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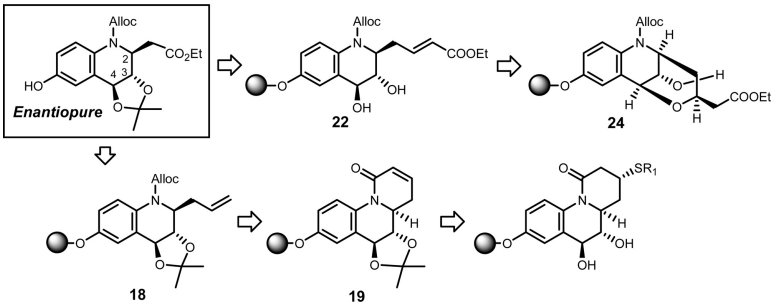

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Stereoselective Diversity-Oriented Solution and Solid-Phase Synthesis of Tetrahydroquinoline-Based Polycyclic Derivatives

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A diversity-oriented solution and solid-phase synthesis of tetrahydroquinoline-based tricyclic derivatives has been achieved from enantiomerically pure, natural product-like bicyclic scaffold. The solution synthesis of enantiopure bicyclic scaffold was developed by asymmetric hetero Michael reaction. Our approach for the synthesis of polycyclic derivatives utilized regio- and stereoselective hetero Michael reaction and ring-closing metathesis as key steps in solution and on solid phase.

In chemical genetics[1]/genomics, small-molecule chemical probes are vital tools for understanding complex cellular processes, such as protein functions and protein−protein interactions.[2] Most natural products that exhibit specific interactions with proteins are chiral and highly complex and possess several stereogenic centers. These properties make them ideal small-molecule candidates that could selectively bind to proteins and act as modulators of protein functions.[3] At present and with few exceptions, most combinatorial methods have utilized the synthesis of rather simple compounds, for example, compounds bearing no stereogenic centers.[4,5]

Herein we describe a solution- and solid-phase synthesis of two polycyclic derivatives, **2** and **3**, from enantiopure tetrahydroquinoline-based β-amino acid **1**. The extensive usefulness of quinoline and tetrahydroquinoline-based natural products[6] prompted us to develop a diversity-oriented synthesis strategy of natural product-like polycyclic derivatives having this privileged structure.

Model compounds **2** and **3** show utilization of enantiopure tetrahydroquinoline β-amino acid, **1** for library generation by solid-phase synthesis. For example, diversity shown in compound **2** could easily derive from the asymmetric enamide functional group by stereoselective Michael reaction followed by trapping of the enol ether with electrophiles. Tetrahydroquinoline-derived polycyclic derivative **3** could be derived from hetero Michael-type reaction from the C_4−OH group to the unsaturated carboxyl ester side chain at C-2. The successful outcome of this reaction may provide a novel route for obtaining highly functionalized tetrahydroquinoline derivatives in which the diversity could be introduced at three sites.

Central to this idea is the development of an efficient solution method to obtain enantiopure tetrahydroquinoline-based β-amino acid (**1**). This derivative is a versatile building block. For model studies, the synthesis of enantiopure tetrahydroquinoline β-amino acid **8** was carried out as follows. 2-Nitropiperonal was converted to unsaturated carboxyl ester by Wittig reaction (95%) and then subjected to Sharpless dihydroxylation reaction, giving enantiopure dihydroxyl derivative **5** (88%, >90% ee, determined by Chiral HPLC). Following the acetonide protection, the carboxyl ester was then reduced by lithium borohydride (**6**). Compound **7** was then obtained from **6**. This was then subjected to nitro group reduction and then treatment with LDA or NaH to obtain the hetero Michael product, **8**, as a single diastereomer. The stereochemistry of the new stereogenic center was assigned by nOe (H-2 and H-4). The reaction seems to be independent of the choice of the base and provides easy access to enantiopure β-amino acid on a large scale. It appears that acetonide protection of vicinal hydroxyls at C_3 and C_4 is an important factor (see **9**, Scheme 2) in the asymmetric hetero Michael reaction. Tetrahydroquinoline β-amino acid **8** contains several important features, (i) vicinal hydroxyls at C_3, C_4 and (ii) a phenolic moiety that could further be utilized as an anchor site in solid-phase synthesis.

Our model studies for the synthesis of tetrahydroquinoline-based tricyclic derivative **11** having an enamide functional group are shown in Scheme 3. Enantiopure tetrahydroquinoline β-amino acid, **8**, was reduced to an alcohol and then subjected to amino group protection (*N*-alloc). Oxidation followed by a Wittig reaction gave the corresponding β-allyl compound. *N*-Acryloyl derivative **10** was then obtained in two steps: (i) *N*-alloc removal and (ii) N-acryloylation with acryloyl chloride. Ring closing metathesis using first-generation Grubbs' catalyst gave the enamide **11** (65%).[7] Further, reaction with thiophenol produced **12** (78%) as a single diastereomer, in which the nucleophile approached the Michael acceptor site from the α-face (no nOe between C_2−H and $C_{4'}$−H).

In a model study for regio- and stereoselective hetero Michael approach shown in Scheme 4, enantiopure tetrahydroquinoline β-amino acid **8** was converted into free dihy-

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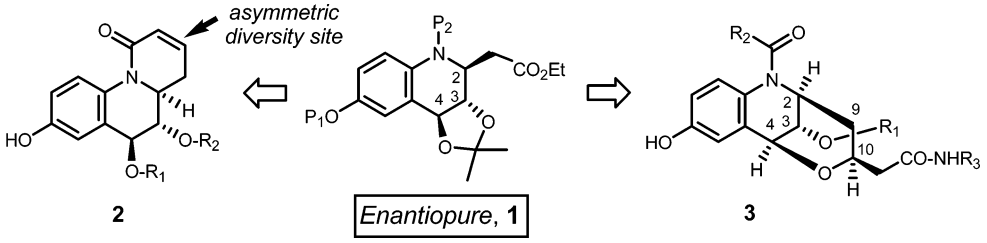
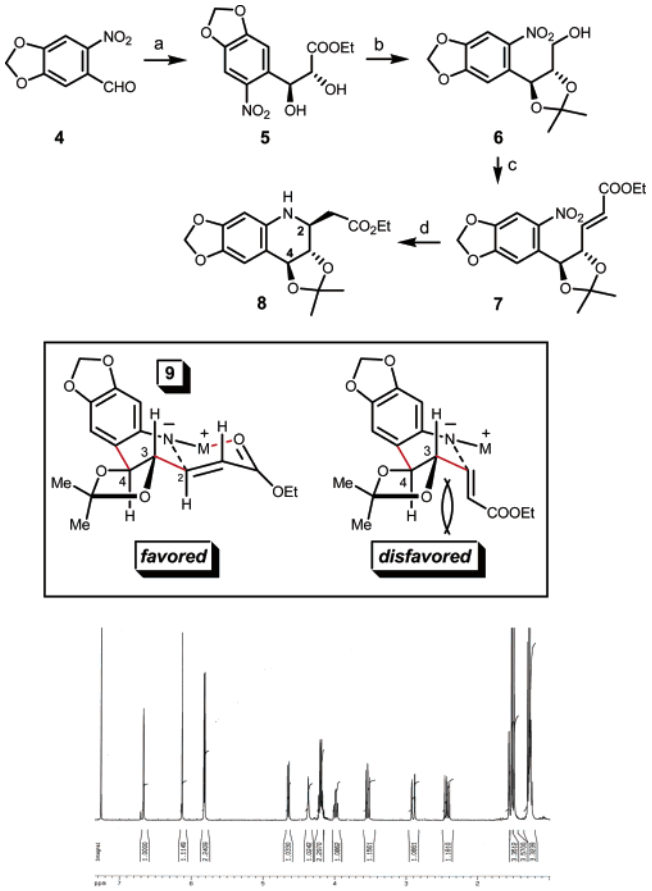
Scheme 1. Diversity-Oriented Synthesis of Enantiopure Tetrahydroquinoline-Based Polycyclic Derivatives

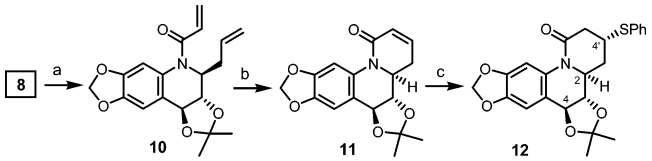


Scheme 2



(a) (i) $Ph_3P{=}CHCOOEt$, room temp 95%; (ii) sharpless enantioselective dihydroxylation reaction: AD-mix-α, $CH_3SO_2NH_2$, 88%. (b) (i) $(OMe)_2C(Me)_2$, *p*-TSA, 95%; (ii) $LiBH_4$, 85%. (c) (i) DMSO, SO_3 pyridine, Et_3N; (ii) $Ph_3P{=}CHCOOEt$, room temp 73% for 2 steps. (d) (i) Zn/HOAc, room temp, 88%; (ii) LDA, THF, −78 °C, 94%.

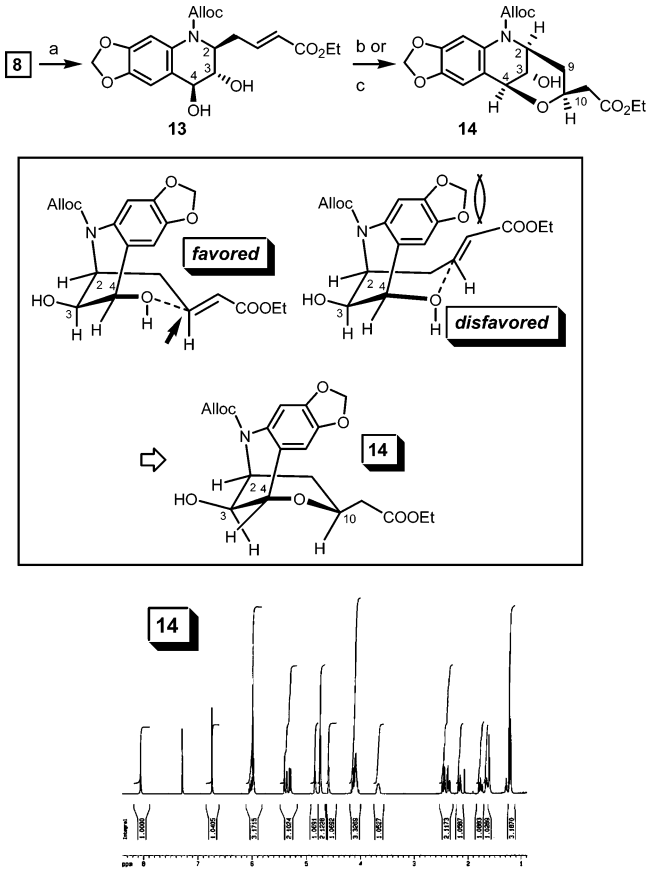
Scheme 3



(a) (i) $LiBH_4$, 87%; (ii) allocCl, pyridine, 0 °C to room temp, 84%; (iii) pyridine SO_3, Et_3N, 83%; (iv) $Ph_3P^+CH_3Br^-$, NaHMDS, 0 °C; (v) $Pd(PPh_3)_4$, room temp; (vi) acryloyl chloride, pyridine, room temp, 36% for 3 steps. (b) 20 mol % 1st generation Grubbs' catalyst: bis(tricyclohexylphosphine)benzylidene-ruthenium(IV) dichloride, CH_2Cl_2, reflux, 65%. (c) PhSH, Et_3N, 78%.

droxyl derivative **13**. With compound **13** as the starting material, the stage was now set to explore the asymmetric hetero Michael reaction. To our pleasant surprise, this reaction proceeded very smoothly, and gave a single dia-

Scheme 4. Model Studies on Regio- and Stereoselective Hetero Michael Approach to Tetrahydroquinoline-Based Polycyclic Derivatives

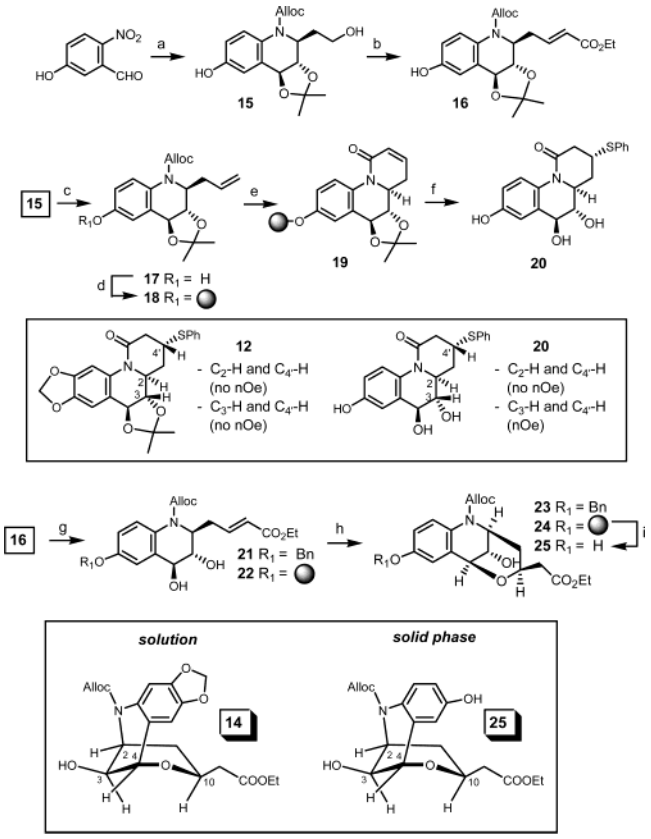


(a) (i) $LiBH_4$; (ii) AllocCl, pyridine; (iii) Pyridine SO_3, Et_3N; (iv) $Ph_3P{=}CHCOOEt$, room temp, 92%; (v) AcOH, THF/H_2O, 97%. (b) LDA, THF, −78 °C to room temp, 65%. (c) NaH, THF, room temp, 84%.

stereomer in high yield (84%)! The tetrahydroquinoline-based tricyclic derivative **14** was well characterized by MS and NMR. As observed earlier, this reaction seems to be independent of the choice of the base and is an excellent example of a highly regio- and stereoselective (reaction with benzylic −OH at C_4 only!) hetero Michael reaction. On the basis of extensive NMR studies that showed no nOe between C_2−H and C_4−H (note: compound **13** showed nOe between C_2−H and C_4−H), we propose a boatlike structure for the newly formed pyran ring via a boatlike transition state. The regio- and stereoselective outcome could be envisioned by a pseudoaxial occupation of functional groups at C-2, C-3, and C-4, allowing facial selective attack of the oxygen nucleophile onto the Michael site.

On the basis of our model studies for enantioselective synthesis of tetrahydroquinoline-derived tricyclic derivatives

Scheme 5



(a) (i) BnBr, K_2CO_3, DMF; (ii) $(Ph)_3P{=}CHCOOEt$; (iii) Sharpless enantioselective dihydroxylation reaction: AD-mix-α, $CH_3SO_2NH_2$, 73%; (iv) $(OMe)_2C(Me)_2$, *p*-TSA; (v) $LiBH_4$, 95%; (vi) DMSO, SO_3 pyridine, Et_3N; (vii) $Ph_3P{=}CHCOOEt$, room temp 83% for 2 steps; (viii) Zn/HOAc, room temp; (ix) LDA, THF, −78 °C, 91%; (x) $LiBH_4$, 85%; (xi) H_2, 10% Pd/C; (xii) AllocCl, 0 °C. (b) Repeat steps (a) vi and vii. (c) (i) DMSO, SO_3 pyridine, Et_3N; (ii) $Ph_3P^+CH_3Br^-$, NaHMDS, 0 °C; (d) 4-(bromomethyl) phenoxymethyl polystyrene resin, Cs_2CO_3, NaI, DMF. (e) (i) $Pd(PPh_3)_4$; (ii) acryloyl chloride, pyridine; (iii) 1st generation Grubbs' catalyst: bis(tricyclohexylphosphine) benzylidene-ruthenium(IV) dichloride. (f) (i) PhSH, Et_3N; (ii) 5% TFA in CH_2Cl_2 (27% for 6 steps). (g) (i) Repeat step d; (ii) PPTS, CH_3CN/CH_2Cl_2. (h) NaH, THF, room temp; (i) 5% TFA in CH_2Cl_2 (25% for four steps).

12 and **14**, we decided to reexamine these studies on solid phase. Solid-phase synthesis of tetrahydroquinoline-based tricyclic derivatives **20** and **25** is shown in Scheme 5. Compound **17** was obtained from hydroxy-nitrobenzaldehyde, as described earlier for nitropiperonal **4**. This was then anchored onto solid support using 4-(bromomethyl)phenoxymethyl polystyrene resin (loading 93%). Following alloc removal and acryloylation, the ring-closing metathesis reaction gave the cyclic enamide product **19**. As observed in solution, **20** was obtained as a single diastereomer (attack from the α-face) on reaction with PhSH after cleavage from the solid support (27% overall yield for 6 steps). The NMR studies with compound **20** showed nOe between C_3-H and $C_{4'}-H$. For the solid-phase synthesis of **25**, **16** was immobilized onto the resin as with the previous example (loading 86%). The free hydroxyl **22** obtained after theacetonide removal was subjected to crucial hetero Michael reaction. The use of NaH as a base at room temperature provided the expected product **24**. After cleavage from the support, the crude sample was purified, giving product **25** (25% overall yield for four steps) that was further assigned by NMR. We were pleased to note that this unusual regio- and stereoselective hetero Michael reaction worked in a manner similar to that in solution synthesis. For comparison, **23** was also synthesized in solution from **16** in a similar manner.

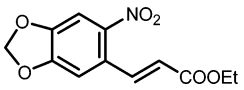
To summarize, with a goal of developing diversity-oriented synthesis of tetrahydroquinoline-based polycylic derivatives having asymmetric enamide functionality, the methodology was successfully developed in solution and on solid phase that utilize RCM strategy. The enamide functional group was further utilized to introduce stereochemical diverse functional groups by asymmetric hetero-Michael reaction. In a second example, we demonstrated the application of a highly unusual, regio- and stereoselective hetero Michael reaction in solution as well as on solid phase. This approach provides a novel entry to highly functionalized tetrahydroquinoline-based tricyclic derivatives that could be subjected to derivatization on solid phase for library generation. Further work is in progress to explore these two templates in solid-phase library synthesis of enantiopure tetrahdyroquinoline-based polycyclic derivatives. In our opinion, these compounds would be useful as small-molecule probes in the chemical genomics arena.

Experimental Section

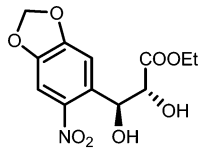
General Methods. Without any specification, materials were obtained from commercial suppliers and used without purification. THF and CH_2Cl_2 were distilled under N_2 over sodium/benzophenone and CaH_2, respectively. All NMR experiments (^1H, ^{13}C, COSY, HMBC, HSQC,NOESY) were recorded on an AC-Brüker instrument DRX 400 (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.

Solution Phase Synthesis. To a solution of the 6-nitropiperonal (20 g, 102 mmol) in dichloromethane (200 mL) was added carbethoxymethylenetriphenylphosphorane (46.4 g, 133 mmol) at room temperature. The reaction mixture was stirred until the starting material disappeared (TLC). The reaction was quenched with saturated NH_4Cl solution and washed with water and brine. The organic phase was dried over anhydrous Na_2SO_4. After solvent evaporation, the crude product was purified by flash chromatography on silica gel (3:1, hexane/ethyl acetate). The product was obtained as white solid (95%). $R_f = 0.71$ (1:1, hexane/ethyl acetate). ^1H NMR: (400 MHz, $CDCl_3$) $\delta = 1.35$ (t, $J = 7.13$ Hz, 3H), 4.28 (q, $J = 7.13$ Hz, 2H), 6.15 (d, $J = 11.33$ Hz, 2H), 6.27

(d, $J = 15.72$ Hz, 1H), 6.99 (s, 1H), 7.66 (s, 1H), 8.10 (d, $J = 15.75$ Hz, 1H) ppm.

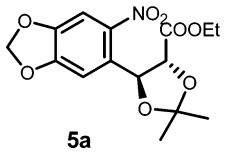


To a solution of the unsaturated carboxyl ester derivative (14.0 g, 52.8 mmol) in *tert*-butyl alcohol (300 mL) was added water (300 mL). The mixture was cooled to 0 °C. This was followed by the addition of methanesulfonamide (5.01 g, 52.7 mmol) and AD-mix-α (74 g). The reaction mixture was brought to room temperature and stirred for an additional 40 h. Following this, sodium thiosulfate (14.5 g, 91.7 mmol) was added, and the mixture was stirred again for 30 min and then extracted with ethyl acetate (5 × 150 mL). The organic phase was washed with 2 M KOH (80 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by column chromatography (40:1 to 20:1, dichloromethane/methanol) afforded the product (13.85 g, 88%) as white solid. $R_f = 0.24$ (1:1, hexane/ethyl acetate). LRMS: MS (ES^+) $m/z = 300.0$ (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) $\delta = 1.25$ (t, $J = 7.12$ Hz, 3H), 4.30 (q, $J = 7.13$ Hz, 2H), 4.55 (d, $J = 2.01$ Hz, 1H), 5.90 (s, 2H), 5.85 (d, $J = 1.96$ Hz, 1H), 6.15 (dd, $J = 0.75$, 10.35 Hz, 2H), 7.38 (s, 1H), 7.62 (s, 1H) ppm. Using a similar approach, the enantiomer of compound 5 was also synthesized, and the enantiomeric excess (ee%) was determined by chiral HPLC.



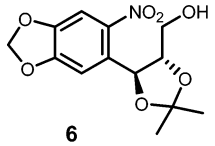
5

To a solution of the carboxyl ester **5** (2.6 g, 8.69 mmol) in acetone (52 mL) at room temperature was added 2,2-dimethoxypropane (52 mL, 44.04 g, 422.89 mmol) and *p*-toluenesulfonic acid monohydrate (260 mg, 1.37 mmol). The reaction mixture was stirred overnight. Following dilution with CH_2Cl_2 and saturated NH_4Cl, the organic layer was collected. It was then washed with water and dried over anhydrous Na_2SO_4. Purification by flash chromatography over silica gel (5:1, hexane/ethyl acetate) afforded the product as a colorless oil in quantitative yield. $R_f = 0.26$ (5:1 hexane/ethyl acetate). LRMS: MS (ES^+) $m/z = 340.1$ (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) $\delta = 1.27$ (t, $J = 7.15$ Hz, 3H), 1.63 (s, 3H), 1.65 (s, 3H), 4.23 (q, $J = 7.14$ Hz, 2H), 4.40 (m, 1H), 5.91 (d, $J = 7.25$ Hz, 1H), 6.16 (dd, $J = 1.05$, 3.44 Hz, 2H), 7.30 (s, 1H), 7.54 (s, 1H) ppm.



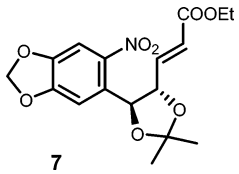
5a

To a solution of the carboxyl ester **5a** (8.6 g, 26.36 mmol) in THF (250 mL) was added lithium borohydride (2.0M solution in THF, 30 mL, 60 mmol) slowly at room temperature. The reaction mixture was stirred at room-temperature overnight. Following this, it was cooled to 0 °C and then quenched with saturated NH_4Cl. After solvent evaporation, the residue was dissolved in dichloromethane, washed with water and brine, and then dried over Na_2SO_4. Purification by flash chromatography over silica gel (2:1, hexane/ethyl acetate) afforded the product (7.3 g, 85%) as a colorless oil. $R_f = 0.26$ (2:1, hexane/ethyl acetate). LRMS: MS (ES^+) $m/z = 298.1$ (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) $\delta = 1.51$ (s, 3H), 1.61 (s, 3H), 2.21 (s, 1H), 3.83∼3.96 (m, 3H), 5.48 (d, $J = 8.00$ Hz, 1H), 6.14 (d, $J = 2.23$ Hz, 2H), 7.24 (s, 1H), 7.43 (s, 1H) ppm.



6

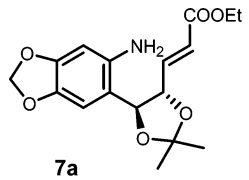
To a solution of **6** (3.9 g, 13.12 mmol) in dichloromethane (120 mL) was added triethylamine (5.48 mL, 39.39 mmol) at room temperature. The solution was cooled to 0 °C and then sulfur trioxide pyridine complex (6.27 g, 39.39 mmol) in DMSO (40 mL) was slowly added. After the addition, the cooling bath was removed, and the reaction mixture was stirred for an additional 3 h at room temperature. Carbethoxymethylenetriphenylphosphorane (13.71 g, 39.35 mmol) was added in one portion, and the mixture was stirred overnight. The reaction was quenched with saturated NH_4Cl, extracted with dichloromethane (3 × 50 mL), dried over Na_2SO_4, and concentrated. Purification by column chromatography over silica gel (7:1, hexane/ethyl acetate) afforded the trans product (3.48 g, 73%) and the cis product (0.68 g, 14%). $R_f = 0.29$ (5:1, hexane/ethyl acetate). LRMS: MS (ES^+) $m/z = 366.0$ (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) $\delta = 1.31$ (t, $J = 7.13$ Hz, 3H), 1.55 (s, 3H), 1.64 (s, 3H), 4.22 (q, $J = 7.13$ Hz, 2H), 4.35 (m, 1H), 5.52 (d, $J = 7.68$ Hz, 1H), 6.04 (dd, $J = 1.29$, 15.58 Hz, 1H), 6.17 (s, 2H), 7.04 (dd, $J = 5.98$, 15.58 Hz, 1H), 7.27 (d, $J = 6.22$ Hz, 1H), 7.48 (s, 1H) ppm.



7

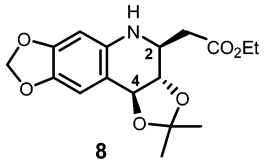
To a solution of **7** (3.48 g, 9.53 mmol) in ethanol (95 mL) was added zinc powder (6.23 g, 95.30 mmol) in one portion at room temperature. This was then followed by dropwise addition of acetic acid (5.45 mL, 95.20 mmol). The reaction mixture was stirred for 15 min, filtered, and concentrated. Purification by flash chromatography over silica gel (5:1, hexane/ethyl acetate) afforded the product in quantitative yield as a yellow oil. $R_f = 0.48$ (4:1, hexane/ethyl acetate) LRMS: MS (ES^+) $m/z = 336.1$ (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) $\delta = 1.30$ (t, $J = 7.12$ Hz, 3H), 1.54 (s, 3H), 1.62 (s, 3H), 4.22 (q, $J = 7.12$ Hz, 2H), 4.68 (d, $J = 8.73$ Hz, 1H), 4.78 (m, 1H), 5.91 (s, 1H), 6.12 (dd, $J = 1.50$,

15.66 Hz, 1H), 6.37 (s, 2H), 6.61 (s, 1H), 6.89 (dd, J = 5.16, 15.62 Hz, 1H) ppm.



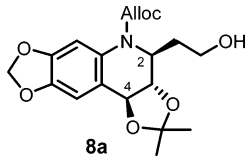
7a

To a solution of **7a** (3.46 g, 10.32 mmol) in anhydrous THF (100 mL) was added LDA (2.0 M solution in THF, 5.16 mL, 10.32 mmol) dropwise at −78 °C. After the mixture was stirred for an additional 30 min at −78 °C, the reaction was quenched with saturated NH_4Cl and extracted with dichloromethane (3 × 50 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography on silica gel (5:1 hexane/ethyl acetate) afforded the product as a yellowish oil (94%). R_f = 0.55 (4:1 hexane/ethyl acetate). LRMS: MS (ES^+) m/z = 336.1 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 1.30 (t, J = 7.13 Hz, 3H), 1.51 (s, 3H), 1.54 (s, 3H), 2.91 (dd, J = 10.28, 16.28 Hz, 1H), 2.91 (dd, J = 2.36, 16.26 Hz, 1H), 3.55 (t, J = 9.45 Hz, 1H), 3.99 (dt, J = 2.25, 10.19 Hz, 1H), 4.22 (m, 2H), 4.65 (d, J = 8.78 Hz, 1H), 5.82 (dd, J = 1.37, 5.39 Hz, 2H), 6.14 (s, 1H), 6.68 (s, 1H) ppm.



8

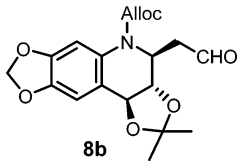
To a stirred solution of 128 mg (3.82×10^{-4} mol) of 8 in 1.5 mL of anhydrous tetrahydrofuran at 0 °C under nitrogen was added lithium borohydride (2 M in tetrahydrofuran, 382 μL, 6.64×10^{-4} mol). After stirring for 20 h at room temperature under nitrogen, the reaction was quenched slowly with saturated aqueous ammonium chloride. Following evaporation of tetrahydrofuran, the mixture was extracted with ethyl acetate. The organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash chromatography over silica gel with hexane and ethyl acetate giving **8a** (87%) as a yellow oil. R_f = 0.34 (hexane/ethyl acetate 1:1). $C_{15}H_{19}NO_5$ 293.32, MS (ES^+) m/z = 294.1 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 6.69 (s, 1H), 6.13 (s, 1H), 5.82 (d, 2H, J = 4.32 Hz), 4.65 (d, 1H, J = 8.72 Hz), 3.90−3.84 (m, 2H), 3.73 (m, 1H), 3.59 (t, 1H, J = 9.34 Hz), 1.95 (m, 1H), 1.85 (m, 1H), 1.56 (s, 3H), 1.53 (s, 3H) ppm.



8a

To a diluted solution of the amino alcohol (92.0 mg) in anhydrous dichloromethane (16.0 mL) at 0 °C was added pyridine (25 μL) and allyl chloroformate (33 μL). After stirring for 20 min at 0 °C, the reaction was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted twice with dichloromethane, and the combined organic layer was dried with anhydrous sodium sulfate, filtered, and then concentrated in vacuo. The residue was purified by flash chromatography over silica gel with hexane and ethyl acetate giving 96.7 mg (84%) of the product as a yellow oil. R_f = 0.51 (hexane/ethyl acetate, 1:1). $C_{19}H_{23}NO_7$ 377.39, MS (ES^+) m/z = 378.1 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 6.86 (s, 1H), 6.81 (s, 1H), 5.96 (d, 2H, J = 13.39 Hz), 5.90 (m, 1H), 5.30−5.22 (m, 2H), 4.72−4.61 (m, 2H), 4.42 (d, 1H, J = 9.14 Hz), 4.37 (m, 1H), 3.74 (m, 2H), 3.25 (t, 1H, J = 8.75 Hz), 1,85 (m, 2H), 1.56 (s, 3H), 1.48 (s, 3H) ppm.

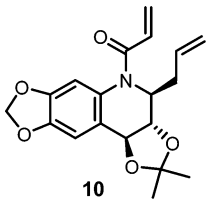
To a solution of the *N*-Alloc-protected alcohol (150 mg, 0.40 mmol) in dry dichloromethane (2.3 mL) at 0 °C under nitrogen was added triethylamine (166 μL, 1.19 mmol) and sulfur trioxide pyridine complex (166 mg, 1.19 mmol) in dimethyl sulfoxide (1.18 mL, 16.7 mmol). After stirring at room temperature for 3.5 h, the reaction was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted three times with dichloromethane. The combined organic layer was dried with anhydrous sodium sulfate, filtered, and then concentrated in vacuo. Purification of the residue by flash chromatography over silica gel with hexane and ethyl acetate afforded aldehyde **8b** (123.3 mg, 83%). R_f = 0.73 (hexane/ethyl acetate 1:1). $C_{19}H_{21}NO_7$ 375.37, MS (ES^+) m/z = 376.2 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 9.79 (s, 1H), 6.90 (s, 1H), 6.80 (s, 1H), 5.98 (d, 2H, J = 11.04 Hz), 5.93 (m, 1H), 5.31−5.23 (m, 2H), 4.68 (m, 1H), 4.61 (m, 2H), 4.43 (d, 1H, J = 9.09 Hz), 3.31 (t, 1H, J = 9.04 Hz), 2.84 (m, 1H), 2.76 (m, 1H), 1.56 (s, 3H), 1.46 (s, 3H) ppm.



8b

To a solution of methyltriphenyl phosphonium bromide (37.7 mg, 1.06×10^{-4} mol, 1.3 equiv) in anhydrous tetrahydrofuran (0.5 mL) at 0 °C under nitrogen was added sodium bis(trimethylsilyl)amide (81 mL, 8.12×10^{-5} mol, 1.0 equiv). The mixture was stirred at 0 °C for 1 h. To this mixture as added *N*-alloc-protected aldehyde (30.5 mg, 8.12×10^{-5} mol) dissolved in dry tetrahydrofuran (1.0 mL). After 30 min, the pH of the mixture was adjusted to 8.0 with 1 N aqueous hydrochloric acid. The organic layer was evaporated, and the aqueous phase was extracted three times with ethyl acetate. The combined organic layers were dried with anhydrous sodium sulfate and then filtered. The residue was kept under high vacuum for 2 h, and the product was used without purification in the next step. R_f = 0.38 (hexane/ethyl acetate 4:1). $C_{20}H_{23}NO_6$ 373.40, MS (ES^+) m/z = 374.3 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 6.93 (s, 1H), 6.79 (s, 1H), 5.96 (d, 2H, J = 5.52 Hz), 5.95 (m, 1H), 5.70 (m, 1H), 5.33−5.23 (m, 2H), 5.12−5.04 (m, 2H), 4.69 (m, 2H), 4.40 (d, 1H, J = 9.08 Hz), 4.32 (m, 1H), 3.30 (t, 1H, J =

8.85 Hz), 2.58−2.54 (m, 2H), 1.56 (s, 3H,), 1.47 (s, 3H) ppm.

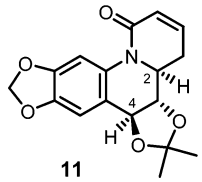


10

To a solution of crude *N*-Alloc-protected product (63.6 mg) in dicholormethane (1.8 mL) at 0 °C under nitrogen was added tetrakis(triphenylphosphine)palladium(0) (5.7 mg, 4.87×10^{-6} mol, 0.06 equiv). To this mixture was added morpholine (14.0 μL, 1.62×10^{-4} mol, 2 equiv). After stirring for 30 min at room temperature, the dichloromethane was evaporated. The crude residue obtained was utilized in the next reaction without purification. $R_f = 0.28$ (hexane/ethyl acetate 4:1). $C_{16}H_{19}NO_4$ 289.33, MS (ES^+) $m/z = 290.2$ (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) $\delta = 6.68$ (s, 1H), 6.10 (s, 1H), 5.84 (m, 1H), 5.79 (d, 2H, $J = 5.65$ Hz), 4.61 (d, 1H, $J = 10.39$ Hz), 3.68−3.61 (dt, 1H, $J = 3.32$, 9.67 Hz), 3.52 (m, 1H), 2.71−2.67 (m, 1H), 2.15 (m, 1H), 1.55 (s, 3H), 1.50 (s, 3H) ppm.

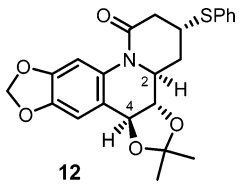
To a solution of *N*-allyl product in dry dichloromethane (1.0 mL) at 0 °C under nitrogen was added pyridine (13 μL, 2.0 equiv) and acryloyl chloride (8.0 μL, 1.2 equiv). After stirring at room temperature for 50 min under nitrogen, the reaction was quenched with aqueous saturated ammonium chloride solution. The aqueous layer was extracted twice with dichloromethane. The combined organic layer was dried with sodium sulfate, filtered, and then concentrated in vacuo. This was then followed by purification by flash chromatography over silica gel with hexane and ethyl acetate, giving the enamide product 10 (10 mg, 36% over 3 steps). $R_f = 0.50$ (hexane/ethyl acetate 3:1). $C_{19}H_{21}NO_5$ 343.37, MS (ES^+) $m/z = 344.1$ (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) $\delta = 6.88$ (s, 1H), 6.61 (s, 1H), 6.43−6.37 (m, 2H), 6.03−6.00 (d, 2H, 9.88 Hz), 5.73−5.66 (m, 2H), 5.12−5.04 (m, 2H), 4.58 (m, 1H), 4.35 (d, 1H, $J = 9.05$ Hz), 3.31 (t, 1H, $J = 8.69$ Hz), 2.64−2.61 (m, 1H), 2.55−2.50 (m, 1H), 1.55 (s, 3H), 1.48 (s, 3H) ppm.

To a solution of **11** (8.0 mg, 2.33×10^{-5} mol) in distilled dichloromethane (0.8 mL) at room temperature under nitrogen was added a solution of benzylidene-bis(tricyclohexyl phosphine)dichlororuthenium (3.8 mg, 20% per mol, 0.2 equiv) in dichloromethane (3.8 mL). After refluxing for 100 min under nitrogen, the reaction mixture was cooled to room temperature, and the solvent was evaporated. The purification of the residue by flash chromatography over silica gel with hexane and ethyl acetate afforded compound **11** (4.8 mg, 65%) as a brown oil. $R_f = 0.19$ (hexane/ethyl acetate 3:1). $C_{17}H_{17}NO_5$ 315.32, MS (ES^+) $m/z = 316.1$(M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) $\delta = 7.58$ (s, 1H), 7.27 (s, 1H), 6.80−6.76 (m, 2H), 6.15−6.12 (dd, 1H, $J = 2.68$, 9.71 Hz), 5.94 (d, 2H, $J = 4.21$ Hz), 4.54 (d, 1H, $J = 8.74$ Hz), 4.06−4.00 (ddd, 1H, $J = 3.11$, 10.40, 13.09 Hz), 3.55−5.51 (dd, 1H, $J = 8.94$, 10.44 Hz), 2.66−2.61 (m, 1H), 2.41−2.37 (m, 1H), 1.56 (s, 3H), 1.52 (s, 3H) ppm.



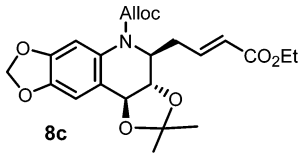
11

To a solution of **11** (3.8 mg, 1.205×10^{-5} mol) in dry dichloromethane (0.88 mL) at room temperature was added of benzenethiol (3.0 mL, 2.0 equiv) and triethylamine (6 μL, 3.0 equiv). The reaction mixture was stirred at room temperature for 10 h. After evaporation, the residue was purified by flash chromatography over silica gel (hexane and ethyl acetate) giving compound **12** as slightly yellow residue (78%). The product was characterized by ESI-MS and NMR. $R_f = 0.79$ (hexane/ethyl acetate 1:1). ($C_{23}H_{23}NO_5S$) LRMS: MS (ES^+) $m/z = 426.1$(M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) $\delta = 7.58$ (s, 1H), 7.44 (m, 2H), 7.34−7.29 (m, 3H), 6.78 (s, 1H), 5.93 (s, 2H), 4.51 (d, $J = 8.73$ Hz, 1H), 3.97−3.93 (dt, $J = 3.59$, 14.20 Hz, 1H), 3.70−3.67 (m, 1H), 3.37−3.32 (t, $J = 9.40$ Hz, 1H), 2.92−2.87 (dd, $J = 5.61$, 15.55 Hz, 1H), 2.70−2.63 (dd, $J = 11.90$, 15 41 Hz, 1H), 2.31−2.23 (td, $J = 4.19$, 14.40 Hz, 1H), 2.20−2.18 (m, 1H), 1.57 (s, 3H), 1.48 (s, 3H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$): $\delta = 170.33$, 146.91, 144.68, 132.95, 129.66, 128.27, 127.60, 121.52, 114.85, 105.82, 103.04, 101.73, 80.01, 77.62, 76.80, 56.63, 40.69, 37.78, 35.23, 27.44, 27.36 ppm. The stereochemistry of the new stereogenic center was assigned by nOe studies.



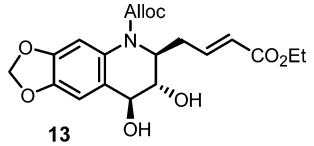
12

To a solution of aldehyde **8b** in dicholoromethane (1.20 mmol) carbethoxymethylenetriphenylphosphorane (0.47 g, 1.35 mmol) was added. The mixture was stirred at room temperature for 10 h. The reaction was quenched with saturated NH_4Cl, extracted with dichloromethane (3 × 10 mL), dried over Na_2SO_4, and concentrated. Purification by flash chromatography over silica gel (4:1, hexane/ethyl acetate) afforded the product **8c** (0.172 g, 86%) as a yellowish oil. $R_f = 0.49$ (2:1 hexane/ethyl acetate). LRMS: MS (ES^+) $m/z = 446.3$ (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) $\delta = 1.24$ (t, $J = 7.14$ Hz, 3H), 1.45 (s, 3H), 1.53 (s, 3H), 2.64 (m, 1H), 2.74 (m, 1H), 3.23 (t, $J = 8.88$ Hz, 1H), 4.10 (m, 2H), 4.38 (m, 2H), 4.65 (m, 2H), 5.23 (d, $J = 10.10$ Hz, 1H), 5.28 (d, $J = 17.15$ Hz, 1H), 5.83∼5.95 (m, 4H), 6.77∼6.90 (m, 3H) ppm.



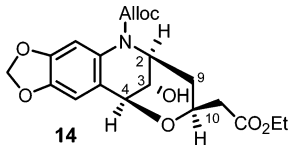
8c

8c (91 mg, 0.204 mmol) was dissolved in a mixture of AcOH/THF/H_2O (11 mL, 9/1/1). The mixture was stirred overnight at room temperature. Purification by column chromatography over silica gel (2:1, hexane/ethyl acetate) afforded the product **13** (80 mg, 97%) as a yellowish oil. R_f = 0.14 (1:1 hexane/ethyl acetate). LRMS: MS (ES^+) *m*/*z* = 406.2 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 1.29 (t, *J* = 7.10 Hz, 3H), 2.54 (m, 2H), 2.90 (m, 2H), 3.37 (t, *J* = 8.06 Hz, 1H), 4.18 (t, *J* = 7.11 Hz, 2H), 4.39 (m, 2H), 4.66 (m, 2H), 5.26 (d, *J* = 10.46 Hz, 1H), 5.32 (d, *J* = 17.15 Hz, 1H), 5.57 (d, *J* = 5.57 Hz, 1H), 5.93∼5.99 (m, 3H), 6.85∼6.96 (m, 3H) ppm.



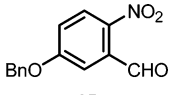
13

To a suspension of NaH (60%, 6 mg, 0.150 mmol) in THF (1 mL) was added a solution of **13** (62 mg, 0.153 mmol) in THF (1 mL) slowly at −15 °C. The reaction mixture was warmed to room temperature and then stirred overnight. The reaction was quenched with saturated NH_4Cl, extracted with dichloromethane (3 × 10 mL), dried over Na_2SO_4, and concentrated. Purification by flash chromatography over silica gel (3:1, hexane/ethyl acetate) afforded the product (52 mg, 84%) as a yellowish oil. R_f = 0.50 (1:1 hexane/ethyl acetate). LRMS: MS (ES^+) *m*/*z* = 406.2 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 1.20 (t, *J* = 7.12 Hz, 3H), 1.65 (d, *J* = 8.02 Hz, 1H), 1.77 (m, 1H), 2.15 (m, 1H), 2.40 (dddd, *J* = 5.65, 7.23, 15.11, 39.55 Hz, 2H), 3.67 (m, 1H), ∼4.07 to 4.13 (m, 3H), 4.58 (m, 1H), 4.73 (d, *J* = 5.60 Hz, 2H), 4.84 (m, 1H), 5.30 (dd, *J* = 0.90, 10.51 Hz, 1H), 5.38 (dd, *J* = 1.35, 17.13 Hz, 1H), ∼5.97 to 6.19 (m, 3H), 6.74 (d, *J* = 5.56 Hz, 1H), 8.05 (s, 1H) ppm.



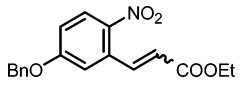
14

To a solution of phenol (10 g, 0.0598 mmol) in DMF (90 mL) was added benzyl bromide (10.7 mL, 0.09 mmol) and potassium carbonate (9.09 g, 0.0716 mmol). The solution was heated to 100 °C for 3 h and then cooled to room temperature. Water (50 mL) was added, and the mixture was extracted with dichloromethane and dried over Na_2SO_4. Purification by flash chromatography over silica gel (6:1, hexane/ethyl acetate) afforded the product (15.5 g, 96%) as a white solid. R_f = 0.62 (4:1 hexane/ethyl acetate). LRMS: MS (ES^+) *m*/*z* = 258.0 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 5.23 (s, 2H), 7.23 (dd, *J* = 2.78, 9.07 Hz, 1H), ∼7.39 to 7.45 (M, 6H), 8.17 (d, *J* = 9.05 Hz, 1H), 10.50 (s, 1H) ppm.



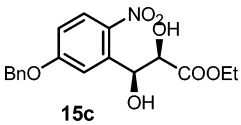
15a

To a solution of aldehyde **15a** (15.4 g, 0.060 mol) in dichloromethane (300 mL) was added carbethoxymethylenetriphenylphosphorane (41.8 g, 0.120 mol). The solution was stirred at room temperature under N_2 overnight. The reaction was quenched with saturated NH_4Cl solution, washed with water and brine. The organic phase was dried over anhydrous Na_2SO_4. After the solvent evaporation, the crude product was purified by flash chromatography over silica gel (7:1, hexane/ethyl acetate). The product was obtained as white solid (trans/cis = 5:1) in quantitative yield. R_f = 0.50 (5:1 hexane/ethyl acetate). LRMS: MS (ES^+) *m*/*z* = 328.2 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 1.13 (t, *J* = 7.14 Hz, 0.6H), 1.19 (t, *J* = 7.14 Hz, 3H), 4.04 (q, *J* = 7.13 Hz, 0.4H), 4.31 (q, *J* = 7.13 Hz, 2H), 5.15 (s, 0.4H), 5.20 (s, 2H), 6.10 (d, *J* = 11.93 Hz, 0.2H), 6.29 (d, *J* = 15.75 Hz, 1H), 7.05 (dd, *J* = 2.75, 9.10 Hz, 1H), 7.12 (d, *J* = 2.71 Hz, 1H), ∼7.41 to 7.45 (m, 6H), 8.14(d, *J* = 9.08 Hz, 1H), 8.22 (d, *J* = 15.88 Hz, 1H).



15b

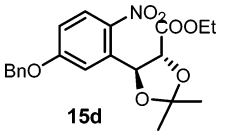
To a solution of the carboxyl ester (19.88 g, 60.7 mmol) in *tert*-butyl alcohol (300 mL) was added water (300 mL). The mixture was cooled to 0 °C. To this mixture was added methanesulfonamide (5.77 g, 60.7 mmol) and AD-mix-α (85 g). After the addition, the cooling bath was removed, and the reaction mixture was stirred at room temperature for 48 h. After this, sodium thiosulfate (16.47 g) was added, and the mixture was stirred for 30 min and then extracted with ethyl acetate (5 × 150 mL). The organic phase was washed with 2 M KOH (80 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by column chromatography (∼40:1 to 20:1 dichloromethane/methanol) afforded the product (16.1 g, 73.4%) as a white solid. R_f = 0.25 (2:1 hexane/ethyl acetate). LRMS: MS (ES^+) *m*/*z* = 362.2 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 1.36 (t, *J* = 7.14 Hz, 3H), 2.89 (d, *J* = 6.79 Hz, 1H), 3.24 (d, *J* = 5.42 Hz, 1H), 4.36 (q, *J* = 7.14 Hz, 2H), 4.53 (d, *J* = 5.11 Hz, 1H), 5.20 (s, 2H), 5.89 (d, *J* = 7.08 Hz, 1H), 7.00 (d, *J* = 9.06 Hz, 1H), ∼7.41 to 7.45 (m, 6H), 8.16 (d, *J* = 8.98 Hz, 1H) ppm.



15c

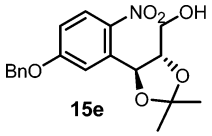
To a solution of the dihydroxyl der (14.5 g, 40.13 mmol) in acetone (290 mL) was added 2,2-dimethoxypropane (290 mL) and *p*-toluenesulfonic acid monohydrate (1.45 g, 7.62 mmol). The mixture was stirred at room temperature overnight and then quenched with saturated NH_4Cl. The organic layer was washed with water, dried over anhydrous Na_2SO_4, and concentrated. Purification by flash chromatography on silica gel (5:1, hexane/ethyl acetate) afforded the product quantitatively as a colorless oil. R_f = 0.51 (3:1, hexane/ethyl acetate). LRMS: MS (ES^+) *m*/*z* = 402.2 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 1.28 (t, *J* = 7.14

Hz, 3H), 1.64 (s, 6H), ~4.18 to 4.36 (m, 3H), 5.23 (s, 2H), 6.04 (d, $J = 7.02$ Hz, 1H), 7.02 (d, $J = 9.12$ Hz, 1H), ~7.41 to 7.49 (m, 6H), 8.13 (d, $J = 9.08$ Hz, 1H) ppm.



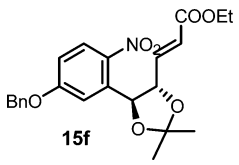
15d

To a solution of the carboxyl ester derivative (16.2 g, 40.36 mmol) in THF (300 mL) was added lithium borohydride (2.0M solution in THF, 40 mL, 80 mmol) slowly at room temperature. The reaction mixture was stirred at room-temperature overnight. After this, the solution was cooled by ice bath and the reaction was quenched with saturated NH_4Cl. After the solvent evaporation, the residue was dissolved in dichloromethane, washed with water and brine, and then dried over Na_2SO_4. Purification by flash chromatography over silica gel (3:1, hexane/ethyl acetate) afforded the product **15e** (13.85 g, 95%) as a colorless oil. $R_f = 0.28$ (2:1, hexane/ethyl acetate). LRMS: MS (ES^+) $m/z = 360.2$ (M + 1).^{1}H NMR: (400 MHz, $CDCl_3$) $\delta = 1.54$ (s, 3H), 1.60 (s, 3H), ~3.88 to 3.95 (m, 3H), 5.19 (s, 2H), 5.61 (d, $J = 7.46$ Hz, 1H), 7.00 (d, $J = 8.58$ Hz, 1H), 7.44 (m, 6H), 8.03 (d, $J = 9.07$ Hz, 1H) ppm.



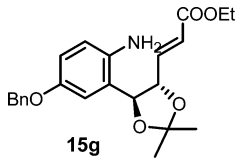
15e

To a solution of the alcohol (2.16 g, 6.01 mmol) in dichloromethane (50 mL) was added triethylamine (2.5 mL, 17.97 mmol) at room temperature. After the solution was cooled to 0 °C, sulfur trioxide pyridine complex (2.87 g, 18.03 mmol) in DMSO (18 mL) was added slowly. After the addition, the cooling bath was removed, and the reaction mixture was stirred for an additional 2 h at room temperature. Carbethoxymethylenetriphenylphosphorane (4.19 g, 12.03 mmol) was added in one portion, and the mixture was stirred overnight. The reaction was quenched with saturated NH_4Cl, extracted with dichloromethane (3 × 50 mL), dried over Na_2SO_4, and concentrated. Purification by column chromatography over silica gel (7:1, hexane/ethyl acetate) afforded the trans product (2.13 g, 83%) as a yellowish oil. $R_f = 0.31$ (4:1 hexane/ethyl acetate). LRMS: MS (ES^+) $m/z = 428.3$ (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) $\delta = 1.31$ (t, $J = 7.14$ Hz, 3H), 1.56 (s, 6H), 4.23 (q, $J = 7.14$ Hz, 2H), 4.33 (m, 1H), 5.20 (s, 2H), 5.65 (d, $J = 7.50$ Hz, 1H), 6.04 (dd, $J = 0.83, 15.57$ Hz, 1H), ~7.00 to 7.08 (m, 2H), ~7.40 to 7.45 (m, 7H), 8.05 (d, $J = 9.07$ Hz, 1H) ppm.



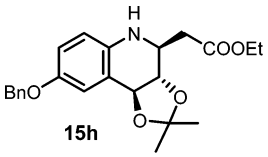
15f

To a solution of the nitro derivative (3.42 g, 80.0 mmol) in ethanol (80 mL) was added zinc powder (5.23 g, 80.0 mmol) at room temperature. This was then followed by dropwise addition of acetic acid (4.58 mL, 80.00 mmol). The reaction mixture was stirred for an additional 15 min, filtered, and concentrated. Purification by flash chromatography over silica gel (5:1, hexane/ethyl acetate) afforded the product (2.86 g, 90%) as a yellowish oil. $R_f = 0.20$ (4:1 hexane/ethyl acetate). LRMS: MS (ES^+) $m/z = 398.1$ (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) $\delta = 1.30$ (t, $J = 7.14$ Hz, 3H), 1.54 (s, 3H), 1.62 (s, 3H), 3.97 (s, br, 2H), 4.21 (q, $J = 7.14$ Hz, 2H), 4.71 (d, $J = 8.66$ Hz, 1H), 4.83 (dddd, $J = 1.30, 1.16, 5.11, 8.72$ Hz, 1H), 6.11 (dd, $J = 1.33, 15.61$ Hz, 2H), 6.65 (d, $J = 8.56$ Hz, 1H), 6.78 (d, $J = 2.79$ Hz, 1H), 6.83 (dd, $J = 2.88, 8.55$ Hz, 1H), 6.89 (dd, $J = 5.10, 15.69$ Hz, 1H), ~7.33 to 7.45 (m, 5H) ppm.



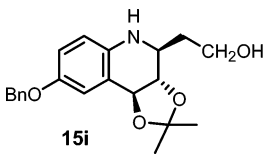
15g

To a solution of the amine derivative (2.08 g, 5.23 mmol) in anhydrous THF (50 mL) was added LDA (2.0 M solution in THF, 2.60 mL, 5.20 mmol) at −78 °C. After the mixture was stirred for an additional 30 min, the reaction was quenched with saturated NH_4Cl and extracted with dichloromethane (3 × 50 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography over silica gel (6:1, hexane/ethyl acetate) afforded the product (1.9 g, 91%) as a yellowish oil. $R_f = 0.71$ (4:1 hexane/ethyl acetate).



15h

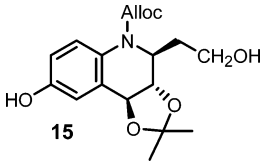
To a solution of β-amino acid derivative (1.10 g, 2.77 mmol) in THF (25 mL) was added lithium borohydride (2.0 M in THF, 2.77 mL, 5.54 mmol) slowly at 0 °C. The reaction mixture was stirred at room temperature overnight. The reaction was quenched with saturated NH_4Cl, extracted with dichloromethane (3 × 10 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography over silica gel (3:1, hexane/ethyl acetate) afforded the product (934 mg, 85%) as a yellowish oil. $R_f = 0.20$ (2:1, hexane/ethyl acetate). LRMS: MS (ES^+) $m/z = 356.3$ (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) $\delta = 1.56$ (s, 3H), 1.59 (s, 3H), 1.89 (m, 1H), 1.97 (m, 1H), 2.63 (br, s, 1H), 3.65 (m, 1H), 3.68 (m,1H), 3.74 (m,3H), 4.74 (d, $J = 8.70$ Hz, 1H), 5.01 (s, 2H), 6.46 (d, $J = 8.03$ Hz, 1H), 6.73 (d, $J = 7.03$ Hz, 1H), 6.91 (s, 1H), 7.28~7.44 (m, 6H) ppm.



15i

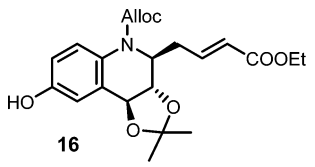
To a solution of β-amino alcohol (700 mg, 1.97 mmol) in ethanol (75 mL) was added palladium on carbon (10%) (100

mg). The solution was stirred under hydrogen overnight at room temperature. The catalyst was removed by filtration, and evaporation of the solvent afforded the crude product, which was not purified and was used directly for the next step. The crude hydrogenation product was dissolved in dichloromethane (200 mL), and pyridine (0.165 mL, 2.04 mmol) was added at room temperature. The solution was cooled to 0 °C, and allyl chloroformate (0.217 mL, 2.045 mmol) was added slowly. After the addition, the solution was stirred at 0 °C for 1 h. The reaction was quenched with saturated NaCl solution, extracted with dichloromethane (3 × 10 mL), and then dried over Na_2SO_4. Purification by flash chromatography on silica gel (3:1, hexane/ethyl acetate) afforded the product 15 (370 mg, 52%) as a yellowish oil. R_f = 0.25 (1:1, hexane/ethyl acetate). LRMS: MS (ES^+) m/z = 350.1 (M + 1). ^1H NMR: (400 MHz, $CDCl_3$) δ = 1.50 (s, 3H), 1.59 (s, 3H), 1.90 (br, s, 2H), 3.31 (t, J = 8.69 Hz, 1H), 3.77 (m,2H), 4.42 (m, 1H), 4.50 (d, J = 9.30 Hz, 1H), 4.61 (m, 1H), 4.71 (dd, J = 5.31, 13.48 Hz, 1H), ~5.22 to 5.30 (m, 2H), 5.64 (s, 1H), 5.93 (m,1H), 6.73 (dd, J = 2.75, 8.63 Hz, 1H), 6.82 (m, 1H), 7.21 (m, 1H) ppm.



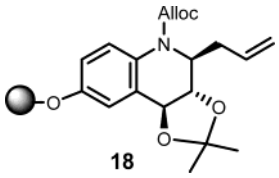
15

To a solution of *N*-Alloc-protected amino alcohol (250 mg, 0.716 mmol) in dichloromethane (7 mL) was added triethylamine (0.3 mL, 2.156 mmol) at room temperature. The mixture was then cooled to 0 °C and sulfur trioxide pyridine complex (343 mg, 2.155 mmol) in DMSO (2.7 mL) was slowly added. After the addition, the cooling bath was removed, and the reaction mixture was stirred for an additional 2 h at room temperature. Carbethoxymethylene-triphenylphosphorane (500 mg, 1.435 mmol) was added in one portion at room temperature, and the mixture was stirred overnight. The reaction was quenched with saturated NH_4-Cl, extracted with dichloromethane (3 × 10 mL), and dried over Na_2SO_4. Purification by column chromatography over silica gel (3:1 hexane/ethyl acetate) afforded the product (250 mg, 84%) as a yellowish oil. R_f = 0.45 (2:1 hexane/ethyl acetate). LRMS: MS (ES^+) m/z = 418.2 (M + 1). ^1H NMR: (400 MHz, $CDCl_3$) δ = 1.26 (t, J = 7.14 Hz, 3H), 1.49 (s, 3H), 1.58 (s, 3H), 2.68 (m, 1H), 2.80 (m, 1H), 3.29 (t, J = 8.60 Hz, 1H), 4.17 (m, 2H), 4.41 (m,1H), 4.48 (d, J = 9.23 Hz, 1H), 4.60~4.75 (m, 2H), 5.21~5.37 (m, 2H), 5.82~6.03 (m, 3H), 6.62 (dd, J = 2.78, 8.68 Hz, 1H), 6.78 (d, J = 2.30 Hz, 1H), 6.85~6.89 (m,1H), 7.21(s, 1H) ppm.



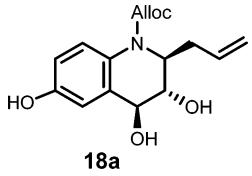
16

Solid-Phase Synthesis. Loading. A 150-mg (1.87×10^{-4} mol) portion of bromo Wang resin (1.19 mmol/g) was washed with dichloromethane (DCM) four times, then swollen 2 × 30 min in DCM and 15 min with dimethylformamide (DMF). To this resin was added oven-dried NaI (56 mg, 2.0 equiv) and anhydrous DMF (5.0 mL), oven dried Cs_2CO_3 (122 mg, 2.0 equiv), and compound **17** (129 mg, 2 equiv) dissolved in anhydrous DMF (7.0 mL). The mixture was bubbled by a controlled flow of argon. After 43 h of bubbling, the resin was washed consecutively two times with DMF, 2 × H_2O, 2 × MeOH, and 3 × DCM, and the resin was dried on high vacuum overnight. The filtrate containing the starting material in DMF was evaporated, and the residue was dissolved in DCM. The organic phase was washed with water, dried with magnesium sulfate, filtered, and evaporated. The residue was purified by flash chromatography on silica gel with hexane/ethyl acetate and DCM/MeOH as eluants. A total of 59.9 mg (1.73×10^{-4} mol) of recovered starting material was obtained, giving an indirect yield for the loading step (93%). A 8.4-mg portion of the resin was mixed with 5% trifluoroacetic acid in DCM (1.0 mL). After stirring at room temperature for 1 h, the mixture was filtered, and the resin was washed two times. The filtrate was evaporated and then dried on a high-vacuum pump overnight.



18

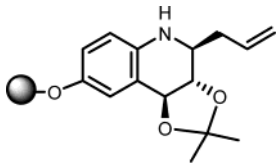
Cleavage Product. 305.33 (mol wt), 305.13 (exact mass) ($C_{16}H_{19}NO_5$). LRMS: MS (ES^+) m/z = 306.1 (M + 1). ^1H NMR: (400 MHz, $CDCl_3$) δ = 6.94 (s, 1H), 6.72 (dd, J = 2.25, 8.25 Hz, 1H), 5.93 (m, 1H), 5.76 (m, 1H), 5.32−5.21 (m, 2H), 5.06−5.03 (m, 2H), 4.66 (m, 2H), 4.47 (d, J = 8.80 Hz, 1H), 4.29 (m, 1H), 3.39 (m, 1H), 2.43−2.34 (m, 2H) ppm. R_f = 0.18 (1:1 hexane/ethyl acetate), 0.26 (2:3 hexane/ethyl acetate).



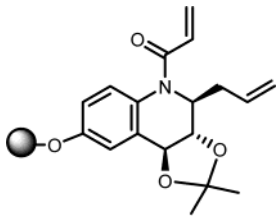
18a

To 150 mg (1.87×10^{-4} mol) of the resin-bound product, 67 mg (0.3 equiv) of tetrakis(triphenylphosphine)palladium-(0) [$(Ph_3P)_4Pd$] dissolved in 8.25 mL of dry DCM was added. To this mixture was added *N*-methylmorpholine (0.25 mL) and anhydride acetic (0.5 mL). The reaction mixture was bubbled under argon for 24 h. The resin was then washed consecutively with 2 × DMF, 2 × H_2O, 2 × MeOH, and 2 × DCM. A small amount of the compound−resin was treated using a solution of 5% of TFA in DCM for 1 h at room temperature. The resin was then washed two times with DCM. The filtrate was evaporated and dried on a high-

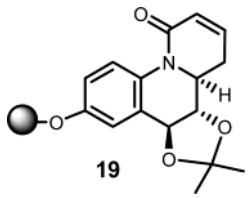
vacuum pump overnight. Molecular weight and formula: 221.25 (mol wt), 221.11 (exact mass) ($C_{12}H_{15}NO_3$). R_f = 0.13 (2:3 hexane/ethyl acetate).



To 150 mg (1.87×10^{-4} mol) of the resin-bound product in anhydrous DCM (5.0 mL) was added 0.720 mL (27 equiv) of triethylamine (Et_3N) and acryloyl chloride (0.30 mL, 20.0 equiv). The mixture was bubbled by a flow of argon for 24 h. The resin was was then washed using 2 × DMF, 2 × MeOH, and four times by DCM and then dried over a high-vacuum pump for 6 h. A small sample of the resin-bound product was treated with 1 mL of a solution of 5% of TFA in DCM for 1 h at room temperature. It was then washed two times with DCM. Molecular weight and formula: 275.30 (mol wt), 275.12 (exact mass) ($C_{15}H_{17}NO_4$) LRMS: MS (ES^+) m/z = 276.1 (M + 1). R_f = 0.06 (1:1 hexane/ethyl acetate).

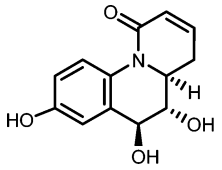


A 22.0-mg (2.618×10^{-5} mol) portion of resin-bound product was added in a flask under N_2 and 2.5 mL of anhydrous DCM. To this mixture, 13.0 mg (0.6 equiv) of benzylidene-bis(tricyclohexyl phosphine)dichlororuthenium (Grubbs' catalyst first generation) dissolved in 2 mL of anhydrous DCM was added. The reaction mixture was warmed at 40 °C under N_2 for 24 h. To this mixture, a new portion of 0.6 equiv of Grubbs' catalyst in 2 mL of anhydrous DCM was added. After 6 h, the mixture was brought to room temperature, then the resin was washed 3 × DCM, 2 × MeOH, and 3 × DCM. This was then treated with 4 mL of a solution of 5% of TFA in anhydrous DCM at room temperature for 1 h. Following this, the resin was washed two times with DCM, and the filtrate was evaporated. The residue was then purified over a small patch of silica gel with hexane/ethyl acetate and DCM/MeOH. The cleaved product was characterized by ESI-MS, 1D-NMR and 2D-NMR COSY, HSQC, HMBC, NOESY, DEPT 135.

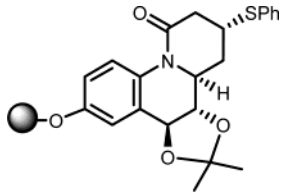


19

Cleavage Product. Molecular weight and formula: 247.25 (mol wt), 247.08 (exact mass) ($C_{13}H_{13}NO_4$). LRMS: MS (ES^+) m/z = 248.0 (M + 1) ^{1}H NMR: (400 MHz, DMSO-d_6) δ = 9.21 (s, 1H), 7.77 (d, J = 8.87 Hz, 1H), 6.91 (s, 1H), 6.76−6.72 (m, 1H), 6.58 (d, J = 8.06 Hz, 1H), 5.88 (d, J = 9.78 Hz, 1H), 5.60 (dd, J = 5.84, 10.63 Hz, 1H), 4.31 (m, 1H), 3.61−3.57 (m, 1H), 3.40 (m, 1H), 3.32 (m, 1H), 2.68 (m, 1H), 2.62 (m, 1H) ppm. ^{13}C NMR: (100 MHz, DMSO-d_6) δ = 154.00, 141.75, 126.06, 125.23, 114.13, 113.70, 72.68, 72.67, 59.45, 26.69 ppm. R_f = 0.07 (1:4, hexane/ethyl acetate).

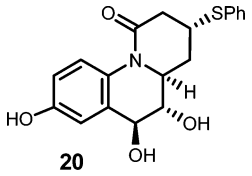


A 79-mg (9.40×10^{-5} mol) portion of resin-bound product in 5 mL of dry dichloromethane was added to benzenethiol (97 μL, 10 equiv) and triethylamine (197.0 μL, 15.0 equiv). The reaction was bubbled at room temperature under N_2 for 24 h. A second cycle of benzenethiol was performed under the same conditions. The resin was washed two times with DCM, two times with methanol, and again four times with DCM. To cleave the compound from the resin, 5% trifluoroacetic acid (5 mL) in DCM was added to the resin and bubbled under N_2 for an additional 1 h. The filtrate was collected, and the resin washed two times with DCM and then dried over a high-vacuum pump. The yellow residue was purified by flash chromatography with silica gel and hexane and ethyl acetate as eluants, giving 27% (over 6 steps) and was characterized by ESI-MS and 2D-NMR experiments. To a solution of 3.8 mg (1.205×10^{-5} mol) in dry dichloromethane at room temperature was added 3 mL (2 equiv) of benzenethiol and 6 mL (3 equiv) of triethylamine. The reaction mixture was stirred at room temperature for 12 h under N_2. After evaporation, the residue was purified by flash chromatography over silica gel, giving a slightly yellow residue, which was then characterized by ESI-MS and NMR, including COSY, HSQC, DEPT 135.



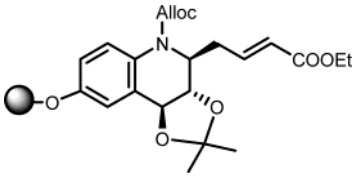
Cleaved Product. Molecular weight and formula: 357.42 (mol wt), 357.10 (exact mass) ($C_{19}H_{19}NO_4S$). LRMS: MS (ES^+) m/z = 358.10 (M + 1). ^{1}H NMR: (400 MHz, DMSO-d_6) δ = 9.29 (s, 1H), 7.47−7.34 (m, 6H), 6.85 (d, J = 2.38 Hz, 1H), 6.58−6.56 (dd, J = 2.75, 8.73 Hz, 1H), 5.60 (s, 2H), 4.31 (d, J = 7.14 Hz, 1H), 3.83 (1H, m), 3.58 (m, 1H), 3.51 (m, 1H), 2.61 (m, 1H), 2.52−2.45 (m, 2H), 1.95 (m, 1H) ppm ^{13}C NMR: (100 MHz, DMSO-d_6) δ = 166.86, 155.12, 134.74, 134.44, 131.53, 130.06, 127.84, 126.05, 115.03, 114.39, 74.68, 74.25, 60.62, 59.41, 40.35, 36.57,

30.39, 21.63, 14.95 ppm. $R_f = 0.26$ (ethyl acetate).

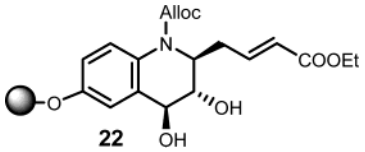


20

Loading. Bromo Wang resin (1.1 mmol/gm, 257 mg, 0.282 mmol) in DMF (10 mL), Cs_2CO_3 (234 mg, 0.719 mmol), and NaI (108 mg, 0.719 mmol) were added. After addition of the starting material phenol (300 mg, 0.719 mmol), the solution was bubbled with nitrogen for 24 h. The DMF solvent was filtered and washed with DMF (2 × 15 mL). The starting material was recovered by column purification, and the loading was 86% (0.94 mmol/gm). The resin was washed with water (2 × 15 mL), MeOH (2 × 15 mL), and DCM (2 × 15 mL) and then dried under vacuum.

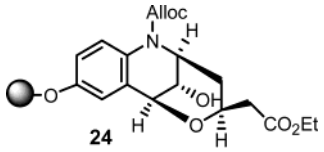


Acetonide Removal. The resin from the loading step was suspended in DCM/CH_3CN (5 mL/5 mL), PPTS was added in one portion, and the mixture solution was shaken for 24 h. The solution was filtered, and the resin was washed with DMF (2 × 15 mL), H_2O (2 × 15 mL), MeOH (2 × 15 mL), and DCM (2 × 15 mL) and then dried under vacuum.



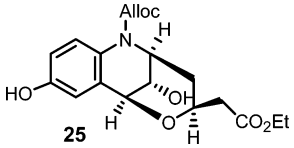
22

Hetero Michael Reaction. The resin from the hydrolysis step was suspended in THF (∼5 to 8 mL), and the NaH (∼10 mg) was added in one portion at room temperature. The mixture was shaken for 24 h, the solution was filtered and washed with DMF (5 × 15 mL) and then DMF (10 mL) with dropwise addition of saturated NH_4Cl solution to destroy the residue of NaH until no gas was evolved. The mixture was filtered and washed with DMF (2 × 15 mL), H_2O (2 × 15 mL), MeOH (2 × 15 mL), and DCM (2 × 15 mL) then dried under vacuum.



24

Cleavage from the Support. The resin was suspended in 5% TFA solution in DCM and shaken for 30 min. The solution was filtered, collected, and evaporated to afford the crude product. Purification over silica gel afforded the product (overall yield ∼25% for four steps), which was confirmed by MS and NMR.



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Acknowledgment. We thank NRC Genomics Program, Special VP-Research NRC Funds for Chemical Biology, and National Cancer Institute of Canada for financial support. Dr. Brady Clark (Sussex Research Labs) is thanked for his valuable comments.

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