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# Solid-Phase Intramolecular *N*-Acyliminium Pictet−Spengler Reactions as Crossroads to Scaffold Diversity

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A novel solid-phase intramolecular Pictet−Spengler reaction is presented. The approach utilizes masked aldehyde building blocks protected as their *N*-Boc-1,3-oxazinanes for the clean generation of solid-supported aldehydes. When exposed to simple acidic treatment, the aldehyde functionality is rapidly released and becomes susceptible to nucleophilic attack from an amide nitrogen of the peptide backbone, which results in the formation of a highly reactive cyclic *N*-acyliminium ion. Subsequently, a quantitative and highly stereoselective Pictet−Spengler reaction takes place by attack of the indole from a neighboring tryptophan, thus appending two new *N*-fused rings to the indole moiety. Extension of this intramolecular reaction to substituted indoles, and other reactive heterocycles, such as furane and thiophenes, provides a convenient and rapid access to a range of pharmacologically interesting tri- and tetracyclic scaffolds. Finally, the reaction products may conveniently be released from the solid support (PEGA) by cleavage of the base-labile linker (HMBA).

## Introduction

Prime goals for solid-phase combinatorial synthesis are to identify and optimize pharmaceutical lead compounds. The high-speed generation of chemical libraries offered by solid-phase synthesis techniques is highly efficient, since workup and purification may be achieved by simple washing and filtration, and combinatorial chemistry is thus becoming an increasingly important tool for drug discovery.[1] It is therefore highly important that the applied reactions proceed in a clean and quantitative fashion. Today, solid-phase peptide synthesis is well-established, fulfilling this requirement with high efficiency and to high levels of sophistication. However, in the search for new drugs, peptide isosters and peptidomimetics incorporating heterocyclic motifs have attracted considerable attention, and the clean transformation of short peptide strands into heterocycles has accordingly emerged as an increasingly important area of research.[2−8]

An illustration of such efforts is provided by the considerable synthetic and medicinal interest in compounds containing the tetrahydro-$\beta$-carboline (THBC), and the related tetrahydroisoquinoline (THIQ) ring systems. Over the past 100 years, these heterocyclic core structures have gained widespread attention due to their presence in many naturally and synthetically derived molecules, which have been found to exhibit a wide range of biological and pharmacological properties. For example, compounds constituted by THIQ ring structures have been reported to display antitumor and antimicrobial activity[9] and stimulation of $\beta_3$ adrenergic receptors,[10] and function as $5HT_{1A}$ receptor agonists.[11] When incorporated within a peptide sequence, THIQ-3-carboxylic acids may restrict the number of conformations of the amino acid backbone,[12] which may enhance pharmacological properties, as illustrated for opioid $\delta$,[13] $\kappa$,[14] and $\mu$ receptor antagonists,[15,16] farnesyl transferase inhibitors,[17,18] dihydrofolate reductase inhibitors,[19] and neuro-

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muscular activity blockers.[20] Significant biological activities have also been noted for compounds containing the THBC skeleton, particularly in the central nervous system, with known interactions at benzodiazepine,[21,22] serotonin,[23−26] and dopamine receptors.[27]

Since its discovery,[28] the Pictet−Spengler reaction has been a widely used tool for the construction of THIQs and THBCs. Without the use of this powerful reaction for C−C bond formation, a large number of total syntheses of highly complicated indole and isoquinoline derived alkaloids would have been difficult to achieve.[29] To date, several solid-phase versions of the Pictet−Spengler reaction have been reported,[30] where the typical approach comprises the Brønsted acid-catalyzed intermolecular condensation of an aldehyde with the amino terminal of a solid-supported amino acid containing the reactive aromatic side chain, most often tryptophan,[31−34] or tryptamine derivatives,[35,36] followed by Pictet−Spengler cyclization to form the THBC ring system. Further solid-phase functionalization of THBCs have involved reactions of the $\beta$-amino group with acylation reagents,[37] which have been utilized in the synthesis of fumitremorgin analogues,[38,39] tetrahydro-$\beta$-carbolinehydantoins,[40,41] and other tetra-, penta-, and hexacyclic fused ring systems.[42,43] When the aldehyde part of the Pictet−Spengler reaction contains a protected amino functionality, the THBC core may also be incorporated between peptide strands,[44−46] ideally to introduce conformational constraints to the overall peptide structure. Fewer reports have dealt with the solid-phase synthesis of THIQs, and both the Bischler−Napieralsky[47,48] and the Pictet−Spengler reaction of electron-rich phenylethylamine derivatives have proven successful.[49−51]

As opposed to general precedent in the field of solid-phase Pictet−Spengler reactions, our research has been focused on the intermolecular condensation of solid-supported aldehydes with tryptophan, tryptamine, and histidine derivatives.[52] Simultaneously, a highly efficient approach was reported for solid-phase generation of aldehydes from masked aldehyde building blocks protected as their *N*-Boc-1,3-oxazinanes.[53] To conduct intermolecular synthetic transformations of such aldehydes attached to solid-supported peptides or peptide isosters, it was necessary to protect the amide nitrogens of the peptide backbone to prevent undesired intramolecular condensation reactions. Similar reactions are well-established in solution-phase synthesis, where the generated cyclic *N*-acyliminium ion subsequently may be trapped in an intramolecular fashion with heteroatom-based nucleophiles, resulting in bicyclic lactam ring systems,[54] or carbon-based nucleophiles in total synthesis,[55,56] and toward natural product-like compounds.[57−59] In the present investigation, the solid-phase version of such an intramolecular condensation reaction for the generation of a cyclic *N*-acyliminium is reported to serve as a highly reactive key intermediate for Pictet−Spengler reactions, provided there is a sufficiently reactive aromatic side chain of the neighboring amino acid, such as the indole of tryptophan (Scheme 1), present.

## Results and Discussion

As an initial choice of substrate, masked aldehyde **3a** was synthesized via standard Fmoc amino acid coupling protocols. Starting from amino-functionalized PEGA resin,[60] the base-labile HMBA linker was attached via

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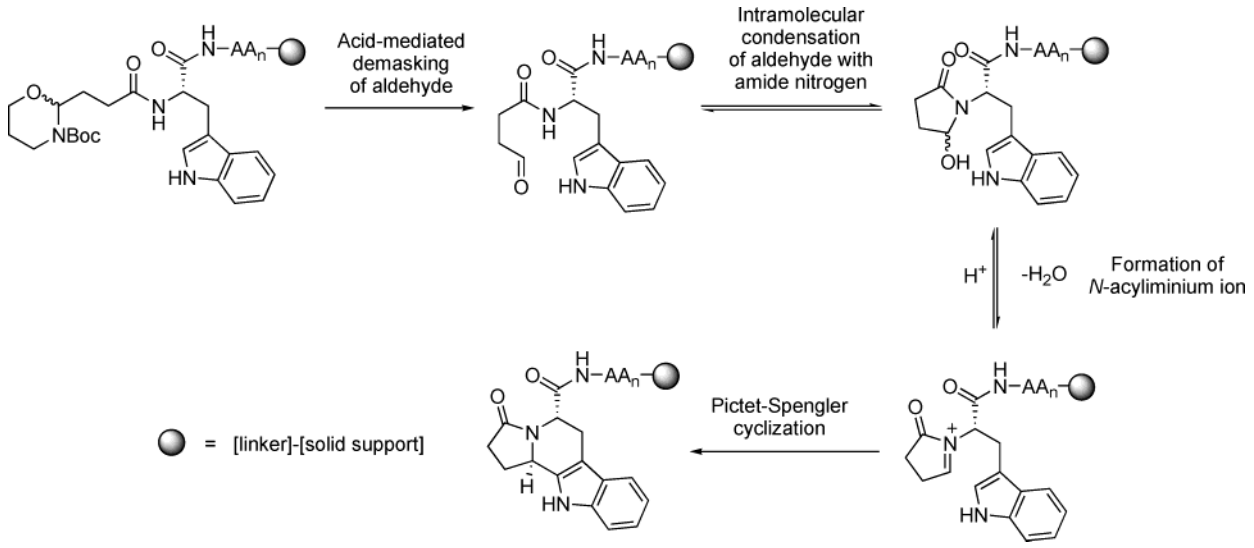
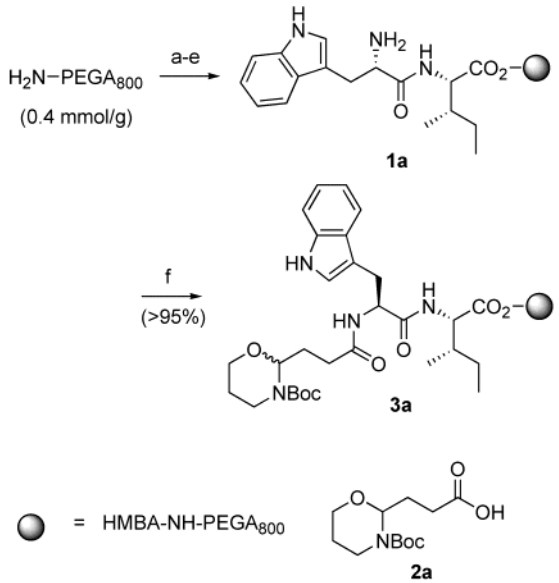
**SCHEME 1. Projected Steps in the Solid-Phase Intramolecular Pictet−Spengler Reaction**

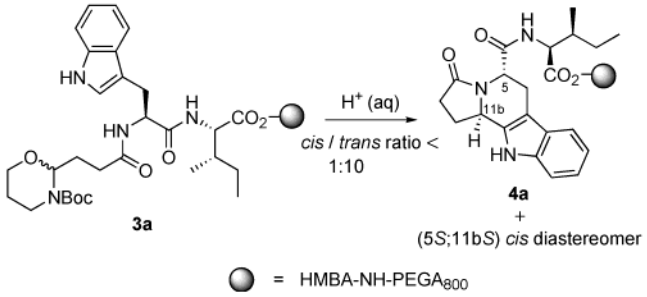



**SCHEME 2. Solid-Phase Synthesis of Pictet−Spengler Reaction Substrate**[a]




[a] Reagents and conditions: (a) HMBA, TBTU, NEM, DMF; (b) Fmoc-Ile-OH, MSNT, MeIm, $CH_2Cl_2$; (c) 20% piperidine (DMF); (d) Fmoc-Trp-OH, TBTU, NEM, DMF; (e) 20% piperidine (DMF); (f) **2a**, TBTU, NEM, DMF.

**TABLE 1. Screening of Aqueous Acidic Reaction Conditions for Intramolecular Pictet−Spengler Reactions**




| | | ratio[a] (**3a**:intermediates[b]:**4a**) | | |
|---|---|---|---|---|
| entry | acid (aq) | 15 min | 1 h | 20 h |
| 1 | 50% HCOOH | 0:10:90 | 0:0:100 | |
| 2 | 50% $CH_3COOH$ | 95:5:0 | 70:20:10 | 0:0:100 |
| 3 | 50% $CH_2ClCOOH$ | 5:40:55 | 0:0:100 | |
| 4 | 20% $CH_2CNCOOH$ | 30:40:30 | 0:20:80 | 0:0:100 |
| 5 | 10% $CCl_3COOH$ | 0:20:80 | 0:0:100 | |
| 6 | 10% TFA | 0:0:100 | | |
| 7 | 20% CSA | 0:20:80 | 0:0:100 | |
| 8 | 10% HCl | 0:0:100 | | |

[a] The diastereomeric ratio and product purity were indicated by analytical RP-HPLC/MS. [b] Presumably lactam−amidal intermediates, which are converted cleanly into **4a**, as the reaction progresses.

the TBTU activation procedure,[61] followed by MSNT-mediated ester bond formation to attach the first amino acid residue (isoleucine).[62] Subsequent cycles of Fmoc deprotection/TBTU-mediated couplings of tryptophan and racemic masked aldehyde building block **2a**, prepared as previously reported,[53] provided the Pictet−Spengler reaction substrate **3a** in the expected 1:1 diastereomeric ratio (Scheme 2).

Optimal reaction conditions for the intramolecular reaction should facilitate a clean demasking of the aldehyde, efficient amide backbone condensation, formation of a cyclic *N*-acyliminium ion, and finally Pictet−Spengler cyclization (Scheme 1). To find such conditions, the substrate was subjected to various aqueous acidic reaction conditions (Table 1).

Pleasingly, the desired hexahydroindolizino[8,7-*b*]indole product **4a** was consistently formed in high product purity (>95%) in a highly stereoselective fashion favoring the (5*S*;11b*R*) trans diastereomer (trans/cis ratio < 10:1), irrespective the nature of the Brønsted acid. Whereas treatment with 50% acetic acid (aq) required several hours for the reaction to reach completion (entry 2), 10% TFA (aq) and 10% HCl (aq) provided the product in less than 15 min (entries 6 and 8, respectively). In fact, treatment of water-preswollen **3a** with 95% TFA (aq) for only 15 s resulted in complete formation of **4a**. Nonaqueous reaction conditions could also be applied in the

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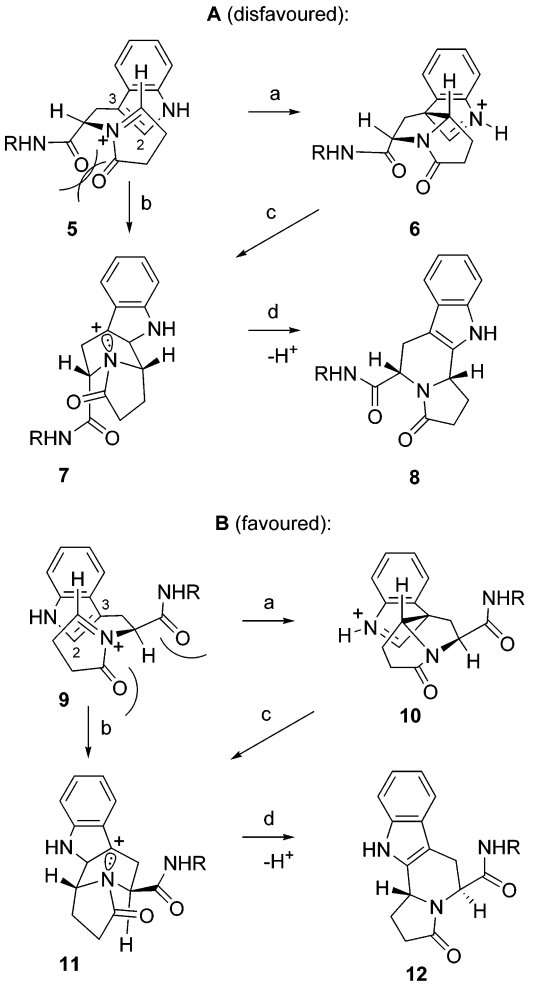
**SCHEME 3. Mechanistic Pathways and Diastereoselectivity of the Pictet−Spengler Reaction**[a]

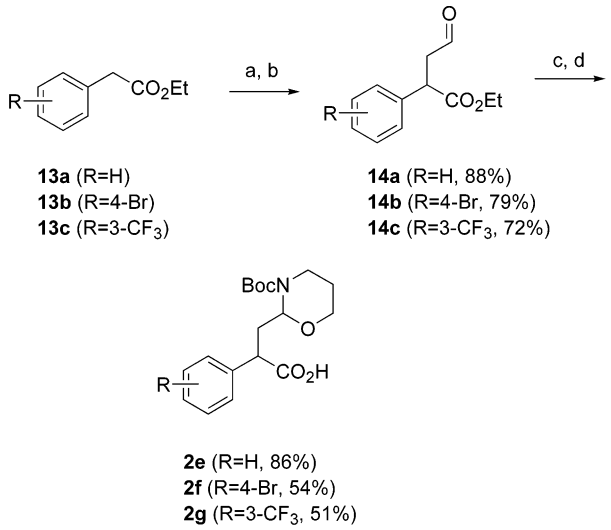



[a] Steps in pathways A and B: (a) attack of C-3 of the indole double bond on the *N*-acyliminium ion; (b) attack of C-2 of the indole double bond on the *N*-acyliminium ion; (c) rearrangement of spiroindolenine; (d) elimination.

reaction, and subjecting **3a** to 10% TFA in solvents, such as $CHCl_3$, $CH_2Cl_2$, or $CH_3CN$, provided clean formation of **4a** within 1 h of reaction time, while solvents comprising DMF, diethyl ether, THF, ethyl acetate, dioxane, and acetone (listed in increasing order of reaction speed) required longer reaction times, although generally resulting in clean product formation. Less polar solvents, such as toluene and petroleum ether, were not efficient, but gave the desired product **4a** (>50%), in addition to substantial amounts of unidentified byproducts (>25%).

In the Pictet−Spengler cyclizations of the present study, a new stereogenic center is formed with excellent diastereocontrol. As we were unable to isolate preparative amounts of the minor diastereomer, comparative NOESY NMR studies could not be carried out. However, a distinct NOE between the amide *N*H and the proton at position 5, and the absence of NOE between the protons at positions 5 and 11b of the tetrahydro-*β*-carboline ring, both support the (5*S*;11b*R*) trans stereochemistry depicted in Table 1. Our work thus complements earlier findings of Cook on the diastereoselective synthesis of

**SCHEME 4. Synthesis of Aryl-Substituted Masked Aldehyde Building Blocks**[a,b]




[a] Reagents and conditions: (a) KHMDS, $BrCH_2CH(OEt)_2$, DMF, rt to 40 °C; (b) TFA:$H_2O$:$CHCl_3$ (3:1:3); (c) $H_2N(CH_2)_3OH$, $Na_2SO_4$, toluene, then $Boc_2O$; (d) KOH, EtOH. [b]Yields for the two steps after flash column chromatography.

1,2,3-trisubstituted-1,2,3,4-tetrahydro-*β*-carbolines,[63] thorough comparative NMR studies by González-Muñiz on (5;11b) cis and trans hexahydroindolizino[8,7-*b*]indole-5-carboxy derivatives,[64,65] investigations by Heaney on fused THBC derivatives,[66] and recent findings by Allin on the formation of the indolizinoindole core.[67]

Given the highly electrophilic nature and the 1,2,3-substitution pattern of the intermediate *N*-acyliminium ion, the reaction may take place by direct attack of carbon-2 of the indole double bond on the *N*-acyliminium ion (step b) to give **11** directly,[63,68,69] followed by elimination of $H^+$ (step d) to furnish the indolizinoindole ring system **12**, as illustrated in pathway B (Scheme 3). The observed diastereoselectivity can be explained by the difference in evolving sterical interactions between the intermediates **5** (sterically disfavored) and **9** (sterically favored), affording either the cis (**8**, pathway A) or trans (**12**, pathway B) isomer, respectively. Alternatively, the mechanism involves the attack of carbon-3 of the indole double bond on the *N*-acyliminium ion (step a) to afford a spiroindolenine **10**, which then rearranges (step c) into **11** prior to the elimination (step d). For both mechanisms, however, the sterically least crowded pathway B is favored and therefore believed to account for the observed trans diastereoselectivity of the reaction.

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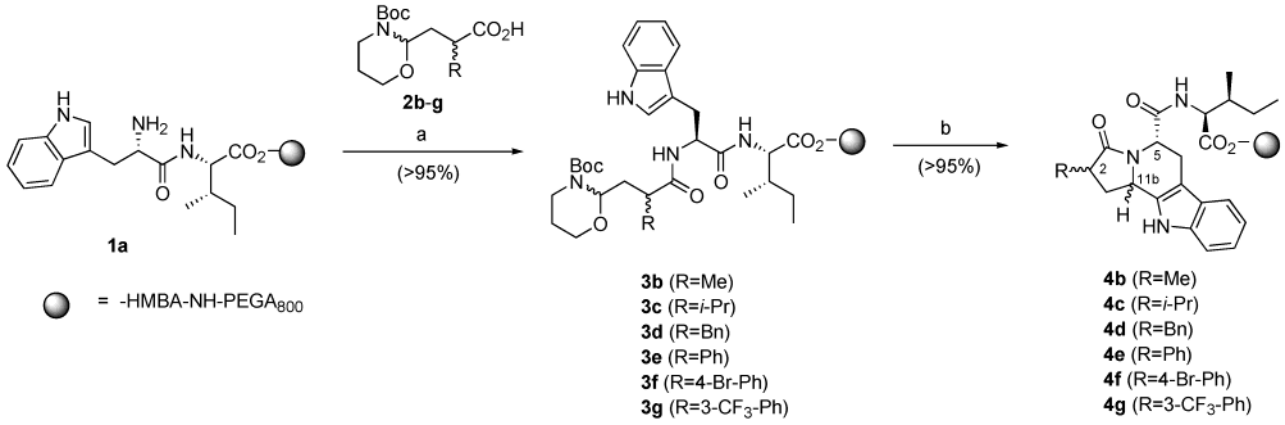
**SCHEME 5. Solid-phase Intramolecular Pictet−Spengler Reactions 1**[a−c]




[a] Reagents and conditions: (a) **2b**−**g**, TBTU, NEM, DMF; (b) 10% TFA (aq). [b]The diastereomeric ratio and product purity were indicated by analytical RP-HPLC/MS. [c]The diastereomeric ratio of **4e**−**g** could not be determined by analytical RP-HPLC/MS (overlapping peaks).

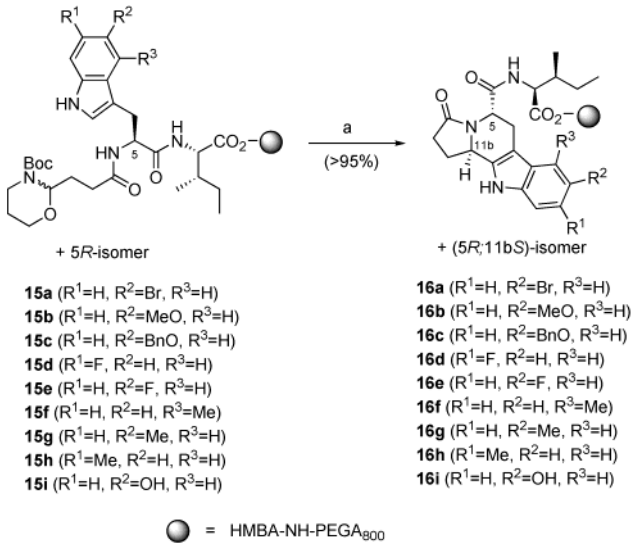
The tetracyclic indolizino[8,7-*b*]indole ring system of **4a** has attracted considerable attention. For example, 3-oxohexahydroindolizino[8,7-*b*]indole-5-carboxylate derivatives have been proposed as mimics of $\beta$-turns,[64] and demonstrated to be potent and selective $CCK_1$ receptor antagonists when attached to peptides.[65] Solid-phase synthesis incorporating the 3-oxohexahydroindolizino-[8,7-*b*]indole-5-carboxyl core within peptide strands has also been reported.[45] The attractive features of this ring system prompted us to introduce substituents around the indolizino[8,7-*b*]indole core structure. For this purpose, the novel aryl-substituted masked aldehyde building blocks **2e**−**g** were made (Scheme 4), in addition to the known masked aldehyde building blocks **2a**−**d**.[53]

Subsequent coupling of **2b**−**g** to the *N*-terminal of a tryptophan moiety and treatment with 10% TFA (aq) efficiently mediated the Pictet−Spengler reaction sequence (Scheme 5). The desired products **4b**−**g** were uniformly formed in high purity (>95%), and the 2-alkyl-substituted products **4b**−**d** were obtained with high stereoselectivity in favor of the (5*S*;11b*R*) trans diastereomer (trans/cis ratio = ∼10:1), as indicated by analytical RP-HPLC/MS, and NOESY NMR studies on the separated (2*S*;5*S*;11b*R*) and (2R;5*S*;11b*R*) stereoisomers of **4d**.

In further rounds of experiments, miscellaneously substituted indoles were also demonstrated to undergo the reaction sequence. Applying reaction conditions similar to those depicted in Scheme 2, a series of commercially available racemic tryptophan derivatives were incorporated between solid-supported isoleucin and masked aldehyde building bock **2a**, and by treatment with 10% TFA (aq), the intramolecular Pictet−Spengler reaction proceeded smoothly with excellent yields (>95%), and high trans diastereoselectivity (trans/cis ratio ≥ 10:1), to afford the products **16a**−**i** (Scheme 6). The only exceptions appear for the formation of **16i** (with lower purity; ∼80%) and **16f** (with lower trans/cis ratio; ∼4:1).

In addition to electron-rich aromatic rings, various heterocycles are known to react in Pictet−Spengler-type condensation reactions, such as furanes[70] and thiophenes.[71] To test such heterocycles in the present intramolecular

**SCHEME 6. Solid-Phase Intramolecular Pictet−Spengler Reactions 2**[a−c]



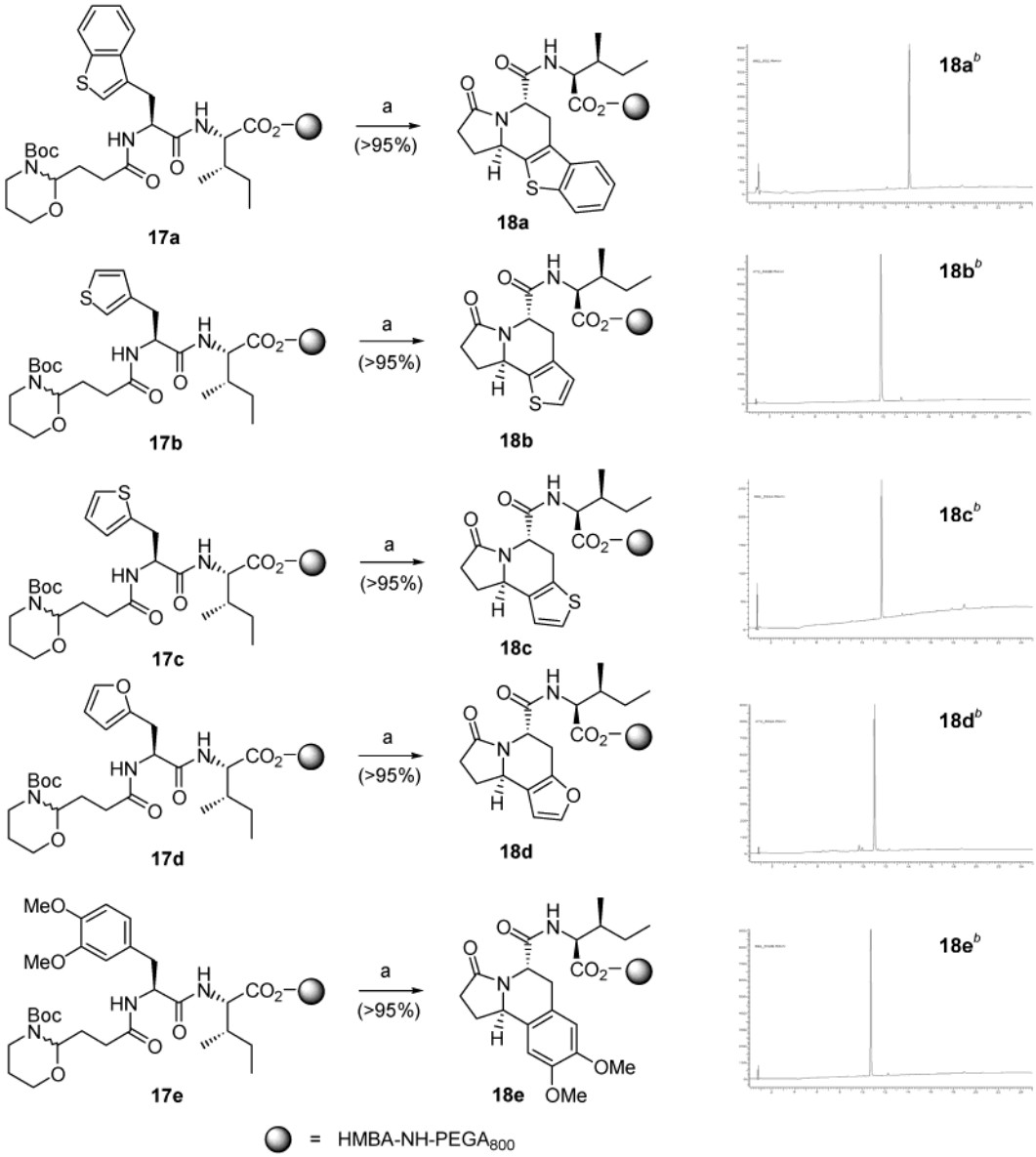

[a] Reagents and conditions: (a) 10% TFA (aq). [b]The diastereomeric ratio and product purity were determined by analytical RP-HPLC/MS. [c]All employed tryptophan derivatives were racemic (except for 5-OH-(L)-Trp), and the products accordingly constituted by equimolar amounts of the (5*S*;11b*R*) and (5*R*;11b*S*) trans diastereomers.

reaction, substrates **17a**−**e** were synthesized analogous to the route depicted in Scheme 2 (using commercially available 3,4-dimethoxyphenyl and heteroaryl-substituted Fmoc-Ala-OH derivatives) and treated with 10% TFA (aq) to provide the cyclized products **18a**−**e** in uniformly excellent yields (>95%) and exclusive trans diastereoselectivity (Scheme 7). The reactivity of the aromatic ring undergoing the intramolecular Pictet−Spengler reaction under the conditions above is highly important. Incorporating phenylalanine, or a tyrosine residue, in the peptide sequence between isoleucine and the masked aldehyde building block did not lead to Pictet−Spengler products, and the reaction presumably stops at the lactam−amidal stage. Clearly, the phenyl and 4-hydroxy-

(70) Miles, W. H.; Heinsohn, S. K.; Brennan, M. K.; Swarr, D. T.; Eidam, P. M.; Gelato, K. A. *Synthesis* **2002**, 1541−1545 and references cited therein.

(71) Othman, M.; Pigeon, P.; Decroix, B. *Tetrahedron* **1997**, *53*, 2495−2504.

**SCHEME 7. Solid-Phase Intramolecular Pictet–Spengler Reactions 3**[a]




[a] Reagents and conditions: (a) 10% TFA (aq). The diastereomeric ratio and product purity were indicated by $^1$H NMR and analytical RP-HPLC/MS. [b]Crude analytical RP-HPLCs (UV detection at 215 nm) of the Pictet–Spengler reaction products cleaved off the solid support as their free carboxylic acids by treatment with 0.1 M NaOH.

phenyl groups are less activated than the more substituted phenyls, such as the 3,4-dimethoxyphenyl functionality, and electronic donation to the reactive carbon seems to be critically important for the reaction outcome. The trans stereochemistry of **18a**–**e** was assigned in analogy to that of **4a** by NOESY NMR studies. The importance of the isoleucin residue of substrates **17a**–**e** was briefly examined. Thus, when introducing glycine instead of isoleucine, the glycine derivatives corresponding to products **18a**–**e** were obtained in the same excellent purity and diastereoselectivity, indicating that the methodology is applicable to a range of natural and unnatural amino acid residues at this position of the peptide sequence. The application of this method to incorporate protected derivatives employed in the general acid labile protecting scheme in Fmoc-based peptide synthesis is currently under investigation and will be described in a forthcoming publication.

## Conclusions

In summary, a novel solid-phase intramolecular *N*-acyliminium Pictet–Spengler reaction has been developed. To a peptide sequence build up from the *N*-terminal may be attached an amino acid containing a reactive aromatic side chain, such as a heteroaryl or dialkoxyphenyl moiety, and immediately terminated by an amide-bonded four-carbon masked aldehyde moiety masked as the *N*-Boc-1,3-oxazinane. In one synthetic step, simple treatment with 10% TFA (aq), an intramolecular Pictet–Spengler reaction sequence, takes place, comprising the steps of (i) aldehyde generation, (ii) amide backbone condensation/formation of *N*-acyliminium ion, and (iii)

Pictet−Spengler cyclization. Overall, two new fused rings are appended to the reactive aromatic side chain in excellent yields (>95%) and trans diastereoselectivity, the latter feature being unprecedented in the solid-phase Pictet−Spengler reaction so far. The reaction provides a smooth and easy access to a range of pharmacologically interesting tri- and tetrasubstituted heterocyclic scaffolds, and the methodology is therefore well-suited for combinatorial library synthesis. Results and applications of this technology in combinatorial chemistry will be reported elsewhere. Key points of diversity are provided by the nature and substituents of the aromatic ring undergoing the Pictet−Spengler cyclization, the substituents of the applied masked aldehyde building blocks, and the building block stereochemistry. Finally, considering the rich chemistry and variety of reactions of *N*-acyliminium ions,[72] we believe that the quantitative *N*-acyliminium ion formation of the present study is worthy of further investigations in intramolecular reactions other than the Pictet−Spengler reaction.

## Experimental Section

**Solid-Phase Synthesis.** Attachment of the 4-hydroxymethylbenzoic acid (HMBA) linker to the amino-functionalized resin was carried out by premixing 4-hydroxymethylbenzoic acid (HMBA, 3.0 equiv), *N*-ethylmorpholine (NEM, 4.0 equiv), and *N*-[(1*H*-benzotriazol-1-yl)-(dimethylamino)methylene]-*N*-methylmethanaminium tetrafluoroborate *N*-oxide (TBTU, 2.88 equiv) for 5 min in DMF. The resulting solution was added to the DMF preswollen resin and allowed to react for 2 h, followed by washing with DMF (6×), and $CH_2Cl_2$ (6×). Coupling of the first amino acid (Ile) to the HMBA-derivatized resin was accomplished by treating the freshly lyophilized resin with a mixture of the Fmoc-Ile-OH (3.0 equiv), 1-methylimidazole (MeIm, 2.25 equiv), and 1-(mesitylene-2-sulfonyl)-3-nitro-1,2,4-triazole (MSNT, 3.0 equiv) in $CH_2Cl_2$:THF (20:1).[62] The 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, TBTU, NEM, DMF),[61] 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 nm. Loadings were then calculated from a calibration curve. HRMS (ESI) analyses were generally performed on collected analytical RP-HPLC fractions. However, HRMS could not be performed on fractions of the Pictet−Spengler reaction substrates **3a**−**g**, **15a**−**i**, and **17a**−**e** due to the acidic nature of the eluent (0.1% TFA), since such temporary storage rapidly yielded the Pictet−Spengler reaction products. Instead, HRMS were performed on **3a**−**g**, **15a**−**i**, and **17a**−**e** directly after basic cleavage and suitable dilution.

**Synthesis of Masked Aldehyde Building Blocks 2e**−**g: General Procedure for α-Alkylation of Aryl Acetic Acid Ethyl Esters/Acid-Mediated Cleavage of Diethylacetals.** A solution of the aryl acetic acid ethyl ester (15 mmol) in DMF (10 mL) was added to a solution of KHMDS (16.5 mmol, 3.29 g) in dry DMF (40 mL). The reaction mixture was stirred at room temperature for 10 min, before dropwise addition of bromoacetaldehyde diethylacetal (16.5 mmol, 3.25 g), followed by heating to 45 °C for 1 h, where TLC indicated complete conversion of the starting material. Upon cooling the reaction mixture to 0 °C, a mixture of sat. $NH_4Cl$ (5 mL) and ice/water (45 mL) was added. The resulting aqueous DMF phase was extracted with hexane (3 × 50 mL). The combined hexane extracts were washed with water (3 × 25 mL) and concentrated. The resulting oil was suspended in water (7.5 mL), cooled to 0 °C, and treated with $CHCl_3$:TFA (1:1, 45 mL) for 2 h. The reaction mixture was poured into a suspension of 1 M aqueous $K_2CO_3$ (115 mL) and $CH_2Cl_2$ (200 mL). Solid $K_2CO_3$ was added until pH 7.5. The organic phase was separated, and the aqueous layer was extracted with a further portion of $CH_2Cl_2$ (120 mL). The combined organic extracts were washed with water (200 mL) and brine (200 mL), then dried over $Na_2SO_4$, filtered, and evaporated to give an oil. The crude product was purified by flash column chromatography on silica gel (petroleum ether:ethyl acetate, 4:1) to give the aldehyde as a colorless oil.

**Analytical Data for Compounds 14a**−**c: Aldehyde 14a.**[73] Yield 88%; $R_f$ 0.21 (petroleum ether:EtOAc, 4:1); $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 9.78 (s, 1H), 7.38−7.21 (m, 5H), 4.25−4.02 (m, 3H), 3.39 (dd, $J$ = 18.5, 10.5 Hz, 1H), 2.80 (dd, $J$ = 18.5, 4.8 Hz, 1H), 1.20 (t, $J$ = 7.5 Hz, 3H); HRMS (ESI) calcd for $C_{12}H_{15}O_3$ $[M + H]^+$ 207.1021, found 207.1037.

**Aldehyde 14b.** Yield 79%; $R_f$ 0.21 (petroleum ether:EtOAc, 4:1); $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 9.77 (s, 1H), 7.51−7.43 (m, 2H), 7.22−7.13 (m, 2H), 4.24−4.02 (m, 3H), 3.36 (dd, $J$ = 18.5, 9.3 Hz, 1H), 2.78 (dd, $J$ = 18.5, 5.0 Hz, 1H), 1.20 (t, $J$ = 7.3 Hz, 3H); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta$ 199.0, 172.3, 136.8, 132.0, 129.4, 121.6, 61.4, 47.0, 44.4, 13.9; HRMS (ESI) calcd for $C_{12}H_{14}BrO_3$ $[M + H]^+$ 285.0126, found 285.0195.

**Aldehyde 14c.** Yield 72%; $R_f$ 0.21 (petroleum ether:EtOAc, 4:1); $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 9.79 (s, 1H), 7.58−7.42 (m, 4H), 4.26−4.04 (m, 3H), 3.42 (dd, $J$ = 18.8, 9.5 Hz, 1H), 2.83 (dd, $J$ = 18.8, $J$ = 7.7, 1H), 1.21 (t, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta$ 198.8, 172.0, 138.8, 131.1, 129.3 (app.s, 2C), 124.4−124.1 (m, 2C), 123.8 (q, $J$(C−$^{19}$F) = 270.5 Hz, 1C), 61.4, 46.8, 44.7, 13.7; HRMS (ESI) calcd for $C_{13}H_{14}F_3O_3$ $[M + H]^+$ 275.0895, found 275.1047.

**General Procedure for *N*-Boc-*N*,*O*-acetalization of Aldehydes with 3-Aminopropan-1-ol and $Boc_2O$/Basic Hydrolysis of Ethyl Esters.** $Na_2SO_4$ (1.14 g, 8.0 mmol) and 3-aminopropanol (158 mg, 2.1 mmol) were added to a solution of the aldehyde (2.0 mmol) in toluene (5 mL). The reaction mixture was stirred for 0.5 h before the addition of $Boc_2O$ (480 mg, 2.2 mmol) in toluene (1 mL), and stirring was continued overnight. The reaction mixture was filtered through Celite, washed with water (2 × 5 mL) and brine (5 mL), dried over $MgSO_4$, filtered through a 2-cm plug of silica gel, and concentrated. The slightly yellow residue was dissolved in ethanol (2 mL), and solid KOH (123 mg, 2.2 mmol) was added in one portion. The resulting solution was stirred overnight, then water (2 mL) was added, and the mixture was cooled to 0 °C. The solution was acidified to pH 4 with 1.0 M HCl (aq) and extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel ($CH_2Cl_2$:MeOH, 20:1) to afford a ∼2:1 diastereomeric mixture of the masked aldehyde building block as a sticky, colorless solid.

**Analytical Data for Compounds 2e**−**g: Masked Aldehyde Building Block 2e (*rac*-MABB5).** Yield 86% (∼2:3 diastereomeric mixture); $R_f$ 0.23 ($CH_2Cl_2$:MeOH, 20:1); $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 7.36−7.16 (m, 5H), 5.50 (dd [app t], $J$ = 7.3 Hz, 0.4H), 5.26 (dd, $J$ = 8.8, 5.3 Hz, 0.6H), 4.02−3.88 (m, 1H), 3.92−3.72 (m, 1H), 3.70−3.52 (m, 2H), 3.14−2.90 (m, 1H), 2.82−2.59 (m, 1H), 2.28−2.10 (m, 0.4H), 2.08−1.95 (m, 0.6H), 1.90−1.67 (m, 1H), 1.52−1.33 (m, 1H), 1.36 (s, 3.6H), 1.29 (s, 5.4H); $^{13}$C NMR (62.5 MHz, $CD_3CN$:$D_2O$, 10:1; major diastereomer) $\delta$ 174.8, 154.2, 139.4, 129.3, 128.6, 127.9, 118.0, 80.4, 59.9, 47.6, 37.3, 32.3, 28.0, 25.6; HRMS (ESI) calcd for $C_{18}H_{26}NO_5$ $[M + H]^+$ 336.1811, found 336.1833.

(72) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817−3856.

(73) Severin, T.; Poehlmann, H. *Chem. Ber.* **1978**, *111*, 1564−1577.

**Masked Aldehyde Building Block 2f (*rac*-MABB6).** Yield 54% (~2:3 diastereomeric mixture); $R_f$ 0.22 ($CH_2Cl_2$:MeOH, 20:1); $^1$H NMR (250 MHz, $CD_3CN$:$D_2O$, 10:1) $\delta$ 7.53−7.44 (m, 2H), 7.32−7.18 (m, 2H), 5.50−5.37 (m, 0.4H), 5.26−5.12 (m, 0.6H), 3.97−3.76 (m, 2H), 3.70−3.56 (m, 1H), 3.55−3.42 (m, 1H), 3.17−2.90 (m, 1H), 2.80−2.63 (m, 0.6H), 2.62−2.47 (m, 0.4H), 2.28−2.12 (m, 0.4H), 2.10−1.95 (m, 0.6H), 1.80−1.57 (m, 1H), 1.56−1.38 (m, 1H), 1.32 (s, 3.6H), 1.27 (s, 5.4H); $^{13}$C NMR (62.5 MHz, $CD_3CN$:$D_2O$, 10:1; major diastereomer) $\delta$ 176.7, 154.9, 139.8, 132.8, 131.4, 121.7, 118.8, 81.0, 60.5, 48.4, 38.0, 33.0, 28.7, 26.2; HRMS (ESI) calcd for $C_{18}H_{24}BrNO_5Na$ [M + Na] 436.0736, found 436.0711.

**Masked Aldehyde Building Block 2g (*rac*-MABB7).** Yield 51% (~2:3 diastereomeric mixture); $R_f$ 0.26 ($CH_2Cl_2$:MeOH, 20:1); $^1$H NMR (250 MHz, $CD_3CN$:$D_2O$, 10:1) $\delta$ 7.68−7.47 (m, 4H), 5.52−5.41 (m, 0.4H), 5.27−5.15 (m, 0.6H), 4.00−3.78 (m, 2H), 3.74−3.56 (m, 2H), 3.29−2.99 (m, 1H), 2.90−2.58 (m, 1H), 2.35−2.19 (m, 0.4H), 2.18−2.02 (m, 0.6H), 1.82−1.56 (m, 1H), 1.55−1.37 (m, 1H), 1.38 (s, 3.6H), 1.31 (s, 5.4H); $^{13}$C NMR (62.5 MHz, $CD_3CN$:$D_2O$, 10:1; major diastereomer) $\delta$ 175.2, 154.6, 141.0, 133.0, 130.5 (app s, 2C), 125.7 (m, 1C), 125.3 (q, $J$(C−$^{19}$F) = 270.4 Hz, 1C), 125.1 (m, 1C), 118.5, 80.7, 60.3, 48.0, 37.7, 32.7, 28.4, 25.9; HRMS (ESI) calcd for $C_{19}H_{24}F_3NO_5Na$ $[M + Na]^+$ 426.1505, found 426.1411.

**Analytical Data for Pictet−Spengler Reaction Substrates: *rac*-MABB1-Trp-Ile-OH (3a).** Purity >95%; $R_t$ = 14.54, 14.67 min; HRMS (ESI) calcd for $C_{29}H_{43}N_4O_7$ $[M + H]^+$ 559.3132, found 559.3166.

***rac*-MABB2-Trp-Ile-OH (3b).** Purity >95%; $R_t$ = 14.94, 15.06 (overlapping peaks), 15.56 min; HRMS (ESI) calcd for $C_{30}H_{45}N_4O_7$ $[M + H]^+$ 573.3288, found 573.3325.

***rac*-MABB3-Trp-Ile-OH (3c).** Purity >95%; $R_t$ = 16.80, 16.92, 17.05, 17.41 min; HRMS (ESI) calcd for $C_{33}H_{51}N_4O_7$ $[M + H]^+$ 615.3758, found 615.3765.

***rac*-MABB4-Trp-Ile-OH (3d).** Purity >95%; $R_t$ = 17.04 (overlapping peaks), 17.20, 17.50 min; HRMS (ESI) calcd for $C_{36}H_{49}N_4O_7$ $[M + H]^+$ 649.3601, found 649.3625.

***rac*-MABB5-Trp-Ile-OH (3e).** Purity >95%; $R_t$ = 16.64 (overlapping peaks), 16.86 min; HRMS (ESI) calcd for $C_{35}H_{47}N_4O_7$ $[M + H]^+$ 635.3445, found 635.3489.

***rac*-MABB6-Trp-Ile-OH (3f).** Purity >95%; $R_t$ = 17.74 (overlapping peaks), 17.97 min; HRMS (ESI) calcd for $C_{35}H_{46}BrN_4O_7$ $[M + H]^+$ 713.2550, found 713.2599.

***rac*-MABB7-Trp-Ile-OH (3g).** Purity >95%; $R_t$ = 17.99 (overlapping peaks), 18.18 min; HRMS (ESI) calcd for $C_{36}H_{46}F_3N_4O_7$ $[M + H]^+$ 703.3318, found 703.3382.

***rac*-MABB1-(5-Br-(D/L))Trp-Ile-OH (15a).** Purity >95%; $R_t$ = 15.69, 15.79 min (overlapping peaks); HRMS (ESI) calcd for $C_{29}H_{42}BrN_4O_7$ $[M + H]^+$ 637.2237, found 637.2281.

***rac*-MABB1-(5-MeO-(D/L))Trp-Ile-OH (15b).** Purity >95%; $R_t$ = 14.18 (overlapping peaks), 14.32 min; HRMS (ESI) calcd for $C_{30}H_{45}N_4O_8$ $[M + H]^+$ 589.3237, found 589.3270.

***rac*-MABB1-(5-BnO-(D/L))Trp-Ile-OH (15c).** Purity >95%; $R_t$ = 16.85 min (overlapping peaks); HRMS (ESI) calcd for $C_{36}H_{49}N_4O_8$ $[M + H]^+$ 665.3550, found 665.3599.

***rac*-MABB1-(5-F-(D/L))Trp-Ile-OH (15d).** Purity >95%; $R_t$ = 14.85 min (overlapping peaks); HRMS (ESI) calcd for $C_{29}H_{42}FN_4O_7$ $[M + H]^+$ 577.3037, found 577.3043.

***rac*-MABB1-(6-F-(D/L))Trp-Ile-OH (15e).** Purity >95%; $R_t$ = 14.81 min (overlapping peaks); HRMS (ESI) calcd for $C_{29}H_{42}FN_4O_7$ $[M + H]^+$ 577.3037, found 577.3356.

***rac*-MABB1-(4-Me-(D/L))Trp)-Ile-OH (15f).** Purity >95%; $R_t$ = 15.05, 15.19 min (overlapping peaks); HRMS (ESI) calcd for $C_{30}H_{45}N_4O_7$ $[M + H]^+$ 573.3288, found 573.3322.

***rac*-MABB1-(5-Me-(D/L))Trp-Ile-OH (15g).** Purity >95%; $R_t$ = 15.15, 15.23 min (overlapping peaks); HRMS (ESI) calcd for $C_{30}H_{45}N_4O_7$ $[M + H]^+$ 573.3288, found 573.3317.

***rac*-MABB1-(6-Me-(D/L))Trp-Ile-OH (15h).** Purity >95%; $R_t$ = 15.23 min (overlapping peaks); HRMS (ESI) calcd for $C_{30}H_{45}N_4O_7$ $[M + H]^+$ 573.3288, found 573.3305.

***rac*-MABB1-(5-OH)Trp-Ile-OH (15i).** Purity >95%; $R_t$ = 12.78, 12.92 min; HRMS (ESI) calcd for $C_{29}H_{43}N_4O_8$ $[M + H]^+$ 575.3081, found 575.3112.

***rac*-MABB1-(3-(2-furyl))Ala-Ile-OH (17a).** Purity >95%; $R_t$ = 13.66, 13.84 min; HRMS (ESI) calcd for $C_{25}H_{40}N_3O_8$ $[M + H]^+$ 510.2815, found 510.2824.

***rac*-MABB1-(3-(2-thienyl))Ala-Ile-OH (17b).** Purity >95%; $R_t$ = 14.17, 14.31 min; HRMS (ESI) calcd for $C_{25}H_{40}N_3O_7S$ $[M + H]^+$ 526.2587, found 526.2635.

***rac*-MABB1-(3-(3-thienyl))Ala-Ile-OH (17c).** Purity >95%; $R_t$ = 14.20, 14.34 min; HRMS (ESI) calcd for $C_{25}H_{40}N_3O_7S$ $[M + H]^+$ 526.2587, found 526.2610.

***rac*-MABB1-(3-(3-benzothienyl))Ala-Ile-OH (17d).** Purity >95%; $R_t$ = 15.84, 15.94 min; HRMS (ESI) calcd for $C_{29}H_{42}N_3O_7S$ $[M + H]^+$ 576.2743, found 576.2798.

***rac*-MABB1-(3-(3,4-dimethoxyphenyl))Ala-Ile-OH (17e).** Purity >95%; $R_t$ = 13.64, 13.73 min; HRMS (ESI) calcd for $C_{29}H_{466}N_3O_9$ $[M + H]^+$ 580.3234, found 580.3267.

**General Procedure for Solid-Phase Pictet−Spengler Reactions.** The solid-supported substrate for the Pictet−Spengler reaction was swelled in 10% TFA (aq) and allowed to react for 2 h, before washing the resin with water (6×), DMF (6×), and $CH_2Cl_2$ (6×). The resin was briefly lyophilized prior to cleavage of the reaction product from the solid support.

**Analytical Data for Pictet−Spengler Reaction Products: Pictet−Spengler Reaction Product of *rac*-MABB1-Trp-Ile-OH (4a).** Purity >95%; $R_t$ = 11.96 min;$^1$H NMR (250 MHz, $CD_3CN$) $\delta$ 7.44 (d, $J$ = 7.5 Hz, 1H), 7.32 (d, $J$ = 8.0 Hz, 1H), 7.14−6.92 (m, 2H), 5.16−5.08 (m, 2H), 4.08 (d, $J$ = 5.8 Hz, 1H), 3.40 (d, $J$ = 15.8 Hz, 1H), 3.01−2.80 (m, 1H), 2.80−2.52 (m, 2H), 2.50.2.29 (m, 1H), 1.95−1.62 (m, 2H), 1.35−1.16 (m, 1H), 1.03−0.78 (m, 1H), 0.76−0.55 (m, 6H); HRMS (ESI) calcd for $C_{21}H_{26}N_3O_4$ $[M + H]^+$ 384.1923, found 384.1911.

**Pictet−Spengler Reaction Products of *rac*-MABB2-Trp-Ile-OH (4b).** Purity >95%; $R_t$ = 12.62 (HRMS (ESI) calcd for $C_{22}H_{28}N_3O_4$ $[M + H]^+$ 398.2080, found 398.2091), 12.89 min (HRMS (ESI) found 398.2089).

**Pictet−Spengler Reaction Products of *rac*-MABB3-Trp-Ile-OH (4c).** Purity >95%; $R_t$ = 15.20 (HRMS (ESI) calcd for $C_{25}H_{34}N_3O_4$ $[M + H]^+$ 440.2549, found 440.2553), 15.59 min (HRMS (ESI) found 440.2564).

**Pictet−Spengler Reaction Products of *rac*-MABB4-Trp-Ile-OH (4d).** Purity >95%; $R_t$ = 15.39 (HRMS (ESI) calcd for $C_{28}H_{32}N_3O_4$ $[M + H]^+$ 474.2393, found 474.2405), 15.76 min (HRMS (ESI) found 474.2406).

**Pictet−Spengler Reaction Products of *rac*-MABB5-Trp-Ile-OH (4e).** Purity >95%; $R_t$ = 14.35 (HRMS (ESI) calcd for $C_{27}H_{30}N_3O_4$ $[M + H]^+$ 460.2236, found 460.2238), 14.53 (HRMS (ESI) found 460.2245), 14.86 min (HRMS (ESI) found 460.2254).

**Pictet−Spengler Reaction Products of *rac*-MABB6-Trp-Ile-OH (4f).** Purity >95%; $R_t$ = 15.64 (HRMS (ESI) calcd for $C_{27}H_{29}N_3O_4$ $[M + H]^+$ 538.1341, found 538.1356), 15.75 (HRMS (ESI) found 538.1366), 16.28 min (HRMS (ESI) found 538.1358).

**Pictet−Spengler Reaction Products of *rac*-MABB7-Trp-Ile-OH (4g).** Purity >95%; $R_t$ = 16.14 (HRMS (ESI) calcd for $C_{28}H_{29}F_3N_3O_4$ $[M + H]^+$ 528.2110, found 528.2100), 16.50 min (HRMS (ESI) found 528.2153).

**Pictet−Spengler Reaction Products of *rac*-MABB1-(5-Br-(D/L))Trp-Ile-OH (16a).** Purity >95%; $R_t$ = 13.64 (HRMS (ESI) calcd for $C_{21}H_{25}BrN_3O_4$ $[M + H]^+$ 462.1028, found 462.0984), 14.19 min (HRMS (ESI) found 462.1051).

**Pictet−Spengler Reaction Products of *rac*-MABB1-(5-MeO-(D/L))Trp-Ile-OH (16b).** Purity >95%; $R_t$ = 11.56 (HRMS (ESI) calcd for $C_{22}H_{28}N_3O_5$ $[M + H]^+$ 414.2029, found 414.2026), 12.01 min (HRMS (ESI) found 414.2021).

**Pictet−Spengler Reaction Products of *rac*-MABB1-(5-BnO-(D/L))Trp-Ile-OH (16c).** Purity >95%; $R_t$ = 14.96 (HRMS (ESI) calcd for $C_{28}H_{32}N_3O_5$ $[M + H]^+$ 490.2342, found 490.2353), 15.19 min (HRMS (ESI) found 490.2340).

**Pictet−Spengler Reaction Products of *rac*-MABB1-(5-F-(D/L))Trp-Ile-OH (16d).** Purity >95%; $R_t$ = 12.38 (HRMS (ESI) calcd for $C_{21}H_{25}FN_3O_4$ [M + H]$^+$ 402.1829, found 402.1830), 12.98 min (HRMS (ESI) found 402.1855).

**Pictet−Spengler Reaction Products of *rac*-MABB1-(6-F-(D/L))Trp-Ile-OH (16e).** Purity >95%; $R_t$ = 12.46 (HRMS (ESI) calcd for $C_{21}H_{25}FN_3O_4$ [M + H]$^+$ 402.1829, found 402.1839), 13.06 min (HRMS (ESI) found 402.1828).

**Pictet−Spengler Reaction Products of *rac*-MABB1-(4-Me-(D/L))Trp)-Ile-OH (16f).** Purity >95%; $R_t$ = 12.64 (HRMS (ESI) calcd for $C_{22}H_{28}N_3O_4$ [M + H]$^+$ 398.2080, found 398.2081), 13.19 min (HRMS (ESI) found 398.2079).

**Pictet−Spengler Reaction Products of *rac*-MABB1-(5-Me-(D/L))Trp-Ile-OH (16 g).** Purity >95%; $R_t$ = 12.98 (HRMS (ESI) calcd for $C_{22}H_{28}N_3O_4$ [M + H]$^+$ 398.2080, found 398.2091), 13.53 min (HRMS (ESI) found 398.2076).

**Pictet−Spengler Reaction Products of *rac*-MABB1-(6-Me-(D/L))Trp-Ile-OH (16h).** Purity >95%; $R_t$ = 12.94 (HRMS (ESI) calcd for $C_{22}H_{28}N_3O_4$ [M + H]$^+$ 398.2080, found 398.2095), 13.53 min (HRMS (ESI) found 398.2067).

**Pictet−Spengler Reaction Products of *rac*-MABB1-(5-OH)Trp-Ile-OH (16i).** Purity ∼80%; $R_t$ = 9.31 min; HRMS (ESI) calcd for $C_{21}H_{26}N_3O_5$ [M + H]$^+$ 400.1872, found 400.1875.

**Pictet−Spengler Reaction Product of *rac*-MABB1-(3-(2-furyl))Ala-Ile-OH (18a).** Purity >95%; $R_t$ = 11.00 min; $^1$H NMR (250 MHz, DMSO-$d_6$) $\delta$ 12.63 (br s, 1H), 8.17 (d, $J$ = 8.3 Hz, 1H), 7.52 (d, $J$ = 1.8 Hz, 1H), 6.39 (d, $J$ = 1.8 Hz, 1H), 5.12 (d, $J$ = 7.3 Hz, 1H), 4.87 (m, 1H), 4.11 (dd, $J$ = 8.3, 6.5 Hz, 1H), (d, $J$ = 16.5 Hz, 1H), 2.88 (dd, $J$ = 16.5, 8.0 Hz), 2.63−2.40 (m, 1H), 2.38−2.16 (m, 2H), 1.90−1.71 (m, 1H), 1.68−1.47 (m, 1H), 1.46−1.25 (m, 1H), 1.24−1.02 (m, 1H), 0.92−0.70 (m, 6H); HRMS (ESI) calcd for $C_{17}H_{23}N_2O5$ [M + H]$^+$ 335.1607, found 335.1627.

**Pictet−Spengler Reaction Products of *rac*-MABB1-(3-(2-thienyl))Ala-Ile-OH (18b).** Purity >95%; tan powder containing 10.96 mg of **18b** (84% isolated yield) after cleavage from the resin (starting from 78.2 mg of PEGA$_{800}$ resin) with 0.1 M aqueous NaOH (1.0 mL), neutralization with 0.1 M aqueous HCl (1.0 mL), dilution with acetonitrile (2 mL), filtration, washing with acetonitrile (3 × 2 mL), and evaporation of the combined filtrates to dryness; $R_t$ = 11.59 min; $^1$H NMR (250 MHz, DMSO-$d_6$) $\delta$ 12.61 (br s, 1H), 8.16 (d, $J$ = 8.5 Hz, 1H), 7.36 (d, $J$ = 5.5 Hz, 1H), 6.90 (d, $J$ = 5.5 Hz, 1H), 5.08 (d, $J$ = 6.5 Hz, 1H), 4.96 (dd [app t], $J$ = 7.0 Hz, 1H), 4.10 (dd, $J$ = 8.0, 6.3 Hz), 3.26 (d, $J$ = 16.3 Hz, 1H), 2.98 (dd, $J$ = 16.3, 7.8 Hz), 2.65−2.46 (m, 2H), 2.35−2.18 (m, 1H), 1.90−1.69 (m, 1H), 1.68−1.45 (m, 1H), 1.42−1.20 (m, 1H), 1.20−1.00 (m, 1H), 0.92−0.65 (m, 6H); HRMS (ESI) calcd for $C_{17}H_{23}N_2O_4S$ [M + H]$^+$ 351.1378, found 351.1384.

**Pictet−Spengler Reaction Product of *rac*-MABB1-(3-(3-thienyl))Ala-Ile-OH (18c).** Purity >95%; $R_t$ = 11.78 min; $^1$H NMR (250 MHz, DMSO-$d_6$) $\delta$ 12.61 (br s, 1H), 8.17 (d, $J$ = 8.5 Hz, 1H), 7.39 (d, $J$ = 5.0 Hz, 1H), 6.84 (d, $J$ = 5.0 Hz, 1H), 5.13 (dd [app t], $J$ = 7.4 Hz, 1H), 5.03 (d, $J$ = 7.3 Hz, 1H), 4.10 (dd, $J$ = 8.3, 6.5 Hz, 1H), 3.13 (d, $J$ = 16.5 Hz, 1H), 2.91−2.75 (m, 1H), 2.65−2.44 (m, 2H), 2.38−2.20 (m, 1H), 1.89−1.58 (m, 2H), 1.44−1.25 (m, 1H), 1.22−1.04 (m, 1H), 0.86−0.70 (m, 6H); HRMS (ESI) calcd for $C_{17}H_{23}N_2O_4S$ [M + H]$^+$ 351.1378, found 351.1383.

**Pictet−Spengler Reaction Products of *rac*-MABB1-(3-(3-benzothienyl))Ala-Ile-OH (18d).** Purity >95%; $R_t$ = 14.09 min; $^1$H NMR (250 MHz, DMSO-$d_6$) $\delta$ 12.59 (br s, 1H), 8.30 (d, $J$ = 8.3 Hz, 1H), 8.00−7.87 (m, 1H), 7.68−7.58 (m, 1H), 7.46−7.28 (m, 2H), 5.30−5.19 (m, 1H), (d, $J$ = 7.3 Hz), 4.09 (dd, $J$ = 8.5, 6.8 Hz, 1H), 3.35 (d, $J$ = 16.5 Hz, 1H), 2.97 (ddd, $J$ = 16.5, 8, 2.4 Hz, 1H), 2.70−2.52 (m, 2H), 2.42−2.25 (m, 1H), 1.92−1.68 (m, 2H), 1.46−1.25 (m, 1H), 1.25−1.03 (m, 1H), 0.91−0.68 (m, 6H); HRMS (ESI) calcd for $C_{21}H_{25}N_2O_4S$ [M + H]$^+$ 401.1535, found 401.1543.

**Pictet−Spengler Reaction Products of *rac*-MABB1-(3-(3,4-dimethoxyphenyl))Ala-Ile-OH (18e).** Purity >95%; white powder containing 6.54 mg of **18e** (79% isolated yield) after cleavage from the resin (starting from 51.2 mg of PEGA$_{800}$ resin) with 0.1 M aqueous NaOH (1.0 mL), neutralization with 0.1 M aqueous HCl (1.0 mL), dilution with acetonitrile (2 mL), filtration, washing with acetonitrile (3 × 2 mL), and evaporation of the combined filtrates to dryness; $R_t$ = 10.56 min; $^1$H NMR (250 MHz, DMSO-$d_6$) $\delta$ 12.61 (br s, 1H), 8.11 (d, $J$ = 8.3 Hz, 1H), 6.73 (d, $J$ = 4.5 Hz, 2H), 4.90 (dd [app t], $J$ = 7.3 Hz, 1H), 4.80 (dd, $J$ = 6.8, 4.0 Hz, 1H), 4.09 (dd, $J$ = 6.5, 8.3 Hz, 1H), 3.72 (s, 6H), 3.07−2.81 (m, 2H), 2.74−2.58 (m, 1H), 2.58−2.40 (m, 1H), 2.32−2.15 (m, 1H), 1.88−1.61 (m, 2H), 1.44−1.25 (m, 1H), 1.23−1.00 (m, 1H), 0.84−0.65 (m, 6H); HRMS (ESI) calcd for $C_{21}H_{29}N_2O_6$ [M + H]$^+$ 405.2025, found 425.2019.

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**Supporting Information Available:** $^1$H NMR spectra for compounds **2e**−**g**, **4a**, **14a**−**c**, and **18a**−**e**, and analytical RP-HPLCs of the Pictet−Spengler reaction products **4a**−**g** and **16a**−**i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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