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Solid-Phase Synthesis of Tetrahydro-β-carbolines and Tetrahydroisoquinolines by Stereoselective Intramolecular *N*-Carbamyliminium Pictet–Spengler Reactions

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Abstract: A solid-phase method for the synthesis of tri-, tetra-, and pentacyclic compounds containing tetrahydro-β-carboline, tetrahydroisoquinoline or analogous scaffolds is presented. The reaction proceeds with high stereoselectivity through an intermediate *N*-carbamyliminium ion that exclusively converts into Pictet–Spengler-type products with a variety of C-nucleophiles. Amino aldehydes masked with 3-Boc-(1,3)-oxazinane (Box) have been synthesized from amino acids, amino alcohols, or 2-nitro benzaldehydes. The amino moiety of these masked aldehydes has been converted into pentafluorophenyl carbamate to serve as a urea precursor. The building blocks were incorporated at the *N*-terminal of a resin-supported dipeptide through urea formation. Subsequent treatment with acid liberated the aldehyde quantitatively. A penultimate tryptophan residue gave rise, under the acetic conditions, to a spontaneous intramolecular Pictet–Spengler reaction with the liberated aldehyde. The reaction proceeded with a high degree of stereoselectivity affording tetrahydro-β-carbolines with a *de* (*de* = diastereomeric excess) above 95% and purity in the range of 90–99%. This reaction has been extended to a range of other aromatic C-nucleophiles, including substituted indoles, benzenes, pyrene, furan, thiophenes, and benzothiophene with comparable stereoselectivity and purity. Prolonged exposure of the benzaldehyde-derived Pictet–Spengler products to strong acid and air lead to quantitative auto-oxidation which yielded compounds with a 3,4-dihydro-β-carboline, a 3,4-dihydroisoquinoline, or a similar core structure.

Keywords: C–C coupling · cyclization · intramolecular cascade reaction · solid-phase synthesis

Introduction

Compounds containing tetrahydro-β-carboline and tetrahydroisoquinoline core structures are of great pharmaceutical interest because of the inherent biological activity of a wide range of both alkaloids and synthetic mimics containing these scaffolds.[1] Among the alkaloids are woodinine,[2] eudistomins,[3–6] eudistomidins,[7] ecteinascidins, and saframycins[8] (Figure 1). Common for most of these alkaloids is an α-aminomethyl substituent at the tetrahydro-β-carboline or tetrahydroisoquinoline core structure.

These compounds are known for their antibiotic[3–6] and anticancer[7–10] properties and the most common method reported for generating these structures is through an intermolecular Pictet–Spengler reaction[11] between aldehydes and hetrocyclic β-ethyl amine derivatives.[8,12–16] The reported syntheses have generally afforded the desired products in acceptable yields, but with few exceptions, as mixtures of diastereomers. Development of a general method for diastereoselective synthesis of these core structures is therefore still a challenge. As a part of ongoing research within solid-phase synthesis, the chemistry of solid-supported aldehydes/ketones has been investigated[17–20] and versions of the Pictet–Spengler reaction in which both the formation of the intermediate *N*-acyliminium ion and the nucleophillic attack are intramolecular have recently been developed.[21–23] The number of reports on solid-phase intramolecular Pictet–Spengler reactions are limited, particularly within solid-phase synthesis. In contrast, the intermolecular Pictet–Spengler reaction in which the iminium ion is formed between two separate molecules has been extensively investigated and is known as one of nature's favored reactions prevalent

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Supporting information for this article contains ^{1}H NMR spectra for all compounds reported and HPLC chromatograms for all compounds synthesized by solid-phase synthesis and is available on the WWW under http://www.chemeurj.org/ or from the author.

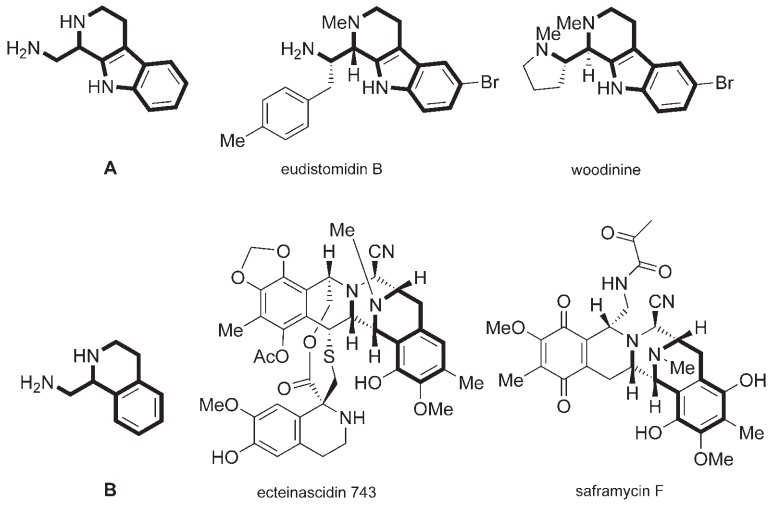
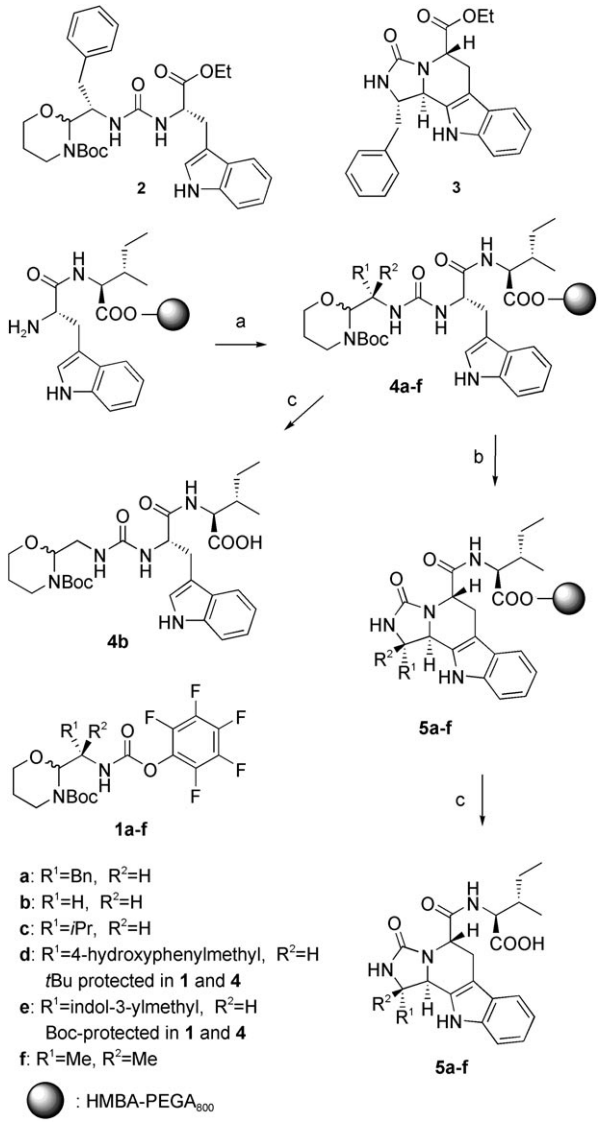


Figure 1. Natural products containing 1-aminomethyl tetrahydro-β-carboline (**A**) and tetrahydroisoquinoline (**B**) substructures.

in the biosynthesis of alkaloids.[24,25] The application of the reaction in the solid-phase synthesis of tetrahydro-β-carbolines and tetrahydroisoquinolines has also been reported as recently reviewed by the present authors.[26] These scaffolds are closely related to other small-constrained peptide mimetics, such as aryl-piperidines and indoles, known as privileged structures for G-protein coupled receptors (GPCR).[27] In our search for novel G-protein coupled receptor agonists that are peptide-derived small-molecules, the intramolecular Pictet–Spengler reaction is interesting, as it generates two new heterocyclic rings in one reaction step. This leads to tetrahydro-β-carbolines and tetrahydroisoquinolines with an additional heterocyclic ring and thereby may result in entropically favored constrained structures with higher activity and selectivity towards a given GPCR target. In the present report, we describe a versatile intramolecular Pictet–Spengler reaction. This reaction provides a facile and fast route from commercially available amino acids, amino alcohols, or nitrobenzaldehydes, to complex tri-, tetra-, and pentacyclic scaffolds by an *N*-carbamyliminium ion intermediate. The reaction proceeds with various sources of C-nucleophiles, thus providing a diverse range of pharmacologically interesting products in excellent stereoselectivity and purity.

Results and Discussion

The present methodology was initially developed for solution-phase reactions by coupling of tryptophan ethyl ester hydrochloride with a urea precursor building block containing a 3-Boc-1,3-oxazinane (Box) masked aldehyde **1a** (Scheme 1).[28] The reaction was performed in DMF by using 4-ethylmorpholine (NEM) for neutralization of the hydrochloride. This cleanly afforded the unsymmetrical urea, **2** in an 85% isolated yield and no major byproduct was detected. The masked aldehyde was then liberated by 10% TFA (TFA = trifluoroacetic acid) in acetonitrile/H_2O. Almost instantaneously, the acid removed the Boc-protecting group and hydrolyzed the 1,3-oxazinane, which gave the free aldehyde. This was followed by intramolecular formation of the *N*,*O*-acetal and acid-promoted elimination of water afforded the highly reactive *N*-carbamyliminium ion, which upon nucleophilic attack by the indole formed the Pictet–Spengler product **3** containing an α-amino methyl tetrahydro-β-carboline skeleton.



Scheme 1. Solid-phase intramolecular Pictet–Spengler reaction with tryptophan: a) **1a–f**; b) TFA (10%, aq); c) NaOH (0.1 M, aq).

The Pictet–Spengler product was obtained in a 92% yield with exclusive formation of the *R* diastereomer.

The mild, quantitative, and stereoselective nature of this reaction prompted for further investigation into the use in solid-phase combinatorial chemistry. Here the reaction could be exploited in combination with highly refined techniques for solid-phase peptide synthesis to generate valuable and diverse small molecule compound collections and split-mix libraries. Libraries of such natural product like compounds have in recent years gained interest as a source of novel drug candidates.[29,30]

Polyethylene glycol acryl amide copolymer (PEGA) resin[31] was selected as the solid-support due to excellent swelling in polar solvents, such as dilute aqueous acid, which was employed during the synthesis. The amino groups of the resin were functionalized with a base-labile HMBA linker[32] (HBMA = hydroxymethylbenzamide) by using TBTU[33] (TBTU = *N*-[(1*H*-benzotriazol-1-yl)-(dimethylamino)methylene]-*N*-methylmethanaminium tetrafluoroborate *N*-oxide) and NEM. The first Fmoc-protected amino acid was esterified to the linker by using MSNT and *N*-methylimidazole.[34] A second amino acid was attached by standard Fmoc-peptide coupling by using TBTU and NEM providing a solid-supported dipeptide.

The pentafluorophenyl carbamate[35–37] building blocks **1a–f**[28] were coupled to the N-terminal of a resin bound Trp-Ile dipeptide by adding three equivalents in DMF. Studies of the coupling reaction showed considerable variation in the rate of reaction; however, after 12 h the reactions were all complete. Addition of DIPEA (DIPEA = diisopropylethylamine) or DMAP (DMAP = 4-dimethylaminopyridine) did not catalyze the reaction significantly. The purities of the crude products **4a–f** were ≈95% as analyzed by HPLC after release from the support. For **4b** the purity was confirmed by ^{1}H NMR spectroscopy.

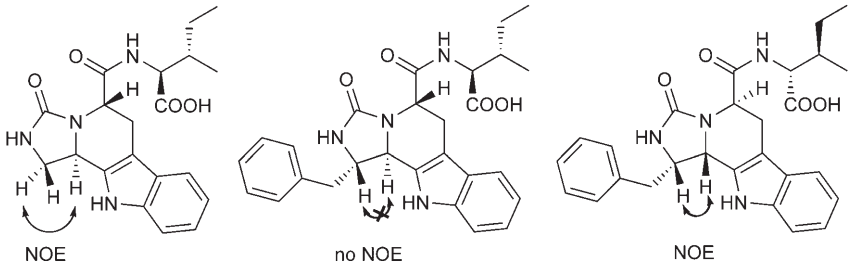
Table 1. Acid concentrations and reaction times for the Pictet–Spengler reaction of **5b**.

Entry	Concentration of TFA [%]	Reaction time [h]	Products **5a**/hemiacetal/other [%][a]
1	0.1	2	89:11:0
2	1	2	36:62:2
3	1	12	0:>95:<5
4	10	2	0:>95:<5
5	95	5	0:>95:<5

[a] The major byproducts were the *S* diastereomer of **7b** and 1,4-substituted imidazolone.

The deprotection and Pictet–Spengler reaction were initially successfully performed by using 10% aqueous TFA. Various acids, acid concentrations, and solvents as well as reaction times were studied. TFA, aqueous HCl (1 N), and aqueous H_2SO_4 (1 N) all performed well in this reaction yielding products with more than 95% purity. Lewis acids, such as $BF_3{\cdot}OEt_2$ or $TiCl_4$ in dichloromethane also yielded the desired product; however, with a slightly lower purity of approximately 85%. The reaction only showed little dependence of the solvent and 10% TFA in MeOH, DMF, THF, acetone, EtOAc, acetonitrile, dichloromethane, toluene, or hexane all gave more than 90% pure product. Application of different concentrations of TFA (Table 1) demonstrated that as little as 1% aqueous TFA could complete the reaction in 12 h. Furthermore, the formed products were found to be stable to prolonged exposure to high concentrations of TFA.

Aqueous TFA (10%) for 1 h was selected as a standard condition for the deprotection and Pictet–Spengler reaction. The six different resin-bound compounds **4a–f** all yielded the expected products **5a–f** with 90–95% purity (Scheme 5 and Table 3). Products containing a side-chain-protecting group **5d–e** were subsequently treated twice with 95% aqueous TFA for 15 min for complete side-chain deprotection before cleavage from the resin. The stereoselectivity is controlled by the transition state of the reaction and was found to be more than 20:1, independent of the selection of building block. The stereochemistry of the products has been determined by NOE studies and by using both L- and D-amino acids in the reactions (Figure 2).

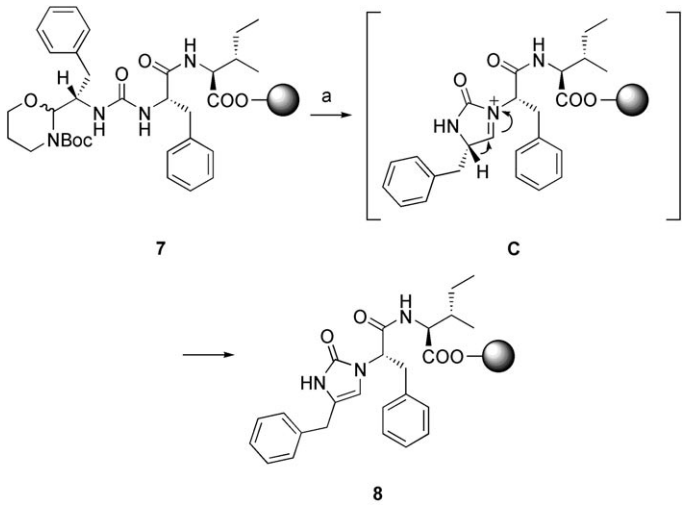


8b **8a** **9**

Figure 2. Elucidation of the stereochemistry by NOE.

In analogy with intramolecular reactions involving *N*-acyliminium ions,[21] the new stereocenter gained the *trans* configuration relative to the configuration of the tryptophan giving rise to either (α-*S*, γ-*R*)- or (α-*R*, γ-*S*)-tetrahydro-β-carboline derivatives.

Imidazolidin-2-one fused Pictet–Spengler products has only been reported for the intramolecular reaction of α,α-disubstituted α-amino aldehydes because the intermediate iminium ions are prone to elimination of an α proton and double bond rearrangement to yield the enamine.[38] In the present investigation, this conversion was also observed when tryptophan was replaced by less reactive phenylalanine as the C-nucleophile **7** (Scheme 2). In preference to reaction with less reactive nucleophiles, the iminium ion **C** rearranges with α-proton abstraction and quantitatively af-



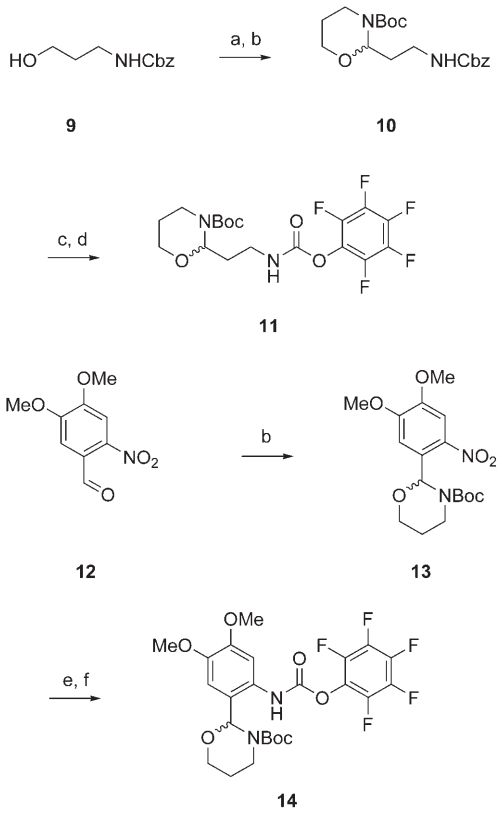
Scheme 2. Formation of imidazolones as a competing reaction in the presence of poor C-nucleophiles and labile α-protons: a) 10% TFA (aq).

fords the uncharged 1,4-substituted imidazolone **8**. Detailed analysis of the crude products of the Pictet–Spengler reaction with more reactive tryptophan **5a–f** showed that the corresponding 1,4-substituted imidazolone was formed as a byproduct in minute amounts by this competing reaction pathway (0–5%). The 1,4-substituted imidazolone is in itself an interesting heterocycle and further investigations on the rearrangement reaction will be reported subsequently.

To extend the scaffold diversity, it was attempted to form two fused six-membered rings (Schemes 4 and 5) in the intramolecular Pictet–Spengler reaction, instead of the five/six-membered bicyclic ring system. Only a few examples of such products have previously been reported.[39–41] The reaction could be accomplished with both aliphatic and aromatic urea building blocks containing Box-protected aldehyde.

Thus 3-aminopropanal building block (ApaBB-OPfp) **11** (Scheme 3) was synthesized from *N*-Cbz-3-amino-1-propanol (**9**)[42] by oxidation with Dess–Martin periodane (DMP) and masking the formed aldehyde by reacting the crude product with 3-amino-1-propanol and sodium sulfate followed by reaction with Boc-anhydride to give 74% overall yield of **10**. The Cbz group was then removed with Pd/C and H_2 and the crude product was reacted with bispentafluorophenylcarbonate affording ApaBB-OPfp **11** in an isolated yield of 82% with no formation of the symmetric urea product.

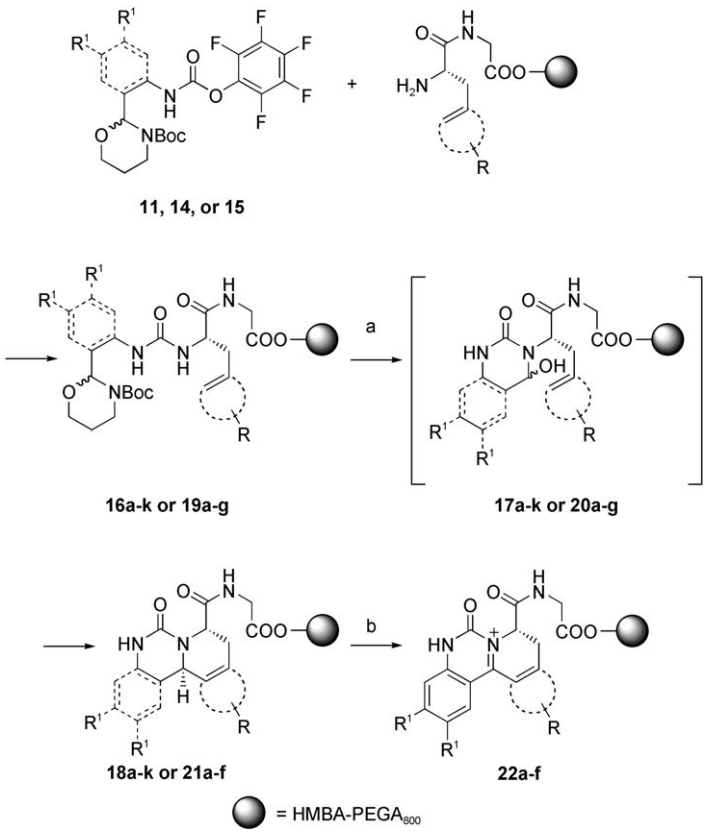
In addition to compound **11**, two 3-Boc-(1,3)-oxazinane (Box) masked 2-amino-benzaldehyde building blocks were synthesized (Scheme 3). The synthesis of the nonsubstituted building block (ApaBB-OPfp) **15** has previously been described[28] and the 4,5-dimethoxy-2-nitro-benzaldehyde derived building block (DMApaBB-OPfp) **14** was synthesized in three steps in a similar manner (Scheme 3). The starting material **12** was protected with the Box-protecting group by reaction with 3-amino-1-propanol and sodium sulfate followed by reaction with Boc-anhydride. This provided 40–70% of compound **13** depending on reaction temperature



Scheme 3. Synthesis of 3-aminopropanal and 2-amino-3,4-dimethoxybenzaldehyde building blocks: a) DMP; b) 3-aminopropanol and Na_2SO_4 then Boc_2O; c) 10% Pd/C, H_2 (1 atm); d) bispentafluorophenyl carbonate; e) 10% Pd/C, H_2 (1 atm), DMAP; f) bispentafluorophenyl carbonate, DMAP.

and timing of reagent addition. The nitro group was hydrogenated in the presence of DMAP as basic conditions were crucial for the stability of the Box-group. The crude product containing DMAP required for catalysis was converted into the pentafluorophenyl carbamate by reaction with bispentafluorophenyl carbonate in 79% overall yield.

The Pictet–Spengler reaction is known to proceed with a range of aromatic heterocycles.[25] To investigate the reactivity of compounds **11**, **14**, and **15**, less prone to elimination of the α proton in the Pictet–Spengler reactions, a series of dipeptides with a terminal β-aryl alanine residue were synthesized on solid support as described above. Compound **11** (ApaBB-OPfp) was coupled to the N-terminus of these peptides under the same conditions as described in Scheme 1. These reactions provided the unsymmetrical ureas **16a–k** (Scheme 4) with purities >95% after cleavage from the resin. Application of 10% aqueous TFA for 1 h liberated the aldehyde, which subsequently underwent Pictet–Spengler reaction with various intramolecular nucleophiles including indole, benzothiophene, and 3-thiophene (**18a–e**) (Schemes 4, 5, and Table 3). In these cases, the deprotection of the aldehyde was the rate-limiting step. With weaker nucleophiles, such as 2-thiophene, furan, and phenyl derivatives the *N,O*-acetal intermediate could be isolated (**17f–k**,



Scheme 4. Pictet–Spengler reaction with 2-amino-benzaldehyde building blocks and oxidation. a) 10–100% TFA (aq); b) Air, TFA (100%) (Table).

Schemes 4 and 5). However, these intermediates could be fully converted to the Pictet–Spengler products by applying more acidic conditions (Table 3). By using optimized TFA concentrations all Pictet–Spengler products were formed within 1 h in 90–99% purity and with a *de* of more than 90% (Table 3).

The 2-amino-4,5-dimethoxy-benzaldehyde (DMAba-OPfp) building block **14** and 2-amino-benzaldehyde (AbaBB-OPfp) **15** were successfully coupled to the N-terminal of the solid-supported dipetide (Scheme 2) The reaction afforded the Pictet–Spengler precursor **19a–h** with the same high purity and similar coupling rates as for the aliphatic amino aldehydes.

During deprotection with various acid concentrations (Table 2) it was demonstrated that the 3-Boc-1,3-oxazinane-masked benzaldehydes were indeed highly acid labile and as little as 0.1% TFA (aq) liberated the aldehyde completely within 1 h.

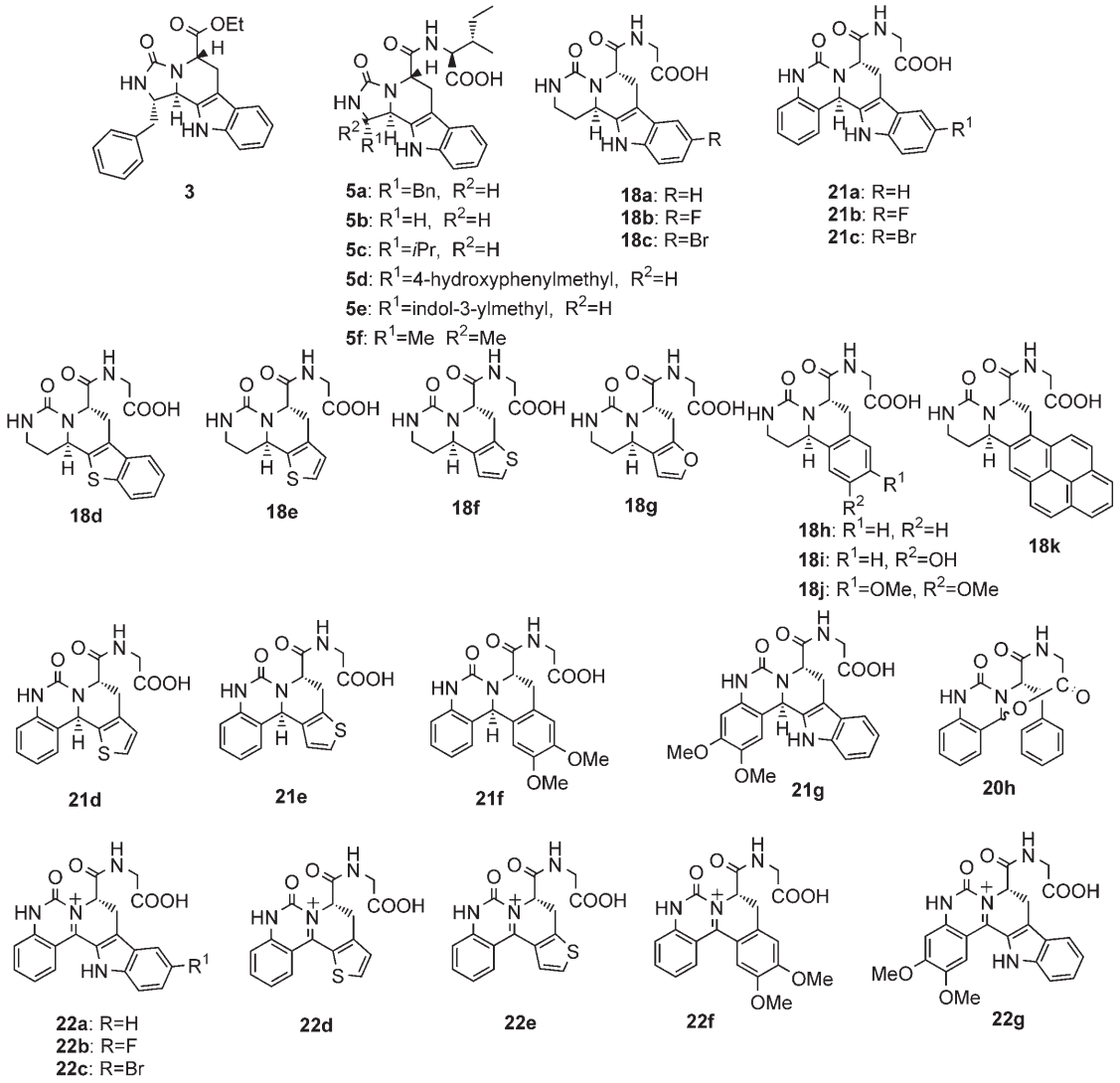
Various C-nucleophiles were tested in this reaction and the indole, thiophene, and 3,4-dimethoxy-phenyl all worked well in this reaction to form only one diastereomer (Scheme 5 and Table 3). The conjugated carbamyliminium ions formed from **20a–h** were found to be less reactive compared to the nonconjugated carbamyliminium ions (from **17a–k**, Scheme 5) and in case of **20e, 20f**, and **20h** the acetal intermediate could be cleaved off the resin and isolated. This observation was also supported by the reaction with the nonsubstituted phenyl group in which only the cyclic acetal (**20h**) could be isolated, even after treatment with 100% TFA for 24 h (Table 3).

Interestingly, prolonged treatment of Pictet–Spengler products **21a–g** derived from the AbaBB and DMAbaBB with 95% TFA (aq) in the presence of oxygen (air) lead to oxidation of the newly formed stereocenter, which yielded **22a–g** as the only products. These products all had an intense color varying from yellow to deep red and were stable to further oxidation. The oxidation of, for example, **21a** to **22a** results in loss of two mass units in high resolution ESI-MS and the loss of the benzylic proton at 6.12 ppm. The spectrophotometric properties of these oxidized products are currently being investigated and are subject to future publication. It was found that the electronic nature of the C-nucleophile, the access to oxygen, and the acidity influenced the oxidation reaction. The indole-derived Pictet–Spengler products **21a–c** were oxidized in less than 5 h, whereas the dimethoxyphenyl product **21f** needed 7 d for completion of the reaction under the same conditions. The reaction rate was greatly enhanced by adding just 1% H_2O_2 to the acid and in this case only 50% TFA was needed to convert **21a** within 1 h. However, prolonged reaction times under these conditions led to decomposition. The reversible reaction was easily accomplished by adding excess of sodium borohydride in DMF with 5% AcOH which gave rise to **21a** from **22a** in about 80% *de* within 5 min.

To the best of our knowledge, the acid-promoted air oxidation of this type of Pictet–Spengler products has not been previously reported as a synthetic reaction; however, a recent report described an oxidized Pictet–Spengler product formed by degradation during storage of an NMR sample.[43] A mechanism for the oxidation may be suggested in which electrophilic oxygen reacts with π-electrons at the 3-position of the indole, assisted by the indole nitrogen followed by formation and elimination of an intermediate oxirane and concurrent elimination of a proton from the benzylic stereocenter formed in the Pictet–Spengler reaction (Scheme 6). The lone pair of the β-nitrogen in the tetrahydro-β-carboline then displaces the formed double bond, which rearranges to form the indole while expelling the oxygen at the 3-position. Stabilization of intermediates similar to that by indole can occur in all the compounds prone to oxidation. However, it should be noted that in the non-oxidizing compounds synthesized from the aliphatic building block **11** that do not contain the benzylic proton no trapping of expected oxirane intermediates could be observed.

Conclusion

We have demonstrated the versatile chemistry of using amino aldehyde building blocks in the *N*-carbamyliminium-ion-mediated intramolecular Pictet–Spengler reaction. This chemistry has led to imidazolidin-2-one fused tetrahydro-β-



Scheme 5. Pictet–Spengler products obtained through acid-catalyzed intramolecular cascade reactions involving intramolecular formation of peptidic *N*-carbamyliminium ions.

carbolines with formation of a five and a six-membered ring in a single reaction. New amino aldehyde building blocks containing 3-Boc-1,3-oxazinane (Box) masking of the aldehyde, and a pentaflourophenyl carbamate moiety could be synthesized from *N*-Cbz-3-aminopropanol and of 3,4-di-methoxy-2-nitro-benzaldehyde in overall yields of 61 and 55% respectively. These two new amino aldehyde building blocks have expanded the scope of the intramolecular version of the Pictet–Spengler reaction and given easy access to tetrahydro-β-carbolines, tetrahydroisoquinolines, and analogues fused with tetrahydropyrimidin-2-one or 1,6-dihydropyrimidin-2-one.

With only one exception, all solid-phase reactions afforded products with 90–99% purity and with a stereoselectivity above 95% *de*. Furthermore, we have demonstrated that electron-rich Pictet–Spengler products are prone to oxidation by a novel acid promoted electrophilic oxygenation. The oxidation proceeds in a quantitative manner and yields colored/fluorescent compounds with a 3,4-dihydro-β-carboline, 3,4-dihydro-isoquinoline, or analogue core structures.

Experimental Section

General aspects: All purchased chemicals were used without further purification. All solvents were HPLC grade. $PEGA_{800}$ resin was from VersaMatrix A/S. All washing steps were performed for a period of 2 min unless stated differently. Flash chromatography was carried out on Merck silica gel 60 (0.040–0.063 mm) and analytical TLC was performed by using Merck silica gel 60 F254 aluminum plates. NMR spectra were recorded on a Bruker AVANCE DPX 250 MHz instrument. $CDCl_3$, CD_3OD, and $[D_6]$DMSO were used as internal standards (7.26, 3.31, and 2.50 ppm for ^1H and 77.0, 49.00, and 39.52 ppm for ^{13}C NMR). High-resolution MS was determined with a Micromass QTOF Global Ultima instrument by using an appropriate internal reference. All reported oxinanes were mixtures of the *R* and *S* isomers at the chiral center of the oxinane ring. Purities of crude materials were accessed by a combination of HPLC and ESIMS to identify all byproducts. The integration of peaks

Table 2. Products formed from **23a** in the presence of air under various conditions.

Entry	Concentration of TFA (aq) [%]	Reaction time [h]	**19a**/**21a**/**22a** [%]
1	0.1	0.16	42:58:0
3	10	0.25	0:100:0
3	10	24	0:90:10
4	95	2	0:71:29
5	95	5	0:0:100
6	50 (+1% H_2O_2)	1	0:0:100
7	10 (then 10% H_2O_2)	0.25 (then 0.5 h)	0:100:0

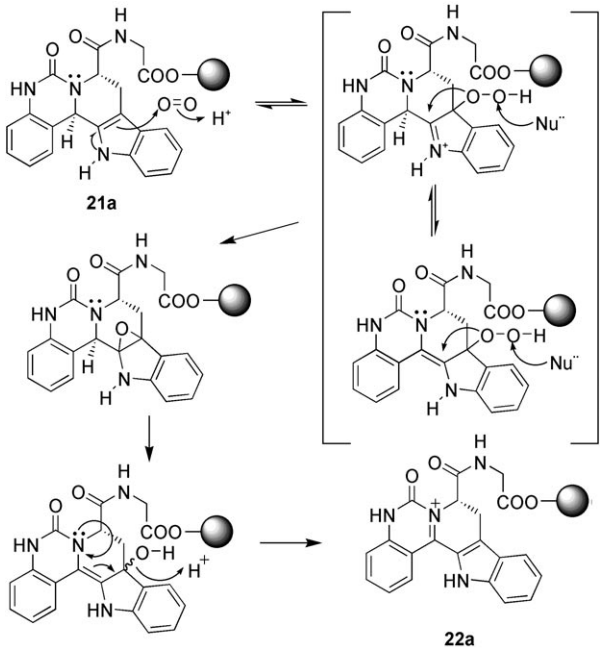
Table 3. Products, conditions, reaction times, and purities/yields for compounds in Scheme 5.

Product	Building block	Conditions (% aq TFA)	Reaction time [h]	Yield[a]/ purity[b] [%]
3	**1a**	10	2	92[a]
5a	**1a**	10	1	92[b]
5b	**1b**	10	1	90[b]
5c	**1c**	10	1	90[b]
5d	**1d**	10	1	92[b]
5e	**1e**	10	1	95[b]
5f	**1f**	10	1	95[b]
18a	**14**	10	1	94[a]
18b	**14**	10	1	>95[b]
18c	**14**	10	1	>95[b]
18d	**14**	10	1	>95[b]
18e	**14**	95	1	>95[b]
18f	**14**	50	1	>95[b]
18g	**14**	95	1	>95[b]
18i	**14**	95	1	>95[b]
18j	**14**	95	1	>95[b]
18k	**14**	95	1	95[b]
20h	**21**	TFA	24	95[b]
21a	**21**	10	2	>95[b]
21b	**21**	10	2	>95[b]
21c	**21**	10	2	>95[b]
21d	**21**	10	2	>95[b]
21e	**21**	95	0.5	>95[b]
21f	**21**	95	2	95[b]
21g	**20**	10	1	70[b,c]
22a	**21**	95/air	5	>95[b]
22b	**21**	95/air	5	>95[b]
22c	**21**	95/air	5	>95[b]
22d	**21**	95/air	120	>95[b]
22e	**21**	95/air	120	>95[b]
22f	**21**	95/air	168	>95[b]
22g	**20**	95/air	5	95[b]

[a] The yield was determined as the yield of isolated pure compound. [b] The purity of the crude product determined by HPLC, ESIMS, and NMR spectroscopy. [c] The remaining ≈30% was the oxidized form (**22g**) and several attempts to isolate the pure **21g** failed. Compounds **19g** and/or **22g** were found as major impurities in all cases.

was used for the determination of purity (±2%) with the assumption that identical chromophores have approximately the same extinction coefficient as determined from selected purified samples. Purities were confirmed by ^{1}H NMR spectroscopy (see Supporting Information).

PheBB-Trp-OEt (2-(1-{3-[1-ethoxycarbonyl-2-(1*H*-indol-3-yl)-ethyl]-ureido}-2-phenyl-ethyl)-[1,3]oxazinane-3-carboxylic acid *tert*-butyl ester) (2): PheBB-OPfp **1a** (105 mg, 203 μmol) was added to a solution of TrpOEt·HCl (54.6 mg, 203 μmol) and NEM (26 μL, 203 μmol) in DMF (2 mL). After stirring for 12 h at RT, the solvent was removed in vacuo at 40 °C and the crude product was purified by flash chromatography by using ethyl acetate/petroleum ether 1:1. The product **2** (98 mg, 85%) was



Scheme 6. Proposed mechanism for oxidation reaction. Similar stabilization can be realized to various degrees for the intermediates obtained during oxidation to form **26b**–**26g**.

obtained as colorless glassy foam. ^{1}H NMR (250 MHz, $CDCl_3$): δ=8.50 (s, 0.5H), 8.3 (s, 0.5H), 7.53 (d, J=7.0 Hz, 1H), 7.41–7.01 (m, 8H), 6.94 (d, J=7.9 Hz, 1H), 5.27–5.06 (m, 1H), 4.91–4.62 (m, 2H), 4.27–3.51 (m, 6H), 3.39–2.59 (m, 6H), 2.01–1.51 (m, 2H), 1.49 (s, 4.5H), 1.34 (s, 4.5H), 1.26–1.09 ppm (m, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=136.8, 129.9, 129.8, 129.5, 129.3, 128.3, 127.6, 126.3, 124.7, 123.4, 122.2, 121.9, 119.6, 119.3, 118.5, 118.3, 111.2, 110.7, 61.4, 59.6, 59.3, 49.9, 37.5, 37.0, 36.5, 32.9, 28.4, 28.2, 27.9, 24.9, 23.6, 14.1, 14.0 ppm; HRMS: m/z: calcd for $C_{31}H_{41}N_4O_6$: 565.3021 $[M+H]^+$; found: 565.3027.

Pictet–Spengler reaction of PheBB-Trp-OEt (1-benzyl-3-oxo-2,3,4,5,10,10b-hexahydro-1*H*-2,3a,10-triaza-cyclopenta[*a*]fluorene-4-carboxylic acid ethyl ester, (3)): 50% TFA (2 mL, aq) was added to a solution of PheBB-Trp-OEt **2** (66 mg, 117 μmol) in acetonitrile (10 mL). After reaction for 2 h, the mixture was neutralized with solid $NaHCO_3$, filtered by using acetonitrile for washing, and the solvent was removed in vacuo. The crude product was purified by RP-HPLC and the product **3** (42 mg, 92%) was obtained as a colorless glass film. ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.58–7.45 (m, 3H), 7.45–7.32 (m, 3H), 7.30–7.16 (m, 1H), 7.15–6.98 (m, 2H), 6.90 (d, J=7.2 Hz, 1H), 5.82 (brs, 1H), 5.25 (brs, 1H), 5.22–5.04 (m, 2H), 4.23–3.88 (m, 3H), 3.44–3.21 (m, 2H), 3.18–2.95 (m, 2H), 1.21 ppm (t, J=7.1 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ= 173.4, 161.0, 136.5, 129.9, 129.7, 129.0, 127.8, 122.4, 119.7, 118.3, 110.8, 106.3, 61.5, 60.0, 55.6, 50.1, 42.2, 23.6, 14.1 ppm; HRMS: m/z: calcd for $C_{23}H_{24}N_3O_3$: 390.1812 $[M+H]^+$; found: 390.1830.

Solid-phase synthesis of Pictet–Spengler products and related products: Dry $PEGA_{800}$ resin (50–150 mg, 0.30–0.38 mmol g^{-1}, 15–57 μmol) derivatized with the HMBA linker and dipeptide (e.g. **6**) was swelled in DMF. The building block-OPfp ester (3.0 equiv) (**1a–f**, **11**, **14**, or **15**) was dissolved in DMF (10 μL mg^{-1} resin) and the solution was added to the resin. After 12 h, the resin was washed with DMF (6×), dichloromethane (6×), and lyophilized. The dry $PEGA_{800}$ resin with HMBA linker, peptide, and building block attached (**4a–f**, **7**, **16a–k**, or **19a–h**) was swelled in 10% TFA (aq, 1 h). The resin was washed with 10% TFA (aq, 2×). Further reaction with TFA was applied when necessary to complete conversion or side-chain deprotection (see below). The resin was then washed with H_2O until the eluate had a pH 5–7. It was then washed with DMF (6×), dichloromethane (6×), and lyophilized. The compound was cleaved from the resin by swelling the dry $PEGA_{800}$ resin with HMBA

linker and compound attached in NaOH (aq, 0.1 M) (10 μL mg^{-1} resin). After 2 h, HCl (aq, 0.1 M) was used for neutralization. The resin was extracted with H_2O (×2) and acetonitrile/H_2O 70:30 (×2). The solvent from the extract was removed in a speedvac giving the crude product (**5a–f**, **6**, **8**, **18a–k**, **20h**, or **21a–g**) as a solid salt with a white to orange color. Yield was in the range of 63–94%.

GlyBB-Trp-Ile-OH (4b): Compound **4b** was synthesized and cleaved as described above, with no TFA treatment applied. Purity >95%; ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ=10.78 (s, 1H), 7.51 (d, 7.7 Hz, 1H), 7.36–7.24 (m, 1H), 7.07 (s, 1H), 7.03 (t, J=8.0 Hz, 1H), 6.93 (t, J=7.9 Hz, 1H), 6.27–6.14 (m, 2H), 5.20 (t, J=6.8 Hz, 1H), 4.34 (m, 1H), 3.93–3.70 (m, 2H), 3.67–3.42 (m, 2H), 3.38–2.99 (m, 3H), 2.98 (dd, J=7.0 and 14.8 Hz, 1H), 1.79–0.98 (m, 13H), 0.80 (t, J=7.4 Hz, 3H), 0.68 ppm (dd, J=2.3 and 6.8, 3H); ^{13}C NMR (62.5 MHz, [D$_6$]DMSO): δ=172.8, 170.4, 161.7, 157.4, 153.4, 136.0, 127.6, 123.5, 120.7, 118.5, 118.1, 111.1, 110.2, 80.5, 79.3, 59.6, 58.5, 54.5, 37.7, 37.4, 27.9, 25.3, 24.8, 15.7, 12.2 ppm; HRMS: m/z: calcd for $C_{28}H_{42}N_5O_7$: 560.3079 [M+H]$^+$; found: 560.3077.

Pictet–Spengler product from PheBB-Trp-Ile-HMBA-PEGA$_{800}$ (5a): Purity >95%; ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ=10.79 (s, 1H), 8.02 (d, J=8.3 Hz, 1H), 7.42–7.20 (m, 7H), 7.12–6.91 (m, 3H), 4.88–4.79 (m, 1H), 4.08 (dd, J=6.4, 8.2 Hz, 1H), 3.98–3.88 (m, 1H), 3.21–2.99 (m, 3H), 2.90–2.75 (m, 1H), 1.90–1.73 (m, 1H), 1.49–1.30 (m, 1H), 1.26–1.04 (m, 1H), 0.88–0.69 ppm (m, 6H). ^{13}C NMR (62.5 MHz, [D$_6$]DMSO): δ= 173.0, 170.8, 160.7, 137.7, 136.2, 131.8, 129.5 128.4, 126.6, 126.4, 121.3, 118.7, 117.8, 111.2, 105.9, 56.5, 56.2, 55.2, 50.5, 41.1, 35.9, 25.0, 21.0, 15.6, 11.1 ppm; HRMS: m/z: calcd for $C_{27}H_{31}N_4O_4$: 457.2340 [M+H]$^+$; found: 457.2373.

Pictet–Spengler product from GlyBB-Trp-Ile-HMBA-PEGA$_{800}$ (5b): Purity >95%; ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ=12.64 (brs, 1H), 10.92 (s, 1H), 8.09 (d, J=8.0 Hz, 1H), 7.43–7.23 (m, 2H), 7.12–6.86 (m, 2H), 6.86 (s, 1H), 5.24–5.09 (m, 1H), 4.84 (d, J=7.2 Hz, 1H), 4.12 (dd, J=6.5 and 8.4 Hz, 1H), 3.77 (t, J=8.9 Hz, 1H), 3.41 (dd, J=3.4 and 8.8 Hz, 1H), 3.17 (d, J=13.9 Hz, 1H), 2.92–2.74 (m, 1H), 1.91–1.71 (m, 1H), 1.48–1.27 (m, 1H), 1.27–1.01 (m, 1H), 0.87–0.71 ppm (m, 6H). ^{13}C NMR (62.5 MHz, [D$_6$]DMSO): δ=172.9, 170.9, 161.5, 136.0, 132.5, 126.5, 122.6, 121.2, 118.6, 117.7, 111.2, 105.6, 56.5, 50.6, 50.0, 40.5, 35.9, 24.9, 21.3, 15.6, 11.1 ppm; HRMS: m/z: calcd for $C_{20}H_{25}N_4O_4$: 385.1876 [M+H]$^+$; found: 385.1891.

Pictet–Spengler product from ValBB-Trp-Ile-HMBA-PEGA$_{800}$ (5c): Purity >95%; ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ=11.04 (s, 1H), 7.51 (d, J=7.1 Hz, 1H), 7.43–7.24 (m, 3H), 7.15–6.87 (m, 2H), 4.70 (s, 1H), 4.64 (d, J=6.9 Hz, 1H), 3.82 (dd, J=3.6, 7.1 Hz, 1H), 3.55–3.30 (m, 2H), 2.82–2.62 (m, 1H), 2.06–1.82 (m, 1H), 1.72–1.56 (m, 1H), 1.54–1.34 (m, 1H), 1.16–0.91 (m, 7H), 0.89–0.68 (m, 4H), 0.65 ppm (d, J=6.8 Hz, 3H); ^{13}C NMR (62.5 MHz, [D$_6$]DMSO) δ=173.6, 168.7, 161.6, 136.8, 132.3, 126.9, 121.7, 119.0, 118.2, 111.7, 106.6, 70.1, 60.7, 58.9, 53.8, 52.0, 38.4, 32.9, 25.7, 19.7, 19.0, 17.1, 16.3, 12.5 ppm; HRMS: m/z: calcd for $C_{23}H_{31}N_4O_4$: 427.2340 [M+H]$^+$; found: 427.2321.

Pictet–Spengler product of TyrBB-Trp-Ile-HMBA-PEGA$_{800}$ (5d): 95% TFA (aq, ×2, 15 min) was used for removal of the *tert*-butyl-protecting group. Purity >95%; ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ=10.91 (s, 1H), 9.47 (brs, 1H), 7.73 (d, J=7.1 Hz, 1H), 7.41–7.28 (m, 2H), 7.22–7.12 (m, 3H), 7.06 (t, J=7.0 Hz, 1H), 6.96 (t, J=7.0 Hz, 1H), 6.74 (d, J=8.4 Hz, 2H), 4.73–4.67 (m, 2H), 3.94–3.81 (m, 2H), 3.03–2.72 (m, 3H), 1.78–1.62 (m, 1H), 1.50–1.66 (m, 1H), 1.14–0.99 (m, 1H), 0.88–0.73 (m, 4H), 0.68 ppm (d, J=2.8 Hz, 3H); ^{13}C NMR (62.5 MHz, [D$_6$]DMSO): δ= 173.4, 168.8, 161.0, 156.1, 136.2, 131.5, 130.5, 127.3, 126.5, 121.3, 118.6, 117.8, 115.3, 111.3, 106.2, 58.4, 56.3, 54.9, 51.3, 37.5, 25.8, 15.9, 11.9 ppm; HRMS: m/z: calcd for $C_{27}H_{31}N_4O_5$: 491.2289 [M+H]$^+$; found: 491.2286.

Pictet–Spengler product from TrpBB-Trp-Ile-HMBA-PEGA$_{800}$ (5e): 95% TFA (aq, ×2, 15 min.) was used for removal of the side chain Boc-protecting group. Purity >95%; ^{1}H NMR (250 MHz, [D$_6$]DMSO) δ= 10.96 (s, 1H), 10.91 (s, 1H), 7.72 (d, J=7.5 Hz, 1H), 7.63 (d, J=7.2 Hz, 1H), 7.42–7.30 (m, 4H), 7.14–6.94 (m, 6H), 4.85 (s, 1H), 4.68 (d, J= 6.9 Hz, 1H), 4.04–3.94 (m, 1H), 3.83–3.77 (m, 1H), 3.35–3.20 (m, 1H), 3.08 (dd, J=8.0 and 14.3 Hz, 1H), 2.81–2.66 (m, 1H), 1.70–1.63 (m, 1H), 1.47–1.33 (m, 1H), 1.06–0.93 (m, 1H), 0.86–0.61 ppm (m, 7H); ^{13}C NMR (62.5 MHz, [D$_6$]DMSO): δ=173.0, 168.3, 160.9, 136.3, 131.5, 127.5, 126.6, 124.6, 123.9, 121.4, 121.0, 118.3, 117.9, 111.4, 109.7, 106.4, 58.6, 55.7, 55.4, 51.5, 37.8, 25.3, 19.7, 15.9, 12.0 ppm; HRMS: m/z: calcd for $C_{29}H_{31}N_5NaO_4$: 536.2268 [M+Na]$^+$; found: 536.2247.

Pictet–Spengler product from AibBB-Trp-Ile-HMBA-PEGA$_{800}$ (5f): Purity >95%; ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ=11.01 (s, 1H), 7.43–7.31 (m, 3H), 7.09–6.93 (m, 3H), 4.75 (s, 1H), 4.69 (d, J=6.4 Hz, 1H), 3.74–3.69 (m, 1H), 3.45 (d, 1H), 2.79–2.66 (m, 1H), 1.54 (S, 3H), 1.43–1.18 (m, 1H), 1.00–0.79 (m, 4H), 0.69 (t, J=7.3 Hz, 3H), 0.52 ppm (d, J=6.8 Hz, 3H); ^{13}C NMR (62.5 MHz, [D$_6$]DMSO): δ=173.7, 169.0, 159.6, 137.0, 129.2, 127.8, 126.8, 124.1, 124.1, 121.5, 118.8, 118.3, 111.5, 107.5, 60.6, 58.6, 57.4, 50.9, 38.0, 28.6, 25.5, 24.3, 22.5, 16.0, 12.4 ppm; HRMS: m/z: calcd for $C_{23}H_{30}N_4NaO_4$: 435.2003 [M+Na]$^+$; found: 435.2003.

Pictet–Spengler product from PheBB-trp-ile-HMBA-PEGA$_{800}$ (6): Purity >95%; ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ=12.61 (brs, 1H), 10.97 (s, 1H), 7.90 (d, J=8.6 Hz, 1H), 7.42–7.25 (m, 2H), 7.24–6.90 (m, 7H), 6.64 (s, 1H), 5.42 (d, J=8.0 Hz, 1H), 4.79 (d, J=6.8 Hz, 1H), 4.28–4.13 (m, 1H), 4.04 (dd, J=6.3 and 8.5 Hz, 1H), 2.84–2.62 (m, 2H), 2.19 (dd, J= 9.7 and 13.6 Hz, 1H), 1.86–1.64 (m, 1H), 1.39–1.20 (m, 1H), 1.16–0.94 (m, 1H), 0.84–0.65 ppm (m, 6H); ^{13}C NMR (62.5 MHz, [D$_6$]DMSO): δ= 172.9, 171.2, 159.3, 137.7, 136.2, 129.2, 129.1 128.0, 126.5, 126.0, 121.1, 118.5, 117.8, 111.1, 107.1, 56.2, 55.0, 53.7, 49.6, 37.4, 36.1, 24.7, 23.4, 15.5, 11.1 ppm; HRMS: m/z: calcd for $C_{27}H_{31}N_4O_4$: 457.2340 [M+H]$^+$; found: 457.2342.

3-Methyl-2-[2-(2-oxo-2,3-dihydro-imidazol-1-yl)-3-phenyl-propionylamino]pentanoic acid (8): The imidazolone product (**8**) was obtained from PheBB-Phe-Ile-HMBA-PEGA$_{800}$ with a purity >95%; ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ=10.16 (s, 1H), 7.31–7.07 (m, 10H), 6.33 (s, 1H), 4.68 (dd, J=4.5, 11.1 Hz, 1H), 3.89 (dd, J=4.0, 8.0 Hz, 1H), 3.57 (d, J=3.3 Hz, 2H), 3.31–3.21 (m, 1H), 3.02 (dd, J=11.3, 14.3 Hz, 1H), 1.85–1.61 (m, 1H), 1.55–1.30 (m, 1H), 1.17–0.92 (m, 1H), 0.90–0.59 ppm (m, 6H); ^{13}C NMR (62.5 MHz, [D$_6$]DMSO): δ=173.7, 168.3, 153.6, 138.7, 137.9, 129.0, 128.3 128.1, 128.0, 126.2, 106.0, 58.5, 56.1, 37.8, 35.9, 31.1, 24.8, 15.9, 12.0 ppm; HRMS: m/z: calcd for $C_{25}H_{30}N_3O_4$: 436.2231 [M+H]$^+$; found: 436.2234.

3-Boc-2-(3-benzyloxycarbonylamino-propyl)-[1,3]oxazinane (10): A solution of Dess–Martin periodinane (12.9 g, 30.4 mmol) in dichloromethane (150 mL) was added dropwise to a solution of *N*-benzyloxycarbonyl-3-aminopropan-1-ol (**9**) (2.97 g, 15.2 mmol) in dichloromethane (50 mL). After 1.5 h, a mixture of 2.1 M aqueous $Na_2S_2O_3$ (85 mL) and saturated aqueous $NaHCO_3$ (85 mL) were added. When a clear solution was obtained, the organic phase was separated and the aqueous phase was extracted with diethyl ether (3×50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (1×50 mL) and brine (1× 50 mL). After drying over $MgSO_4$, the solvent was evaporated in vacuo and the crude aldehyde (3.0 g, quant.) was obtained. R_f=0.47 (ethyl acetate/petroleum ether 1:1); ^{1}H NMR (250 MHz, $CDCl_3$) was found to be as reported.[42] 3-Amino-propanol (0.75 mL, 9.9 mmol) and anhydrous sodium sulfate (14.1 g, 99 mmol) were added to a solution of the aldehyde (2.05 g, 9.9 mmol) described above in toluene (40 mL). The mixture was stirred for 3 h, and then Boc_2O (2.27 g, 10.4 mmol) was added. After a further 3 h, the mixture was filtered and the solvent removed in vacuo. The crude product was purified by flash-column chromatography by using ethyl acetate/petroleum ether 1:2. The product **10** (2.66 g, 7.3 mmol, 74%) was obtained as a colorless syrup which solidified upon storage in the refrigerator. ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.34–7.13 (m, 5H), 5.43 (t, J=7.0 Hz, 1H), 5.28–5.13 (m, 1H), 5.02 (s, 2H), 3.97–3.85 (m, 1H), 3.84–3.70 (m, 1H), 3.66–3.53 (m, 1H), 3.44–2.87 (m, 3H), 2.13–1.51 (m, 3H), 1.51–1.23 ppm (m, 10H); ^{13}C NMR (62.9 MHz, [D$_6$]DMSO): δ=156.3, 153.7, 136.6, 128.4, 128.0, 80.8, 80.3, 66.5, 59.9, 37.4, 36.8, 29.2, 28.2, 25.0 ppm; HRMS: m/z: calcd for $C_{20}H_{25}N_2O_5$: 365.2071 [M+H]$^+$; found: 365.2061.

3-Boc-2-(1-pentafluorophenyloxycarbonylamino-propyl)-[1,3]oxazinane (ApaBB-OPfp) (11): Compound **10** (2.37 g, 6.5 mmol) and 10% Pd/C (200 mg) were mixed in ethanol (50 mL) and H_2 (1 atm) was applied under vigorous stirring for 4.5 h. After this time, the mixture was filtered through Celite and the solvent was removed in vacuo. The crude product

was dissolved in dichloromethane (30 mL) and bispentafluorophenyl carbonate (2.57 g, 6.5 mmol) was added to the mixture. After reaction for 12 h, the mixture was concentrated in vacuo. The crude product was purified by flash-column chromatography by using ethyl acetate/petroleum ether 1:5. The product **11** (2.35 g, 5.3 mmol, 82%) was obtained as a colorless syrup which solidified upon storage in the refrigerator. ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 6.07$–5.86 (m, 1H), 5.56 (t, $J = 6.9$ Hz, 1H), 4.08–3.82 (m, 2H), 3.81–3.37 (m, 2H), 3.33–3.00 (m, 2H), 2.26–1.77 (m, 3H), 1.75–1.52 (m, 1H), 1.48 ppm (s, 9H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta =$ 81.1, 80.8, 66.5, 60.3, 38.3, 37.0, 29.0, 28.3, 25.1 ppm; HRMS: *m/z*: calcd for $C_{20}H_{25}N_2O_5$: 441.1443 $[M+H]^+$; found: 441.1438.

3-Boc-2-(4,5-dimethoxy-2-nitro-phenyl)-[1,3]oxazinane (13): 3-Aminopropanol (2.00 mL, 26.1 mmol) and anhydrous sodium sulfate (37.0 g, 261 mmol) were added to a solution of technical quality (80% pure) 4,5-dimethoxy-2-nitrobenzaldehyde (**12**) (5.50 g, 20.84 mmol) in toluene (150 mL). The mixture was stirred for 3 h and then Boc_2O (5.69 g, 26.1 mmol) was added. After 3 h, the mixture was filtered and the solvent removed in vacuo. The crude product was purified by flash-column chromatography by using ethyl acetate/petroleum ether 1:5. The product **13** (5.28 g, 14.3 mmol, 69%) was obtained as a light yellow liquid, which solidified upon storage in the refrigerator. ^{1}H NMR (250 MHz, CD_3OD): $\delta = 7.46$ (s, 1H), 6.87 (s, 1H), 6.81 (s, 1H), 3.98 (dt, $J = 9.1$, 17.9 Hz, 1H), 3.90 (s, 6H), 3.81–3.69 (m, 1H), 3.68–3.54 (m, 1H), 3.44–3.30 (m, 1H), 1.91–1.70 (m, 1H), 1.69–1.54 (m, 1H), 1.42 ppm (s, 9H); ^{13}C NMR (62.5 MHz, CD_3OD): $\delta = 156.0$, 153.3, 150.3, 126.5, 111.5, 109.7, 82.2, 63.9, 57.0, 56.8, 41.2, 28.5, 25.9 ppm; HRMS: *m/z*: calcd for $C_{17}H_{25}N_2O_7$: 369.1656 $[M+H]^+$; found: 369.1659.

3-Boc-2-(4,5-dimethoxy-2-pentafluorophenyloxycarbonyl-aminophenyl)-[1,3]oxazinane (14): Compound **13** (3.70 g, 10.0 mmol), DMAP (122 mg), and 10% Pd/C (370 mg) in MeOH (100 mL) were stirred under a H_2 atmosphere (1 atm) for 2.5 h. After this time, the mixture was filtered through Celite and solvent removed in vacuo. The crude product was dissolved in dichloromethane (50 mL) and a solution of bispentafluorophenyl carbonate (3.94 g, 10.0 mmol) in dichloromethane (10 mL) was added. After 5 h, the solvent was removed in vacuo and the crude product was purified by column chromatography by using ethyl acetate/petroleum ether 1:8. The product **14** (4.33 g, 7.9 mmol, 79%) was obtained as a light yellow syrup, which solidified upon storage in the refrigerator. ^{1}H NMR (250 MHz, CD_3OD): $\delta = 7.62$ (br s, 1H), 6.66 (s, 1H), 6.58 (s, 1H), 4.20–4.03 (m, 1H), 3.93–3.71 (m, 8H), 3.42–3.26 (m, 1H), 2.05–1.81 (m, 1H), 1.69–1.50 (m, 1H), 1.49 ppm (s, 9H); ^{13}C NMR (62.5 MHz, CD_3OD): $\delta =$ 112.9, 109.1, 82.9, 62.1, 57.0, 56.5, 39.9, 28.6, 26.0 ppm; HRMS: *m/z*: calcd for $C_{24}H_{26}F_5N_2O_7$: 549.1655 $[M+H]^+$; found: 549.1651.

Pictet–Spengler product from ApaBB-Trp-Gly-HMBA-PEGA$_{800}$ (18a): Resin (154 mg, theoretical loading: 0.27 mmol g^{-1}) was cleaved and yielded 13.4 mg of product **17a** (94%); Purity >95%; ^{1}H NMR (250 MHz, [D$_6$]DMSO): $\delta = 12.72$ (br s, 1H), 11.11 (s, 1H), 8.14 (t, $J = 5.8$ 1H), 7.38 (d, $J = 7.4$ Hz, 1H), 7.28 (d, $J = 7.9$ Hz, 1H), 7.09–6.90 (m, 2H), 6.67 (d, $J = 3.7$ Hz, 1H), 5.51 (d, $J = 5.6$ Hz, 1H), 5.03–4.89 (m, 1H), 3.65 (d, $J =$ 3.9 Hz, 2H), 3.57–3.01 (m), 2.81–2.68 (m, 1H), 2.64–2.53 (m, 1H), 1.74–1.54 ppm (m, 1H); ^{13}C NMR (62.5 MHz, [D$_6$]DMSO): $\delta = 171.5$, 171.2, 155.3, 136.3, 133.5, 126.5, 120.9, 118.4, 117.7, 111.0, 105.1, 50.5, 49.4, 40.8, 37.8, 28.9, 22.3 ppm; HRMS: *m/z*: calcd for $C_{17}H_{19}N_4O_4$: 343.1401 $[M+H]^+$; found: 343.1452.

Pictet–Spengler product from ApaBB-Trp(5-F)-Gly-HMBA-PEGA$_{800}$ (18b): Resin (150 mg, theoretical loading: 0.38 mmol g^{-1}) was cleaved to yield the product **17b** (15 mg, 63%); Purity >95%; ^{1}H NMR (250 MHz, [D$_6$]DMSO): $\delta = 11.08$ (s, 1H), 8.11 (t, $J = 6.7$, 1H), 7.27 (dd, $J = 4.5$, 8.8 Hz, 1H), 7.13 (dd, $J = 2.5$, 9.9 Hz, 1H), 6.87 (dt, $J = 2.4$, 9.1 Hz, 1H), 6.69 (d, $J = 3.8$ Hz, 1H), 5.50 (d, $J = 6.6$ Hz, 1H), 5.00–4.87 (m, 1H), 3.63 (d, $J = 5.8$ Hz, 2H), 3.45–3.09 (m, 4H), 2.72 (dd, $J = 9.9$, 15.5 Hz, 1H), 2.46–2.39 (m), 1.65 ppm (dq, $J = 4.4$, 12.0 Hz, 1H); ^{13}C NMR (62.5 MHz, [D$_6$]DMSO): $\delta = 171.2$, 158.5, 155.2, 154.9, 135.6, 132.9, 126.8, 126.6, 122.6, 122.6, 111.9, 111.7, 108.9, 108.5, 105.6, 105.5, 102.8, 102.5, 50.3, 49.3, 41.0, 37.7, 28.7, 22.2 ppm; HRMS: *m/z*: calcd for $C_{17}H_{17}FN_4O_4$: 361.1307 $[M+H]^+$; found: 361.1304.

Pictet–Spengler product from ApaBB-Trp(5-Br)-Gly-HMBA-PEGA$_{800}$ (18c): Resin (150 mg, theoretical loading: 0.38 mmol g^{-1}); cleaved yield: 16 mg, 79%; purity >95%; ^{1}H NMR (250 MHz, [D$_6$]DMSO): $\delta = 11.27$ (s, 1H), 8.10 (t, $J = 5.7$, 1H), 7.55 (d, $J = 1.8$ Hz, 1H), 7.25 (d, $J = 8.5$ Hz, 1H), 7.15 (dd, $J = 1.9$, 8.6 Hz, 1H), 6.70 (d, $J = 3.6$ Hz, 1H), 5.50 (d, $J =$ 5.6 Hz, 1H), 5.01–4.88 (m, 1H), 3.62 (d, $J = 5.8$ Hz, 2H), 3.45–3.09 (m, 4H), 2.72 (dd, $J = 6.6$, 15.6 Hz, 1H), 2.58 (d, $J = 12.4$, 1H), 1.65 ppm (dq, $J = 4.6$, 12.0 Hz, 1H); ^{13}C NMR (62.5 MHz, [D$_6$]DMSO): $\delta = 171.1$, 155.1, 135.2, 134.9, 128.3, 123.2, 120.1, 117.6, 115.9, 113.0, 111.0, 105.2, 50.3, 49.3, 41.0, 37.7, 28.7, 22.1 ppm; HRMS: *m/z*: calcd for $C_{17}H_{17}BrN_4O_4$: 421.0506 $[M+H]^+$; found: 421.0493.

Pictet–Spengler product from ApaBB-Ala(benzothiophen-3-yl)-Gly-HMBA-PEGA$_{800}$ (18d): Purity >95%; ^{1}H NMR (250 MHz, [D$_6$]DMSO): $\delta = 8.23$–8.11 (m, 1H), 7.92 (d, $J = 7.2$ Hz, 1H), 7.68 (d, $J = 7.0$ Hz, 1H), 7.45–7.29 (m, 2H), 6.76 (d, $J = 3.4$ Hz, 1H), 5.55 (d, $J = 5.9$ Hz, 1H), 5.08–4.96 (m, 1H), 3.65 (d, $J = 4.4$ Hz, 2H), 3.51–2.88 (m), 2.87–2.74 (m, 1H), 2.44–2.32 (m, 1H), 1.90–1.69 ppm (m, 1H); HRMS: *m/z*: calcd for $C_{17}H_{18}N_3O_4S$: 360.1018 $[M+H]^+$; found: 360.1011.

Pictet–Spengler product from ApaBB-Ala(thiophen-3-yl)-Gly-HMBA-PEGA$_{800}$ (18e): Purity >95%; ^{1}H NMR (250 MHz, [D$_6$]DMSO): $\delta = 8.14$ (t, $J = 5.9$ Hz, 1H), 7.35 (d, $J = 5.1$ Hz, 1H), 6.81 (d, $J = 5.0$ Hz, 1H), 6.67 (s, 1H), 5.40 (d, $J = 5.7$ Hz, 1H), 4.97–4.85 (m, 1H), 3.68 (d, $J = 5.9$ Hz, 2H), 3.44–3.02 (m, 3H), 2.76–2.63 (m, 1H), 2.37–2.24 (m, 1H), 1.82–1.62 ppm (m, 1H); HRMS: *m/z*: calcd for $C_{13}H_{16}N_3O_4S$: 310.0862 $[M+H]^+$; found: 310.0852.

Pictet–Spengler product from ApaBB-Ala(thiophen-2-yl)-Gly-HMBA-PEGA$_{800}$ (18f): Purity >95%; ^{1}H NMR (250 MHz, [D$_6$]DMSO): $\delta = 8.13$ (t, $J = 5.8$ Hz, 1H), 7.29 (d, $J = 5.1$ Hz, 1H), 6.92 (d, $J = 5.2$ Hz, 1H), 6.66 (s, 1H), 5.48 (d, $J = 5.4$ Hz, 1H), 4.83–4.65 (m, 1H), 3.68 (d, $J = 5.8$ Hz, 2H), 3.50–3.05 (m, 3H), 2.90–2.75 (m, 1H), 2.50–2.38 (m, 1H), 1.66–1.38 ppm (m, 1H); HRMS: *m/z*: calcd for $C_{13}H_{16}N_3O_4S$: 310.0862 $[M+H]^+$; found: 310.0853.

Pictet–Spengler product from ApaBB-Ala(furan-2-yl)-Gly-HMBA-PEGA$_{800}$ (18g): Purity >95%; ^{1}H NMR (250 MHz, [D$_6$]DMSO): $\delta = 8.11$ (t, $J = 4.8$ Hz, 1H), 7.47 (d, $J = 1.8$ Hz, 1H), 6.65 (s, 1H), 6.39 (d, $J =$ 1.9 Hz, 1H), 5.51 (d, $J = 5.9$ Hz, 1H), 4.67–4.55 (m, 1H), 3.72 (d, $J =$ 6.1 Hz, 2H), 3.56–3.02 (m, 3H), 2.80–2.68 (m, 1H), 2.40–2.16 (m, 1H), 1.61–1.37 ppm (m, 1H); HRMS: *m/z*: calcd for $C_{13}H_{16}N_3O_5$: 294.1090 $[M+H]^+$; found: 294.1073.

Pictet–Spengler product from ApaBB-Phe-Gly-HMBA-PEGA$_{800}$ (18h): Purity >95%; ^{1}H NMR (250 MHz, [D$_6$]DMSO): $\delta = 8.18$–8.06 (m, 1H), 7.27–7.04 (m, 4H), 6.64 (s, 1H), 5.29–5.25 (m, 1H), 4.81 (d, $J = 10.5$ Hz, 1H), 3.50–3.30 (m, 3H), 3.16 (d, $J = 15.6$ Hz, 1H), 2.90 (dd, $J = 5.7$, 15.2 Hz, 1H), 2.42–2.33 (m, 1H), 1.72–1.58 ppm (m, 1H); HRMS: *m/z*: calcd for $C_{15}H_{18}N_3O_4$: 304.1297 $[M+H]^+$; found: 304.1298.

Pictet–Spengler product from ApaBB-Tyr-Gly-HMBA-PEGA$_{800}$ (18i): Purity >95%; ^{1}H NMR (250 MHz, [D$_6$]DMSO): $\delta = 9.18$ (s, 1H), 8.07 (t, $J = 6.0$ Hz, 1H), 6.90 (d, $J = 8.9$ Hz, 1H), 6.65–6.50 (m, 3H), 5.21 (dd, $J =$ 2.7, 6.0 Hz, 1H), 4.76–4.64 (m, 1H), 3.63 (dd, $J = 2.0$, 5.9 Hz, 1H), 3.21–2.95 (m, 3H), 2.82–2.71 (m, 1H), 2.32–2.20 (m, 1H), 1.72–1.55 (m, 1H); HRMS: *m/z*: calcd for $C_{15}H_{18}N_3S_4$ $[M+H]^+$: 320.1246; found: 320.1227.

Pictet–Spengler product from ApaBB-3,4-Di-MeO-Phe-Gly-HMBA-PEGA$_{800}$ (18j): Purity >95%; ^{1}H NMR (250 MHz, [D$_6$]DMSO): $\delta = 8.04$ (t, $J = 5.7$ Hz, 1H), 6.77 (s, 1H), 6.65–6.62 (m, 2H), 5.26 (m, 1H), 4.76–4.68 (m, 1H), 3.71 (s, 3H), 3.60 (dd, $J = 2.7$, 5.7 Hz, 1H), 3.42–3.07 (m, 4H), 2.78 (dd, $J = 6.2$, 15.6 Hz, 1H), 2.46–2.37 (m, 1H), 1.62–1.46 ppm (m, 1H); HRMS: *m/z*: calcd for $C_{17}H_{22}N_3O_6$ $[M+H]^+$: 364.1509; found: 364.1499.

Pictet–Spengler product from ApaBB-1-pyrenyl-Ala-Gly-HMBA-PEGA$_{800}$ (18k): Purity >95%; ^{1}H NMR (250 MHz, [D$_6$]DMSO): $\delta =$ 8.39–8.17 (m, 6H), 8.15–7.99 (m, 3H), 6.77 (d, $J = 3.2$ Hz, 1H), 5.62 (d, $J = 4.2$ Hz, 1H), 5.34 (dd, $J = 2.5$, 10.5 Hz, 1H), 4.14 (d, $J = 15.0$ Hz, 1H), 3.63–3.20 (m, 5H), 2.67 (d, $J = 11.3$ Hz, 1H), 1.91–1.70 ppm (m, 1H); HRMS: *m/z*: calcd for $C_{25}H_{22}N_3O_4$: 428.1605 $[M+H]^+$; found: 428.1611.

The cyclic *N,O*-acetal product from AbaBB-Phe-Gly-HMBA-PEGA$_{800}$ (20h): Purity >95%; ^{1}H NMR (250 MHz, [D$_6$]DMSO): $\delta = 13.00$ (br s, 1H), 9.96 (s, 1H), 7.46–7.13 (m, 8H), 7.01 (t, $J = 7.5$ Hz, 1H), 6.88 (d, $J =$ 8.0 Hz, 1H), 6.03 (s, 1H), 4.81 (t, $J = 6.9$ Hz, 1H), 4.11 (d, $J = 18.0$ Hz, 1H), 3.76 (d, $J = 18.0$ Hz, 1H), 2.96 ppm (d, $J = 7.0$ Hz, 1H); ^{13}C NMR

(62.5 MHz, [D$_6$]DMSO): δ = 172.6, 169.6, 152.3, 137.1, 136.4, 130.6, 129.3, 128.2, 127.5, 126.5, 121.7, 116.4, 114.6, 112.4, 70.3, 60.3, 41.6, 33.2 ppm; HRMS: *m*/*z*: calcd for $C_{19}H_{18}N_3O_4$: 352.1292 $[M+H]^+$; found: 352.1282.

Pictet–Spengler product from AbaBB-Trp-Gly-HMBA-PEGA$_{800}$ (21a): Purity >95%; ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 10.86 (s, 1H), 9.78 (s, 1H), 7.54 (t, *J* = 4.4 Hz, 1H), 7.47–7.31 (m, 3H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.11–6.89 (m, 4H), 6.12 (s, 1H), 5.29 (d, *J* = 6.1 Hz, 1H), 3.45–3.29 (m, 2H), 3.23 (dd, *J* = 4.2, 16.7 Hz, 1H), 3.01–2.84 ppm (m, 1H); ^{13}C NMR (62.5 MHz, [D$_6$]DMSO): δ = 171.7, 169.1, 155.1, 137.3, 136.3, 130.6, 128.4, 126.6, 125.9, 121.6, 121.1, 119.8, 118.7, 117.8, 115.9, 113.7, 111.5, 106.4, 52.5, 51.7, 44.0, 21.2 ppm; HRMS: *m*/*z*: calcd for $C_{21}H_{18}N_4O_4$: 391.1401 $[M+H]^+$; found: 391.1426.

Pictet–Spengler product from AbaBB-Trp(5-F)-Gly-HMBA-PEGA$_{800}$ (21b): Purity >95%; resin (150 mg, theoretical loading: 0.38 mmol g^{-1}); cleaved yield: 21 mg, 90%; ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 10.89 (s, 1H), 9.77 (s, 1H), 7.54 (t, *J* = 4.5 Hz, 1H), 7.40 (d, *J* = 6.6 Hz, 1H), 7.33 (dd, *J* = 4.6, 8.8 Hz, 1H), 7.29–7.13 (m, 2H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.95–6.82 (m, 2H), 6.15 (s, 1H), 5.29 (d, *J* = 6.2 Hz, 1H), 3.47–3.14 (m, 3H), 2.98–2.80 ppm (m, 1H); ^{13}C NMR (62.5 MHz, [D$_6$]DMSO): δ = 171.5, 168.8, 158.7, 155.0, 154.9, 137.1, 132.9, 132.8, 128.5, 126.9, 126.7, 126.1, 121.6, 119.2, 113.6, 112.5, 112.3 109.2, 108.8, 106.7, 102.8, 102.4, 52.4, 51.6, 43.9, 20.8 ppm; HRMS: *m*/*z*: calcd for $C_{21}H_{17}FN_4O_4$: 409.1307 $[M+H]^+$; found: 409.1297.

Pictet–Spengler product from AbaBB-Trp(5-Br)-Gly-HMBA-PEGA$_{800}$ (21c): Resin (150 mg, theoretical loading: 0.38 mmol g^{-1}); cleaved yield: 22 mg, 82%; purity >95%; ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 11.06 (s, 1H), 9.78 (s, 1H), 7.62 (d, *J* = 1.8 Hz, 1H), 7.55 (t, *J* = 4.6 Hz, 1H), 7.40 (d, *J* = 7.4 Hz, 1H), 7.32 (d, *J* = 8.6 Hz, 1H), 7.25 (t, *J* = 7.7 Hz, 1H), 7.17 (dd, *J* = 1.9, 8.6 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 7.8 Hz, 1H), 6.16 (s, 1H), 5.29 (d, *J* = 6.2 Hz, 1H), 3.47–3.12 (m, 3H), 2.97–2.81 ppm (m, 1H); ^{13}C NMR (62.5 MHz, [D$_6$]DMSO): δ = 171.4, 168.7, 154.8, 137.1, 134.9, 132.5, 128.5, 128.4, 126.8, 123.5, 121.6, 120.1, 119.2, 113.7, 113.5, 111.3, 106.3, 52.4, 51.6, 44.0, 20.8 ppm; HRMS: *m*/*z*: calcd for $C_{21}H_{17}BrN_4O_4$ $[M+H]^+$: 469.0506; found: 469.0494.

Pictet–Spengler product from AbaBB-Ala(3-thiophen-3-yl)-Gly-HMBA-PEGA$_{800}$ (21d): Purity >95%; ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 9.72 (s, 1H), 8.59 (t, *J* = 6.0 Hz, 1H), 7.32–7.18 (m, 3H), 7.02 (dt, *J* = 1.1, 7.5 Hz, 1H), 6.95–6.79 (m, 2H), 6.06 (s, 1H), 5.33 (d, *J* = 6.9 Hz, 1H), 3.88 (dd, *J* = 6.6, 17.3 Hz, 1H), 3.63 (dd, *J* = 5.5, 17.3 Hz, 1H), 3.27 (d, *J* = 15.0 Hz, 1H), 2.97–2.81 ppm (m, 1H); ^{13}C NMR (62.5 MHz, [D$_6$]DMSO): δ = 171.4, 170.0, 153.3, 136.2, 135.5, 133.3, 128.9, 128.1, 126.2, 123.7, 122.3, 119.4, 113.9, 52.7, 52.1, 23.2 ppm; HRMS: *m*/*z*: calcd for $C_{17}H_{16}N_3O_4S$: 358.0856 $[M+H]^+$; found: 358.0832.

Pictet–Spengler product from AbaBB-Ala(thionphen-2-yl)-Gly-HMBA-PEGA$_{800}$ (21e): Purity >95%; ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 12.54 (br s, 1H), 9.68 (s, 1H), 8.54 (t, *J* = 5.9 Hz, 1H), 7.31–7.18 (m, 3H), 6.99 (dt, *J* = 1.1, 7.5 Hz, 1H), 6.86 (d, *J* = 7.9 Hz, 1H), 6.65 (d, *J* = 5.2 Hz, 1H), 5.85 (s, 1H), 5.32 (d, *J* = 6.2 Hz, 1H), 3.84 (dd, *J* = 6.4, 17.3 Hz, 1H), 3.64 (dd, *J* = 5.6, 17.3 Hz, 1H), 3.46 (d, *J* = 22.2 Hz, 1H), 3.13–2.97 ppm (m, 1H); ^{13}C NMR (62.5 MHz, [D$_6$]DMSO): δ = 171.3, 169.9, 153.2, 136.8, 134.2, 133.2, 128.4, 126.6, 124.9, 122.8, 121.4, 119.8, 113.8, 53.2, 52.2, 23.2 ppm; HRMS: *m*/*z*: calcd for $C_{17}H_{16}N_3O_4S$: 358.0856 $[M+H]^+$; found: 358.0806.

Pictet–Spengler product from AbaBB-Phe(3,4-di-MeO)-Gly-HMBA-PEGA$_{800}$ (21f): Purity >95%; ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 9.54 (s, 1H), 8.30 (m, 1H), 7.27 (t, 7.7 Hz, 1H), 7.21 (d, *J* = 7.5 Hz, 1H), 7.01 (t, *J* = 7.4 Hz, 1H), 6.94 (s, 1H), 6.92 (d, *J* = 7.7 Hz, 1H), 6.19 (s, 1H), 5.62 (s, 1H), 4.79 (t, *J* = 6.6 and 17.3 Hz, 1H), 3.76–3.67 (m, 5H), 3.50 (s, 3H), 3.23–3.09 (m, 1H), 3.00 ppm (dd, *J* = 7.5, 15.6 Hz, 1H); HRMS: *m*/*z*: calcd for $C_{21}H_{22}N_3O_6$: 412.1503 $[M+H]^+$; found: 412.1481.

Pictet–Spengler product from DMAbaBB-Trp-Gly-HMBA-PEGA$_{800}$ (21g): Purity 70%; ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 12.62 (s, 1H), 10.53 (s, 1H), 9.41 (s, 1H), 8.45 (t, *J* = 6.1 Hz, 1H), 7.42 (d, *J* = 7.4 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.07–6.91 (m, 3H), 6.04 (s, 1H), 5.35 (d, 6.0 Hz, 1H), 3.84–3.70 (m, 8H), 3.31 (d, *J* = 16.0 Hz, 1H), 3.73–3.56 ppm (ddd, *J* = 1.8, 7.0, 15.9 Hz, 1H); HRMS: *m*/*z*: calcd for $C_{23}H_{23}N_4O_6$: 451.1612 $[M+H]^+$; found: 451.1599.

Oxidation of Pictet–Spengler products on solid phase (22a–g): The dry PEGA$_{800}$ resin with HMBA linker and Pictet–Spengler product attached (50–150 mg, 0.30–0.38 mmol g^{-1}, 15–57 mmol) **21a–g** was swelled in TFA (95%, aq) in an open syringe fitted with a Teflon frit and the mixture was shaken vigorously (reaction time see below). The resin was then washed with H_2O until the eluate had a pH 5–7. It was washed with DMF (6×), dichloromethane (6×), and lyophilized. The compound was cleaved from the resin by swelling the dry PEGA$_{800}$ resin with HMBA linker and the compound attached in NaOH (aq, 0.1 M, 10 μL mg^{-1} resin). After 2 h, HCl (aq, 0.1 M) was used for neutralization. The resin was extracted with H_2O (×2) and acetonitrile/H_2O 70:30 (×2). The solvent from the extract was removed in a speedvac to give the crude product (**22a–g**) as a solid salt with a yellow to intensive red color.

Oxidized Pictet–Spengler product from AbaBB-Trp-Gly-HMBA-PEGA$_{800}$ (22a): Reaction time: 5 h; purity >95%; ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 13.60 (br s, 1H), 12.74–12.39 (m, 2H), 8.84 (t, *J* = 5.7 Hz, 1H), 8.67 (d, *J* = 8.4 Hz, 1H), 8.11 (t, *J* = 7.7 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.74–7.46 (m, 4H), 7.27 (t, *J* = 7.0 Hz, 1H), 6.03 (d, *J* = 6.6 Hz, 1H), 3.88 (d, *J* = 18.0 Hz, 1H), 3.73–3.56 ppm (m, 4H); HRMS: *m*/*z*: calcd for $C_{21}H_{17}N_4O_4$: 389.1244 $[M]^+$; found: 389.1237.

Oxidized Pictet–Spengler product from AbaBB-Trp(5-F)-Gly-HMBA-PEGA$_{800}$ (22b): Reaction time: 5 h; purity >95%; ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 12.80 (s, 1H), 12.53 (br s, 1H), 8.86 (t, *J* = 5.8 Hz, 1H), 8.68 (d, *J* = 8.3 Hz, 1H), 8.13 (t, *J* = 7.4 Hz, 1H), 7.73–7.53 (m, 4H), 7.46 (dt, *J* = 5.1, 18.3 Hz, 1H), 6.04 (d, *J* = 6.5 Hz, 1H), 4.01 (d, *J* = 17.6 Hz, 1H), 3.68 (d, *J* = 5.9 Hz, 2H), 3.62–3.48 ppm (m, 1H); HRMS: *m*/*z*: calcd for $C_{21}H_{15}N_4O_4$: 407.1150 $[M]^+$; found: 407.1145.

Oxidized Pictet–Spengler product from AbaBB-Trp(5-Br)-Gly-HMBA-PEGA$_{800}$ (22c): Reaction time: 5 h; purity >95%; ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 12.86 (s, 1H), 8.84 (t, *J* = 5.7 Hz, 1H), 8.67 (d, *J* = 8.3 Hz, 1H), 8.24–8.06 (m 2H), 7.75–7.52 (m, 4H), 6.04 (d, *J* = 6.7 Hz, 1H), 4.04 (d, *J* = 17.7 Hz, 1H), 3.75–3.52 ppm (m, 3H); HRMS: *m*/*z*: calcd for $C_{21}H_{15}BrN_4O_4$: 467.0349 $[M]^+$; found: 467.0341.

Oxidized Pictet–Spengler product of AbaBB-Ala(thiophen-3-yl)-Gly-HMBA-PEGA$_{800}$ (22d): Reaction time: 5 d; purity >95%; ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 8.92–8.73 (m, 3H), 8.23–8.06 (m, 2H), 7.69 (dd, *J* = 7.5, 8.5 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 5.0 Hz, 1H), 6.02 (d, *J* = 6.5 Hz, 1H), 3.97–3.80 (m, 1H), 3.49 ppm (dd, *J* = 1.8, 5.7 Hz, 1H), 3.65–3.55 ppm (m, 1H); HRMS: *m*/*z*: calcd for $C_{17}H_{14}N_3O_4S$: 356.0700 $[M]^+$; found: 356.0702.

Oxidized Pictet–Spengler product from AbaBB-Ala(thiophen-2-yl)-Gly-HMBA-PEGA$_{800}$ (22e): Reaction time: 5 d; purity >95%; ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 8.80 (t, *J* = 5.8 Hz, 1H), 8.50 (d, *J* = 8.3 Hz, 1H), 8.18 (t, *J* = 7.4 Hz, 1H), 8.01 (d, *J* = 5.3 Hz, 1H), 7.85 (d, *J* = 5.4 Hz, 1H), 7.59 (m, 2H), 6.00 (d, *J* = 8.1 Hz, 1H), 4.03 (d, *J* = 16.9 Hz, 1H), 3.76–3.63 ppm (m, 4H); HRMS: *m*/*z*: calcd for $C_{17}H_{14}N_3O_4S$: 356.0700 $[M+H]^+$; found: 356.0725.

Oxidized Pictet–Spengler product from AbaBB-Phe(3,4-di-MeO)-Gly-HMBA-PEGA$_{800}$ (22f): Reaction time: 7 d.; purity >95%; ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 13.55 (br s, 1H), 8.75 (t, *J* = 5.8 Hz, 1H), 8.45 (d, *J* = 8.3 Hz, 1H), 8.15 (t, *J* = 7.4 Hz, 1H), 7.68–7.52 (m, 2H), 7.46 (s, 1H), 7.27 (s, 1H), 5.86–5.73 (m, 1H), 3.99 (s, 3H), 3.89 (s, 3H), 3.70–3.55 ppm (m, 4H); HRMS: *m*/*z* calcd for $C_{21}H_{20}N_3O_6$: 410.1347 $[M]^+$; found: 410.1357.

Oxidized Pictet–Spengler product of DMAbaBB-Trp-Gly-OH (22g): Reaction time: 5 h; purity >95%; ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 12.75 (s, 1H), 8.84 (t, *J* = 5.7 Hz, 1H), 7.86 (s, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.65 (d, *J* = 8.5 Hz, 1H), 7.51 (ddd, *J* = 1.0, 7.0, 8.3 Hz, 1H), 7.51 (dd, *J* = 7.2, 7.9 Hz, 1H), 7.07 (s, 1H), 6.54 (s, 1H), 5.95 (d, *J* = 6.3 Hz, 1H), 4.07 (s, 3H), 4.04 (s, 3H), 3.69–3.55 ppm (m, 4H); HRMS: *m*/*z*: calcd for $C_{23}H_{21}N_4O_6$: 449.1456 $[M]^+$; found: 449.1447.

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