_5Na$ $[M + Na]^+$ 407.0, found 407.0.

5-Hydroxylactam from *rac*-MABB1-(4-Br)Phe-Gly-OH (39c). Purity: >95%; R_t = 11.54, 11.78 min; MS (ESI) calcd for $C_{15}H_{17}N_3O_5Na$ $[M + Na]^+$ 407.0, found 407.0.

5-Hydroxylactam from *rac*-MABB1-(4-I)Phe-Gly-OH (39d). Purity: >95%; R_t = 12.22, 12.45 min; MS (ESI) calcd for $C_{15}H_{17}IN_2O_5Na$ $[M + Na]^+$ 455.0, found 455.0.

5-Hydroxylactam from *rac*-MABB1-(4-Cl)Phe-Gly-OH (39e). Purity: >95%; R_t = 11.10, 11.32 min; MS (ESI) calcd for $C_{15}H_{17}ClN_2O_5Na$ $[M + Na]^+$ 363.1, found 363.1.

5-Hydroxylactam from *rac*-MABB1-(3-Cl)Phe-Gly-OH (39f). Purity: >95%; R_t = 11.14, 11.39 min; MS (ESI) calcd for $C_{15}H_{17}ClN_2O_5Na$ $[M + Na]^+$ 363.1, found 363.0.

5-Hydroxylactam from *rac*-MABB1-(3,4-dichloro)Phe-Gly-OH (39g). Purity: >95%; R_t = 12.53, 12.69 min; MS (ESI) calcd for $C_{15}H_{16}Cl_2N_2O_5Na$ $[M + Na]^+$ 397.0, found 397.0.

5-Hydroxylactam from *rac*-MABB1-(3,5-dibromo)Tyr-Gly-OH (39h). Purity: >95%; R_t = 10.34, 10.75 min; MS (ESI) calcd for $C_{15}H_{16}Br_2N_2O_6Na$ $[M + Na]^+$ 500.9, found 500.9.

5-Hydroxylactam from *rac*-MABB1-Nal(1)-Gly-OH (45a). Purity: >95%; R_t = 12.10, 12.31 min; MS (ESI) calcd for $C_{19}H_{20}N_2O_5Na$ $[M + Na]^+$ 379.1, found 379.1.

5-Hydroxylactam from *rac*-MABB1-Nal(2)-Gly-OH (45b). Purity: >95%; R_t = 12.27, 12.57 min; MS (ESI) calcd for $C_{19}H_{20}N_2O_5Na$ $[M + Na]^+$ 379.1, found 379.1.

5-Hydroxylactam from *rac*-MABB1-(1-pyrenyl)Ala-Gly-OH (45c). Purity: >95%; R_t = 14.90, 15.16 min; MS (ESI) calcd for $C_{25}H_{22}N_2O_5Na$ $[M + Na]^+$ 453.1, found 453.1.

General Procedure for Solid-Phase Intramolecular Pictet−Spengler Cyclization. The solid-supported 5-hydroxylactams were treated with acid (e.g., 50% TFA (CH_2Cl_2) or 10% H_2SO_4 in acetic acid) overnight before washing the resin with CH_2Cl_2 (×6), DMF (×6), water (×6), DMF (×6), and CH_2Cl_2 (×6). The resin was lyophilized overnight prior to cleavage of the reaction product from the solid support with 0.1 M NaOH (aq).

Analytical Data for Pictet−Spengler Reaction Products. [((5*S*,10b*R*)-3-Oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]-isoquinoline-5-carbonyl)amino]acetic Acid (20). Purity: >95%; R_t = 10.30 min; ^{1}H NMR (250 MHz, DMSO-d_6) δ 10.35 (bs, 1H), 8.36 (dd [app. t], J = 6 Hz, 1H), 7.20−7.14 (m, 4H), 4.94 (dd [app. t], J = 8 Hz, 1H), 4.75 (dd, J = 3 Hz, J = 7 Hz, 1H), 3.69 (d, J = 6 Hz, 2H), 3.18 (dd, J = 3 Hz, J = 16 Hz, 1H), 2.95 (dd, J = 7 Hz, J = 16 Hz, 1H), 2.76−2.55 (m, 2H), 2.30−2.20 (m, 1H), 1.83−1.68 (m, 1H); HRMS (ESI) calcd for $C_{15}H_{17}N_2O_4$ $[M + H]^+$ 289.1188, found 289.1178.

[((5*S*,10b*R*)-8,9-Dimethoxy-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carbonyl)amino]acetic Acid (27a). Purity: >95%; R_t = 9.68 min; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.27 (dd [app. t], J = 6 Hz, 1H), 6.73 (s, 1H), 6.72 (s, 1H), 4.87 (dd [app. t], J = 8 Hz, 1H), 4.78 (dd, J = 2 Hz, J = 7 Hz, 1H), 3.73 (2 × s, 6H), 3.67 (d, J = 6 Hz, 2H), 3.15 (dd, J = 2 Hz, J = 16 Hz, 1H), 2.85 (dd, J = 6 Hz, J = 15 Hz, 1H), 2.75−2.50 (m, 2H), 2.31−2.21 (m, 1H), 1.77−1.62 (m, 1H); HRMS (ESI) calcd for $C_{17}H_{21}N_2O_6$ $[M + H]^+$ 349.1400, found 349.1399.

[((5*S*,10b*R*)-9-Methoxy-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carbonyl)amino]acetic Acid (27b). Purity: >95%; R_t = 10.33 min; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.29 (dd [app. t], J = 6 Hz, 1H), 7.04−7.00 (m, 1H), 6.74−6.70 (m, 2H), 4.87 (dd [app. t], J = 8 Hz, 1H), 4.71 (dd, J = 3 Hz, J = 7 Hz, 1H), 3.68 (s, 3H), 3.63 (d, J = 6 Hz, 2H), 3.08 (dd, J = 3 Hz, J = 16 Hz, 1H), 2.82 (dd, J = 7, J = 16 Hz, 1H), 2.70−2.50 (m, 2H), 2.26−2.16 (m, 1H), 1.79−1.63 (m, 1H); HRMS (ESI) calcd for $C_{16}H_{19}N_2O_5$ $[M + H]^+$ 319.1294, found 319.1282.

Regioisomeric Mixture of Pictet−Spengler Reaction Products [((5*S*,10b*R*)-8-Methoxy-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carbonyl)amino]acetic Acid (27c) and [((5*S*,10b*R*)-10-Methoxy-3-oxo-1,2,3,5,6,-10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carbonyl)amino]acetic Acid (28c) (82:18). Purity: >95%, R_t = 10.60 (82%), 11.19 min (18%); ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.38 (dd [app. t], J = 6 Hz, 1H), 7.13 (t, J = 8 Hz, 0.18H), 7.09 (d, J = 9 Hz, 0.82H), 6.82 (d, J = 8 Hz, 0.18H), 6.79 (dd, J = 3 Hz, J = 9 Hz, 0.82H), 6.72 (d, J = 2 Hz, 0.82H), 6.70 (d, J = 8 Hz, 0.18H), 4.99−4.85 (m, 1.2 H), 4.74 (dd, J = 3 Hz, J = 7 Hz, 0.8H), 3.78−3.64 (m, 5H), 3.28−3.14 (m, 1H), 2.98−2.77 (m, 1H), 2.71−2.50 (m, 2H), 2.32−2.18 (m, 1H), 1.82−1.48 (m, 1H); HRMS (ESI) calcd for $C_{16}H_{19}N_2O_5$ $[M + H]^+$ 319.1294, found 319.1291.

[((5*S*,10b*R*)-9-Hydroxy-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carbonyl)amino]acetic Acid (27d). Purity: >95%; R_t = 8.20 min; ^{1}H NMR (250 MHz, DMSO-d_6) δ 9.30 (s, 1H), 8.28 (dd [app. t], J = 6 Hz, 1H), 6.89 (d, J = 8 Hz, 1H), 6.55 (dd, J = 2 Hz, J = 9 Hz, 1H), 6.53 (d, J = 2 Hz, 1H), 4.81 (dd [app. t], J = 8 Hz, 1H), 4.66 (dd, J = 3 Hz, J = 7 Hz, 1H), 3.65 (d, J = 6 Hz, 2H), 3.03 (dd, J = 3 Hz, J = 16 Hz, 1H), 2.79 (dd, J = 7, J = 15 Hz, 1H), 2.64−2.50 (m, 2H), 2.28−2.16 (m, 1H), 1.76−1.62 (m, 1H); HRMS (ESI) calcd for $C_{15}H_{17}N_2O_5$ $[M + H]^+$ 305.1137, found 305.1143.

[((5*S*,10b*R*)-8-Hydroxy-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carbonyl)amino]acetic Acid (27e). Purity: >95%, R_t = 6.92 min; ^{1}H NMR (250 MHz, DMSO-d_6) δ 9.28 (bs, 1H), 8.27 (dd [app. t], J = 6 Hz, 1H), 6.98 (d, J = 9 Hz, 1H), 6.63 (dd, J = 3 Hz, J = 9 Hz, 1H), 6.54 (d, J = 3 Hz, 1H), 4.84 (dd [app. t], J = 8 Hz, 1H), 4.70 (dd, J = 3 Hz, J = 7 Hz, 1H), 3.70 (d, J = 6 Hz, 2H), 3.08 (dd, J = 3 Hz, J = 16 Hz, 1H), 2.88 (dd, J = 7 Hz, J = 16 Hz, 1H), 2.66−2.51 (m, 2H), 2.32−2.20 (m, 1H), 1.80−1.68 (m, 1H); HRMS (ESI) calcd for $C_{15}H_{17}N_2O_5$ $[M + H]^+$ 305.1137, found 305.1138.

[((5*S*,10b*R*)-10-Hydroxy-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carbonyl)amino]acetic Acid (28e). Purity: >95%, R_t = 7.47 min; ^{1}H NMR (250 MHz, DMSO-d_6) δ 9.55 (bs, 1H), 8.25 (dd [app. t], J = 6 Hz, 1H), 6.95 (t, J = 8 Hz, 1H), 6.63 (d, J = 8 Hz, 1H), 6.54 (d, J = 8 Hz, 1H), 4.96−4.88 (m, 2H), 3.66 (d, J = 5 Hz, 1H),

3.64 (d, $J = 5$ Hz, 1H), 3.20 (d, $J = 16$ Hz, 1H), 2.88−2.71 (m, 2H), 2.61−2.50 (m, 1H), 2.27−2.17 (m, 1H), 1.64−1.47 (m, 1H); HRMS (ESI) calcd for $C_{15}H_{17}N_2O_5$ $[M + H]^+$ 305.1137, found 305.1133.

[((5*S*,10b*R*)-9-Methyl-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carbonyl)amino]acetic Acid (34a). Purity: >95%; $R_t = 11.48$ min; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.29 (dd [app. t], $J = 6$ Hz, 1H), 7.04−7.01 (m, 1H), 6.74−6.70 (m, 2H), 4.87 (dd [app. t], $J = 8$ Hz, 1H), 4.70 (dd, $J = 3$ Hz, $J = 7$ Hz, 1H), 3.68 (s, 3H), 3.64 (d, $J = 6$ Hz, 2H), 3.10 (dd, $J = 3$ Hz, $J = 16$ Hz, 1H), 2.85 (dd, $J = 7$ Hz, $J = 16$ Hz, 1H), 2.69−2.50 (m, 2H), 2.26−2.16 (m, 1H), 2.22 (s, 3H), 1.78−1.62 (m, 1H); HRMS (ESI) calcd for $C_{16}H_{19}N_2O_4$ $[M + H]^+$ 303.1345, found 303.1337.

[((5*S*,10b*R*)-8-Methyl-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carbonyl)amino]acetic Acid (34b). Purity: >95%; $R_t = 11.50$ min; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.31 (dd [app. t], $J = 6$ Hz, 1H), 7.04−6.95 (m, 3H), 4.86 (dd [app. t], $J = 8$ Hz, 1H), 4.71 (dd, $J = 3$ Hz, $J = 7$ Hz, 1H), 3.64 (d, $J = 6$ Hz, 2H), 3.10 (dd, $J = 3$ Hz, $J = 16$ Hz, 1H), 2.86 (dd, $J = 7$ Hz, $J = 16$ Hz, 1H), 2.67−2.50 (m, 2H), 2.25−2.15 (m, 1H), 2.20 (s, 3H), 1.75−1.60 (m, 1H); HRMS (ESI) calcd for $C_{16}H_{19}N_2O_4$ $[M + H]^+$ 303.1345, found 303.1336.

[((5*S*,10b*R*)-7-Methyl-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carbonyl)amino]acetic Acid (34c). Purity: >95%; $R_t = 11.36$ min; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.35 (dd [app. t], $J = 6$ Hz, 1H), 7.11−6.95 (m, 3H), 4.91 (dd [app. t], $J = 8$ Hz, 1H), 4.81 (dd, $J = 2$ Hz, $J = 7$ Hz, 1H), 3.66 (d, $J = 6$ Hz, 2H), 3.14 (dd, $J = 3$ Hz, $J = 17$ Hz, 1H), 2.80−2.51 (m, 3H), 2.26−2.21 (m, 1H), 2.16 (s, 3H), 1.71−1.60 (m, 1H); HRMS (ESI) calcd for $C_{16}H_{19}N_2O_4$ $[M + H]^+$ 303.1345, found 303.1342.

[((5*S*,10b*R*)-3-Oxo-9-phenyl-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carbonyl)amino]acetic Acid (34d). Purity: >95%; $R_t = 14.03$ min; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.38 (dd [app. t], $J = 6$ Hz, 1H), 7.62−7.59 (m, 2H), 7.44−7.19 (m, 6H), 4.98 (dd [app. t], $J = 8$ Hz, 1H), 4.78 (dd, $J = 3$ Hz, $J = 7$ Hz, 1H), 3.66 (d, $J = 6$ Hz, 2H), 3.21 (dd, $J = 3$ Hz, $J = 17$ Hz, 1H), 2.95 (dd, $J = 7$ Hz, $J = 16$ Hz, 1H), 2.80−2.69 (m, 1H), 2.63−2.51 (m, 1H), 2.29−2.20 (m, 1H), 1.87−1.70 (m, 1H); HRMS (ESI) calcd for $C_{21}H_{21}N_2O_4$ $[M + H]^+$ 365.1501, found 365.1495.

[((5*S*,10b*R*)-7-Fluoro-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carbonyl)amino]acetic Acid (40a). Purity: >95%; $R_t = 10.80$ min; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.36 (dd [app. t], $J = 6$ Hz, 1H), 7.27−7.18 (m, 1H), 7.03−6.96 (m, 2H), 4.96−4.87 (m, 2H), 3.66 (d, $J = 6$ Hz, 2H), 2.80−2.50 (4H, m), 2.30−2.19 (m, 1H), 1.75−1.59 (m, 1H); HRMS (ESI) calcd for $C_{15}H_{16}FN_2O_4$ $[M + H]^+$ 307.1094, found 307.1083.

[((5*S*,10b*R*)-7-Bromo-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carbonyl)amino]acetic Acid (40b). Purity: >95%; $R_t = 11.85$ min; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.36 (dd [app. t], $J = 6$ Hz, 1H), 7.48−7.45 (m, 1H), 7.21−7.11 (m, 2H), 4.96−4.86 (m, 2H), 3.66 (d, $J = 6$ Hz, 2H), 2.82−2.50 (4H, m), 2.30−2.20 (m, 1H), 1.74−1.58 (m, 1H); HRMS (ESI) calcd for $C_{15}H_{16}BrN_2O_4$ $[M + H]^+$ 367.0293, found 367.0291.

[((5*S*,10b*R*)-9-Bromo-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carbonyl)amino]acetic Acid (40c). Purity: >95%; $R_t = 12.10$ min; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.39 (dd [app. t], $J = 6$ Hz, 1H), 7.42−7.07 (m, 3H), 4.90 (dd [app. t], $J = 8$ Hz, 1H), 4.76 (dd, $J = 2$ Hz, $J = 7$ Hz, 1H), 3.64 (d, $J = 6$ Hz, 2H), 3.12 (dd, $J = 3$ Hz, $J = 17$ Hz, 1H), 2.95−2.50 (m, 3H), 2.26−2.17 (m, 1H), 1.79−1.63 (m, 1H); HRMS (ESI) calcd for $C_{15}H_{16}BrN_2O_4$ $[M + H]^+$ 367.0293, found 367.0285.

[((5*S*,10b*R*)-9-Iodo-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carbonyl)amino]acetic Acid (40d). Purity: >95%; $R_t = 12.67$ min; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.38 (dd [app. t], $J = 6$ Hz, 1H), 7.58−7.45 (m, 2H), 7.02−6.92 (m, 1H), 4.88 (dd [app. t], $J = 8$ Hz, 1H), 4.75 (dd, $J = 3$ Hz, $J = 7$ Hz, 1H), 3.65 (d, $J = 6$ Hz, 2H), 3.11 (dd, $J = 3$ Hz, $J = 17$ Hz, 1H), 2.84 (dd, $J = 7$ Hz, $J = 17$ Hz, 1H), 2.72−2.50 (m, 2H), 2.26−2.17 (m, 1H), 1.79−1.63 (m, 1H); HRMS (ESI) calcd for $C_{15}H_{16}IN_2O_4$ $[M + H]^+$ 415.0155, found 415.0150.

[((5*S*,10b*R*)-9-Chloro-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carbonyl)amino]acetic Acid (40e). Purity: >95%; $R_t = 11.74$ min; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.38 (dd [app. t], $J = 6$ Hz, 1H), 7.32−7.16 (m, 3H), 4.93 (dd [app. t], $J = 8$ Hz, 1H), 4.76 (dd, $J = 2$ Hz, $J = 7$ Hz, 1H), 3.64 (d, $J = 6$ Hz, 2H), 3.14 (dd, $J = 3$ Hz, $J = 17$ Hz, 1H), 2.95−2.50 (m, 3H), 2.27−2.17 (m, 1H), 1.81−1.61 (m, 1H); HRMS (ESI) calcd for $C_{15}H_{16}ClN_2O_4$ $[M + H]^+$ 323.0799, found 323.0791.

[((5*S*,10b*R*)-8-Chloro-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carbonyl)amino]acetic Acid (40f). Purity: >95%; $R_t = 11.73$ min; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.43 (dd [app. t], $J = 6$ Hz, 1H), 7.35−7.20 (m, 3H), 4.92 (dd [app. t], $J = 8$ Hz, 1H), 4.79 (dd, $J = 3$ Hz, $J = 7$ Hz, 1H), 3.69 (d, $J = 6$ Hz, 2H), 3.20 (dd, $J = 2$ Hz, $J = 17$ Hz, 1H), 2.94 (dd, $J = 7$, $J = 17$ Hz, 1H), 2.81−2.50 (m, 2H), 2.30−2.21 (m, 1H), 1.83−1.63 (m, 1H); HRMS (ESI) calcd for $C_{15}H_{16}ClN_2O_4$ $[M + H]^+$ 323.0799, found 323.0789.

[((5*S*,10b*R*)-8,9-Dichloro-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carbonyl)amino]acetic Acid (40g). Purity: >95%; $R_t = 13.08$ min; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.40 (dd [app. t], $J = 6$ Hz, 1H), 7.54 (s, 1H), 7.51 (s, 1H), 4.93 (dd [app. t], $J = 8$ Hz, 1H), 4.84 (dd, $J = 3$ Hz, $J = 7$ Hz, 1H), 3.70 (d, $J = 6$ Hz, 2H), 3.21 (dd, $J = 2$ Hz, $J = 16$ Hz, 1H), 2.92 (dd, $J = 7$, $J = 17$ Hz, 1H), 2.81−2.50 (m, 2H), 2.33−2.23 (m, 1H), 1.83−1.66 (m, 1H); HRMS (ESI) calcd for $C_{15}H_{15}N_2O_4$ $[M + H]^+$ 357.0409, found 357.0398.

[((5*S*,10b*R*)-8,10-Dibromo-9-hydroxy-3-oxo-1,2,3,5,6,-10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carbonyl)amino]acetic Acid (40h). Purity: >95%; $R_t = 10.83$ min; ^{1}H NMR (250 MHz, DMSO-d_6) δ 9.78 (s, 1H), 8.44 (dd [app. t], $J = 6$ Hz, 1H), 7.43 (s, 1H), 5.04−4.93 (m, 2H), 3.67 (d, $J = 6$ Hz, 2H), 3.20−3.05 (m, 2H), 2.90−2.50 (m, 2H), 2.31−2.21 (m, 1H), 1.66−1.50 (m, 1H); HRMS (ESI) calcd for $C_{15}H_{15}Br_2N_2O_5$ $[M + H]^+$ 460.9348, found 460.9345.

[((6*S*,10a*R*)-8-Oxo-5,6,8,9,10,10a-hexahydrobenzo[*f*]pyrrolo[2,1-*a*]isoquinoline-6-carbonyl)amino]acetic Acid (44a). Purity: >95%; $R_t = 12.79$ min; ^{1}H NMR (250 MHz, DMSO-

d_6) δ 8.43 (dd [app. t], J = 6 Hz, 1H), 7.96 (d, J = 8 Hz, 1H), 7.86 (dd, J = 1 Hz, J = 8 Hz, 1H), 7.77 (d, J = 9 Hz, 1H), 7.58−7.45 (m, 2H), 7.28 (d, J = 9 Hz, 1H), 5.12−5.02 (m, 2H), 3.82 (d, J = 17 Hz, 1H), 3.63 (dd, J = 2 Hz, J = 6 Hz, 2H), 3.06 (dd, J = 8 Hz, 17 Hz, 1H), 2.81−2.54 (m, 2H), 2.36−2.22 (m, 1H), 1.71−1.55 (m, 1H); HRMS (ESI) calcd for $C_{19}H_{19}N_2O_4$ $[M + H]^+$ 339.1345, found 339.1332.

[((5*S*,12b*R*)-3-Oxo-1,2,3,5,6,12b-hexahydrobenzo[*g*]pyrrolo[2,1-*a*]isoquinoline-5-carbonyl)amino]acetic Acid (44b). Purity: >95%; R_t = 12.38 min; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.47 (dd [app. t], J = 6 Hz, 1H), 7.99 (d, J = 8 Hz, 1H), 7.90 (d, J = 8 Hz, 1H), 7.74 (d, J = 8 Hz, 1H), 7.52 (m, 2H), 7.27 (d, J = 8 Hz, 1H), 5.61 (dd [app. t], J = 8 Hz, 1H), 5.06 (d, J = 7 Hz, 1H), 3.64 (d, J = 6 Hz, 2H), 3.15−3.00 (m, 2H), 2.82−2.65 (m, 2H), 2.34−2.26 (m, 1H), 1.72−1.52 (m, 1H); HRMS (ESI) calcd for $C_{19}H_{19}N_2O_4$ $[M + H]^+$ 339.1345, found 339.1342.

Pictet−Spengler Reaction Product of *rac*-MABB1-(1-pyrenyl)Ala-Gly-OH (44c). Purity: >95%; R_t = 15.46 min; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.59 (dd [app. t], J = 6 Hz, 1H), 8.37−8.25 (m, 4H), 8.18−8.02 (m, 4H), 5.45 (dd [app. t], J = 8 Hz, 1H), 5.06 (d, J = 6 Hz, 1H), 4.12 (d, J = 16 Hz, 1H), 3.71−3.68 (m, 2H), 3.54−3.40 (m, 1H), 3.02−2.91 (m, 1H), 2.81−2.67 (m, 1H), 2.42−2.32 (m, 1H), 2.02−1.85 (m, 1H); HRMS (ESI) calcd for $C_{25}H_{21}N_2O_4$ $[M + H]^+$ 413.1501, found 413.1495.

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Supporting Information Available. Crude analytical RP-HPLCs of 5-hydroxylactams **15**, **25b**, **25d**, **32a**−**f**, **39a**−**h**, and **45a**−**c** and crude ^{1}H NMR spectra and analytical RP-HPLCs of Pictet−Spengler products **20**, **27a**−**e**, **28c**, **28e**, **34a**−**d**, **40a**−**h**, and **44a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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