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Publisher's version / Version de l'éditeur:

<https://doi.org/10.1021/cc060059n>

Journal of Combinatorial Chemistry, 8, 5, pp. 762-773, 2006-09-11

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Part 3. A Novel Stereocontrolled, In Situ, Solution- and Solid-Phase, Aza Michael Approach for High-Throughput Generation of Tetrahydroaminoquinoline-Derived Natural-Product-like Architectures

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Received April 24, 2006

With the goal of rapidly accessing tetrahydroquinoline-based natural-product-like polycyclic architectures, herein, we report an unprecedented, in situ, stereocontrolled Aza Michael approach in solution and on the solid phase. The mild reaction conditions required to reach the desired target are highly attractive for the use of this method in library generation. To our knowledge, this approach has not been used before, and it opens a novel route leading to a wide variety of tetrahydroquinoline-derived bridged tricyclic derivatives.

Introduction

The dissection of protein–protein interaction-based signaling networks using small molecules is an activity of an immense interest.^{1–3} In general, these interactions are complex, dynamic in nature, and present tremendous challenges in developing an understanding of their role at the molecular level.^{4,5} Because small molecules have the ability to modulate these interactions in a reversible, temporal, and nondestructive manner, there is a growing desire to use small molecules to obtain a better understanding of multiple protein–protein interaction-based signaling networks.^{6–8} In the absence of the structural information of a protein involved in protein–protein interactions, high-throughput generation of small-molecule chemical probes remains the method of choice. In particular, inspired by bioactive natural products that have been shown to act as inhibitors of protein–protein interactions, the development of solid-phase synthesis methods leading to the high-throughput generation of natural-product-like compounds seems to be an attractive undertaking.^{9–11}

With the goal of having rapid access to tetrahydroquinoline alkaloid, natural-product-like, polycyclic architectures, we reveal a method that uses an unprecedented in situ aza Michael reaction to obtain this objective. The wide abundance of quinoline and tetrahydroquinoline alkaloid natural products showing promising properties for modulating protein–protein interactions¹² was the motivation behind the development of this method. Another objective was to validate our hypothesis that the compounds generated from this project were highly likely to yield interesting biological

properties because these derivatives were anticipated to occupy the chemical space currently being championed by quinoline and tetrahydroquinoline alkaloids.¹³

Results and Discussion

A practical *enantioselective* synthesis of a highly functionalized, tetrahydroaminoquinoline-derived artificial amino acid, **1** (Figure 1) was previously reported by us.^{14,15} This scaffold is highly versatile and contains several attractive features. These include (i) the presence of orthogonally protected functional groups, (ii) β - and δ -amino acid functionality, (iii) 1,2-*trans*-amino alcohol moiety, and (iv) 1,3-hydroxyl carboxyl ester functionality. The phenolic hydroxyl group provided a site that could be used for immobilization of the scaffold onto the solid support. Furthermore, as shown in compound **2**, an extension of the side chain to obtain an unsaturated carboxyl ester functional group could be used to build the additional functionalized ring derivative that could lead to the tricyclic architecture (**3**) suitable for high-throughput generation of various analogs. At the time of the proposed plan, it was not clear that the desirable aza Michael reaction would lead to the additional ring in either the chair or boat form (see **3.1** and **3.2** in Figure 1). If successful in solution and on the solid phase, the approach described herein would lead to an interesting tetrahydroquinoline-derived natural-product-like tricyclic architecture that could then be subjected to combinatorial chemistry to obtain several analogs in a high-throughput manner.

Our initial approach to obtain the tetrahydroaminoquinoline-based aldehyde did not provide us the desired product, **6** (Scheme 1), from **4**. In our hands, the corresponding hydroxyl derivative, **5**, which was easily obtained from **4**, failed to oxidize under several reaction conditions. As an alternative, compound **4** was first subjected to side-chain extension, giving the unsaturated carboxyl derivative **7**. after

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Figure 1. Approach to high-throughput generation of tetrahydroaminoquinoline-based polycyclic architectures (3) from an *enantioenriched* scaffold (1).

Scheme 1

^a (i) CBz and acetonide deprotection, (ii) alloc protection, (iii) TBSOTf, (iv) LiBH₄. ^b Dess–Martin. ^c (i) H₂, 10% Pd/C; SiO₂, 56%, (ii) allocCl, DIPEA, 91%, (iii) 2-methoxypropene, PPTS, molecular sieves 4 Å, 60 °C, 81%, (iv) LiBH₄, RT, 81%, (v) Dess–Martin, RT, (vi) Ph₃P=CHCOOEt, RT, 87% for 2 steps. ^d (i) Acetonide removal, (ii) TESOTf, (iii) alloc removal. ^e Benzoylation. ^f Cinnamoylation.

the acetonide deprotection and the hydroxyl group protection, the desired starting material containing an *N*-Alloc-protected system was then obtained; this allowed the exploration of the crucial aza Michael reaction. Interestingly, when compound **7b** (not shown in the scheme) was subjected to *N*-Alloc removal, there was no sign of the free amine derivative **8**. Instead, the tricyclic product **9** was isolated as a single diastereomer! *The discovery of an in situ aza Michael reaction with complete stereocontrol was a pleasant surprise indeed.* To our knowledge, this approach is highly intriguing and has not been used in the past in related systems to obtain functionalized polycyclic architectures. These reaction conditions (i.e., the removal of the *N*-Alloc group using Pd(0), PPh₃) are very mild, and it would be excellent if this approach could be developed for the solid phase.

After the discovery of this beautiful in situ cyclization, the next set of challenges involved the assignment of the stereochemistry of the newly generated asymmetric center and the determination of the shape of the additional piperidine ring containing a β -amino acid functionality. Figure 2 shows the four plausible transition states that could be considered to lead to the product formation. A careful NMR analysis allowed us to assign the unique structure of compound **9**. In contrast to compound **7**, which showed a NOE between the protons at C₂ and C₄, the bridged tricyclic derivative **9** did not show a NOE. This suggested that, in

the starting material **9**, the substituents at C₂, C₃, and C₄ occupy the pseudoequatorial positions. The formation of the bridged compound **9** could be explained as follows: to proceed with the aza Michael reaction, the substituents at C₂, C₃, and C₄ adopt a pseudoaxial position to facilitate this reaction. As shown in Figure 2, there are four plausible transition states which may be involved in the formation of the desired product. For steric reasons, the chairlike transition states are not considered to be favorable (see **10** and **11**). The NOE between the protons at C₃ and C₇ allowed us to assign the stereochemistry and to predict a boat-type structure for the third ring (see Figure 2). A similar product with all the chair-type ring structures would not show any NOE between these two protons at C₃ and C₇. The ease of the solution-phase method for obtaining this highly functionalized, tetrahydroquinoline-based tricyclic derivative, having a β -amino acid functionality, prompted us to develop this approach on solid phase. The development of the manual solid-phase synthesis for further use in the library generation is shown in Scheme 2.

The starting material for the solid-phase synthesis, compound **15**, was obtained from **6** through easy transformations, and the details are provided in the Experimental Section. Additional analytical data are also provided in the Supporting Information.¹⁶ When subjecting compound **15** to the standard loading conditions using Broad Institute alkylsilyl-based

Figure 2. Proposed transition states to explain the diastereoselective outcome of the aza Michael reaction.

Scheme 2

^a (i) pTSA, 60 °C, 96%, (ii) Cs₂CO₃, 3-bromo-propanol, RT, 58%. ^b(i) TBAF, RT, 94%, (ii) FmocCl, NaHCO₃, RT, 60%, (c) (4-methoxyphenyl)diisopropylsilyl propyl polystyrene macrobeads (loading 1.365 mmol/g, 500–560 μm), 75% determined by an increase in the weight of the loaded alkylsilyl macrobeads. ^d(i) 3,4-(Methylenedioxy)phenylacetic acid, DCC, DMAP, RT, (ii) Pd(PPh₃)₄, PPh₃, 4-methyl morpholine, CH₃CO₂H, RT, (iii) PhCOCl, 2,4,6-collidine, RT, (iv) morpholine, RT, (v) 4-methoxyphenylacetyl chloride, 2,4,6-collidine, RT. ^eHF pyridine.

polystyrene macrobeads (560–560 μm, loading capacity 1.365 mmol/g), we were pleased to note that it could be immobilized in a high yield (85–90% loading determined after cleavage of the product from the solid support) and with complete regiocontrol. The hydroxyl group of loaded compound **16** was then acylated (i.e., first diversity) and subjected to *N*-Alloc removal. To our delight, as we observed in solution synthesis, the in situ formation of the additional piperidine ring by an aza Michael also worked very well in the solid phase. The final product, **18**, was obtained, following the three-step sequence that includes (i) *N*-amidation, (ii) *N*-Fmoc removal, and (iii) *N*-amidation, after a cleavage from the solid support. The extensive NMR studies of compound **18** revealed similar results to those obtained with the product **9a**, generated by solution-phase synthesis. Our successful solid-phase efforts provide an attractive route to obtain a high-throughput access to several analogs of tetrahydroquinoline-based bridged tricyclic natural-product-like compounds.

Conclusion

To summarize, herein, we disclose an unprecedented, stereocontrolled, in situ, aza Michael approach in solution and on the solid phase to obtain tetrahydroquinoline-derived

bridged tricyclic architectures. Furthermore, work is in progress to generate a 200-member library by using IRORI 2D-bar coded technology and to develop new small-molecule microarrays using these library members. In addition, the scope of these library members as chemical dissectors of several protein–protein interaction-based signaling networks will be investigated, and these studies will be reported as they become available.

Experimental Procedures

All reactions were carried out in flame-dried glassware under an atmosphere of nitrogen with magnetic stirring. Thin-layer chromatography (TLC) was done on EMD (Art. 5715-7) precoated silica gel 60 F₂₅₄ glass plates (layer thickness = 0.25 mm). Visualization was affected with a UV lamp (254 nm) or either by staining with a vanillin, KMnO₄, or ammonium molybdate/ceric sulfate solution. Flash column chromatography was performed using silica gel 60 (40–63 μm, Silicycle) or the Biotage Horizon Flash Chromatography System. Solvents were purified as follows: the trace amounts of water and oxygen in THF, DMF, and dichloromethane were removed using columns containing activated alumina and copper under N₂. Triethylamine, pyridine, ethyl ether, and toluene were obtained from commercial suppliers (EMD

and Aldrich) and used without further purification. NMR spectra were recorded on a Bruker DRX 400 MHz spectrometer. All chemical shifts are reported in parts per million (δ). ^1H NMR (400 MHz) spectra were recorded at room temperature in CDCl_3 or C_6D_6 solutions and referenced to residual CHCl_3 (7.27 ppm) or C_6H_6 (7.16 ppm). Fully decoupled ^{13}C NMR (100 MHz) spectra were recorded in CDCl_3 or C_6D_6 solutions. The center peaks of CDCl_3 (77.0 ppm) and C_6D_6 (128.7 ppm) were used as the internal reference. Mass spectra were carried out on a VG Quattro I (Micromass) mass spectrometer equipped with a pneumatically assisted electrospray ionization source, operating in positive mode. HPLC were performed using a Hewlett-Packard (Agilent) 1100 Series equipped with a diode array detector and a NovaPack C18 (3.9×300 mm) column. The enantiomeric excess was determined by chiral HPLC, using a Hewlett-Packard (Agilent) 1090 Series II Liquid Chromatograph equipped with a diode array detector and a CHIRACELOD column. HPLC/MS were performed using Waters equipment: Waters micromass ZQ ESCI multimode ionization, Waters 996 photodiode array detector (254 nm), and a Waters 2795 separation module with Phenomenex Spherisorb 3 ODS-2 column.

Colorless oil. R_f : 0.54 (1/1 hexane/ethyl acetate). ^1H NMR (CDCl_3 , 400 MHz): δ 7.42–7.26 (m, 5H, Ph), 6.86 (broad s, 1H, MEMOC–CH=C), 6.78 (dd, $J = 8.5$ Hz, $J = 2.3$ Hz, 1H, CH–CH=C–N), 6.44 (d, $J = 8.5$ Hz, 1H, CH–CH=C–N), 5.29 (d, $J = 12.3$ Hz, 1H, PhCH_2OCO), 5.20 (d, $J = 12.3$ Hz, 1H, PhCH_2OCO), 5.06 (broad s, 2H, OMEM), 4.47 (d, $J = 9.8$ Hz, 1H, CH–NCO), 4.42 (broad s, 1H, NH), 4.16 (2q, $J = 7.0$ Hz, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.95 (td, $J = 9.8$ Hz, $J = 2.5$ Hz, 1H, CHCH $_2$ CO $_2$ Et), 3.79–3.74 (m, 2H, OMEM), 3.66 (t, $J = 9.8$ Hz, 1H, CHOCMe $_2$), 3.54–3.49 (m, 2H, OMEM), 3.34 (s, 3H, OMEM), 2.84 (dd, $J = 16.0$ Hz, $J = 2.5$ Hz, 1H, CHCH $_2$ CO $_2$ Et), 2.38 (dd, $J = 16.0$ Hz, $J = 9.8$ Hz, 1H, CHCH $_2$ CO $_2$ Et), 1.66 (broad s, 3H, CMe $_2$), 1.56 (s, 3H, CMe $_2$), 1.25 (t, $J = 7.0$ Hz, 3H, CO $_2$ CH $_2$ CH $_3$). ^{13}C NMR (CDCl_3 , 100 MHz): δ 171.4, 154.6 (broad), 149.2, 137.0, 135.8, 128.2 (2C), 128.0 (2C), 127.9, 122.9 (broad), 115.7, 114.1 (broad), 113.8, 99.0 (broad), 94.4, 78.5 (broad), 71.4, 67.1, 66.9 (broad), 60.6, 60.1 (broad), 58.7, 52.2, 39.4, 26.1 (broad, 2C), 13.9. LRMS: MS (ES $^+$) $m/z = 529.4$ (M + 1).

Triphosgene (192 mg, 0.63 mmol) was added to the round-bottom flask and cooled to -78°C . This was then followed by the slow addition of 10 mL of anhydrous CH_2Cl_2 , and the solution was vigorously stirred for 30 min. The 2-(trimethylsilyl) ethanol (265 μL , 1.84 mmol) was added to the reaction mixture in one portion at -78°C , and the mixture was then warmed to -10°C . Then pyridine (150 μL , 1.84 mmol) was added dropwise to the reaction mixture and stirred for 2 h at -10°C . The reaction mixture was cooled to -45°C , and a solution of free amine (485 mg, 0.92 mmol) and pyridine (225 μL , 2.75 mmol) in 3 mL of anhydrous CH_2Cl_2 was added via cannula over a period of 5 min. The stirring was continuous for 1 h at -30°C and for 15 min at 0°C . When the TLC showed no starting material, the reaction mixture was quenched via the addition of 40 mL of a saturated solution of NaHCO_3 , and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The organic layer was dried over MgSO_4 , filtered, and concentrated under vacuum, and the crude product was chromatographed on neutralized silica gel with hexane/triethylamine, 9/1 (eluent = hexane/ethyl acetate, 8/2) to give **4** (470 mg, 77%) (Figure 4). Colorless oil. R_f : 0.59 (1/1 hexane/ethyl acetate). ^1H NMR (CDCl_3 , 400 MHz): δ 7.44–7.23 (m, 6H, 5H $_{\text{Ph}}$ and CH–CH=C–N), 6.96 (dd, $J = 8.8$ Hz, $J = 2.5$ Hz, 1H, CH–CH=C–N), 6.82 (broad s, 1H, MEMOC–CH=C), 5.30–5.09 (m, 4H, 2H from OMEM and PhCH_2OCO), 4.56 (broad m, 1H, CHCH $_2$ CO $_2$ Et), 4.35–4.26 (m, 2H, TMSCH $_2$ CH $_2$ O), 4.29–4.19 (m, 1H, CH–NCO), 4.10–3.96 (m, 2H, CO $_2$ CH $_2$ CH $_3$), 3.84–3.76 (m, 2H, OMEM), 3.71 (t, $J = 9.5$ Hz, 1H, CHOCMe $_2$), 3.57–3.51 (m, 2H, OMEM), 3.37 (s, 3H, OMEM), 2.81–2.71 (m, 2H, CHCH $_2$ CO $_2$ Et), 1.73 (broad s, 3H, CMe $_2$), 1.57 (s, 3H, CMe $_2$), 1.16 (t, $J = 7.0$ Hz, 3H, CO $_2$ CH $_2$ CH $_3$), 1.06 (broad s, 2H, TMSCH $_2$ CH $_2$ O), 0.03 (s, 9H, TMS). ^{13}C NMR (CDCl_3 , 100 MHz): δ 169.5, 154.8, 154.4, 153.7 (broad), 135.7, 132.6 (broad), 128.6, 128.3 (2C), 128.1 (2C), 127.9, 127.1 (broad), 113.8 (broad), 111.1 (broad), 99.5 (broad), 93.4, 80.4 (broad), 71.3, 67.4, 66.9 (broad), 64.3, 60.3, 59.5, 58.7, 54.3, 37.9 (broad), 25.8

Figure 3.

Figure 4. NOE between H₂ and H₄ for compound **4**.

(broad, 2C), 17.5, 13.7, -1.8 (3C). LRMS: MS (ES+) *m/z* = 673.5 (*M* + 1).

Palladium 10 wt % on activated carbon (63 mg) was added to a solution of Teoc-protected amine (503 mg, 075 mmol) in 15 mL of anhydrous ethanol, and the mixture was stirred for 8.5 h in a hydrogen atmosphere. The reaction mixture was filtered through celite and concentrated under vacuum. The crude product was chromatographed on silica gel (eluent: CH₂Cl₂/methanol, 98/2) to give **4a** (210 mg, 56%). Colorless oil. *R_f*: 0.16 (98/2 CH₂Cl₂/methanol). ¹H NMR (CDCl₃, 400 MHz): δ 7.26 (broad d, *J* = 8.5 Hz, 1H, CH-CH=C-N), 7.05 (d, *J* = 2.5 Hz, 1H, MEMOC-CH=C), 6.89 (dd, *J* = 8.5 Hz, *J* = 2.5 Hz, 1H, CH-CH=C-N), 5.24–5.19 (m, 2H, OMEM), 4.46–4.44 (m, 1H, CHCH₂-CO₂Et), 4.28–4.12 (m, 2H, TMSCH₂CH₂O), 4.05–3.95 (m, 2H, CO₂CH₂CH₃), 3.80–3.75 (m, 2H, OMEM), 3.65 (t, *J* = 9.8 Hz, 1H, CHOH), 3.54–3.49 (m, 2H, OMEM), 3.33 (s, 3H, OMEM), 3.20 (ddd, *J* = 9.8 Hz, *J* = 6.0 Hz, *J* = 3.3 Hz, 1H, CHNH₂), 2.74–2.64 (m, 1H, OH), 2.71 (dd, *J* = 15.3 Hz, *J* = 4.5 Hz, 1H, CHCH₂CO₂Et), 2.52 (dd, *J* = 15.3 Hz, *J* = 8.5 Hz, 1H, CHCH₂CO₂Et), 2.01 (broad s, 2H, NH₂), 1.14 (t, *J* = 7.0 Hz, 3H, CO₂CH₂CH₃), 0.99 (t, *J* = 8.5 Hz, 2H, TMSCH₂CH₂O), -0.03 (s, 9H, TMS). ¹³C NMR (CDCl₃, 100 MHz): δ 171.9, 155.0, 154.3, 135.1, 129.3, 126.3, 114.3, 111.1, 93.5, 78.8, 71.4, 67.4, 64.2, 60.7, 58.8, 57.4, 53.0, 38.7, 17.6, 13.9, -1.7 (3C). LRMS: MS (ES+) *m/z* = 499.4 (*M* + 1).

N,N-Diisopropylethylamine (135 μL, 0.77 mmol), one portion, and allylchloroformate (77 μL, 0.71 mmol), dropwise, were added to a solution of free amine **4a** (320 mg, 0.64 mmol) in 50 mL of anhydrous CH₂Cl₂ at -70 °C. The reaction mixture was slowly warmed to room temperature in 3 h, stirred for an additional 2.5 h, and quenched via the addition of 40 mL of a saturated solution of NH₄Cl. The

aqueous layer was extracted with CH₂Cl₂ (3 × 30 mL), and the organic layer was dried over MgSO₄. After filtration and concentration under vacuum, the crude product was chromatographed on silica gel (eluent = CH₂Cl₂/methanol, 98/2) to give **4b** (340 mg, 91%). Colorless oil. *R_f*: 0.19 (1/1 hexane/ethyl acetate). ¹H NMR (CDCl₃, 400 MHz): δ 7.27 (broad d, *J* = 8.8 Hz, 1H, CH-CH=C-N), 6.94 (dd, *J* = 8.8 Hz, *J* = 2.5 Hz, 1H, CH-CH=C-N), 6.92 (broad s, 1H, MEMOC-CH=C), 6.00–5.87 (m, 1H, H₂C=CH-CH₂O), 5.36 (broad d, *J* = 7.5 Hz, 1H, NH), 5.33 (broad d, *J* = 17.1 Hz, 1H, H₂C=CH-CH₂O), 5.24–5.20 (m, 1H, H₂C=CH-CH₂O), 5.25–5.19 (m, 2H, OMEM), 4.70–4.62 (m, 1H, CH-NH), 4.62 (d, *J* = 5.5 Hz, 2H, H₂C=CH-CH₂O), 4.62–4.56 (m, 1H, CHCH₂CO₂Et), 4.32–4.16 (m, 2H, OCH₂CH₂TMS), 4.10–3.97 (m, 2H, CO₂CH₂CH₃), 3.93 (broad s, 1H, OH), 3.80 (dd, *J* = 6.0 Hz, *J* = 4.5 Hz, 2H, OMEM), 3.61–3.54 (m, 1H, CH-OH), 3.55 (dd, *J* = 6.0 Hz, *J* = 4.5 Hz, 2H, OMEM), 3.36 (s, 3H, OMEM), 2.73 (dd, *J* = 15.1 Hz, *J* = 4.8 Hz, 1H, CHCH₂CO₂Et), 2.54 (dd, *J* = 15.1 Hz, *J* = 8.3 Hz, 1H, CHCH₂CO₂Et), 1.17 (t, *J* = 7.0 Hz, 3H, CO₂CH₂CH₃), 1.03 (t, *J* = 8.5 Hz, 2H, OCH₂CH₂TMS), 0.01 (s, 9H, TMS). ¹³C NMR (CDCl₃, 100 MHz): δ 171.8, 156.7, 154.9, 154.4, 132.6, 131.8, 129.3, 126.7, 117.9, 114.9, 111.8, 93.6, 76.4, 71.5, 67.5, 66.0, 64.5, 60.9, 58.9, 57.1, 53.8, 38.4, 17.7, 13.9, -1.62 (3C). LRMS: MS (ES+) *m/z* = 583.4 (*M* + 1).

2-Methoxypropene (0.79 mL, 8.02 mmol) was added to a solution of the alloc-protected compound **4b** (468 mg, 0.80 mmol) in 10 mL of toluene, and the mixture was stirred for 15 min. Molecular sieves (4 Å, 50 mg) and pyridinium *p*-toluenesulfonate (10 mg, 0.04 mmol) were then added to the reaction mixture, and the mixture was warmed to 60 °C for 140 min. The reaction mixture was cooled, filtered, and concentrated under vacuum. The crude product was chromatographed using the Biotage chromatograph system (A = hexane, B = ethyl acetate, CV = 48 mL, vol fract = 15 mL, flow = 19 mL/min, neutralization of the column using 2 CV with hexane/triethylamine, 9/1, EQ[5CV] 10%B, 1CV¹ 10%B, 10CV² 10%B to 40%B, 10CV³ 40%B) to give the title compound (404 mg, 81%). Colorless oil. *R_f*: 0.60 (1/1 hexane/ethyl acetate using neutralized TLC silica plate with triethylamine). ¹H NMR (CDCl₃, 400 MHz): δ 7.17 (broad s, 1H, CH-CH=C-N), 6.85 (dd, *J* = 8.8 Hz, *J* = 2.5 Hz, 1H, CH-CH=C-N), 6.74 (d, *J* = 2.5 Hz, 1H, MEMOC-CH=C), 5.85 (broad s, 1H, H₂C=CH-), 5.26–5.05 (m, 4H, OMEM and H₂C=CH-), 4.58 (broad s, 2H, H₂C=CH-CH₂O), 4.46 (broad s, 1H, CHCH₂CO₂Et), 4.26–4.14 (m, 2H, TMSCH₂CH₂O), 4.17–4.08 (m, 1H, CH-NCO), 3.99–3.86 (m, 2H, CO₂CH₂CH₃), 3.74–3.70 (m, 2H, OMEM), 3.61 (t, *J* = 9.5 Hz, 1H, CHOCMe₂), 3.48–3.44 (m, 2H, OMEM), 3.27 (s, 3H, OMEM), 2.70–2.62 (m, 2H, CHCH₂-CO₂Et), 1.62 (broad s, 3H, CMe₂), 1.47 (s, 3H, CMe₂), 1.06 (t, *J* = 7.3 Hz, 3H, CO₂CH₂CH₃), 0.97 (broad s, 2H,

TMSCH₂CH₂O), -0.07 (broad s, 9H, TMS). ¹³C NMR (CDCl₃, 100 MHz): δ 169.4, 154.8, 154.3, 153.3 (broad), 132.6 (broad), 132.1, 128.5, 127.0 (broad), 118.0, 113.8 (broad), 110.9 (broad), 99.3 (broad), 93.4, 80.3 (broad), 71.3, 67.3, 65.9 (broad), 64.2, 60.2, 59.4 (broad), 58.6, 54.3, 37.9 (broad), 25.7 (broad, 2C), 17.4, 13.7, -1.9 (3C). LRMS: MS (ES⁺) m/z = 623.6 (M + 1). HPLC: 12.59 min.

A 2 M lithium borohydride solution in THF (0.80 mL, 1.61 mmol) was added to a solution of ester **4c** (400 mg, 0.64 mmol) in 5 mL of anhydrous THF at room temperature, and the mixture was stirred for 15 h. Then more lithium borohydride solution in THF (2.00 mL, 4.00 mmol) was added and stirred for an additional 2 h. The reaction mixture was quenched by reverse addition onto ice-cold saturated NH₄Cl solution. The aqueous layer was extracted with Et₂O (3 $\times$ 20 mL), and the organic layer was dried over MgSO₄. After filtration and concentration under vacuum, the crude product was chromatographed using the Biotage chromatograph system (A = hexane, B = ethyl acetate, CV = 48 mL, vol fract = 42 mL, flow = 19 mL/min, neutralization of the column using 2 CV with hexane/triethylamine, 9/1, EQ[5CV] 10%B, 1CV¹ 10%B, 10CV² 10%B to 50%B, 10CV³ 50%B) to give the title compound (301 mg, 81%). Colorless oil. *R*_f: 0.45 (1/1 hexane/ethyl acetate using neutralized TLC silica plate with triethylamine). ¹H NMR (CDCl₃, 400 MHz): δ 7.13 (broad s, 1H, CH=CH=C-N), 6.90 (dd, *J* = 8.8 Hz, *J* = 2.5 Hz, 1H, CH=CH=C-N), 6.80 (d, *J* = 2.5 Hz, 1H, MEMOC-CH=C), 5.90 (broad s, 1H, H₂C=CH-), 5.35–5.06 (m, 4H, OMEM and H₂C=CH-), 4.63 (broad s, 2H, H₂C=CH-CH₂O), 4.38 (broad s, 1H, CHCH₂CO₂Et), 4.28–4.18 (m, 2H, TMSCH₂CH₂O), 4.15 (m, 1H, CH-NCO), 3.79–3.75 (m, 2H, OMEM), 3.73–3.60 (m, 2H, CHCH₂CH₂OH), 3.54–3.49 (m, 2H, OMEM), 3.42–3.33 (broad m, 1H, CHOCMe₂), 3.32 (s, 3H, OMEM), 3.03 (broad s, 1H, OH), 1.87 (broad s, 1H, CHCH₂-CH₂OH), 1.75–1.56 (m, 1H, CHCH₂CH₂OH), 1.67 (broad s, 3H, CMe₂), 1.52 (s, 3H, CMe₂), 0.95 (broad s, 2H, TMSCH₂CH₂O), -0.05 (broad s, 9H, TMS). ¹³C NMR (CDCl₃, 100 MHz): δ 155.9 (broad), 155.3 (broad), 153.5 (broad), 133.5 (broad), 132.2, 128.3 (broad), 127.7 (broad), 118.2, 113.9 (broad), 111.3 (broad), 99.5 (broad), 93.5, 83.0 (broad), 71.4, 67.5, 66.1 (broad), 64.6 (broad), 59.6, 58.8, 58.5 (broad), 54.3 (broad), 37.6, 25.9 (broad, 2C), 17.4, -1.8 (3C). LRMS: MS (ES⁺) m/z = 581.6 (M + 1). HPLC: 11.43 min.

Compound 4e.

Dess–Martin reagent (272 mg, 0.62 mmol) was added to a solution of alcohol **4d** (301 mg, 0.52 mmol) in 5 mL of anhydrous CH₂Cl₂ at room temperature, and the mixture was stirred for 1 h. Then 10 mL of a saturated solution of NaHCO₃ was added; the aqueous layer was extracted with CH₂Cl₂ (3 $\times$ 10 mL), and the organic layer was dried over MgSO₄. After filtration and concentration under vacuum, the crude aldehyde was used for the next reaction without purification. Yellow oil. *R*_f: 0.58 (1/1 hexane/ethyl acetate using neutralized TLC silica plate with triethylamine). LRMS: MS (ES⁺) m/z = 579.5 (M + 1), 596.6 (M + 18). HPLC: 11.76 min.

Compound 7.

The (carbethoxymethylene) triphenylphosphorane (285 mg, 0.78 mmol) was added to a solution of crude aldehyde **4e** in 10 mL of anhydrous CH₂Cl₂, and the reaction mixture was stirred for 5 h. Then 20 mL of a saturated solution of Na₂CO₃ was added; the aqueous layer was extracted with CH₂Cl₂ (3 $\times$ 20 mL), and the organic layer was dried over MgSO₄. After filtration and concentration under vacuum, the crude product was chromatographed using the Biotage chromatograph system (A = hexane, B = ethyl acetate, CV = 48 mL, vol fract = 42 mL, flow = 19 mL/min, neutralization of the column using 2 CV with hexane/triethylamine, 9/1, EQ[5CV] 10%B, 1CV¹ 10%B, 10CV² 10%B to 40%B, 10CV³ 40%B) to give the title compound (295 mg, 87% for 2 steps). Colorless oil. *R*_f: 0.62 (1/1 hexane/ethyl acetate using neutralized TLC silica plate with triethylamine). ¹H NMR (CDCl₃, 400 MHz): δ 7.40–7.06 (broad m, 1H, CH=CH=C-N), 6.89 (dd, *J* = 8.8 Hz, *J* = 2.0 Hz, 1H, CH=CH=C-N), 6.79 (dt, *J* = 15.6 Hz, *J* = 7.5 Hz, 1H, CH=CHCO₂Et), 6.77 (d, *J* = 2.0 Hz, 1H, MEMOC-CH=C), 5.88 (broad s, 1H, H₂C=CH-), 5.79 (d, *J* = 15.6 Hz, 1H, CH=CHCO₂Et), 5.31–5.07 (m, 4H, OMEM and H₂C=CH-), 4.61 (broad s, 2H, H₂C=CH-CH₂O), 4.35 (broad s, 1H, CHCH₂CH=CHCO₂Et), 4.27–4.13 (m, 3H, TMSCH₂CH₂O and CH-NCO), 4.13–4.03 (m, 2H, CO₂CH₂CH₃), 3.78–3.73 (m, 2H, OMEM), 3.52–3.48 (m, 2H, OMEM), 3.36 (t, *J* = 9.3 Hz, 1H, CHOCMe₂), 3.31 (s, 3H, OMEM), 2.71–2.61 (m, 1H, CHCH₂CH=CHCO₂Et), 2.61–2.51 (broad m, 1H, CHCH₂CH=CHCO₂Et), 1.65 (broad s, 3H, CMe₂), 1.49 (s, 3H, CMe₂), 1.19 (t, *J* = 7.0 Hz, 3H, CO₂CH₂CH₃), 0.99 (broad s, 2H, TMSCH₂CH₂O), -0.03 (broad s, 9H, TMS). ¹³C NMR (CDCl₃, 100 MHz): δ 165.6, 155.0, 154.6, 153.5 (broad), 142.9, 132.9 (broad), 132.2, 128.7, 128.3 (broad), 127.2 (broad), 124.1, 118.2, 113.9 (broad), 111.1 (broad), 99.4 (broad), 93.5, 80.9 (broad), 71.4, 67.5, 66.0 (broad), 64.3, 59.9, 59.5 (broad), 58.8, 55.8 (broad), 35.8 (broad), 25.9 (broad, 2C), 17.5 (broad), 14.0, -1.8 (2C). LRMS: MS (ES⁺) m/z = 649.7 (M + 1), 621.6 (M – 27), 581.4 (M – 67). HPLC: 12.70 min.

Compound 7a.

A solution of acetic acid/THF/water (8/1/1, 5.0 mL) was added to compound **9** (100 mg) at room temperature, and the mixture was stirred for 24 h. Again, 3 mL of the above-mentioned solution was added to the reaction mixture, and it was stirred for another 24 h. The reaction mixture was extracted with ethyl acetate (3 × 30 mL) and dried over anhydrous MgSO_4 . The solvent was removed under reduced pressure, and the crude product was purified by flash column chromatography using 45/55 ethyl acetate/hexane to obtain compound **7a** (80 mg, 85%). Molecular Formula: $\text{C}_{29}\text{H}_{44}\text{N}_2\text{O}_{10}\text{Si}$. LRMS: MS (ES+) m/z = 609 ($M + 1$). ^1H NMR (400 MHz, CDCl_3): δ 7.36 (br d, 1H, J = 9.0 Hz, $\text{CHCH}-\text{C}-\text{N}$), 7.03–6.97 (dd, 1H, J = 8.7 Hz and 3.0 Hz, $\text{CHCH}-\text{C}-\text{N}$), 6.92 (br d, 1H, J = 2.0 Hz, $\text{MEMOC}=\text{CH}-\text{C}$), 6.91–6.84 (m, 1H, $\text{CH}=\text{CHCO}_2\text{Et}$), 6.02–5.92 (m, 1H, $\text{OCH}_2\text{CH}=\text{CH}_2$), 5.80 (d, 1H, J = 15.5 Hz, $\text{CH}=\text{CHCO}_2\text{Et}$), 5.37 (d, 1H, J = 16.8 Hz, $\text{OCH}_2\text{CH}=\text{CH}_2$), 5.31–5.24 (m, 3H, 1H from $\text{OCH}_2\text{CH}=\text{CH}_2$ and MEM), 5.12 (br d, 1H, J = 8.7 Hz, NHCHCH), 4.72–4.62 (m, 3H, NH, $\text{OCH}_2\text{CH}=\text{CH}_2$), 4.53–4.45 (m, 1H, NCHCH_2), 4.33–4.21 (q, 2H, J = 9.5 Hz, $\text{TMSCH}_2\text{CH}_2\text{O}$), 4.20–4.11 (q, 2H, J = 7.2 Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.84 (m, 2H, MEM), 3.58 (m, 2H, MEM), 3.50–3.42 (m, 1H, CHOH), 3.39 (s, 3H, MEM), 2.62–2.53 (m, 1H, NCHCH_2), 2.52–2.42 (m, 1H, NCHCH_2), 1.27 (t, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.06 (t, 2H, $\text{TMSCH}_2\text{CH}_2\text{O}$), 0.07–0.00 (br s, 9H, TMS). ^{13}C NMR (400 MHz, CDCl_3): δ 166.42, 151.13, 155.33, 155.13, 144.17, 132.80, 131.40, 130.11, 127.66, 124.52, 118.72, 115.91, 112.04, 94.08, 77.63, 71.99, 68.05, 66.71, 65.08, 60.70, 59.46, 59.11, 54.69, 36.61, 18.14, 14.60, –1.11(3C).

Compound 7b.

Pyridine (16.1 μL , 0.19 mmol) was added to a solution of compound **7a** (80 mg, 0.13 mmol) in 40 mL of dry CH_2Cl_2 , cooled to -40°C , followed by the addition of TESOTf (39.1 μL , 0.17 mmol). The reaction mixture was allowed to stir at -40°C for 3.5 h. The reaction mixture was then quenched with saturated NaHCO_3 , extracted with CH_2Cl_2 (3 × 30 mL), and dried over anhydrous MgSO_4 . The solvent was removed under reduced pressure, and the crude product was purified by flash column chromatography using 30/70 ethyl acetate/hexane to obtain compound **7b** (55 mg, 84%). Molecular Formula: $\text{C}_{35}\text{H}_{58}\text{N}_2\text{O}_{10}\text{Si}_2$. LRMS: MS (ES+) m/z = 723 ($M + 1$). ^1H NMR (400 MHz, CDCl_3): δ 7.49–7.33 (m, 1H, $\text{CHCH}-\text{C}-\text{N}$), 7.03–6.97 (dd, 1H, J = 8.7 Hz, J = 2.7 Hz, $\text{CHCH}-\text{C}-\text{N}$), 6.96 (br s, 1H, $\text{MEMOC}=\text{CH}-\text{C}$), 6.91–6.82 (m, 1H, $\text{CH}=\text{CHCO}_2\text{Et}$), 6.02–5.92 (m, 1H,

$\text{OCH}_2\text{CH}=\text{CH}_2$), 5.77 (d, 1H, J = 15.8 Hz, $\text{CH}=\text{CHCO}_2\text{Et}$), 5.36 (br d, 1H, J = 17.3 Hz, $\text{OCH}_2\text{CH}=\text{CH}_2$), 5.28–5.24 (m, 3H, 1H from $\text{OCH}_2\text{CH}=\text{CH}_2$ and MEM), 4.76 (br d, 1H, J = 8.0 Hz, NHCHCH), 4.70–4.60 (m, 3H, NH, $\text{OCH}_2\text{CH}=\text{CH}_2$), 4.59–4.53 (m, 1H, NCHCH_2), 4.29–4.14 (m, 4H, $\text{TMSCH}_2\text{CH}_2\text{O}$, $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.88–3.79 (m, 3H, CHOTES , 2H from MEM), 3.61–3.55 (m, 2H, MEM), 3.40 (s, 3H, MEM), 2.47–2.39 (m, 1H, NCHCH_2), 2.28–2.21 (m, 1H, NCHCH_2), 1.29 (t, 3H, J = 7.2 Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.09–1.00 (m, 2H, $\text{TMSCH}_2\text{CH}_2\text{O}$), 1.00–0.93 (br t, 9H, J = 7.7 Hz, TES), 0.71–0.60 (br q, 6H, TES), 0.08–0.00 (br s, 9H, TMS).

Compound 9.

Morpholine (13 μL , 0.14 mmol) was added to a solution of compound **7b** (54 mg, 0.07 mmol) in 30 mL of dry CH_2Cl_2 at room temperature, followed by the addition of $\text{Pd}(\text{PPh}_3)_4$ (8.5 mg, 0.007 mmol), and the mixture was stirred vigorously for 1 h. The solvent was removed under reduced pressure, and the crude product was purified by flash column chromatography using 45/55 ethyl acetate/hexane to give **9** (44 mg, 92%). Molecular Formula: $\text{C}_{31}\text{H}_{54}\text{N}_2\text{O}_8\text{Si}_2$. LRMS: MS (ES+) m/z = 639 ($M + 1$). ^1H NMR (400 MHz, CDCl_3): δ 8.27 (br d, 1H, J = 10.0 Hz, $\text{CHCH}-\text{C}-\text{N}$), 7.18 (m, 1H, $\text{MEMOC}=\text{CH}-\text{C}$), 7.12 (br d, 1H, J = 10.0 Hz, $\text{CHCH}-\text{C}-\text{N}$), 5.35–5.23 (m, 3H, NH, MEM), 4.87 (m, 1H, $\text{NHCHCH}-\text{O}$), 4.78 (m, 1H, TeocNCHCH_2), 4.50 (m, 1H, CHOTES), 4.33 (t, 2H, J = 8.0 Hz, $\text{TMSCH}_2\text{CH}_2\text{O}$), 4.18–4.06 (br q, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.84 (m, 2H, MEM), 3.59 (m, 2H, MEM), 3.39 (s, 3H, MEM), 3.23 (m, 1H, $\text{CHCH}_2\text{CO}_2\text{Et}$), 2.68 (br d, 1H, J = 11.5 Hz, $\text{CHCH}_2\text{CO}_2\text{Et}$), 2.54 (m, 1H, $\text{CHCH}_2\text{CO}_2\text{Et}$), 2.28 (m, 2H, TeocNCHCH_2), 1.22 (t, 3H, J = 7.0 Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.10 (m, 2H, $\text{TMSCH}_2\text{CH}_2\text{O}$), 0.92–0.83 (t, 9H, J = 7.5 Hz, TES), 0.70–0.56 (br q, 6H, TES), 0.12–0.02 (br s, 9H, TMS). ^{13}C NMR (400 MHz, CDCl_3): δ 172.03, 156.56, 153.28, 136.04, 133.96, 121.77, 117.06, 116.07, 94.25, 77.63, 72.03, 67.89, 64.53, 60.90, 59.43, 57.34, 54.63, 43.04, 40.48, 37.31, 18.21, 14.54, 7.07 (3C), 5.18 (3C), –1.08 (3C).

Compound 9a.

Triethyl amine (6.5 μL , 0.046 mmol), followed by benzoyl chloride (3.6 μL , 0.031 mmol), was added to a solution of compound **9** (10 mg, 0.015 mmol) in 10 mL of dry CH_2Cl_2 , cooled to 0°C . The reaction mixture was allowed to stir from 0°C to room temperature for 3.5 h. The reaction

mixture was then quenched with saturated NaHCO_3 , extracted with CH_2Cl_2 ($3 \times 30 \text{ mL}$), and dried over anhydrous MgSO_4 . The solvent was removed under reduced pressure, and the crude product was purified by flash column chromatography using 30/70 ethyl acetate/hexane to obtain compound **9a** (7 mg, 60%). Molecular Formula: $\text{C}_{38}\text{H}_{58}\text{N}_2\text{O}_9\text{Si}_2$. LRMS: MS (ES+) $m/z = 743$ ($M + 1$). ^1H NMR (400 MHz, CDCl_3): δ 8.09 (br d, 1H, $J = 8.5 \text{ Hz}$, $\text{CHCH}-\text{C}-\text{N}$), 7.74 (m, 2H, Ph), 7.56–7.47 (m, 3H, Ph), 7.01–6.97 (dd, 1H, $J = 9.5 \text{ Hz}$, $J = 3.0 \text{ Hz}$, $\text{CHCH}-\text{C}-\text{N}$), 6.64 (d, 1H, $J = 3.0 \text{ Hz}$, $\text{MEMOC}=\text{CH}-\text{C}$), 5.21 (m, 2H, MEM), 4.80 (m, 1H, TeocNCHCH_2), 4.67 (m, 1H, PhCOHCHCH), 4.29 (t, 2H, $J = 8.0 \text{ Hz}$, $\text{TMSCH}_2\text{CH}_2\text{O}$), 4.12 (t, 1H, $J = 3.5 \text{ Hz}$, CHOTES), 4.08 (q, 2H, $J = 7.0 \text{ Hz}$, $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.84 (m, 2H, MEM), 3.60 (m, 2H, MEM), 3.46 (m, 1H, $\text{CHCH}_2\text{CO}_2\text{Et}$), 3.39 (s, 3H, MEM), 3.02 (dd, 1H, $J = 16.5 \text{ Hz}$, $J = 5.5 \text{ Hz}$, $\text{CHCH}_2\text{CO}_2\text{Et}$), 2.85 (dd, 1H, $J = 16.0 \text{ Hz}$, $J = 6.0 \text{ Hz}$, $\text{CHCH}_2\text{CO}_2\text{Et}$), 2.17 (m 2H, TeocNCHCH_2), 1.19 (t, 3H, $J = 7.0 \text{ Hz}$, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.09 (m, 2H, $\text{TMSCH}_2\text{CH}_2\text{O}$), 0.74 (t, 9H, $J = 7.5 \text{ Hz}$, TES), 0.42 (br q, 6H, TES), 0.07 (br s, 9H, TMS). ^{13}C NMR (400 MHz, CDCl_3): δ 174.87, 171.60, 155.54, 153.25, 137.36, 133.58, 131.22, 129.35 (2C), 128.42 (2C), 127.69, 123.97, 122.80, 116.82, 94.23, 72.00, 68.00, 65.90, 64.77, 60.67, 59.59, 59.46, 53.81, 46.29, 38.64, 36.76, 18.20, 14.57, 6.94 (3C), 4.95 (3C), -1.08 (3C).

Compound 9b.

Triethyl amine (4.3 μL , 0.031 mmol), followed by cinnamoyl chloride (3.8 mg, 0.023 mmol), was added to a solution of compound **9** (10 mg, 0.015 mmol) in 10 mL of dry CH_2Cl_2 , cooled to 0°C . The reaction mixture was allowed to stir from 0°C to room temperature for 3.5 h. The reaction mixture was then quenched with saturated NaHCO_3 , extracted with CH_2Cl_2 ($3 \times 30 \text{ mL}$), and dried over anhydrous MgSO_4 . The solvent was removed under reduced pressure, and the crude product was purified by flash column chromatography using 25/75 ethylacetate/hexane to obtain compound **9b** (13 mg, 80%) (Figures 5 and 6). Molecular Formula: $\text{C}_{40}\text{H}_{60}\text{N}_2\text{O}_9\text{Si}_2$. LRMS: MS (ES+) $m/z = 769$ ($M + 1$). ^1H NMR (400 MHz, CDCl_3): δ 7.94 (br d, 1H, $J = 9.0 \text{ Hz}$, $\text{CHCH}-\text{C}-\text{N}$), 7.72 (d, 1H, $J = 15.0 \text{ Hz}$, $\text{CH}=\text{CHPh}$), 7.57 (br d, 2H, $J = 6.0 \text{ Hz}$, Ph), 7.42–7.36 (m, 3H, Ph), 7.09 (m, 1H, $\text{MEMOC}=\text{CH}-\text{C}$), 7.03–6.96 (1 set of d, 1H, $J = 15.0 \text{ Hz}$, $\text{CH}=\text{CHPh}$ and 1 set of dd, 1H, $J = 9.0 \text{ Hz}$, $J = 2.5 \text{ Hz}$, $\text{CHCH}-\text{C}-\text{N}$), 5.20 (m, 2H, MEM), 5.16 (m, 1H, $\text{CONCHCH}-\text{O}$), 4.93 (m, 1H, TeocNCHCH_2), 4.31 (t, 2H, $J = 8.5 \text{ Hz}$, $\text{TMSCH}_2\text{CH}_2\text{O}$), 4.17–4.09 (m, 3H, CHOTES , $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.91–3.83 (m, 1H, $\text{CHCH}_2\text{CO}_2\text{Et}$), 3.81 (t, 2H, $J = 5.0 \text{ Hz}$, MEM), 3.60 (t, 2H, $J = 5.0 \text{ Hz}$, MEM), 3.35 (br s, 3H, MEM), 2.97 (dd, 1H, $J =$

When the sample was heated to 58°C , the ^1H spectrum gave sharper lines and the COSY was also improved. We attribute this improvement to faster rotation of some of the protecting groups.

Figure 5. COSY of compound **9b**.

Molecular model for **9b**. The protecting groups are hidden to make the core of the molecule easier to visualize.

NOESY of **9b** at 58°C . Some of the important distances in the molecular model are correlated with cross peaks in the NOESY. Note that there are no cross peaks for the distances labeled D and E.

Figure 6. NOESY of compound **9b**.

16.0 Hz, $J = 4.0 \text{ Hz}$, $\text{CHCH}_2\text{CO}_2\text{Et}$), 2.71–2.63 (dd, 1H, $J = 16.0 \text{ Hz}$, $J = 8.5 \text{ Hz}$, $\text{CHCH}_2\text{CO}_2\text{Et}$), 2.27–2.17 (m 1H, TeocNCHCH_2), 2.10–2.02 (t, 1H, TeocNCHCH_2), 1.24 (t, 3H, $J = 7.0 \text{ Hz}$, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.10 (m, 2H, $\text{TMSCH}_2\text{CH}_2\text{O}$), 0.89 (t, 9H, $J = 8.0 \text{ Hz}$, TES), 0.59 (q, 6H, $J = 8.0 \text{ Hz}$, TES), 0.09 (br s, 9H, TMS). ^{13}C NMR (400 MHz, CDCl_3): δ 173.29, 171.31, 155.70, 153.57, 146.94, 143.88, 135.45, 130.28, 129.29 (2C), 128.67, 128.31 (2C), 124.19, 119.43,

118.13, 116.73, 94.26, 72.00, 68.00, 65.73, 64.75, 61.11, 59.41 (2C), 53.95, 46.50, 41.72, 30.10, 18.20, 14.60, 7.08 (3C), 5.16 (3C), -1.1 (3C).

Starting Material for Solid-Phase Synthesis. Compound 7c.

p-Toluenesulfonic acid monohydrate (80 mg, 0.41 mmol) was added to a solution of MEM-protected compound **7a** (269 mg, 0.41 mmol) in a mixture of 20 mL of anhydrous ethanol and 8 mL of anhydrous CH_2Cl_2 at room temperature. The reaction mixture was stirred for 13 h at 60 °C. After the mixture was cooled to room temperature, a saturated solution of NaHCO_3 (10 mL) was added, and the reaction mixture was concentrated under vacuum to remove the ethanol. Then CH_2Cl_2 (10 mL) was added; the aqueous layer was extracted with CH_2Cl_2 (3×20 mL), and the organic layer was dried over MgSO_4 . After filtration and concentration under vacuum, the crude product was chromatographed using the Biotage chromatograph system (A = hexane, B = ethyl acetate, CV = 48 mL, vol fract = 42 mL, flow = 6 mL/min, EQ[5CV] 15%B, 1CV¹ 15%B, 10CV² 15%B to 60%B, 10CV³ 60%B) to give the title compound (208 mg, 96%). White solid. *R*_f: 0.24 (1/1 hexane/ethyl acetate), 0.48 (3/7 hexane/ethyl acetate). ¹H NMR (CDCl_3 , 400 MHz): δ 7.95–7.52 (broad s, 1H, OH phenol), 7.24–7.08 (broad m, 1H, CH=CH=C–N), 6.82 (dt, *J* = 15.3 Hz, *J* = 7.3 Hz, 1H, CH=CHCO₂Et), 6.69–6.56 (broad m, 2H, CH=CH=C–N and HOC–CH=C), 5.99–5.90 (broad s, 1H, NH), 5.89–5.72 (m, 1H, H₂C=CH–), 5.74 (d, *J* = 15.3 Hz, 1H, CH=CHCO₂Et), 5.24 (broad d, *J* = 17.1 Hz, 1H, *H*_{trans2}C=CH–), 5.13 (broad d, *J* = 10.6 Hz, 1H, *H*_{cis2}C=CH–), 5.12–5.04 (m, 1H, CH–NHCO), 4.57 (broad t, *J* = 8.3 Hz, 1H, CHOH), 4.55–4.46 (m, 2H, H₂C=CH–CH₂O), 4.44–4.30 (broad m, 1H, CHCH₂CH=CHCO₂Et), 4.25–4.12 (broad m, 2H, TMSCH₂CH₂O), 4.12–4.02 (m, 2H, CO₂CH₂CH₃), 3.30 (broad s, 1H, OH), 2.58–2.46 (broad m, 1H, CHCH₂CH=CHCO₂Et), 2.45–2.33 (broad m, 1H, CHCH₂CH=CHCO₂Et), 1.20 (t, *J* = 7.0 Hz, 3H, CO₂CH₂CH₃), 1.05–0.95 (broad m, 2H, TMSCH₂CH₂O), -0.02 (s, 9H, TMS). ¹³C NMR (CDCl_3 , 100 MHz): δ 166.6, 157.1, 155.0, 154.1, 144.7, 132.3, 127.3, 126.7 (broad), 123.5, 118.0, 114.5, 110.7 (broad), 110.1 (broad), 75.9 (broad), 66.0, 64.6, 60.4, 58.5 (broad), 54.1 (broad), 36.0 (broad), 17.5, 14.0, -1.7 (3C). LRMS: MS (ES⁺) *m/z* = 521.4 (M + 1), 493.3 (M - 27). HPLC: 10.08 min.

Compound 14.

3-Bromo propanol (43 μL , 0.48 mmol) and the phenol

compound **7c** (208 mg, 0.40 mmol) were added to a solution of cesium carbonate (823 mg, 2.53 mmol) in 10 mL of anhydrous DMF at room temperature via canula (1 mL of anhydrous DMF was used to wash the round-bottom flasks). The reaction mixture was stirred for 4 h at room temperature, and the DMF was removed under vacuum. Et₂O (10 mL) and a solution of NaHCO_3 (20 mL) were added, and the aqueous layer was extracted with Et₂O (3×30 mL) and CH_2Cl_2 (1×30 mL). The organic layer was dried over MgSO_4 , filtered, and concentrated under vacuum. The crude product was chromatographed using the Biotage chromatograph system (A = hexane, B = ethyl acetate, CV = 48 mL, vol fract = 42 mL, flow = 19 mL/min, EQ[5CV] 17%B, 1CV¹ 17%B, 10CV² 17%B to 70%B, 10CV³ 70%B) to give the title compound (133 mg, 58%). Colorless oil. *R*_f: 0.29 (3/7 hexane/ethyl acetate), 0.45 (2/8, hexane/ethyl acetate), ¹H NMR (CDCl_3 , 400 MHz): δ 7.25 (broad s, 1H, CH=CH=C–N), 6.82 (dt, *J* = 15.6 Hz, *J* = 7.8 Hz, 1H, CH=CHCO₂Et), 6.78–6.70 (broad m, 2H, CH=CH=C–N and HOC–CH=C), 5.97–5.79 (broad m, 1H, H₂C=CH–), 5.82 (broad d, *J* = 8.3 Hz, 1H, NH), 5.73 (d, *J* = 15.6 Hz, 1H, CH=CHCO₂Et), 5.29 (d, *J* = 17.1 Hz, 1H, *H*_{trans2}C=CH–), 5.17 (d, *J* = 10.3 Hz, 1H, *H*_{cis2}C=CH–), 4.60–4.51 (broad m, 3H, CH–NHCO and H₂C=CH–CH₂O), 4.44–4.36 (broad m, 1H, CHCH₂CH=CHCO₂Et), 4.25–4.12 (m, 3H, CHOH and TMSCH₂CH₂O), 4.08 (q, *J* = 7.0 Hz, 2H, CO₂CH₂CH₃), 4.06–3.96 (broad m, 2H, HOCH₂CH₂CH₂), 3.75 (broad t, *J* = 5.8 Hz, 2H, HOCH₂CH₂CH₂), 3.37–3.26 (broad s, 1H, OH), 2.59–2.49 (broad m, 1H, CHCH₂CH=CHCO₂Et), 2.57 (broad s, 1H, HOCH₂CH₂CH₂), 2.43–2.33 (broad m, 1H, CHCH₂CH=CHCO₂Et), 1.99–1.91 (m, 2H, HOCH₂CH₂CH₂), 1.20 (t, *J* = 7.0 Hz, 3H, CO₂CH₂CH₃), 1.04–0.95 (m, 2H, TMSCH₂CH₂O), -0.01 (s, 9H, TMS). ¹³C NMR (CDCl_3 , 100 MHz): δ 166.1, 156.8, 156.4, 154.7, 144.3, 132.6, 132.0, 128.4, 126.8, 123.6, 117.8, 113.0, 109.9, 76.0, 65.9, 65.4, 64.4, 60.1, 59.5, 58.6, 54.3, 36.2 (broad), 31.9, 17.5, 14.1, -1.7 (3C). LRMS: MS (ES⁺) *m/z* = 579.5 (M + 1), 551.4 (M - 27). HPLC: 10.45 min.

Compound 14b.

A solution of TBAF (460 μL , 0.46 mmol) was added to a solution of Teoc-protected compound **14a** (133 mg, 0.23 mmol) in 10 mL of anhydrous THF at room temperature. The reaction mixture was stirred for 4.5 h at room temperature, and then brine (10 mL) was added. The aqueous layer was extracted with Et₂O (3×20 mL) and CH_2Cl_2 (1×20 mL). The organic layer was dried over MgSO_4 , filtered, and concentrated under vacuum. The crude product was chromatographed using the Biotage chromatograph system (A = hexane, B = ethyl acetate, CV = 12 mL, vol fract = 30 mL, flow = 9 mL/min, EQ[5CV] 17%B, 1CV¹ 17%B, 10CV² 17%B to 70%B, 10CV³ 70%B) to give the title compound (94 mg, 94%). White solid. *R*_f: 0.30 (2/8 hexane/ethyl acetate). ¹H NMR (CDCl_3 , 400 MHz): δ 6.97 (ddd, *J* = 15.8 Hz, *J* = 2.5 Hz, *J* = 8.5 Hz, 1H, CH=CHCO₂Et),

6.70 (d, $J = 2.3$ Hz, 1H, $\text{CH}_2\text{OC}-\text{CH}=\text{C}$), 6.63 (dd, $J = 8.5$ Hz, $J = 2.3$ Hz, 1H, $\text{CH}-\text{CH}=\text{C}-\text{NH}$), 6.44 (d, $J = 8.5$ Hz, 1H, $\text{CH}-\text{CH}=\text{C}-\text{NH}$), 5.98 (d, $J = 15.8$ Hz, 1H, $\text{CH}=\text{CHCO}_2\text{Et}$), 5.93 (ddt, $J = 17.1$ Hz, $J = 10.6$ Hz, $J = 5.5$ Hz, 1H, $\text{H}_2\text{C}=\text{CH}-$), 5.43 (broad d, $J = 8.3$ Hz, 1H, CONH), 5.33 (d, $J = 17.1$ Hz, 1H, $H_{\text{trans}2}\text{C}=\text{CH}-$), 5.23 (d, $J = 10.6$ Hz, 1H, $H_{\text{cis}2}\text{C}=\text{CH}-$), 4.82 (t, $J = 8.3$ Hz, 1H, $\text{CH}-\text{NHCO}$), 4.61 (broad d, $J = 5.5$ Hz, 2H, $\text{H}_2\text{C}=\text{CH}-\text{CH}_2\text{O}$), 4.19 (q, $J = 7.3$ Hz, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 4.00 (broad s, 1H, NH), 3.70–3.50 (broad s, 1H, CHOH), 3.98 (t, $J = 5.8$ Hz, 2H, $\text{HOCH}_2\text{CH}_2\text{CH}_2$), 3.79 (t, $J = 5.8$ Hz, 2H, $\text{HOCH}_2\text{CH}_2\text{CH}_2$), 3.50 (dd, $J = 8.5$ Hz, $J = 8.3$ Hz, 1H, CHOH), 3.28 (td, $J = 8.5$ Hz, $J = 2.5$ Hz, 1H, $\text{CHCH}_2-\text{CH}=\text{CHCO}_2\text{Et}$), 2.86 (broad dt, $J = 14.6$ Hz, $J = 2.5$ Hz, 1H, $\text{CHCH}_2\text{CH}=\text{CHCO}_2\text{Et}$), 2.50–2.35 (broad s, 1H, $\text{HOCH}_2-\text{CH}_2\text{CH}_2$), 2.36 (dt, $J = 14.6$ Hz, $J = 8.5$ Hz, 1H, $\text{CHCH}_2-\text{CH}=\text{CHCO}_2\text{Et}$), 1.96 (pent, $J = 5.8$ Hz, 2H, $\text{HOCH}_2\text{CH}_2-\text{CH}_2$), 1.29 (t, $J = 7.3$ Hz, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$). ^{13}C NMR (CDCl_3 , 100 MHz): δ 166.2, 158.3, 151.8, 145.0, 138.3, 132.4, 124.6, 121.1, 118.2, 115.63, 115.55, 113.5, 74.5, 66.3, 66.2, 60.4, 60.1, 56.3, 55.8, 34.7, 32.0, 14.2. LRMS: MS (ES+) $m/z = 435.4$. HPLC: 8.35 min.

Compound 15.

A solution of 5 N sodium bicarbonate (1 mL) and 9-fluorenylmethyl chloroformate (144 mg, 0.54 mmol) were added to a solution of free amine **14b** (94 mg, 0.22 mmol) in 5 mL of ethyl acetate at room temperature. The reaction mixture was stirred for 20 h at room temperature, and a solution of NaHCO_3 (5 mL) was added. The aqueous layer was extracted with AcOEt (3×10 mL). The organic layer was dried over MgSO_4 . After filtration and concentration under vacuum, the crude product was chromatographed using the Biotage chromatograph system (A = hexane, B = ethyl acetate, CV = 12 mL, vol fract = 42 mL, flow = 9 mL/min, EQ[5CV] 20%B, 1CV¹ 20%B, 10CV² 20%B to 80%B, 10CV³ 80%B) to give the title compound (75 mg, 60%). White solid. R_f : 0.30 (2/8, hexane/ethyl acetate). ^1H NMR (CDCl_3 , 400 MHz): δ 7.74 (m, 2H, Fmoc), 7.47 (broad s, 2H, Fmoc), 7.41–7.34 (m, 2H, Fmoc), 7.32–7.24 (broad m, 3H, Fmoc and $\text{CH}-\text{CH}=\text{C}-\text{N}$), 6.75 (broad m, 1H, $\text{CH}=\text{CHCO}_2\text{Et}$), 6.76–6.60 (broad m, 2H, $\text{CH}_2\text{OC}-\text{CH}=\text{C}$ and $\text{CH}-\text{CH}=\text{C}-\text{N}$), 5.96–5.82 (m, 1H, $\text{H}_2\text{C}=\text{CH}-$), 5.67 (d, $J = 15.3$ Hz, 1H, $\text{CH}=\text{CHCO}_2\text{Et}$), 5.49 (broad d, $J = 8.3$ Hz, 1H, CONH), 5.30 (d, $J = 17.1$ Hz, 1H, $H_{\text{trans}2}\text{C}=\text{CH}-$), 5.20 (d, $J = 10.3$ Hz, 1H, $H_{\text{cis}2}\text{C}=\text{CH}-$), 4.68–4.61 (m, 2H, Fmoc), 4.60–4.50 (m, 3H, $\text{CH}-\text{NHCO}$ and $\text{H}_2\text{C}=\text{CH}-\text{CH}_2\text{O}$), 4.40–4.25 (m, 2H, Fmoc and $\text{CHCH}_2\text{CH}=\text{CHCO}_2\text{Et}$), 4.12 (q, $J = 7.0$ Hz, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 4.12–4.00 (m, 3H, CHOH and $\text{HOCH}_2\text{CH}_2\text{CH}_2$), 3.83–3.77 (broad m, 2H, $\text{HOCH}_2\text{CH}_2\text{CH}_2$), 3.30 (broad s, 1H, CHOH), 2.43–2.20 (broad m, 3H, $\text{CHCH}_2\text{CH}=\text{CHCO}_2\text{Et}$ and $\text{HOCH}_2\text{CH}_2\text{CH}_2$),

2.03–1.94 (m, 2H, $\text{HOCH}_2\text{CH}_2\text{CH}_2$), 1.23 (t, $J = 7.0$ Hz, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$). ^{13}C NMR (CDCl_3 , 100 MHz): δ 166.1, 156.8, 156.5, 154.4, 143.8, 143.6, 141.31, 141.28, 132.4, 132.3, 128.1, 127.69, 127.65, 127.11, 127.06, 126.9, 124.9, 124.8, 123.8, 119.9 (2C), 118.1, 113.2, 110.0 (broad), 76.0 (broad), 67.3, 66.1, 65.6, 60.3, 59.8, 58.8, 54.1 (broad), 47.2, 35.7 (broad), 31.9, 14.1. LRMS: MS (ES+) $m/z = 657.6$. HPLC: 10.54 min.

Solid-Phase Synthesis. Loading. Compound 16.

The resin (25.9 mg, 0.035 mmol of free loading site) and compound **15** (46.4 mg, 0.071 mmol) were dried on freeze dryer for 24 h hours. The beads were placed in a vial, and 1 mL of anhydrous CH_2Cl_2 was added at room temperature to allow the beads to swell. The solution containing the beads was gently shaken for 30 min. The CH_2Cl_2 was then removed, and a 0.45 M trifluoromethanesulfonate solution (0.47 mL, 0.2118 mmol) was added to resin and kept for 20 min (shaking gently). The beads and the solution became an orange-red color. The trifluoromethanesulfonate solution was removed completely, and the resin was washed with anhydrous CH_2Cl_2 twice (1 mL). Then 1 mL of anhydrous CH_2Cl_2 was added to the resin, followed by the addition of 2,6-lutidine (33 μL , 0.2824 mmol). The beads became colorless and were left to stand for 10 min. Compound **16** was dissolved in a minimum of solvent (0.5 mL of anhydrous CH_2Cl_2) and added to the resin. The resulting mixture was gently shaken for 1 h. Then the vial was capped and kept on a tumble shaker for 12 h. The vial was removed from the tumble shaker, and the contents were washed with DCM (5 mL) 3 times, THF 3 times, and DCM, again, 3 times. Finally, the resin was dried on vacuum pump for 6 h and in the freeze dryer for 12 h (34 mg, 75%). The compound was obtained after cleavage of 3 beads. LRMS: MS (ES+) $m/z = 657.6$ ($M + 1$). HPLC: 10.58 min.

Compound 16a.

The compound loaded on resin **16** (34 mg, 0.0348 mmol) was swelled in 3 mL of anhydrous CH_2Cl_2 for 30 min. The solvent was removed and replaced with 1 mL of anhydrous CH_2Cl_2 . 1,3-Diisopropylcarbodiimide (11 μL , 0.0696 mmol), 3,4-(methylenedioxy)phenylacetic acid (9.6 mg, 0.0522 mmol), and 4-(dimethylamino)-pyridine (0.4 mg, 0.0035 mmol) were added at once to the beads at room temperature. The mixture was shaken with a tumble shaker for 15 h. The mixture was filtered; the resin was washed with CH_2Cl_2 (3×5 mL), THF (3×5 mL), and CH_2Cl_2 (3×5 mL) and dried under vacuum overnight. The compound was obtained after cleavage of 3 beads. LRMS: MS (ES+) $m/z = 819.7$ ($M + 1$), 836.8 ($M + 18$). HPLC: 12.65 min.

NCOCH₂Ph), 2.89 (dd, $J = 16.6$ Hz, $J = 5.0$ Hz, 1H, NCHCH₂CHCH₂), 2.61 (dd, $J = 16.6$ Hz, $J = 6.0$ Hz, 1H, NCHCH₂CHCH₂), 2.18–2.09 (m, 1H, NCHCH₂CHCH₂), 2.03 (quint, $J = 6.0$ Hz, 2H, HOCH₂CH₂CH₂), 1.96–1.85 (m, 1H, NCHCH₂CHCH₂), 1.92 (broad s, 1H, OH), 1.16 (t, $J = 7.3$ Hz, 3H, CO₂CH₂CH₃). LRMS: MS (ES+) $m/z = 765.4$ ($M + 1$), 782.5 ($M + 8$). HPLC: 10.81 min. ¹³C NMR (CDCl₃, 100 MHz): δ 174.3, 170.9, 170.7, 158.6, 155.6, 147.7, 146.8, 135.8, 131.3, 130.8, 130.4, 129.9 (2C), 129.0 (2C), 128.5, 128.2 (2C), 126.5, 124.5, 122.2, 115.3, 114.2 (2C), 114.11, 114.06, 113.7, 109.5, 108.2, 101.0, 67.0, 65.6, 60.4, 60.1, 55.3, 55.0, 45.9, 40.5, 38.8, 35.5, 31.9, 29.7, 14.1.

Acknowledgment. We thank the Chemical Biology program at the Broad Institute of Harvard University and MIT for providing us the alkylsilyl linker-based macrobeads and for sharing the solid-phase synthesis loading protocol used with this resin. This work was supported by the NRC Genomics and Health Initiative, National Cancer Institute of Canada (NCIC), and the Canadian Institutes of Health Research (CIHR). M.P. and S.S. contributed equally to this article.

Supporting Information Available. Analytical data is provided on the key compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (16) See the Supporting Information for further information on the analytical data on key compounds.

CC060059N