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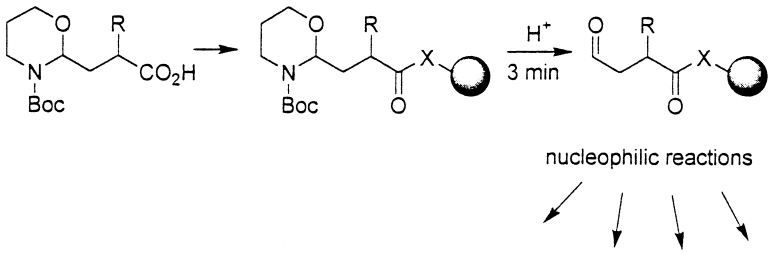

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Synthesis of Aldehyde Building Blocks Protected as Acid Labile *N*-Boc *N,O*-Acetals: Toward Combinatorial Solid Phase Synthesis of Novel Peptide Isosteres[1,†]

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The synthesis of (*RS*)-3′-*tert*-butoxycarbonyl-perhydro-1′,3′-oxazine-2′-yl acetic acid and the syntheses of the simple and C-2 substituted 3′-*tert*-butoxycarbonyl-perhydro-1′,3′-oxazine-2′(*RS*)-yl propionic acids from simple starting materials are presented. The simple compounds were prepared from 1,3-propanediol and 1,4-butanediol, respectively, via a short series of facile steps, in 70% overall yield in both cases. For the syntheses of the C-2 substituted compounds of the longer homologue, (*RS*)-3′-*tert*-butoxycarbonyl-perhydro-1′,3′-oxazine-2′-yl propionic acid, a malonic ester route was selected, thus allowing easy incorporation of various side chains. The stability of the novel aldehyde protection group, the *N*-Boc *N,O*-acetal moiety, under various acidic conditions was investigated, and it was found to cleanly and rapidly yield the aldehyde under strong acidic conditions or, if desired, slower under less harsh conditions. As a demonstration of the use of the building blocks, one building block was coupled to a solid support and, after unmasking of the aldehyde, submitted to three different types of nucleophilic reactions (Pictet−Spengler condensation, reductive amination, Horner−Wadsworth−Emmons olefination) followed by further chemical modification, and the identity of the structures were verified after cleavage from the resin.

Introduction

With the understanding of how proteolytic enzymes are involved in essential processes of various pathological phenomena such as viral interactions, cancer, osteoporosis, etc., the interest in proteolytic enzymes and their application as drug targets has increased. The appearance of combinatorial chemistry as a tool to generate lead compounds has facilitated the drug discovery process. The active sites of many proteases are well-defined cavities, and small molecules mimicking the interaction of the natural macromolecular substrates may act as high affinity inhibitors.[2,3] Inhibitors of both peptidic and nonpeptidic natures may be synthesized by combinatorial methods on a solid support by use of peptide isosteric building blocks. In a program to produce the isosters directly on solid support in a combinatorial fashion, building blocks of the type **1** and **2** (Figure 1) may be promising as versatile precursors. These building blocks were designed so that they contain three essential functionalities: (1) a carboxylic acid for attachment onto a peptide; (2) a C-2 side chain that mimics the side chain of an amino acid; and (3) a masked aldehyde, which when unmasked may act as a strong electrophile with a large variety of nucleophiles. The reaction between *n* differently substituted aldehydes and *m* different nucleophiles will thus produce $n \times m$ isosters, which will be positioned at the *N*-terminus of a peptide, or centrally in the peptide if peptide synthesis can be continued after the nucleophilic reaction. Examples of compounds with the properties similar to those of the type **2** building block have been described;[4−8] however, none are suitable for the present purpose.

Since removal of side products is not possible on solid phase, a method of generating an aldehyde *quantitatively* on solid phase was desired, or in other words, without formation of any side products or unreacted starting material. Another requirement was *rapid* generation of the aldehyde, and furthermore, it was desired that the unmasking step only employ mild reagents and conditions practical to use on solid phase.

Aldehydes can be masked in a variety of ways,[9,10] for example, as *O,O*-acetals,[4,7,8] *O,S*-acetals, *S,N*-acetals, *S,S*-acetals,[5,6] *Se,Se*-acetals, as a thiazole,[11,12] and more, or they can simply be "masked" as an alcohol or an ester or amide which may be converted to an aldehyde upon oxidation or reduction, respectively. Oxidation of an alcohol is not preferred since it requires protection of all other alcohols present in the peptide, and furthermore, initial test oxidations

† **Abbreviations.** ESMS: electrospray mass spectrometry; HATU: *N*-[(dimethylamino)-1*H*-1,2,3-triazolo-[4,5-*b*]pyridin-1-yl-methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide; HOAt: 1-hydroxy-7-azabenzotriazole; HSQC: heteronuclear single quantum coherence spectroscopy; KHMDS: potassium hexamethyldisilazane; MAS NMR: magic angle spinning nanoprobe nuclear magnetic resonance; MSNT: 2,4,6-mesitylenesulfonyl-3-nitro-1,2,4-triazolide; NEM: *N*-ethylmorpholine; POE-POP: polyoxyethylene-polyoxypropylene copolymer; RP-HPLC: reversed phase high performance liquid chromatography; TBABr: tetra-*n*-butylammonium bromide; TBAF: tetra-*n*-butylammonium fluoride; TCA: trichloroacetic acid; TEMPO: 2,2,6,6-tetramethyl-1-piperidinyloxy.

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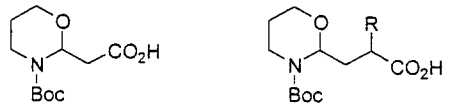


Figure 1. Versatile peptide isostere precursors.

using Py·SO_3/DMSO/TEA[13] resulted in resin bound aldehyde, though not of a satisfactory purity and not sufficiently rapid. The unmasking of thio and selenium acetals has the disadvantage of requiring, e.g., heavy atom compounds (Hg, Ag, Cu)[9] or nonselective reagents such as methyl iodide, and are hence impractical for use on solid phase. The ease of hydrolysis of cyclic *O*,*O*-acetals is variable and may be dependent on the nature of the compound,[9] and acyclic *O*,*O*-acetals are too acid labile. Finally, the protection group should also be able to withstand the chemical manipulations used at a later stage of the building block synthesis.

For these reasons, focus was directed toward masking the aldehyde as an *N*,*O*-acetal, namely as a perhydro-1,3-oxazine.[14] The interest in protecting the aldehyde as an *N*-Boc *N*,*O*-acetal was inspired by the work of Agami et al.,[15,16] in which an aldehyde was converted into a chiral *N*-Boc oxazolidine, in order to act as an auxiliary, and at a later stage converted back into the aldehyde by treatment with TFA and water. *N*,*O*-Acetals are exceedingly susceptible to hydrolysis, yet this can be conquered by protecting the nitrogen atom. Employing the Boc group for this results in a masked aldehyde which is stable under very harsh basic conditions and rapidly removed with, e.g., TFA.[9]

The present work has resulted in a practical procedure for the synthesis of unsubstituted building blocks **1** and **2** (R = H) as well as an expeditious and general route to C-2 substituted building blocks of type **2** (R ≠ H) (Figure 1).

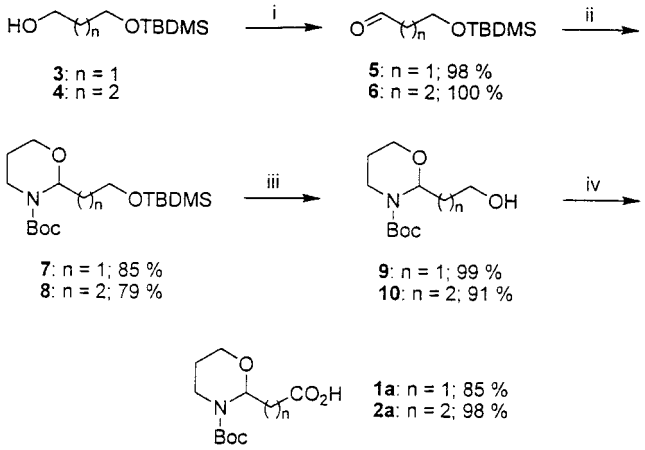
Results and Discussion

Two distinct routes toward the building blocks were selected, one starting from either 1,3-propanediol or 1,4-butanediol, the other one from diethylmalonate. The advantage of the first route is that it readily can be used for synthesizing both of the simple building block homologues **1a** and **2a** (Scheme 1); the disadvantage is that it is somewhat impractical for synthesis of the C-2 substituted type **2** building blocks. For C-2 substituted type **1** compounds the starting compounds, 2-substituted 1,3-propanediols, are easily available prepared from malonic esters. Since nearly all interest lies in the building blocks of type **2**, C-2 substituted type **1** building blocks were not synthesized.

The second route only leads to building blocks of type **2**, yet has the advantage that a large number of side chains can be introduced at a relatively late stage of the synthesis.

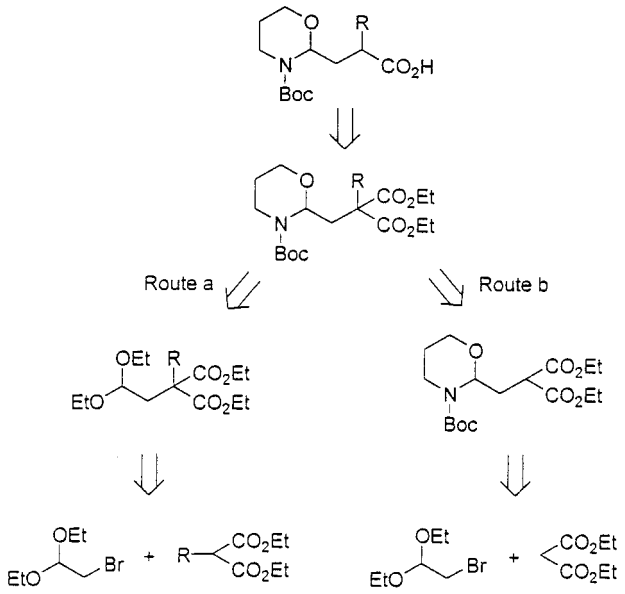
Building Block Synthesis via Diols. *tert*-Butyl dimethyl silyl ethers **3** and **4** were prepared according to literature methods from the corresponding diols,[17,18] and oxidation of the unprotected alcohols to aldehydes was conveniently accomplished using TEMPO/NaOCl[19] (Scheme 1). The crude aldehydes **5** and **6** were sufficiently pure to be used directly in the following protection of the aldehyde carbonyl, which proceeded in good yields (n = 1, 85%; n = 2, 79%). To fully preserve the acid sensitive Boc group, the silyl

Scheme 1[a]



[a] Reagents and conditions: (i) TEMPO, NaOCl, NaBr, 0 °C, 8 min; (ii) (a) 3-aminopropanol, K_2CO_3, toluene, (b) Boc_2O; (iii) TBAF, THF; (iv) TEMPO, NaOCl, NaBr, TBABr, 0 °C, 30 min.

Scheme 2

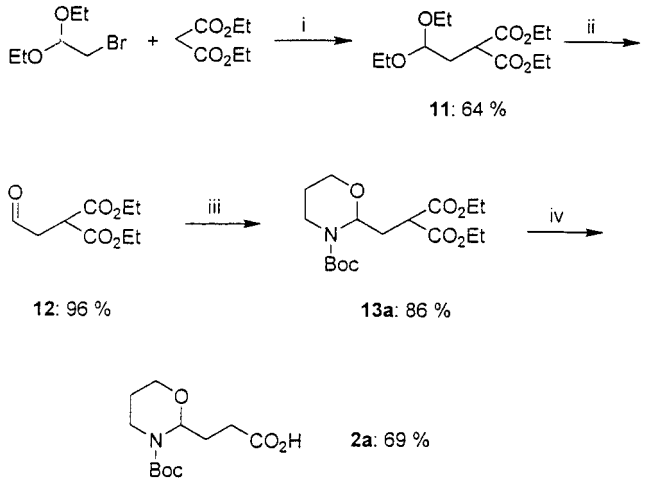


protection group was removed using basic TBAF,[20] which afforded alcohols **9** and **10** in excellent yields. To oxidize the alcohols, the TEMPO/NaOCl protocol was used again, this time in the presence of catalytic amounts of the phase-transfer reagent TBABr, thus catalyzing the oxidation to the carboxylic acid.[21]

Although synthesizing building blocks **1a** and **2a** was convenient and proceeded with good overall yields (**3** → **1a** and **4** → **2a**: 70%), the method cannot directly be adapted to synthesize C-2 substituted type **2** building blocks. To incorporate side chains at this position, esterification of **2a** (MeI/Cs_2CO_3/DMF) followed by alkylation at C-2 with LDA/BnBr in HMPA/THF was performed. This approach was inefficient since the alkylation step yielded only 27% of the methyl ester of **2d** but also since this route toward incorporation of side chains requires three extra steps (esterification, alkylation, ester cleavage).

Building Block Synthesis via Malonic Esters. The considered route a (Scheme 2) benefits from the fact that a large number of substituted malonic esters are commercially available, thus decreasing the number of synthetic steps. First,

Scheme 3[a]



[a] Reagents and conditions: (i) K_2CO_3, DMF, reflux; (ii) TFA:H_2O:$HCCl_3$ 3:1:3, 0 °C; (iii) (a) 3-aminopropanol, Na_2SO_4, toluene, (b) Boc_2O; (iv) (a) KOH, EtOH, 20 °C, (b) pyridine, reflux, 3 h.

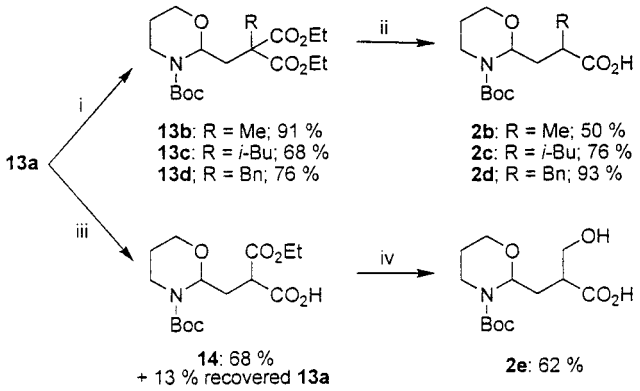
alkylations of benzyl and *iso*-butyl substituted malonic acid diethylester with bromoacetaldehyde diethylacetal were attempted, but purification of the crude products by either flash chromatography or distillation did not furnish the expected compounds.

Instead, route b was attempted. Diethyl malonate was coupled with bromoacetaldehyde diethylacetal to give **11** in good yield (64%) after distillation (Scheme 3). This reaction is described in the literature employing sodium ethoxide[22−25] or sodium hydride[26,27] as base; nevertheless, we attempted the alkylation using potassium carbonate, a modified procedure which was found to be very practical. The diethyl acetal moiety of **11** was cleaved using aqueous TFA, and the resulting aldehyde, which by TLC and NMR was shown to be pure, was immediately protected as an *N*-Boc *N*,*O*-acetal. Where potassium carbonate previously had been employed as drying agent in the acetalization step, sodium sulfate was preferred due to its lower basicity. The product from this reaction, **13a**, did not need purification and was therefore used directly in the following steps.

Deprotonation of **13a** with KHMDS and alkylation with either MeI, *i*-BuI, or BnBr in DMF proceeded in good to excellent yields of compounds **13b**−**d** (91%, 68%, and 76%, respectively, Scheme 4). Esters **13a**−**d** were hydrolyzed with potassium hydroxide in a 10:1 ethanol:water mixture; however, only the tertiary malonic ester **13a** (Scheme 3) was fully hydrolyzed to give the diacid. In contrast, treatment of the quaternary malonic esters **13b**−**d** in this manner resulted in mixtures of diacids and the corresponding malonic acid monoesters.

In the case of the two esters with the more bulky side chains (**13c** and **13d)**, heating to reflux was necessary in order to achieve a satisfactory degree of ester hydrolysis (Scheme 4). Decarboxylations were performed on the crude monoacid/diacid mixtures (pyridine, reflux, 3 h), and the resulting acid/ester mixtures were again treated with potassium hydroxide solution, thus furnishing building blocks **2b**−**d**. Hydroxymethyl substituted building block **2e** was prepared in two steps from **13a**. Partial hydrolysis of **13a** using a slight excess of potassium hydroxide yielded the malonic acid monoester

Scheme 4[a]



[a] Reagents and conditions: (i) MeI (→**13b**)/*i*-BuI (→**13c**)/BnBr (→**13d**), KHMDS, DMF, Δ; (ii) (a) KOH, EtOH, reflux, (b) pyridine, reflux, 3 h, (c) KOH, EtOH; (iii) KOH, EtOH, 20 °C; (iv) $NaBH_4$, THF:EtOH 10:1, 45 min.

Table 1. Levels of Hydrolysis of **13a** after Treatment with Selected Acid/Solvent Mixtures[a]

acid/solvent	2 min	10 min	30 min	1 h	20 h
80% AcOH/H_2O	-	-	-	-	+
100% AcOH	-	-	-	-	-
10% HCO_2H/CH_2Cl_2	-	-	+	+	++[b]
80% HCO_2H/CH_2Cl_2	-	+	++	+++	
10% TCA/CH_2Cl_2	-	+	++	++	+++
10% TCA/H_2O	-	+	+++		
1% TFA/CH_2Cl_2	-	+	+	++	++[b]
10% TFA/CH_2Cl_2	+	++	++	+++	
10% TFA/H_2O	+	+++			
95% TFA/H_2O	+++				

[a] Observed hydrolysis: +++ complete; ++ more than 50%; + less than 50%; - none. [b] A single side product was detected.

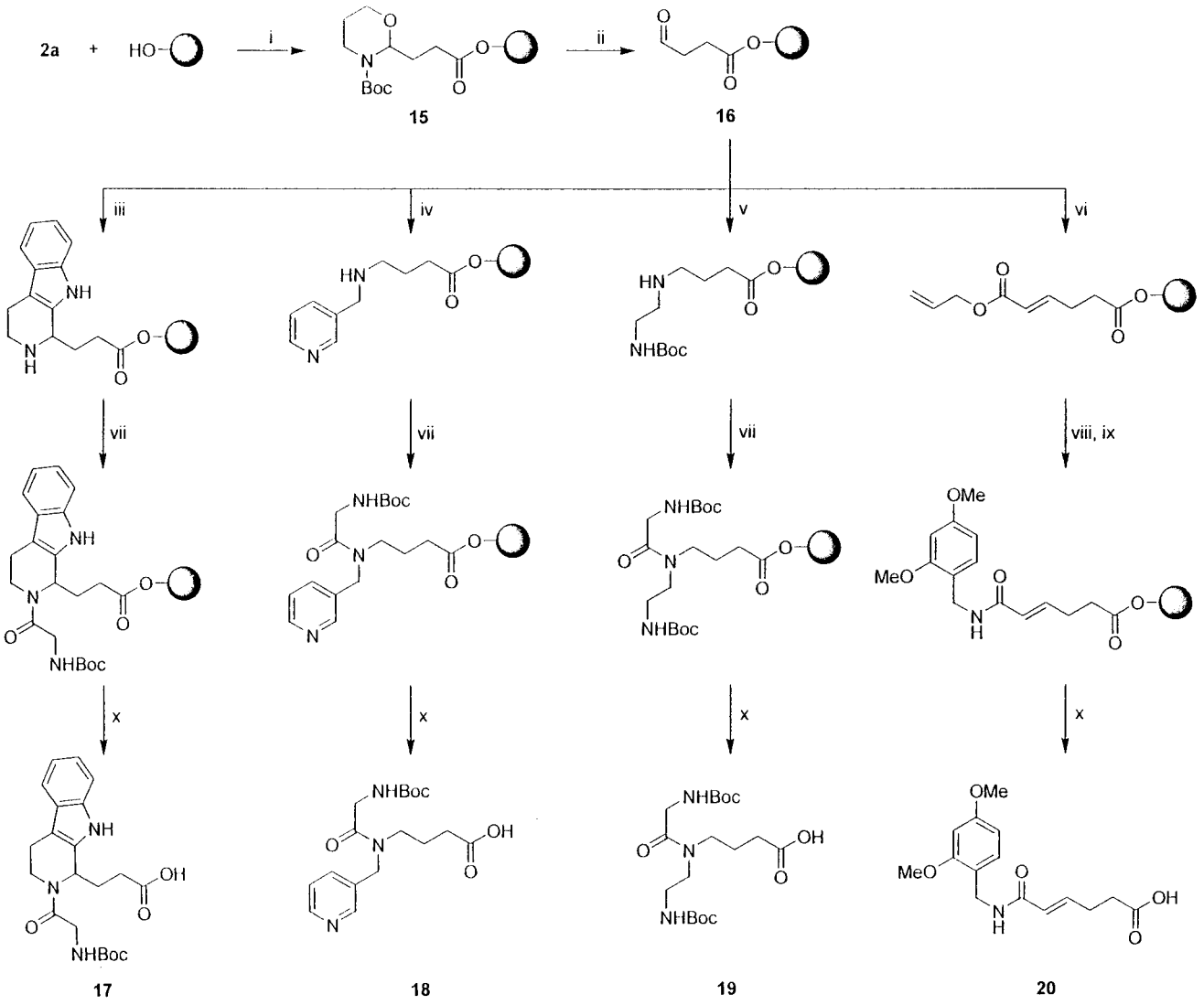
14, and the ester moiety was selectively reduced with sodium borohydride.[28]

Compounds **14** and **2b**−**e** exhibit multiple and frequently overlapping ^1H and ^{13}C NMR signals since the synthesized products all are enantiomeric mixtures of two diastereomers; nevertheless, peak assignment was possible by COSY and ^1H-^{13}C correlation spectroscopy (HSQC). It was not possible to separate the products into pairs of enantiomers by conventional flash chromatography procedures. However, the use of diastereomeric pairs of building blocks in combinatorial peptide mimetic libraries is generally not a problem.[29]

Aldehyde Demasking. The acid lability of the 3-Boc perhydro-1,3-oxazine moiety was investigated with four different acids: acetic, formic, trichloroacetic, and trifluoroacetic acid in either water or dichloromethane (Table 1). Compound **13a** was treated with the various acids, and the approximate ratios of **13a** to the generated aldehyde **12** were estimated at 2 min, 10 min, 30 min, 1 h, and 20 h.

TFA:water (95:5) unmasked the aldehyde fully in less than 2 min, and the requirement of rapid and clean demasking[30] of the aldehyde can thus be fulfilled. In addition, unmasking using 10% TFA in water occurred within 10 min and 10% trichloroacetic acid in water within 30 min. As expected, unmasking with the same acids in dichloromethane proceeded slower, namely within approximately 1 h in both cases. Surprisingly, an unidentified side product was observed after 20 h when using 1% TFA in dichloromethane, a phenomenon also observed with 10% formic acid in

Scheme 5[a]



[a] Reagents and conditions: (i) MSNT, *N*-methylimidazole, CH_2Cl_2; (ii) TFA:H_2O 95:5, 3 min; (iii) tryptamine hydrochloride (20 equiv), toluene:DMSO 1:1, 50 °C, 3 days; (iv) 3-picolylamine (20 equiv), $NaBH(OAc)_3$ (18 equiv), DMSO:CH_2Cl_2:AcOH 50:50:1, overnight; (v) as iv, with *N*-Boc diaminoethylene in stead of 3-picolylamine; (vi) allyl-*P*,*P*-diethylphosphonoacetate (30 equiv), LiBr (25 equiv), TEA (20 equiv), MeCN, 20 °C, overnight; (vii) Boc-Gly-OH (5 equiv), HATU (4.8 equiv), HOAt (1 equiv), NEM (5 equiv), DMF; (viii) $Pd[PPh_3]_4$ (3 equiv), $HCCl_3$:AcOH:NEM (37:2:1), 1 h; (ix) HATU, HOAt and NEM in DMF (10 min), then 2,5-dimethoxybenzylamine, 18 h; (x) 0.1 M NaOH, 20 °C, 1 h.

dichloromethane; however, the side product was not the same in the two cases. At a formic acid concentration of 80%, this problem is not observed and the necessary cleavage time was decreased to 1 h. Glacial acetic acid did not show any aldehyde demasking even after 20 h; however, 80% acetic acid showed a high degree of deprotection of **13a** within this period of time. The 3-Boc perhydro-1,3-oxazine can therefore be cleaved rapidly under strong acidic conditions or, if desired, slower under less harsh conditions, thus allowing the possibility for orthogonal deprotection in the presence of other acid labile groups.

Solid Phase Aldehyde Reactions. Although the general utilization of the building blocks is described in a separate article,[31] unmasking of the aldehyde and transformation of this functionality is demonstrated here by a few simple synthetic steps. Since these reactions serve solely as a demonstration of the perhydro-1,3-oxazine as an aldehyde protection group, as well as a demonstration of the usefulness of the resin bound aldehydes, it was considered sufficient to employ only one building block, namely **2a**, directly linked by an ester bond to the resin. First, **2a** was esterified onto a solid support (Scheme 5). The resin selected was POE-POP_{1500}, which is a hydroxy functionalized PEG-1500 based resin suitable for a broad range of conditions, including aqueous solvents.[32−34] The resin bound perhydro-1,3-oxazine was treated with TFA:H_2O (95:5) for 3 min, and the aldehyde was characterized by ^{1}H MAS NMR while still attached to the resin and showed a distinct aldehyde signal at δ 9.83 ppm. From this experiment it was also shown that no remaining perhydro-1,3-oxazine was present. Aldehyde **16** was submitted to three different types of reactions which all are investigated in great detail in the succeeding article,[31] and a discussion on conditions and reaction optimization are presented there. The reactions used were Pictet−Spengler condensation, reductive amination, and Horner−Wadsworth−Emmons olefin synthesis.

In the first reaction, **16** was treated with 20 equiv of tryptamine hydrochloride, and the resulting secondary cyclic

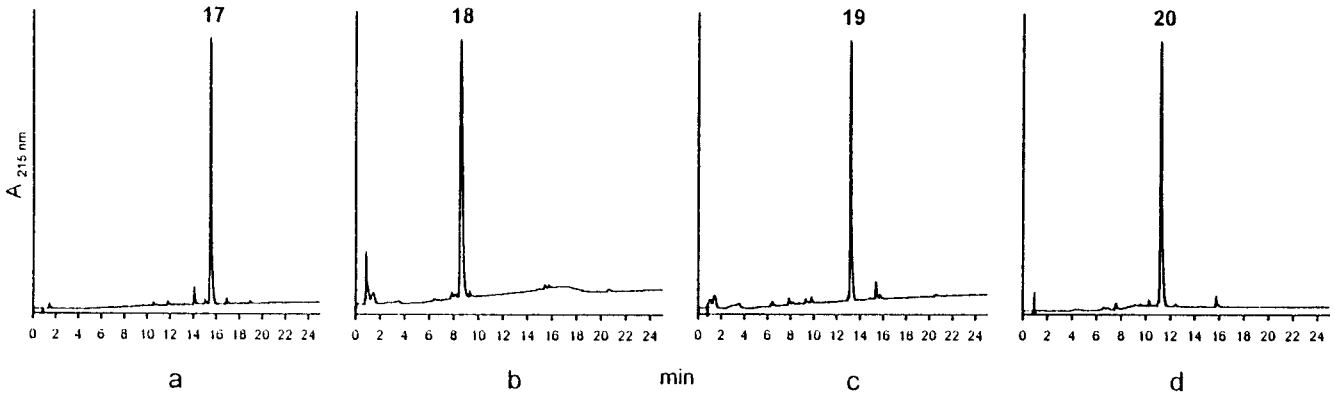


Figure 2. Analytical RP-HPLC diagrams of crude products **17**−**20**.

amine was acylated with Boc-glycine. After cleavage from the solid support with 0.1 M NaOH, analytical RP-HPLC of the crude product revealed that **17** was formed in high purity (Figure 2a). Reductive amination of aldehyde **16** was performed with a benzylic and an aliphatic amine, namely 3-picolylamine and *N*-Boc-diaminoethylene, in the presence of sodium triacetoxyborohydride (DMSO:dichloromethane: acetic acid (50:50:1), 20 °C, overnight). Also here the products were acylated with Boc-glycine prior to cleavage from the resin, and again the products were formed in high crude purity (Figure 2b,c). This was also the case in the synthesis of **20**, which consisted of three steps: (i) Horner−Wadsworth−Emmons olefination of **16** with allyl-*P*,*P*-diethylphosphonoacetate in the presence of lithium bromide and triethylamine, (ii) cleavage of the ally ester with palladium(0), and (iii) coupling of an amine to the acid moiety.

It has hereby been demonstrated that the building blocks offer a convenient and rapid route toward resin bound aldehydes, which successfully can be transformed by various types of reactions with nucleophiles.

Conclusions

In summary, facile routes toward (*RS*)-3′-*tert*-butoxycarbonyl-perhydro-1′,3′-oxazine-2′-yl acetic acid (**1a**) and the simple and C-2 substituted 3′-*tert*-butoxycarbonyl-perhydro-1′,3′-oxazine-2′(*RS*)-yl propionic acid (**2a**−**e**) starting from easily available starting materials are introduced. A general procedure for the synthesis of C-2 substituted building blocks of type **2** has been presented, relying on the ease of incorporation of various side chains in the malonic ester intermediate **13a**, and furthermore, a hydroxymethyl substituted analogue of **2** was also prepared from **13a** via partial ester hydrolysis and reduction. The novel aldehyde protection group, the 3-*tert*-butoxycarbonyl-perhydro-1,3-oxazine, was shown to liberate the aldehyde moiety under a variety of different acid/solvent mixtures, with the possibility of completing this transformation cleanly in less than 2 min with TFA:H_2O (95:5). The protection group was stable under several harsh basic conditions, such as refluxing 6 M NaOH, KHMDS in DMF at 150 °C for 3.5 h, and $NaBH_4$ at 70 °C for 45 min. It was shown that coupling of **2a** to a solid support, liberation of the aldehyde followed by a series of selected nucleophilic reactions (Pictet−Spengler condensation, reductive amination, Horner−Wadsworth−Emmons olefination), and successive amide bond coupling yielded compounds of high crude purity. The presented work offers a simple and general route toward C-2 substituted type **2** building blocks, and use of these in a combinatorial synthesis of peptide isosteres as putative protease inhibitors is described in a separate article.[31]

Experimental Section

General. All solvents were stored over molecular sieves. Solution phase experiments were conducted under argon in oven dried glassware equipped with rubber septa. All starting materials and reagents were commercially available, except compounds **3**[17] and **4**.[18] Flash chromatography was carried out using Merck silica gel 60 (0.040−0.063 mm) and analytical TLC analysis using Merck C-60 F_{254} plates. All solid phase reactions were performed in flat-bottom polyethylene syringes equipped with sintered Teflon filters (50 μm pores), Teflon tubing, and Teflon valves for applying suction to the syringes from below.[35]

Standard NMR spectra were taken at 250 MHz (^{1}H) and 62.5 MHz (^{13}C) in $CDCl_3$, and were recorded on a Bruker DPX 250 MHz instrument. Proton shifts are downfield from TMS (0.00 ppm) as internal standard, and carbon shifts are relative to $CDCl_3$ (76.93 ppm). Where assignments are reported, COSY, HSQC,[36] and in most cases DEPT spectra were also recorded for the compound in question. ^{1}H high resolution MAS NMR was recorded on a Varian Unity Inova 500 MHz spectrometer equipped with a 4 mm ^{1}H-observe nano NMR probe, at 25 °C, using a spin rate of approximately 2 kHz. The spectrum was recorded as a one-pulse experiment with presaturation of the main PEG resonance. Acquisition data for the spectrum was as follows: 2.0 s acquisition time, 2.0 s presaturation delay, sweep width of 8000 Hz. Resin particles were transferred into a nanotube, dried overnight in vacuo, and added the $DCCl_3$ (40 μL).

Analytical RP-HPLC was performed on a Zorbax column (C-18, 300 Å, 50 mm × 0.45 mm) with a linear gradient of 100% A (0.1% TFA in water) to 100% B (0.1% TFA in 1:9 water:MeCN) in 25 min, 1 mL min^{-1}, with detection at 215 and 280 nm by a programmable multiwavelength detector (Waters 490E). Elemental analyses were performed at the University of Copenhagen, Denmark.

(*RS*)-1-*tert*-Butyldimethylsilyloxy 2-(3′-*tert*-butoxycarbonyl-perhydro-1′,3′-oxazine-2′-yl) ethane (7): Alcohol **3**

(8.44 g, 44.34 mmol) and TEMPO (277 mg, 1.77 mmol, 0.04 equiv) were dissolved in CH_2Cl_2 (700 mL) at 0 °C, and a mixture of NaBr (684 mg, 6.65 mmol, 0.15 equiv), water (117 mL), saturated aqueous $NaHCO_3$ (113 mL), and NaOCl (1.3 M, 44.3 mL, 57.6 mmol, 1.3 equiv) was added. After vigorous stirring for 8 min, the reaction was quenched with MeOH (80 mL), and the aqueous phase was extracted with CH_2Cl_2 (250 mL) and then EtOAc (250 mL). The combined organic phases were dried over $MgSO_4$ and concentrated to a slightly yellow oil of **5** (8.15 g, 43.3 mmol, 98%). R_f 0.56 (15% EtOAc in petrol ether); ESMS *m*/*z* calcd for $C_9H_{21}O_2Si$ $(M + H)^+$: 189.3. Found: 189.2.

A total of 7.20 g (38.27 mmol) of **5** was dissolved in toluene (100 mL) and stirred with 3-aminopropanol (3.20 mL, 42.1 mmol, 1.10 equiv) and K_2CO_3 (10.6 g, 76.6 mmol, 2.0 equiv) for 5 h. Boc_2O (9.61 g, 1.15 equiv) was added, and the mixture was stirred at 90 °C for 2 h, diluted with EtOAc (50 mL), washed with water (2 × 50 mL) and brine (50 mL), dried over $MgSO_4$, and concentrated to a syrup which was purified by flash chromatography (15% EtOAc in petrol ether) yielding colorless crystals of **7** (11.22 g, 32.5 mmol, 85%). R_f 0.39 (15% EtOAc in petrol ether); mp 46.7−46.9 °C; ^{1}H NMR δ 5.61 (dd, 1H J = 5.9, 8.2, OCHN), 4.02 (m, 1H, CH*H*N), 3.87 (dt, 1H, J = 3.4, J = 11.6, CH*H*OC), 3.72 (m, 1H, C*H*HOC), 3.66 (m, 2H, CH_2OSi), 3.13 (ddd, 1H, J = 3.6, 12.5, 13.5, C*H*HN), 2.28−2.13 (m, 1H, CH*H*CH_2OSi), 2.01−1.77 (m, 2H, C*H*HCH_2OSi + CH*H*CH_2N), 1.56−1.44 (m, 1H, C*H*HCH_2N), 1.46 (s, 9H, *t*-BuO), 0.90 (s, 9H, *t*-BuSi), 0.06 (s, 6H, Me_2Si); ^{13}C NMR δ 154.3 (C═O), 80.0 (Me_3CO), 79.6 (OCHN), 59.7 (CH_2-OC), 59.2 (CH_2OSi), 37.0 (CH_2N), 32.3 (CH_2CH_2OSi), 28.3 (Me_3CO), 25.9 (Me_3CSi), 25.3 (CH_2CH_2N), 18.2 (Me_3CSi), −5.5 (Me_2Si); ESMS *m*/*z* calcd for $C_{17}H_{36}NO_4Si$ $(M + H)^+$: 346.6. Found: 346.5. Anal. calcd for $C_{17}H_{35}NO_4Si$: C, 59.09; H, 10.21; N, 4.05. Found: C, 59.18; H, 10.59; N, 4.06.

(*RS*)-2-(3′-*tert*-Butoxycarbonyl-perhydro-1′,3′-oxazine-2′-yl) ethanol (9): To a 0 °C solution of **7** (11.21 g, 32.4 mmol) in THF (60 mL) was added a solution of TBAF in THF (1 M, 65 mL, 65 mmol, 2 equiv). After 10 min the temperature was allowed to rise to 20 °C and stirred overnight. The mixture was concentrated and purified by flash chromatography (gradient 7:3 to 8:2 EtOAc:petrol ether), yielding a colorless oil of **9** (7.40 g, 32.0 mmol, 99%). R_f 0.38 (70% EtOAc in petrol ether); ^{1}H NMR δ 5.64 (t, 1H, J = 7.0, OCHN), 4.01 (m, 1H, CH*H*N), 3.92 (ddd, J = 4.0, 10.5, 11.7, CH*H*OC), 3.76−3.58 (m, 3H, C*H*HOC + CH_2OH), 3.11 (ddd, 1H, J = 3.9, 12.5, 13.5, C*H*HN), 2.47 (bs, 1H, OH), 2.22−1.79 (m, 3H, CH_2CH_2OH + CH*H*CH_2N), 1.63−1.52 (m, 1H, C*H*HCH_2N), 1.47 (s, 9H, *t*-Bu); ^{13}C NMR δ 154.0 (C═O), 80.9 (OCHN), 80.5 (Me_3C), 60.1 (CH_2OC), 59.1 (CH_2OH), 36.9 (CH_2N), 31.9 (CH_2CH_2OH), 28.2 (Me_3C), 25.0 (CH_2CH_2N); ESMS *m*/*z* calcd for $C_{11}H_{22}NO_4$ $(M + H)^+$: 231.3. Found: 231.2; Anal. calcd for $C_{11}H_{21}NO_4$: C, 57.12; H, 9.15; N, 6.06. Found: C, 56.54; H, 9.46; N, 5.92.

(*RS*)-3′-*tert*-Butoxycarbonyl-perhydro-1′,3′-oxazine-2′-yl acetic acid (1a): To a 0 °C cold solution of **9** (310 mg, 1.34 mmol) in CH_2Cl_2 (25 mL) was added TEMPO (8.4 mg, 54 μmol, 0.04 equiv) followed by a mixture of NaBr (20.7 mg, 0.20 mmol, 0.15 equiv), TBABr (21.6 mg, 67 μmol, 0.05 equiv), water (4.2 mL), saturated aqueous $NaHCO_3$ (7.8 mL), and NaOCl (∼1.3 M, 3.1 mL, 4.02 mmol, 3 equiv). The mixture was stirred vigorously at 0 °C for 30 min, quenched with MeOH (1 mL), acidified to pH 4 with 1 M HCl, and extracted with CH_2Cl_2 (10 mL) followed by EtOAc (10 mL). The combined extracts were dried over Na_2SO_4 and concentrated to an oil which was purified by flash chromatography (1:30:70 AcOH:EtOAc:petrol ether), affording **1a** as a white solid (279 mg, 1.14 mmol, 85%). R_f 0.33 (1:30:70 AcOH:EtOAc:petrol ether); mp 105.2−105.4 °C; ^{1}H NMR δ 10−9 (bs, 1H, CO_2H), 5.88 (dd, 1H, J = 5.6, 8.2, OCHN), 4.00 (m, 1H, CH*H*N), 3.92 (ddd, J = 3.9, 10.2, 11.8, CH*H*O), 3.77 (m, 1H, C*H*HO), 3.19 (ddd, 1H, J = 3.8, 11.8, 13.8, C*H*HN), 3.02 (dd, 1H, J = 8.2, 14.6, CH*H*CO_2H), 2.81 (dd, 1H, J = 5.6, 14.6, C*H*HCO_2H), 1.96−1.78 (m, 1H, CH*H*CH_2N), 1.66−1.53 (m, 1H, C*H*HCH_2N), 1.46 (s, 9H, *t*-Bu); ^{13}C NMR δ 174.9 (CO_2H), 153.4 (Boc C═O), 80.7 (Me_3C), 79.6 (OCHN), 60.7 (CH_2O), 37.3 (CH_2N), 35.7 (CH_2CO_2H), 28.2 (Me_3C), 24.8 (CH_2CH_2N); ESMS *m*/*z* calcd for $C_{11}H_{20}NO_5$ $(M + H)^+$: 246.3. Found: 246.1. Anal. calcd for $C_{11}H_{19}NO_5$: C, 53.87; H, 7.81; N, 5.71. Found: C, 53.88; H, 7.78; N, 5.63.

(*RS*)-1-*tert*-Butyldimethylsilyloxy 3-(3′-*tert*-butoxycarbonyl-perhydro-1′,3′-oxazine-2′-yl) propane (8): Following the procedure for the synthesis of **7**, alcohol **4** (3.03 g, 14.8 mmol) was oxidized to aldehyde **6** (3.00 g, 14.8 mmol, 100%). R_f 0.71 (15% EtOAc in petrol ether); ^{1}H NMR δ 9.79 (t, 1H, J = 1.7), 3.65 (t, 2H, J = 6.0), 2.50 (dt, 2H, J = 1.7, J = 7.1), 1.86 (tt, 2H, J = 6.0, 7.1), 0.86 (s, 9H), 0.04 (s, 6H); ^{13}C NMR δ 202.0, 61.4, 40.2, 25.3, 24.9, 17.6, −6.1; ESMS *m*/*z* calcd for $C_{10}H_{22}O_2Si$ $(M + H)^+$: 203.4. Found: 203.1.

Treatment of **6** with 3-aminopropanol was carried out for 24 h, and the succeeding reaction with Boc_2O was performed at 20 °C overnight. Purification by flash chromatography (gradient 12−15% EtOAc in petrol ether) afforded **8** as an oil (4.19 g, 11.6 mmol, 79%). R_f 0.15 (15% EtOAc in petrol ether); ^{1}H NMR δ 5.48 (t, 1H, J = 7.1, OCHN), 4.02 (m, 1H, CH*H*N), 3.89 (dt, 1H, J = 3.4, J = 11.6, CH*H*OC), 3.69 (m, 1H, C*H*HOC), 3.65 (t, 2H, J = 6.3, CH_2OSi), 3.11 (dt, 1H, J = 3.5, J = 13.0, C*H*HN), 2.04−1.77 (m, 3H, $CH_2(CH_2)_2OSi$ + CH*H*CH_2N), 1.62−1.45 (m, 3H, C*H*HCH_2N + CH_2CH_2OSi), 1.46 (s, 9H, *t*-BuO), 0.90 (s, 9H, *t*-BuSi), 0.05 (s, 6H, Me_2Si); ^{13}C NMR δ 154.3 (C═O), 82.5 (OCHN), 80.4 (Me_3CO), 62.9 (CH_2OSi), 59.9 (CH_2OC), 37.1 (CH_2N), 28.8 (Me_3CO), 28.7 ($CH_2(CH_2)_2OSi$), 26.3 (Me_3-CSi), 25.8 (CH_2CH_2OSi + CH_2CH_2N), 18.7 (Me_3CSi), −4.9 (Me_2Si); ESMS *m*/*z* calcd for $C_{18}H_{38}NO_4Si$ $(M + H)^+$: 360.6. Found: 360.5. Anal. calcd for $C_{18}H_{37}NO_4Si$: C, 60.12; H, 10.37; N, 3.90. Found: C, 59.93; H, 10.47; N, 3.88.

(*RS*)-3-(3′-*tert*-Butoxycarbonyl-perhydro-1′,3′-oxazine-2′-yl) propan-1-ol (10): Silyl ether **8** (4.18 g, 11.6 mmol) was cleaved as described for **7**. Purification by flash chromatography (7:3 EtOAc:petrol ether) yielded **7** as a colorless oil (2.60 g, 10.6 mmol, 91%). R_f 0.33 (70% EtOAc in petrol ether); ^{1}H NMR δ 5.50 (t, 1H, J = 7.0, OCHN), 4.01 (m, 1H, CH*H*N), 3.91 (dt, J = 1.2, J = 11.3, CH*H*OC),

3.74−3.67 (m, 3H, C*H*HOC + C*H*$_2$OH), 3.13 (dt, 1H, J = 3.7, J = 12.6, C*H*HN), 2.23 (bs, 1H, OH), 2.10−1.78 (m, 3H, C*H*$_2$(CH$_2$)$_2$OH + CH*H*CH$_2$N), 1.72−1.48 (m, 3H, C*H*$_2$-CH$_2$OH + C*H*HCH$_2$N), 1.46 (s, 9H, *t*-Bu); ^{13}C NMR δ 153.8 (C═O), 82.0 (OCHN), 80.0 (Me$_3$*C*), 62.1 (CH$_2$OH), 59.5 (*C*H$_2$OC), 36.7 (CH$_2$N), 28.2 (*Me*$_3$C), 28.1 (*C*H$_2$CH$_2$N), 25.6 (*C*H$_2$(CH$_2$) $_2$OH), 25.0 (*C*H$_2$CH$_2$OH); ESMS *m*/*z* calcd for $C_{12}H_{24}NO_4$ $(M + H)^+$: 246.3. Found: 246.2. Anal. calcd for $C_{12}H_{23}NO_4$: C, 58.75; H, 9.45; N, 5.71. Found: C, 58.00; H, 9.73; N, 5.46.

(*RS*)-3-(3′-*tert*-Butoxycarbonyl-perhydro-1′,3′-oxazine-2′-yl) propanoic acid (2a): By oxidation of 10: Following the procedure for the preparation of **1a**, alcohol **10** (2.19 g, 8.93 mmol) was oxidized to **2a** which was purified by flash chromatography (gradient 1:30:70 to 1:50:50 AcOH:EtOAc: petrol ether) affording a white solid (2.27 g, 8.93 mmol, 98%). R_f 0.18 (1:30:70 AcOH:EtOAc:petrol ether); mp 92.1−92.5 °C; ^{1}H NMR δ 10−9 (bs, 1H, CO$_2$H), 5.51 (t, 1H, J = 7.1, OCHN), 4.03 (m, 1H, CH*H*N), 3.88 (dt, J = 3.6, 11.5, CH*H*O), 3.71 (m, 1H, C*H*HO), 3.12 (ddd, 1H, J = 3.7, 12.7, 13.6, C*H*HN), 2.45−2.36 (m, 2H, C*H*$_2$CH$_2$CO$_2$H), 2.32−2.04 (m, 2H, C*H*$_2$CO$_2$H), 1.94−1.78 (m, 1H, CH*H*CH$_2$N), 1.57−1.49 (m, 1H, C*H*HCH$_2$N), 1.49 (s, 9H, *t*-Bu); ^{13}C NMR δ 178.2 (CO$_2$H), 153.8 (Boc C═O), 81.2 (OCHN), 80.4 (Me$_3$*C*), 59.7 (*C*H$_2$O), 36.7 (CH$_2$N), 29.5 (*C*H$_2$CH$_2$CO$_2$H), 28.2 (*Me*$_3$C), 25.0 (*C*H$_2$CH$_2$N), 24.2 (*C*H$_2$CO$_2$H); ESMS *m*/*z* calcd for $C_{12}H_{22}NO_5$ $(M + H)^+$: 260.3. Found: 260.1. Anal. calcd for $C_{12}H_{21}NO_5$: C, 55.58; H, 8.16; N, 5.40. Found: C, 55.86; H, 8.22; N, 5.36.

By hydrolysis and decarboxylation of 13a: General procedure B below was employed on **13a** yielding **2a** in 69% yield (1.12 g, 4.33 mmol).

2-(2,2-Diethoxy-ethyl)-malonic acid diethyl ester (11): Bromoacetaldehyde diethylacetal (6.35 g, 32.2 mmol) was dissolved in DMF (50 mL), diethyl malonate (10.32 g, 64.4 mmol, 2.0 equiv) and K_2CO_3 (5.34, 1.2 equiv) were added. and the mixture was refluxed overnight. The mixture was cooled to 20 °C, filtered, and concentrated to an oil (traces of DMF removed azeotropically with toluene). The oil was dissolved in 2 mL of toluene and filtered through a 5 cm plug of silica gel which then was washed with toluene. The colorless toluene extract was distilled, yielding compound **11** as a colorless oil (5.71 g, 20.7 mmol, 64%). R_f 0.38 (10% EtOAc in petrol ether); bp 104−107 °C/0.50 mmHg; ^{1}H NMR δ 4.55 (t, 1H, J = 5.6, C*H*(OEt)), 4.20 (qt, 2H, J = 7.2, C*H*$_2$OCH), 4.19 (qt, 2H, J = 7.1, C*H*$_2$OCH), 3.57 (m, 4H, 2 × CO$_2$CH$_2$), 3.52 (t, 1H, J = 7.2, CHCO$_2$), 2.22 (dd, 2H, J = 5.7, 7.3, C*H*$_2$CH), 1.27 (t, 6H, J = 7.1, C*H*$_3$CH$_2$-OCH), 1.19 (t, 6H, J = 7.0, CO$_2$CH$_2$C*H*$_3$); ^{13}C NMR δ 169.2 (C═O), 100.7 (*C*H(OEt)), 61.7 (CO$_2$*C*H$_2$), 61.2 (*C*H$_2$OCH), 48.0 (*C*HCO$_2$), 32.7 (*C*H$_2$CH), 15.1 (CO$_2$CH$_2$*C*H$_3$), 13.9 (OCH$_2$*C*H$_3$). ESMS *m*/*z* calcd for $C_{13}H_{25}O_6$ $(M + H)^+$: 277.3. Found: 277.2. Anal. calcd for $C_{13}H_{24}O_6$: C, 56.51; H, 8.75. Found: C, 56.32; H, 9.17.

(*RS*)-3′-*tert*-Butoxycarbonyl-perhydro-1′,3′-oxazine-2′-ylmethyl malonic acid diethyl ester (13a): Compound **11** (6.46 g, 23.4 mmol) was treated with TFA:H$_2$O:HCCl$_3$ (30:10:30 mL) at 0 °C for 50 min. The mixture was poured into 1 M K_2CO_3 (150 mL) and CH_2Cl_2 (250 mL), and K_2CO_3 (s) was added until the pH reached 7.5. The organic phase was washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$, and concentrated to a pale yellow oil of aldehyde **12** (4.56 g, 22.5 mmol, 96%). R_f 0.30 (20% EtOAc in petrol ether); ^{1}H NMR δ 9.79 (s, 1H), 4.24 (t, 2H, J = 7.2), 4.20 (t, 2H, J = 7.2), 3.88 (t, 1H, J = 7.0), 3.10 (d, 2H, J = 7.0), 1.28 (t, 6H, J = 7.2); ^{13}C NMR δ 198.0, 168.3, 61.7, 45.6, 42.2, 13.8.

Aldehyde **12** (4.56 g, 22.5 mmol) was dissolved in toluene (100 mL), Na_2SO_4 (12.8 g, 90 mmol, 4 equiv) and 3-aminopropanol (1.80 mL, 23.7 mmol, 1.05 equiv) were added, and the mixture was stirred for 15 min. A solution of Boc_2O (5.41 g, 24.8 mmol, 1.10 equiv) in toluene (10 mL) was added to the reaction mixture, and it was stirred overnight. The reaction mixture was filtered through a 1 cm plug of silica gel, washed with water (2 × 50 mL) and brine (50 mL), dried over $MgSO_4$, filtered through a 1 cm plug of silica gel, and concentrated to a colorless oil of pure **13a** (6.94 g, 19.3 mmol, 86%). R_f 0.32 (20% EtOAc in petrol ether); ^{1}H NMR δ 5.54 (t, 1H, J = 7.1, OCHN), 4.26−4.09 (m, 4H, 2 × C*H*$_2$CH$_3$), 4.01 (m, 1H, CH*H*N), 3.88 (dt, 1H, J = 3.5, J = 11.4, CH*H*O), 3.68 (m, 1H, C*H*HOCH), 3.41 (dd, 1H, J = 6.7, 7.4, C*H*(CO$_2$Et)), 3.11 (dd, 1H, J = 3.6, J = 12.7, 13.4, C*H*HN), 2.56 (ddd, 1H, J = 6.6, 7.9, 14.2, C*H*HCH-(CO$_2$Et)), 2.38 (ddd, 1H, J = 6.4, 7.5, 14.2, CH*H*CH(CO$_2$-Et)), 1.94−1.75 (m, 1H, C*H*HCH$_2$N), 1.55−1.47 (m, 1H, CH*H*CH$_2$N), 1.46 (s, 9H, *t*-Bu), 1.30 (t, 3H, J = 7.1, CH$_2$C*H*$_3$); 1.28 (t, 3H, J = 7.1, CH$_2$C*H*$_3$); ^{13}C NMR δ 168.9 + 168.7 (2 × *C*O$_2$Et), 153.5 (Boc C═O), 80.3 (Me$_3$*C* + OCHN), 61.5 (*C*H$_2$CH$_3$), 59.9 (2 × *C*H$_2$OCH), 48.3 (*C*H-(CO$_2$Et)$_2$), 36.7 (CH$_2$N), 28.2 (*Me*$_3$C, *C*H$_2$CH(CO$_2$Et)$_2$), 24.9 (*C*H$_2$CH$_2$N), 13.9 (2 × *C*H$_3$CH$_2$); ESMS *m*/*z* calcd for $C_{17}H_{30}NO_7$ $(M + H)^+$: 360.4. Found: 360.4. Anal. calcd for $C_{17}H_{29}NO_7$: C, 56.81; H, 8.13; N, 3.90. Found: C, 56.70; H, 8.44; N, 3.88.

General Procedure A. 3′-*tert*-Butoxycarbonyl-perhydro-1′,3′-oxazine-2′(*RS*)-ylmethyl methyl malonic acid diethyl ester (13b): Malonic ester **13a** (2.00 g, 5.57 mmol) was dissolved in DMF (40 mL), KHMDS (1.34 g, 6.71 mmol, 1.20 equiv) in DMF (10 mL) was added, the mixture was stirred for 10 min, and MeI (417 μL, 6.69 mmol, 1.20 equiv) was added. The mixture was stirred at 50 °C for 3 h after which NMR of a small sample of the reaction mixture proved the reaction to be completed. Toluene (50 mL) and water (1 mL) were added, and the mixture was concentrated. Toluene was added and evaporated several times in order to remove all DMF. The residue was purified by flash chromatography (20% EtOAc in petrol ether) to give **13b** as a colorless oil (1.89 g, 5.07 mmol, 91%). R_f 0.38 (20% EtOAc in petrol ether); ^{1}H NMR δ 5.66 (dd, 1H, J = 5.5, 8.0, OCHN), 4.24−4.08 (m, 4H, 2 × CO$_2$CH$_2$), 4.01 (m, 1H, CH*H*N), 3.90 (dt, 1H, J = 3.5, J = 11.5, C*H*HOCH), 3.64 (m, 1H, CH*H*OCH), 3.12 (dt, J = 3.5, J = 11.5, C*H*HN), 2.68 (dd, 1H, J = 8.1, 14.5, CH*H*CHMe), 2.29 (dd, 1H, J = 5.4, 14.5, C*H*HCHMe), 1.92−1.71 (m, 1H, CH*H*CH$_2$N), 1.52 (s, 3H, *Me*C(CO$_2$Et)$_2$), 1.54−1.44 (m, 1H, C*H*HCH$_2$N), 1.47 (s, 9H, *t*-Bu), 1.26 (t, 3H, J = 7.1, CH$_2$C*H*$_3$), 1.25 (t, 3H, J = 7.1, CH$_2$C*H*$_3$); ^{13}C NMR δ 171.5 + 171.4 (2 × *C*O$_2$Et), 153.2 (Boc C═O), 80.1 (Me$_3$*C*), 78.3 (OCHN), 61.1 + 61.2

(2 × CO_2CH_2), 59.7 (CH_2OCH), 51.4 (CH_2CMe), 36.8 (CH_2N), 34.1 (CH_2CMe), 28.1 (Me_3C), 24.9 (CH_2CH_2N), 13.9 + 13.7 (2 × CH_2CH_3); ESMS *m/z* calcd for $C_{18}H_{32}NO_7$ $(M + H)^+$: 374.4. Found: 374.5. Anal. calcd for $C_{18}H_{31}NO_7$: C, 57.89; H, 8.37; N, 3.75. Found: C, 57.92; H, 8.35; N, 3.74.

Isobutyl 3′-*tert*-butoxycarbonyl-perhydro-1′,3′-oxazine-2′(*RS*)-ylmethyl malonic acid diethyl ester (13c): The reaction was carried out using general procedure A with 5.60 mmol (2.01 g) of **13a** and 0.78 mL (6.72 mmol, 1.20 equiv) of *i*-BuI at 150 °C for 3.5 h. Purification by flash chromatography (15% EtOAc in petrol ether) yielded **13c** as a slightly yellow oil (1.59 g, 3.83 mmol, 68%). R_f 0.38 (15% EtOAc in petrol ether); ^{1}H NMR δ 5.60 (t, 1H, J = 6.7, OCHN), 4.25−4.08 (m, 4H, 2 × CO_2CH_2), 4.02 (m, 1H, CH*H*N), 3.92 (dt, 1H, J = 3.3, J = 11.7, CH*H*OCH), 3.64 (m, 1H, C*H*HOCH), 3.12 (ddd, J = 3.4, 10.2, 12.8, C*H*HN), 2.66 (dd, 1H, J = 7.4, 14.8, CH*H*CCO_2Et), 2.48 (dd, 1H, J = 6.1, 14.8, C*H*$HCCO_2$Et), 2.03 (d, 1H, J = 6.8, CH*H*CH_2-Me_2), 2.01 (d, 1H, J = 6.8, C*H*HCH_2Me_2), 1.86−1.63 (m, 2H, C*H*Me_2 + CH*H*CH_2N), 1.48 (s, 9H, *t*-Bu), 1.47−1.39 (m, 1H, C*H*HCH_2N), 1.25 (t, 3H, J = 7.1, CH_2CH_3), 1.24 (t, 3H, J = 7.1, CH_2CH_3); ^{13}C NMR δ 171.6 (CO_2Et), 153.6 (Boc C═O), 80.1 (Me_3C), 78.4 (OCHN), 61.2 (CO_2CH_2), 60.0 (CH_2OCH), 54.6 (CCO_2Et), 39.6 (CH_2CHMe_2), 36.9 (CH_2N), 31.6 (CH_2CCO_2Et), 28.3 (Me_3C), 25.2 (CH_2CH_2N), 23.9 + 23.6 (CHMe_2), 23.2 (CHMe_2), 13.8 (CH_2CH_3); ESMS *m/z* calcd for $C_{21}H_{38}NO_7$ $(M + H)^+$: 416.5. Found: 416.3. Anal. calcd for $C_{21}H_{37}NO_7$: C, 60.70; H, 8.98; N, 3.37. Found: C, 60.37; H, 9.20; N, 3.33.

Benzyl 3′-*tert*-butoxycarbonyl-perhydro-1′,3′-oxazine-2′(*RS*)-ylmethyl malonic acid diethyl ester (13d): The reaction was carried out using general procedure A with 5.59 mmol (2.01 g) of **13a** and 0.80 mL (6.71 mmol, 1.20 equiv) of BnBr at 150 °C for 1.25 h. Purification by flash chromatography (gradient 15−20% EtOAc in petrol ether) yielded **13d** as a colorless syrup (1.91 g, 4.24 mmol, 76%). R_f 0.33 (20% EtOAc in petrol ether); ^{1}H NMR δ 7.29−7.14 (m, 5H, Ph), 5.93 (t, 1H, J = 6.6, OCHN), 4.24−4.07 (m, 4H, 2 × CO_2CH_2), 4.02 (m, 1H, CH*H*N), 3.93 (dt, 1H, J = 3.1, J = 11.8, CH*H*OCH), 3.66 (m, 1H, C*H*HOCH), 3.40 (d, 1H, J = 16.9, CH*H*Ph), 3.35 (d, 1H, J = 16.9, CH*H*Ph), 3.11 (ddd, J = 3.3, 12.8, 13.6, C*H*HN), 2.55 (dd, 1H, J = 7.5, 14.8, CH*H*CCO_2Et), 2.30 (dd, 1H, J = 5.7, 14.8, C*H*$HCCO_2$Et), 1.95−1.75 (m, 1H, CH*H*CH_2N), 1.52 (s, 9H, *t*-Bu), 1.51−1.38 (m, 1H, C*H*HCH_2N), 1.25 (t, 3H, J = 7.1, CH_2CH_3), 1.22 (t, 3H, J = 7.1, CH_2CH_3); ^{13}C NMR δ 170.7 + 170.3 (2 × CO_2Et), 153.5 (Boc C═O), 135.8 + 130.0 + 128.2 + 126.9 (Ph), 80.6 (Me_3C), 78.1 (OCHN), 61.3 (CO_2CH_2), 59.9 (CH_2OCH), 56.6 (CCO_2Et), 37.4 (CH_2Ph), 37.1 (CH_2N), 31.1 (CH_2CCO_2Et), 28.3 (Me_3C), 25.2 (CH_2CH_2N), 13.8 (OCH_2CH_3); ESMS *m/z* calcd for $C_{24}H_{36}NO_7$ $(M + H)^+$: 450.5. Found: 450.3. Anal. calcd for $C_{24}H_{35}NO_7$: C, 64.12; H, 7.85; N, 3.12. Found: C, 63.90; H, 8.19; N, 3.09.

General Procedure B. 3-(3′-*tert*-Butoxycarbonyl-perhydro-1′,3′-oxazine-2′(*RS*)-yl) 2(*RS*)-methyl propanoic acid (2b): Malonic ester **13b** (1.11 g, 2.98 mmol) was treated with KOH (1 M in EtOH, 17.9 mL, 6.0 equiv) and water (1.8 mL) for 15 h at 20 °C after which TLC showed complete consumption of starting material. The mixture was diluted with water (50 mL), cooled to 0 °C, acidified to pH 3 with 1 M HCl, and extracted with cold CH_2Cl_2 (4 × 100 mL). The extracts were dried over Na_2SO_4 and concentrated to 1.13 g of a thick residue. The residue was refluxed in pyridine (10 mL) for 3 h, cooled to 20 °C, and concentrated with toluene to 0.92 g of a reddish oil which was stirred with KOH (1 M in EtOH, 10 mL) for 30 min, diluted with water (10 mL), cooled, acidified to pH 3, and worked up as described above. The residue was purified by flash chromatography (1:30:70 AcOH:EtOAc:petrol ether), affording **2b** as a white paste (407 mg, 1.49 mmol, 50%). R_f 0.36 (1:30:70 AcOH:EtOAc:petrol ether); ^{1}H NMR δ 10−9 (bs, 1H, CO_2H), 5.60 + 5.56 (2 t, 1H, J = 7.2, OCHN), 4.02 (m, 1H, CH*H*N), 3.89 (dt, 1H, J = 3.4, 11.5, CH*H*O), 3.76−3.64 (m, 1H, C*H*HO), 3.11 (dt, 1H, J = 3.8, 13.0, C*H*HN), 2.61−2.43 (m, 1H, C*H*CO_2H), 2.45−2.28 (m, 1H, CH*H*$CHCO_2$H), 1.96−1.78 (m, 1H, CH*H*CH_2N), 1.75−1.63 (C*H*$HCHCO_2$H), 1.58−1.45 (m, 1H, C*H*HCH_2N), 1.46 (s, 9H, *t*-Bu), 1.27 + 1.26 (2 d, 3H, J = 7.0, C*H*$_3$CH); ^{13}C NMR δ 180.5 (CO_2H), 153.8 (Boc C═O), 80.4 (Me_3C), 79.2 + 79.0 (OCHN), 58.8 + 58.5 (CH_2O), 35.7 + 35.5 (CH_2N), 34.4 ($CHCO_2$H), 31.5 + 31.4 (CH_2CHCO_2H), 27.1 (Me_3C), 24.0 + 23.9 (CH_2CH_2N), 16.0 + 15.5 (CH_3CH); ESMS *m/z* calcd for $C_{13}H_{24}NO_5$ $(M + H)^+$: 274.3. Found: 274.2. Anal. calcd for $C_{13}H_{23}NO_5$: C, 57.13; H, 8.48; N, 5.12. Found: C, 56.84; H, 8.69; N, 5.33.

2(*RS*)-Isobutyl 3-(3′-*tert*-butoxycarbonyl-perhydro-1′,3′-oxazine-2′(*RS*)-yl) propanoic acid (2c): Following general procedure B, malonic ester **13c** (2.40 g, 5.78 mmol) was treated with KOH under reflux for 4 h. The second KOH treatment also proceeded under reflux. After purification by flash chromatography (1:30:70 AcOH:EtOAc:petrol ether), compound **2c** was collected as a slightly yellow thick syrup (1.42 g, 4.48 mmol, 76%). R_f 0.50 (1:30:70 AcOH:EtOAc:petrol ether); ^{1}H NMR δ 5.55 + 5.52 (2 t, J = 7.1, 1H, OCHN), 4.01 (m, 1H, CH*H*N), 3.88 (m, 1H, CH*H*O), 3.69 (m, 1H, C*H*HO), 3.09 (m, 1H, C*H*HN), 2.51 (m, 1H, C*H*CO_2H), 2.5−1.7 (m, 2H, CH_2CHCO_2H), 2.0−1.4 (m, 2 H, CH_2CH_2N), 1.8 (m, 1H, C*H*Me_2), 1.46 (s, 9H, *t*-Bu), 1.4 (m, 2H, CH_2CHMe_2), 0.92 (m, 6H, CHMe_2); ^{13}C NMR δ 181.4 + 181.1 (CO_2H), 154.0 (Boc C═O), 80.8 + 80.5 (OCHN), 80.4 (Me_3C), 59.9 + 59.7 (CH_2O), 41.6 + 41.3 (CH_2CHMe_2), 39.8 + 39.3 ($CHCO_2$H), 31.7 (CH_2CHCO_2H), 28.2 (Me_3C), 25.9 ($CHMe_2$), 25.0 + 24.9 (CH_2CH_2N), 22.8 + 21.9 (CHMe_2); ESMS *m/z* calcd for $C_{16}H_{30}NO_5$ $(M + H)^+$: 316.4. Found: 316.3. Anal. calcd for $C_{16}H_{29}NO_5$: C, 60.93; H, 9.27; N, 4.44. Found: C, 60.36; H, 9.36; N, 4.34.

2(*RS*)-Benzyl 3-(3′-*tert*-butoxycarbonyl-perhydro-1′,3′-oxazine-2′(*RS*)-yl) propanoic acid (2d): Malonic ester **13d** (1.49 g, 3.32 mmol) was treated exactly as **13c** above. After purification by flash chromatography (gradient 1:25:75 (R_f 0.26) to 1:30:70 (R_f 0.42) AcOH:EtOAc:petrol ether), compound **2d** was collected as a pale yellow extremely thick syrup which was difficult to fully free of solvent (1.08 g, 3.09 mmol, 93%). ^{1}H NMR δ 10−9 (bs, 1H, CO_2H), 5.57 + 5.54 (2 t, 1H, J = 7.4, OCHN), 3.94 (m, 1H, CH*H*N),

3.80 (dt, 0.5 H, J = 3.8, 11.4, CH*H*O), 3.61 (m, 1.5 H, CH*H*O), 3.1−2.6 (m, 4H, C*H*HN + C*H*CH_2Ph), 2.4−1.8 (m, 2H, CH_2CHCO$_2$H), 1.9−1.7 + 1.5−1.4 (m, 2H, CH_2-CH_2N), 1.44 + 1.41 (2 s, 9H, *t*-Bu); ^{13}C NMR δ 180.0 (CO_2H), 153.7 (Boc C═O), 138.4 + 128.9 + 128.5 + 126.5 (Ph), 80.7 + 80.3 (OCHN), 80.4 (Me$_3$*C*), 59.7 (CH_2O), 43.5 + 42.9 (*C*HCO$_2$H), 38.0 + 37.8 (*C*H$_2$Ph), 36.6 (CH_2N), 30.3 + 30.2 (*C*H$_2$CHCO$_2$H), 28.2 (*Me*$_3$C), 25.0 + 24.9 (*C*H$_2$-CH_2N); ESMS *m*/*z* calcd for $C_{19}H_{28}NO_5$ $(M + H)^+$: 350.4. Found: 350.3. Anal. calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 64.67; H, 7.99; N, 3.94.

2(*RS*)-(3′-*tert*-Butoxycarbonyl-perhydro-1′,3′-oxazin-2′-(*RS*)-ylmethyl)-malonic acid monoethyl ester (14): Malonic ester **13a** (1.35 g, 3.76 mmol) was stirred with KOH (4.25 mmol, 1.13 equiv) in EtOH (7 mL) for 2 days. The reaction mixture was partitioned between water (25 mL) and CH_2Cl_2 (25 mL), and the aqueous phase was cooled to 0 °C, acidified to pH 2 with 1 M HCl, and extracted with cold CH_2Cl_2 (3 × 50 mL). The combined extracts were dried over Na_2SO_4, concentrated, and purified by flash chromatography (0.25% AcOH in EtOAc) to give **14** as a colorless oil (849 mg, 2.56 mmol, 68%) and 172 mg of starting material **13a** (0.48 mmol, 13%). R_f 0.32 (0.25% AcOH in EtOAc); ^{1}H NMR 7.8 (bs, 1H), 5.59 + 5.56 (2 t, 1H, J = 7.1), 4.22 (m, 2H), 4.01 (m, 1H), 3.88 (m, 1H), 3.61 (m, 1H), 3.46 (m, 1H), 3.11 (m, 1H), 2.65−2.31 (m, 2H), 1.84 (m, 1H), 1.50 (m, 1H), 1.47 (s, 9H), 1.29 (m, 3H); ^{13}C NMR δ 172.7 + 172.5, 169.0 + 168.7, 153.7, 80.7, 80.3 + 80.5, 61.7 + 61.5, 59.9, 48.0 + 47.5, 36.7, 28.2, 28.1, 24.8, 13.8; ESMS *m*/*z* calcd for $C_{15}H_{26}NO_7$ $(M + H)^+$: 332.4. Found: 332.2. Anal. calcd for $C_{15}H_{25}NO_7$: C, 54.37; H, 7.60; N, 4.23. Found: C, 54.13; H, 7.89; N, 4.37.

2(*RS*)-Hydroxymethyl 3-(3′-*tert*-butoxycarbonyl-perhydro-1′,3′-oxazine-2′(*RS*)-yl) propanoic acid (2e): Ester **14** (845 mg, 2.55 mmol) was dissolved in THF:EtOH (25:2.5 mL), and $NaBH_4$ (193 mg, 5.10 mmol, 2.0 equiv) was added in several small portions at 20 °C. It was stirred at 70 °C for 45 min, cooled to 20 °C, quenched with acetone, and concentrated to a white solid which was suspended in water (20 mL), cooled to 0 °C, acidified with 1 M HCl to pH 2, and extracted with CH_2Cl_2 (4 × 50 mL). The combined extracts were dried over Na_2SO_4, concentrated, and purified by flash chromatography (gradient 0.5 to 3.0% AcOH in EtOAc) yielding **2e** as a colorless syrup (455 mg, 1.57 mmol, 62%). R_f 0.40 (1.5% AcOH in EtOAc); ^{1}H NMR δ 6.1 (bs, 2H, OH), 5.61 + 5.58 (2 t, 1H, J = 7.1, OCHN), 3.98 (m, 1H, CH*H*N), 3.93 (m, 1H, CH*H*OCH), 3.85 (m, 2H, CH_2-OH), 3.72 (m, 1H, C*H*HOCH), 2.96 (m, 1H, C*H*HN), 2.65 (m, 1H, C*H*CO$_2$H), 2.46−2.27 (m, 1H, CH*H*CHCO$_2$H), 2.15−1.9 (m, 1H, C*H*HCHCO$_2$H), 1.95−1.75 (m, 1H, CH*H*CH_2N), 1.60−1.45 (m, 1H, C*H*HCH_2N), 1.46 (s, 9H, *t*-Bu); ^{13}C NMR δ 178.0 (CO_2H), 154 (Boc C═O), 80.8 + 80.7 (OCHN), 80.4 (Me$_3$*C*), 63.0 + 62.6 (CH_2OH), 60.1 + 59.9 (*C*H$_2$COCH), 43.8 + 43.5 (*C*HCO$_2$H), 36.9 + 36.8 (CH_2N), 28.2 (*Me*$_3$C), 27.9 + 27.8 (*C*H$_2$CHCO$_2$H), 25.0 + 24.9 (*C*H$_2$CH$_2$N); ESMS *m*/*z* calcd for $C_{13}H_{24}NO_6$ $(M + H)^+$: 290.3. Found: 290.2. Anal. calcd for $C_{13}H_{23}NO_6 \cdot {}^1/_2H_2O$: C, 52.34; H, 8.11; N, 4.70. Found: C, 52.24; H, 8.10; N, 4.51.

Acid Lability Experiments. A total of 4.0 mg of **13a** was placed in a small vial, and 0.50 mL of an acid-solvent mixture was added (cf. Table 1). At 2 min, 10 min, 30 min, 1 h, and 20 h, TLC analysis (40% EtOAc in petrol ether, R_f 0.73 (**13a**), R_f 0.67 (**12**)) was performed; the spots were visualized with ninhydrin spray (5 g ninhydrin in 100 mL EtOH), rendering the acetal spot brown and the aldehyde spot yellow. The ratio of **13a** to **12** was estimated visually.

Attachment of 2a to the Solid Support To Give 15. $POEPOP_{1500}$[33] resin (801 mg, 0.45 mmol -OH/g, 0.36 mmol) was swollen in CH_2Cl_2, drained, and functionalized with **2a** (187 mg, 2.0 equiv), MSNT (214 mg, 2.0 equiv), and *N*-methylimidazole (115 μL, 4.0 equiv) in CH_2Cl_2 (2.5 mL) for 4.25 h. The resin was washed with CH_2Cl_2 (3×), DMF (3×), and CH_2Cl_2 (6×) and dried. A total of 13.5 mg of resin was treated with 0.1 M NaOH (2 × 100 μL, 2 × 1 h) and washed with water (3 × 100 μL), MeCN (3 × 100 μL), and 1,4-dioxane (3 × 100 μL). The combined extracts were added to 40 μL of saturated aqueous NH_4Cl, cooled to −20 °C, and freeze-dried. The residue was taken up in $DCCl_3$, filtered, and analyzed by ^{1}H NMR, showing a spectrum identical to that of **2a**. The spectrum was recorded again after addition of a well-defined amount of EtOAc in $DCCl_3$ as internal reference, allowing calculation of the loading of **2a** on the resin to be 0.56 mmol/g.

Resin Bound Aldehyde 16. Resin **15** was treated with 95:5 TFA:H_2O for 3 min, washed with MeCN (3×), DMF (3×), and MeCN (6×), and dried in vacuo. ^{1}H MAS NMR δ 9.83 (s, 1H, CHO), 2.82 (t, 2H, J = 6.5, C*H*$_2$CHO), 2.68 (t, 2H, J = 6.5, C*H*$_2$CH$_2$CHO) + various resin peaks.

Pictet−Spengler Product 17. Resin bound aldehyde **16** (31 mg, 17 μmol) was treated with tryptamine hydrochloride (69 mg, 20 equiv) in a 1:1 mixture of toluene and DMSO (1 mL) at 50 °C for 3 days after which the resin was washed with DMSO (3×), CH_2Cl_2 (3×), MeCN (3×), and DMF (6×). Boc-Gly-OH (15 mg, 5 equiv), HATU (32 mg, 4.8 equiv), HOAt (2.4 mg, 1 equiv), and NEM (11 μL, 5 equiv) were incubated in DMF (100 μL) for 2 min, added to the resin, and kept at 20 °C overnight. The resin was washed with DMF (6×) and MeCN (6×), and 1−2 mg resin was treated with 0.1 M NaOH (50 μL) for 1 h, neutralized with saturated aqueous NH_4Cl (10 μL), and added MeCN (50 μL), and the supernatant was analyzed by analytical RP-HPLC. R_t = 15.4 min, ESMS *m*/*z* calcd for $C_{21}H_{28}N_3O_5$ $(M + H)^+$: 402.5. Found: 402.1

Reductive Amination Product 18. Resin bound aldehyde **16** (35 mg, 19 μmol) was treated with a mixture of 3-picolylamine (39 μL, 20 equiv) and $NaBH(OAc)_3$ (74 mg, 18 equiv) in 750 μL of 50:50:1 DMSO:CH_2Cl_2:AcOH overnight at 20 °C after which the resin was washed with DMF (3×), H_2O (1×), and DMF (8×) and acylated with Boc-Gly-OH as described for the synthesis of **17**. The compound was cleaved off the resin, and analysis was performed as described for **17**. R_t = 8.5 min, ESMS *m*/*z* calcd for $C_{18}H_{26}N_3O_7$ $(M + H)^+$: 352.4. Found: 352.1

Reductive Amination Product 19. Resin bound aldehyde **16** (37 mg, 20 μmol) was treated with a mixture of *N*-Boc diaminoethylene (66 μL, 20 equiv) and $NaBH(OAc)_3$ (79 mg, 18 equiv) in 750 μL of 50:50:1 DMSO:CH_2Cl_2:AcOH

overnight after which the resin was washed with DMF (3×), H_2O (1×), and DMF (8×) and acylated with Boc-Gly-OH as described for the synthesis of **17**. The compound was cleaved off the resin, and analysis was performed as described for **17**. R_t = 13.1 min, ESMS *m*/*z* calcd for $C_{18}H_{34}N_3O_7$ $(M + H)^+$: 404.5. Found: 404.1

Horner−Wadsworth−Emmons Product 20. Resin bound aldehyde **16** (32 mg, 18 μmol) was treated with a mixture of allyl-*P*,*P*-diethylphosphonoacetate (112 mg, 30 equiv), LiBr (39 mg, 25 equiv), and TEA (50 μL, 20 equiv) in MeCN (500 μL) overnight. The resin was washed with DMF (5×) and MeCN (5×), treated with an argon bubbled solution of $Pd[PPh_3]_4$ (62 mg, 3 equiv) in $HCCl_3$:AcOH:NEM (37:2:1, 600 μL) for 1 h, and washed with DCM (6×) and DMF (3×). To the resin was then added 400 μL of a DMF solution containing HATU (0.3 M), HOAt (0.1 M), and NEM (0.3 M), and 10 min later 200 μL of a DMF solution containing 2,4-dimethoxybenzylamine (1 M) and NEM (1 M) was added (the resin was not drained prior to amine addition). After incubation overnight, the resin was washed with DMF (6×) and MeCN (6×) and analyzed as described for **17**. R_t = 11.2 min, ESMS *m*/*z* calcd for $C_{15}H_{19}NNaO_5$ $(M + Na)^+$: 316.3. Found: 316.0.

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