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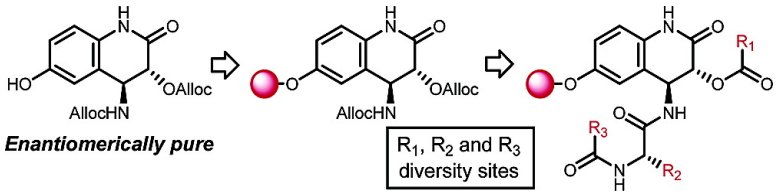

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A Solid-Phase, Library Synthesis of Natural-Product-Like Derivatives from an Enantiomerically Pure Tetrahydroquinoline Scaffold

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With the goal of developing a library synthesis of tetrahydroquinoline-derived natural-product-like small molecules, a practical synthesis of enantiomerically pure tetrahydroquinoline scaffold was achieved. An asymmetric aminohydroxylation reaction was the key step in this strategy. This scaffold was further immobilized onto the solid support for the library generation. The library was obtained from three diversity sites: (i) acylation of the hydroxyl group (R_1), (ii) coupling of the Fmoc-protected amino acid to the amino group (R_2), and (iii) amidation of the N-terminal amine group (R_3).

Introduction

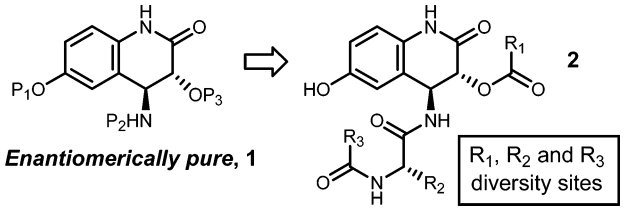
Chemical genetics/genomics is an emerging area of research that relies heavily on the use of small-molecule chemical probes in understanding complex cellular processes, such as protein functions.[1] Over the years, natural products have proven to be useful small-molecule probes in the medicinal community. A rapid access to small molecules that are guided by natural products appears to be quintessential for the success of chemical genetics/genomics-based research programs. The design and synthesis of novel scaffolds as chiral core structures for the library generation of natural-product-like derivatives is an essential step in accessing a wide variety of structurally complex derivatives in an efficient manner.[2]

Solid-phase synthesis combined with IRORI combinatorial split-and-mix technology[3] provides an efficient method for synthesizing numerous compounds in a parallel manner. With few exceptions, the field of combinatorial chemistry has been mostly successful in the synthesis of simple compounds, that is, compounds bearing no stereogenic centers.[4] Herein, we report an efficient method to obtain enantiomerically pure, tetrahydroquinoline-derived amino alcohol scaffold **1** (Scheme 1) that has further been utilized in the small library generation (**2**) using the IRORI split-and-mix approach by solid-phase synthesis.

Tetrahydroquinoline-based natural products are commonly found in nature and are considered to be valuable building blocks in medicinal chemistry.[5] Several of these derivatives have been shown to exhibit a wide range of biological activities. Because of the broad biological applications that are associated with tetrahydroquinolines, we chose to embark on a combinatorial chemistry program that utilized an enantiopure scaffold **1**.

The first milestone in our plan was the development of the solution phase-enantioselective synthesis of the tetrahydroquinoline-based amino alcohol scaffold **1**. The next step was to immobilize this scaffold onto a solid support and then to explore the amino alcohol functionalities for the library generation. The phenolic hydroxyl group in this scaffold could act as an anchor site, and the amino alcohol may then be utilized in diversity synthesis. The diversity shown in compound **2** could be easily derived from (i) *O*-acylation of the corresponding secondary hydroxyl group, (ii) amino acid coupling, and (iii) N-terminal acylation. Using this strategy, one could easily synthesize functionalized, substituted tetrahydroquinoline-based natural-product-like bicyclic derivatives with three diversity sites as shown in **2**. One could also synthesize the diastereomeric libraries by selecting the appropriate chirality that is derived from natural or unnatural amino acids. Following the successful solid-phase synthesis method development, the plan was to obtain a modest test library (27 compounds) by using the IRORI split-and-mix approach.

Scheme 1. Library of Tetrahydroquinoline-Derived, Natural-Product-Like Derivatives



Results and Discussion

The development of an efficient, enantioselective synthesis in order to obtain the versatile tetrahydroquinoline-based amino alcohol scaffold **8** (Scheme 2) is key to this project. Using a diversity-oriented approach on solid phase, compound **8** can be utilized in the synthesis of tetrahydroquinoline-based, natural-product-like derivatives. The fully protected scaffold derivative **7** has three orthogonal functional groups, including a phenolic hydroxyl moiety that is protected as −OMEM. Upon deprotection, this functional group could serve as an anchor site for solid phase synthesis. Our

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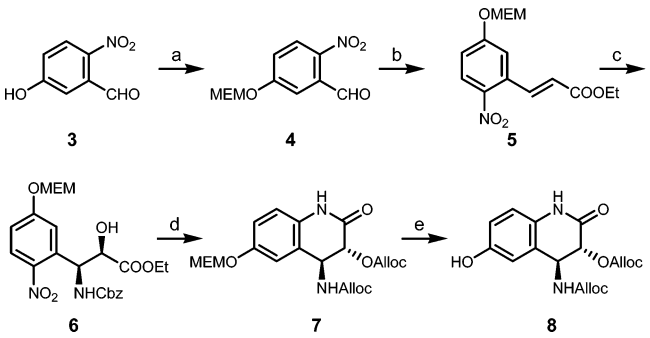
Scheme 2. Enantioselective Synthesis of Tetrahydroquinoline Derivative **8**



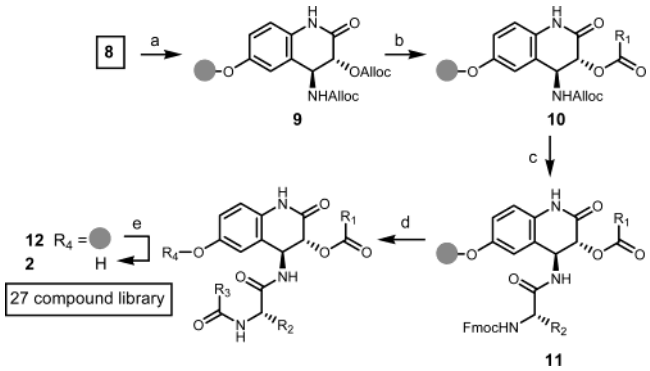
(a) MEM-Cl, DIPEA, CH_2Cl_2, (97%). (b) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, (99%). (c) $(DHQ)_2PHAL$, $K_2OsO_2(OH)_4$, BnOCONClNa, *n*-PrOH/H_2O, (80%). (d) (i) 10% Pd over carbon, H_2, EtOH; (ii) NaOH (0.1 M), THF/H_2O (9:1); (iii) Alloc-Cl, (68% after three steps). (e) *p*-TsOH, EtOH, 50 °C, (98%).

synthetic approach is highly practical, and it allows one to obtain large-scale product (i.e., 10−20 g) with high enantiomeric excess (>90% ee). Moreover, the tetrahydroquinoline-based scaffold is quite stable at room temperature and does not require extra precautions to store this compound.

Enantioselective, Solution-Phase Synthesis of Scaffold. The synthesis of enantiopure, tetrahydroquinoline-based amino alcohol **8** was carried out as follows. The starting material, 5-hydroxy-2-nitrobenzaldehyde (**3**) was subjected to the phenolic hydroxyl protection as −OMEM (**4**, 97%). Following carbon homologation by the Wittig reaction gave the expected product **5** in high yields (99%, 85:15, trans/cis ratio of isomers by ^{1}HNMR and GC analysis). The Wittig product was then subjected to asymmetric aminohydroxylation reaction giving the desired compound **6** in good yields and high enantiomeric excess (yield 80%, ee >90%, determined by chiral HPLC).[6] Compound **6** was then subjected to a series of transformations: (i) H_2 in the presence of 10% Pd over carbon for the reduction of nitro to amino group and the *N*-Cbz removal; (ii) treatment with NaOH (0.1 M), giving the six-membered ring; and (iii) the protection of the amino and alcohol functional groups as *N*-Alloc and *O*-Alloc derivatives. Thus, compound **7** was obtained from **6** in three steps in 68% isolated yields. Removal of the −OMEM group regenerated the phenolic functionality (98%), thus providing compound **8** as the starting material for solid-phase synthesis. All of the products were well characterized by NMR (^{1}H, COSY, HMBC, HSQC, ^{13}C) and MS. A unique feature of the chiral scaffold **8** is the use of *N*-Alloc and *O*-Alloc as orthogonal protecting groups. The ease of the selective removal of the *O*-Alloc in the presence of the *N*-Alloc in solution and on solid phase is an attractive strategy, and it has been utilized in our library synthesis planning.

Solid-Phase Synthesis and Library Generation by IRORI Split-and-Mix Approach. The manual solid-phase synthesis of the quinoline-based bicyclic derivative **2**, followed by the generation of a small library (27 compounds) by the IRORI split-and-mix approach is shown in Scheme 3. Compound **8** was anchored onto a solid support using bromo-Wang resin or (bromomethyl)phenoxymethyl polystyrene (loading 1.4 mmol/g). The resin in DMF was mixed

Scheme 3. A Split-and-Mix-Type, Solid-Phase Library Synthesis of Natural-Product-Like Derivatives from Tetrahydroquinoline Scaffold



(a) Cs_2CO_3, NaI, DMF. (b) (i) NaOMe, MeOH; (ii) DMAP, DIC, CH_2Cl_2, R_1CO_2H. (c) (i) $Pd(PPh_3)_4$, *N*-methyl morpholine, CH_2Cl_2; (ii) HBTU, DIPEA, Fmoc-protected amino acid, DMF. (d) (i) 20% piperidine, DMF; (ii) HBTU, DIPEA, R_3CO_2H, DMF. (e) 10% TFA, CH_2Cl_2.

with free phenol derivative, Cs_2CO_3, and sodium iodide. The mixture was bubbled vigorously under nitrogen for 24 h and then filtered. The resin was washed with CH_3OH, DMF, H_2O, CH_3OH, and CH_2Cl_2 (three times with each solvent) and dried under vacuum, giving compound **9** (loading 80−85%). The resin was then subjected to *O*-Alloc removal by treatment with NaOMe in MeOH. Following the removal of the *O*-Alloc group, the resin was then treated with a mixture of DIC, DMAP, and carboxylic acid in CH_2Cl_2 to provide compound **10** (first diversity, R_1). The next step was the *N*-Alloc removal by $Pd(PPh_3)_4$ in CH_2Cl_2 in the presence of *N*-methylmorpholine as the trapping agent. The free amine was then subjected to amino acid coupling (second diversity, R_2) with HBTU and DIPEA reaction conditions, giving compound **11** as the *N*-Fmoc-protected amino acid conjugate. To complete the solid-phase synthesis, the *N*-Fmoc group was removed, and the generated free amine group was then coupled with the carboxylic acids to introduce the third diversity (compound **12**). Cleavage under acidic conditions (5−10% TFA) gave product **2** (confirmed by HPLC/MS). Thus, it was possible to synthesize the tetrahydroquinoline-based bicyclic derivatives **2** in eight steps while introducing three sites of diversity. Using an IRORI split-and-mix approach, the manual solid phase synthesis method was further applied to obtain a modest 27-compound library. Further work is in progress to explore the use of these derivatives as small-molecule probes in understanding biological functions. For example, currently the tetrahydroquinoline-based library is being tested in the search for small-molecule inhibitors of eukaryotic protein translation synthesis, and the biological findings will be reported later as appropriate.[7]

To summarize, an efficient synthesis to obtain enantiomerically pure tetrahydroquinoline-based amino alcohol scaffold **8** was developed. A solid-phase synthesis followed by IRORI split-and-mix approach leading to the modest size library generation was obtained from this scaffold. Further work is ongoing in the development of complex, polycyclic, natural-product-like derivatives (in solution and on solid phase) that utilize a tetrahydroquinoline-based scaffold as the starting material.

Experimental Section

General Methods. Without any specification, materials were obtained from commercial suppliers and used without purification. THF and CH_2Cl_2 were distilled under N_2 over sodium/benzophenone and CaH_2 respectively. All NMR experiments (^1H, ^{13}C, COSY, HMBC, HSQC) were recorded on an AC-Brüker instrument (400 MHz). Unless otherwise noted, proton and carbon chemical shifts are reported in parts per million using residual $CHCl_3$ as an internal standard at 7.26 and 77.0 ppm, respectively. Analysis by mass spectrometry was performed on a VG Quattro I (Micromass) mass spectrometer equipped with a pneumatically assisted electrospray ionization source, operating in positive mode. The enantiomeric excess was determined by chiral HPLC using a Hewlett-Packard (Agilent) 1090 LC equipped with a diode array detector and Chiracel-OD column. The HPLC spectra were recorded on a Gilson Combinatorial Chromatography System with 215 Liquid Handler/Injector and equipped with a Vydac C-18 monomeric column and a diode array detector. The split-and-mix-like combinatorial chemistry was achieved by use of the IRORI Technology (Accutag-100 Combinatorial Chemistry System, Accucleave-96 Cleavage Station, Microkan Reactor Pk96, Radio frequency Tag Pk500).

Solution Phase Synthesis. Compound 4. To a solution of 5-hydroxy-2-nitro-benzaldehyde (**3**, 13.9 g, 83.2 mmol) in CH_2Cl_2 (500 mL) at 0 °C were added DIPEA (35.6 mL, 204 mmol) and MEM chloride (17.5 mL, 153 mmol). The mixture was warmed to room temperature and stirred further at this temperature for 4 h. The reaction was quenched with saturated NH_4Cl solution and then extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The crude product was purified over silica gel (solvent system: ethyl acetate/hexanes, 1:3) to give the pure product as a pale yellow oil (20.5 g, 97%). ^1H NMR (400 MHz, $CDCl_3$) δ 10.46 (s, 1H), 8.16 (d, $J = 9.0$ Hz, 1H), 7.48 (s, 1H), 7.34 (d, $J = 8.9$ Hz, 1H), 5.40 (s, 2H), 3.84 (d, $J = 3.0$ Hz, 2H), 3.56 (d, $J = 2.9$ Hz, 2H), 3.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7, 162.1, 143.3, 134.7, 127.5, 120.2, 116.7, 93.9, 71.8, 68.9, 59.4. LRMS: MS (ES^+) $m/z = 256.1$ $(M + 1)^+$.

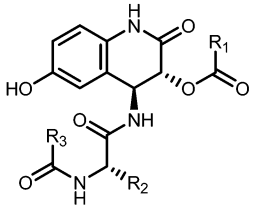
Compound 5. To a solution of the above aldehyde **4** (20.5 g, 80.4 mmol) in dry CH_2Cl_2 (300 mL), (carbethoxymethylene)triphenylphosphorane (33.6 g, 96.44 mmol) was added, and the reaction mixture was stirred at room temperature for 12 h. The solvent was evaporated under reduced pressure to obtain a yellow solid. The crude product was purified by flash column chromatography on silica gel (solvent system: ethyl acetate/hexanes, 1:3) to give a pale yellow-green oil (26.0 g, 99%). The relative ratio of the trans/cis isomers from the Wittig reaction was determined as 85:15 by ^1H NMR. ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, $J = 15.7$ Hz, 1H), 8.12 (d, $J = 9.1$ Hz, 1H), 7.22 (d, $J = 2.6$ Hz, 1H), 7.16 (dd, $J = 2.8$, 9.1 Hz, 1H), 6.32 (d, $J = 15.7$ Hz, 1H), 5.37 (s, 2H), 4.30 (q, $J = 7.1$ Hz, 2H), 3.86 (t, $J = 4.6$ Hz, 2H), 3.57 (t, $J = 4.6$ Hz, 2H), 3.38 (s, 3H), 1.36 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 161.5, 142.3, 141.1, 133.9, 127.8, 123.7, 117.4, 116.5, 93.8, 71.8, 68.6, 61.2, 59.4, 14.6. LRMS: MS (ES^+) $m/z = 326.2$ $(M + 1)^+$.

Compound 6. The Wittig product **5** was subjected to Sharpless asymmetric aminohydroxylation reaction. Benzyl carbamate (3.63 g, 24 mmol) was dissolved in *n*-propyl alcohol (32.0 mL). To this stirred solution was added a freshly prepared solution of NaOH (0.96 g, 24 mmol) in water (60 mL), followed by a freshly prepared solution of *tert*-butyl hypochlorite (2.60 g, 24 mmol, ca. 2.8 mL). Then a solution of the chiral ligand $(DHQ)_2PHAL$ (312 mg, 0.4 mmol, 5 mol %) in *n*-propyl alcohol (28 mL) was added. The mixture was stirred in an ice bath for a few minutes. To this mixture, the Wittig product (2.60 g, 8 mmol) and the potassium osmate dihydrate (118 mg, 0.32 mmol, 4 mol %) were added. The reaction mixture was further stirred for 1 h. After disappearance of starting material monitored by GC, ethyl acetate (60 mL) was added, and the two phases were separated. The aqueous phase was further extracted by ethyl acetate (2×15 mL). The combined organic extracts were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated to dryness. Purification by flash column chromatography (solvent system: ethyl acetate/hexanes 1:1) gave the Cbz-protected amino hydroxyl product as yellow syrup (2.93 g, 79%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, $J = 9.1$ Hz, 1H), 7.38−7.30 (m, 5H), 7.19 (d, $J = 2.4$ Hz, 1H), 7.11 (dd, $J = 2.4$, 9.1 Hz, 1H), 6.09 (d, $J = 8.9$ Hz, 1H), 5.88 (d, $J = 8.9$ Hz, 1H (NH)), 5.33 (s, 2H), 5.11 (d, $J = 12.1$ Hz, 1H), 5.03 (d, $J = 11.9$ Hz, 1H), 4.66 (s, 1H), 4.31 (q, $J = 7.2$ Hz, 2H), 3.82 (t, $J = 4.6$ Hz, 2H), 3.54 (t, $J = 4.7$ Hz, 2H) 3.36 (s, 3H), 3.31 (s, 1H (OH)), 1.28 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 161.6, 155.7, 142.1, 138.5, 136.5, 128.9, 128.6, 128.5, 128.1, 117.4, 115.4, 93.7, 72.4, 71.8, 68.4, 67.5, 63.2, 59.4, 53.3, 14.4. LRMS: MS (ES^+) $m/z = 493.3$ $(M + 1)^+$.

Compound 7. To a solution of compound **6** (3.50 g, 7.57 mmol) in ethanol (180 mL) under nitrogen was added 10% palladium over activated carbon (0.525 g). The reaction mixture was then subjected to hydrogenation under atmospheric pressure until TLC indicated the complete reduction of the nitro group as well as removal of the *N*-Cbz group. The resulting mixture was then filtered through Celite, the catalyst was removed, and the solvent was evaporated under reduced pressure to obtain the product as a pale yellow solid. The crude product was dissolved in 0.1 M NaOH solution (prepared in THF/H_2O, 9:1, 315.0 mL). The mixture was stirred for 1 h and then cooled to 0 °C. To this mixture, allyl chloroformate (2.0 mL, 19.0 mmol) was added, and the solution was stirred at room temperature for 1−2 h. The reaction mixture was diluted with ethyl acetate, and the organic layer was separated. The aqueous layer was washed further with ethyl acetate. The combined organic layers were washed with brine and dried over $Na_2S_2O_4$. After solvent removal, the crude product was purified by flash column chromatography (silica gel: ethyl acetate/hexanes 3:1) to give a pale yellow solid (2.32 g, 68%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H (NH)), 7.02 (s, 1H), 7.01 (d, $J = 8.4$ Hz, 1H), 6.77 (d, $J = 8.5$ Hz, 1H), 5.98 (m, 2H), 5.44−5.26 (m, 6H), 5.24 (s, 2H), 5.16, (d, $J = 7.3$ Hz, 1H (NH)), 4.73 (d, $J = 5.4$ Hz, 2H), 4.67 (d, $J = 4.5$ Hz, 2H), 3.83 (t, $J = 4.6$ Hz, 2H), 3.58 (t, $J = 4.5$ Hz, 2H), 3.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 156.6, 154.7, 154.1, 133.9,

Scheme 4. 27-Compound Library by IRORI Split-and-Mix Approach

R_1	R_2	R_3	R_1	R_2	R_3
4-MPAA	Benzyl	4-MPAA	*p*-TAA	*i*-Propyl	PAA
4-MPAA	Benzyl	*p*-TAA	*p*-TAA	Methyl	4-MPAA
4-MPAA	Benzyl	PAA	*p*-TAA	Methyl	*p*-TAA
4-MPAA	*i*-Propyl	4-MPAA	*p*-TAA	Methyl	PAA
4-MPAA	*i*-Propyl	*p*-TAA	PAA	Benzyl	4-MPAA
4-MPAA	*i*-Propyl	PAA	PAA	Benzyl	*p*-TAA
4-MPAA	Methyl	4-MPAA	PAA	Benzyl	PAA
4-MPAA	Methyl	*p*-TAA	PAA	*i*-Propyl	4-MPAA
4-MPAA	Methyl	PAA	PAA	*i*-Propyl	*p*-TAA
p-TAA	Benzyl	4-MPAA	PAA	*i*-Propyl	PAA
p-TAA	Benzyl	*p*-TAA	PAA	Methyl	4-MPAA
p-TAA	Benzyl	PAA	PAA	Methyl	*p*-TAA
p-TAA	*i*-Propyl	4-MPAA	PAA	Methyl	PAA
p-TAA	*i*-Propyl	*p*-TAA			



2

4-MPAA: 4-Methoxy Phenyl Acetic Acid

p-TAA: *para*-Tolyl Acetic Acid

PAA: Phenyl Acetic Acid

132.4, 130.5, 125.1, 118.1, 117.2, 117.1, 116.9, 114.9, 94.3, 74.1, 71.9, 68.7, 68.0, 65.5, 58.3, 51.8. LRMS: MS (ES^+) $m/z = 451.2$ $(M + 1)^+$.

Compound 8. To a solution of compound **7** (0.68 g, 1.51 mmol) in ethanol (45.0 mL), *p*-toluenesulfonic acid monohydrate (0.29 g, 1.51 mmol) was added. The reaction mixture was stirred at 50 °C overnight. Following the evaporation of the solvent, the crude product was diluted with ethyl acetate, washed with brine, and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by flash column chromatography (solvent system: ethyl acetate/hexanes 3:1) to give compound **8** as white solid in 99% yield (0.54 g). ^1H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, $J = 8.6$ Hz, 1H (NH)), 6.91 (d, $J = 8.5$ Hz, 1H), 6.85 (d, $J = 2.5$ Hz, 1H), 6.79 (dd, $J = 2.4$, 8.5 Hz, 1H), 5.99 (m, 2H), 5.43−5.2 (m, 6H), 7.71 (d, $J = 5.4$ Hz, 2H), 4.62 (d, $J = 5.2$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 156.6, 154.7, 153.9, 133.8, 132.4, 128.3, 125.1, 118.1, 117.3, 116.9, 115.9, 113.0, 74.2, 68.7, 65.5, 51.7. LRMS: MS (ES^+) $m/z = 363.2$ $(M + 1)^+$.

Solid-Phase Synthesis. Compound 9. (a) To a suspension of bromo-Wang resin or 4-(bromomethyl) phenoxymethyl polystyrene (0.400 g, 1.4 mmol/g, 0.560 mmol) in dry DMF (17 mL) was added compound **8** (0.507 g, 1.40 mmol), cesium carbonate (0.456 g, 1.40 mmol), and sodium iodide (0.210 g, 1.40 mmol). The mixture was bubbled under nitrogen at room temperature for 24 h. Then the resin was filtered, washed with CH_3OH (3×), DMF (3×), H_2O (3×), CH_3OH (3×), and CH_2Cl_2 (3×), and dried under vacuum to give resin **9**. The loading of the compound was found to be 81%. This was determined by cleavage from the support (5−10% TFA) followed by purification of the product **8** by flash column chromatography.

Compound 10. (b) (i) To a suspension of resin **9** (0.400 g, 0.560 mmol) in MeOH (15 mL) was added NaOMe (0.5 M in MeOH, 2.24 mL, 1.12 mmol) at room temperature. The mixture was stirred gently for 1.5 h. Following this, the resin was filtered; washed with CH_3OH (3×), DMF (3×), H_2O (3×), CH_3OH (3×), and CH_2Cl_2 (3×); and dried under vacuum. (ii) To a suspension of the above resin (0.300 g, 0.420 mmol) in dry CH_2Cl_2 (19 mL) was added carboxylic acid (4.0 equiv), DIC (329 μL, 2.1 mmol) and DMAP (0.026 g, 0.210 mmol). The mixture was stirred gently overnight and then filtered. The resin was washed with CH_3OH (3×), DMF (3×), H_2O (3×), CH_3OH (3×), and CH_2Cl_2 (3×) and then dried under vacuum to give resin **10**.

Compound 11. (c) (i) To a suspension of resin **10** (0.300 g, 0.420 mmol), acetic acid (0.8 mL) and 4-methylmorpholine (0.4 mL) in dry CH_2Cl_2 (13.9 mL) was added $Pd(PPh_3)_4$ (0.146 g, 0.126 mmol). The resulting mixture was stirred at room temperature overnight and filtered. The resin was washed with CH_3OH (3×), DMF (3×), H_2O (3×), CH_3OH (3×), and CH_2Cl_2 (3×) and dried under vacuum. (ii) To a suspension of the above resin (0.250 g, 0.350 mmol) in dry DMF (14 mL) were successively added HBTU (0.531 g, 1.40 mmol), Fmoc-protected amino acid (4 equiv) and DIPEA (490 μL, 2.80 mmol). The mixture was stirred gently overnight and filtered. The resin was washed with CH_3OH (3×), DMF (3×), H_2O (3×), CH_3OH (3×), and CH_2Cl_2 (3×) and dried under vacuum to give resin **11**.

Compound 12. (d) (i) To a suspension of resin **11** (0.140 g, 0.196 mmol) in dry DMF (4.8 mL) was added piperidine (1.2 mL). The mixture was stirred gently for 2 h and then filtered. The resin was washed with CH_3OH (3×), DMF (3×), H_2O (3×), CH_3OH (3×), and CH_2Cl_2 (3×), and dried under vacuum. (ii) To a suspension of the above resin (0.070 g, 0.098 mmol) in dry DMF (4 mL) were successively added HBTU (0.149 g, 0.392 mmol), carboxylic acid (4 equiv), and DIPEA (137 μL, 0.784 mmol). The mixture was stirred gently overnight and filtered. The resin was washed with CH_3OH (3×), DMF (3×), H_2O (3×), CH_3OH (3×), and CH_2Cl_2 (3×) and dried under vacuum to give resin **12**.

Compound 2, Cleavage from the Support. (e) Resin **12** (0.030 mg, 0.042 mmol) was stirred in 10% TFA in CH_2Cl_2 (2 mL) for 1 h and then filtered. After removal of solvents, the residue was dried under vacuum, giving the crude product **2** in 16−35% yield. Scheme 4.

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