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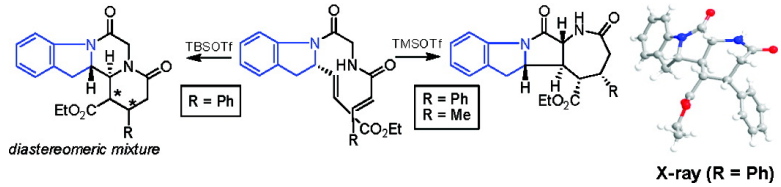

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Reagent-Based, Modular, Tandem Michael Approach for Obtaining Different Indoline Alkaloid-Inspired Polycyclic Architectures

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A modular, reagent-based approach to obtain different indoline alkaloid-inspired, tetracyclic architectures is developed. With the use of TBSOTf as a Lewis acid, we report here a tandem Michael-based approach that led to the synthesis of a diastereomeric mixture of tetracyclic derivatives with two additional six-membered rings. By simply changing the Lewis acid to TMSOTf, we were able to obtain a different tetracyclic compound having additional functionalized 5- and 7-membered rings with complete stereocontrol.

With the rapid rise in utilization of small molecule probes in understanding biological functions, the need for accessing natural products, natural product analogs and natural product-inspired small molecules has also grown.[1] In particular, the development of modular approaches on solid phase is attractive because they allow the possibility of generating different architectures in a high-throughput manner.[2]

Herein, we report a modular, reagent-based approach for developing the synthesis of enantio-enriched, alkaloid-inspired, polycyclic derivatives. The key reaction in our approach is the tandem Michael/Aza−Michael reaction that was reported in the literature.[3] In particular, we were interested in developing this methodology on the indoline/aminoindoline scaffolds because of our interest in having a wide access to different indoline alkaloid natural product-inspired polycyclic architectures.[4] In addition to developing this modular approach in solution, we were also interested in solid-phase synthesis leading to high-throughput generation of several derivatives.

In a model study, the commercially available (*S*)-indoline-2-carboxylic acid **1** (Scheme 1) yielded compound **2** in four steps. Following *N*-Alloc removal, coupling of modified amino acid **3** was then carried out giving compound **4** as the starting material to explore the tandem Michael reaction. The first reaction conditions, TBSOTf/NEt_3 at a low temperature, produced a mixture of tetracyclic derivatives (48%, see products **5a**, **5b**, and **5c**) and the tricyclic compounds (20%, **5d**). All the products were assigned by 2D NMR studies. To increase the yield of the tetracyclic compounds in this reaction, other Lewis acids, TESOTf and TMSOTf, were then used.

With the use of TMSOTf, we were pleased to observe the complete transformation, yielding only one tetracyclic compound. Another surprise came from the structural assignment that revealed a totally different architecture (Scheme 2, compounds **7** and **8**). In addition to the NMR studies, the X-ray structure of the unique compound **7** finally confirmed the stereochemistry (Figure 3). Compound **7** crystallizes as a solvate from chloroform in the orthorhombic space group $P2_12_12_1$ with $a = 17.1257$ (13) Å, $b = 29.451(2)$ Å, and $c = 39.372(3)$ Å (Table 1). There are eight molecules of **7** in the asymmetric unit. All exhibit the same stereochemistry. Complete X-ray data for **7** can be found in the Supporting Information. With the use of TMSOTf, the reaction was very fast and the complete disappearance of the starting material took place in a less than 20 min yielding compound **7**. This reaction was repeated with the other starting material, **6**, and as observed previously, only a single tetracyclic compound **8** was obtained with a complete stereocontrol.

To explain the stereochemical outcome of this reaction, four transition states could be postulated as shown in Figure 1 (**A**, **B**, **C** and **D**). In structures **A** and **B**, the first enol adopts the Z configuration, which is less stable than the E configuration shown in structures **C** and **D**. Moreover, in the **B** and **D** structures, the disfavored interaction between an electron-deficient alkene and the equatorial proton from the indoline core allows us to postulate that it is the privileged structure **C** that leads to the correct stereochemistry. The generation of next two stereocenters could be explained by consideration of the four privileged conformations of the precursor of the 7-membered ring (Figure 1). Transition states **E** and **F** (Figure 1) indicate a strong disfavored interaction from the ester group in the less stable axial position with the Lewis Acid complex. Finally, a strong disfavored interaction between the side chain and an electron-deficient olefin in transition state **G** led us to propose structure **H** as the favored one leading to the observed stereochemistry.

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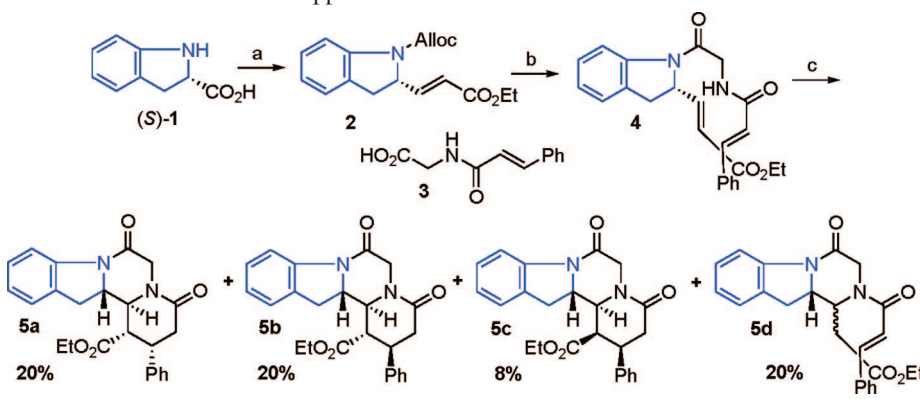
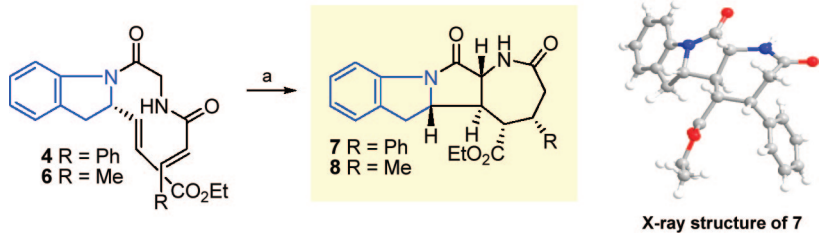
Scheme 1. TBSOTf-Mediated Tandem Michael Approach[a]



[a] Reagents and conditions: (a) (i) $LiAlH_4$, 84% (ii) Alloc-Cl, DIPEA, 99% (iii) SO_3−pyridine, DMSO, Et_3N, 84% (iv) $Ph_3C{=}CHCO_2Et$, 95%; (b) (i) $Pd(Ph_3)_4$, morpholine, 90% (ii) **3**, HATU, DIPEA, 83%; (c) TBSOTf, Et_3N, 68%.

Scheme 2. TMSOTf-Mediated Tandem Michael Approach[a]



[a] Reagents and conditions: (a) TESOTf or TMSOTf, Et_3N (for **7**, 91% and **8**, 80%).

Table 1. Crystal Data and Structure Refinement for the Compound **7**

identification code	sadf
empirical formula	$C_{99.24}H_{99.24}C_{19.71}N_8O_{16}$
fw	2004.26
temp	398(2) K
wavelength	0.71073 Å
cryst syst	orthorhombic
space group	$P2_12_12_1$
unit cell dimensions	
a	17.1257(13) Å
b	29.451(2) Å
c	39.372(3) Å
α	90°
β	90°
γ	90°
vol	19858(3) Å^3
Z	8
density (calcd)	1.341 Mg m^{-3}
abs coeff	0.341 mm^{-1}
F(000)	8350
cryst size	0.50 × 0.40 × 0.10 mm^3
θ range for data collection	1.03−20.75°
index ranges	$-17 \le h \le 16$
	$-29 \le k \le 29$
	$-39 \le l \le 39$
reflns collected	118 886
independent reflns	20 487 [R_{int} = 0.0585]
completeness to θ = 20.75°	99.8%
abs correction;	semiempirical from equivalents
refinement method	full-matrix least-squares on F^2
data/restraints/params	20 487/1680/2095
GOF on F^2	1.026
final R indices [$I > 2\sigma(I)$]	R1 = 0.0891, wR2 = 0.2320
R indices (all data)	R1 = 0.1251, wR2 = 0.2713
absolute structure parameter	0.05(10)
extinction coeff	0.00069(10)
largest diff. peak and hole	0.727 and −0.456 e Å^{-3}

The next series of experiments was then tried with a starting material in which the Gly-moiety in the side chain (**9**, Scheme 3) was replaced by another amino acids. The cyclization of compound **10** led to a mixture of **11a** and **11b** in a ratio of 3:1. It appears that the bulky isobutyl group induces the cyclization to occur through the pathway shown in Scheme 1. After this, we then decided to work with the systems that were derived from aminoindoline derivatives **13** and **15** (Scheme 4), which could be easily obtained from the starting material **12**. When TBSOTf was used as the Lewis acid, there was no sign of the cyclization reaction. This may be attributed to steric effects because this study only led to the tricyclic **14** with the predictable stereochemistry (see the Supporting Information). When the Lewis acid used was changed to TMSOTf, two isomers of tetracyclic compounds **16a/17a** and **16b/17b** were formed in a 2:1 ratio with the same architecture observed with the model study. At this stage it was difficult to assign the stereochemistry because the *N*-Alloc group usually results in broad signals in NMR. To solve this problem, the *N*-Alloc group was replaced with the *N*-benzoyl group and this replacement gave sharp NMR signals.

After the successful development of the tandem reaction-based method in solution, the method was then applied to the solid phase. To our knowledge, there are no examples in the literature that describe the application of this approach on the solid phase leading to library generation. For this study, compound **19** (Scheme 5) was prepared with the three-carbon spacer and the appropriate protecting groups to be compatible for the solid-phase synthesis. The loading of compound **19** was near quantitative, giving compound **20** anchored onto the solid support. After a few steps on the solid phase support, compounds **21**−**24** were obtained. Compound **21** (Scheme 5) was subjected to cyclization to

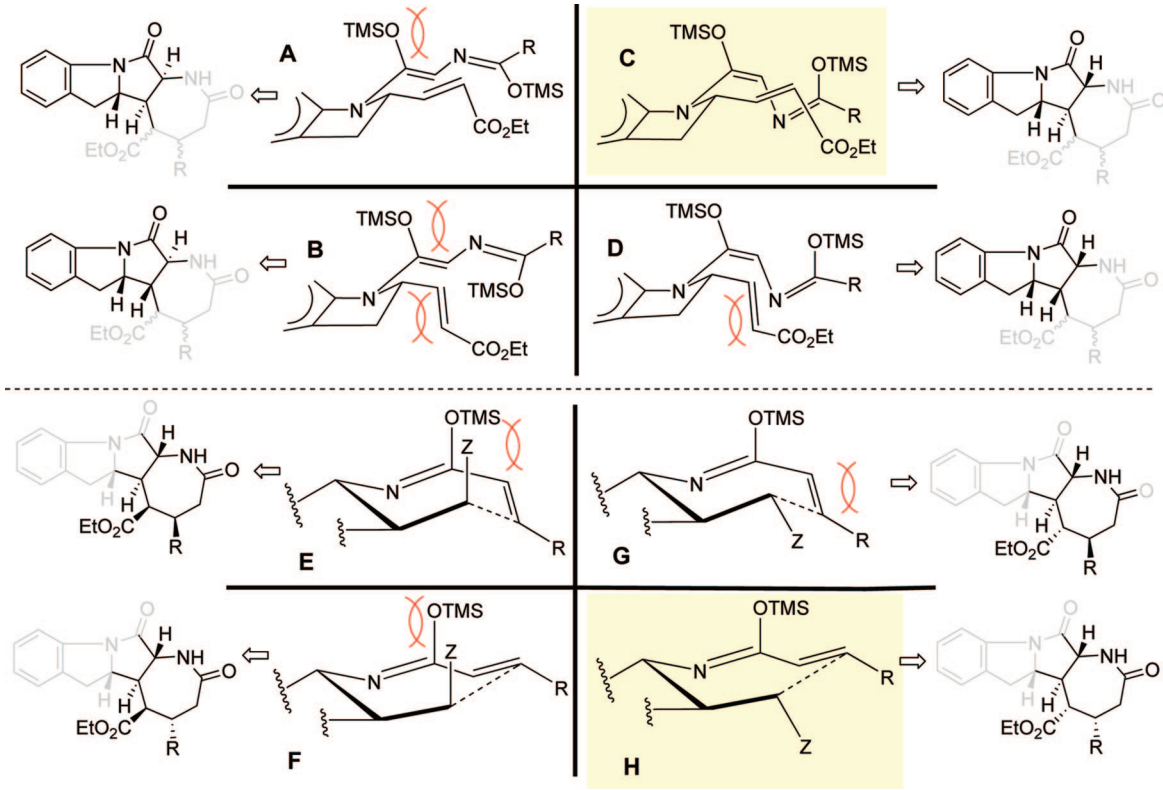


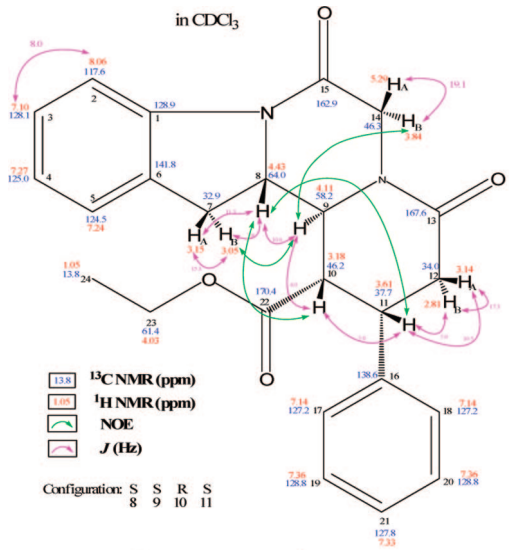
Figure 1. Proposed transition states to explain the observed trans-fused system and the seven-membered ring stereochemistry.

give a mixture of four isomers in an excellent yield (98%) with a ratio of 7.4:1.2:0.3:1.1. The major isomer **25a** was separated by preparative HPLC, and the stereochemistry was thoroughly assigned using 2D NMR. Compounds **22**, **23**, and **24**, upon cyclization reaction, gave the corresponding desired tetracyclic products **26**, **27**, and **28** in moderate to good yields (60%, 45%, and 72%) as diastereomeric mixtures (**26** = 6.7:1.6:0.9:0.8, **27** = 2.2:7.8, and **28** = 2:5:1.9:1.1). For **26** and **27**, the major isomers were separated by preparative HPLC, but their stereochemistry could not be assigned because of an overlap of signals in NMR even in various solvents. Further work, using this solid-phase methodology, is ongoing in library generation, and applications of these compounds will be reported in the near future.

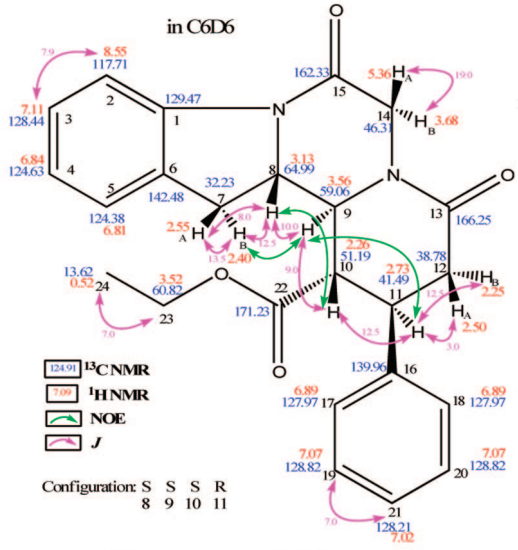
Experimental Section

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. no. 5715-7) precoated silica gel 60 F_{254} glass plates (layer thickness 0.25 mm). Visualization was achieved with a UV lamp (254 nm) or by staining with vanillin, $KMnO_4$ solution, ammonium molybdate/ceric sulfate solution. Flash column chromatography was performed using silica gel 60 (40−63 μm, Silicycle) or Biotage Horizon Flash Chromatography System. Solvents were purified as follows: trace amounts of water and oxygen from THF, DMF, and dichloromethane were removed using columns containing activated alumina and copper under N_2. 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). ^{1}H NMR (400 MHz) spectra were recorded at room temperature in $CDCl_3$, C_6D_6, or DMSO-d_6 solutions and referenced to residual $CHCl_3$ (7.27 ppm) or C_6H_6 (7.16 ppm) or DMSO (2.50 ppm). Fully decoupled ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$, C_6D_6, or DMSO-d_6 solutions. The center peaks of $CDCl_3$ (77.0 ppm), C_6D_6 (128.7 ppm), and DMSO-d_6 (39.43 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 CHIRACEL-OD column. HPLC/MS were performed using Waters equipment: Waters micromass ZQ ESCI Multi-Mode ionization, Waters 996 Photodiode Array Detector (254 nm), and Waters 2795 Separation Module with Phenomenex Spherisorb 3 ODS-2 column.

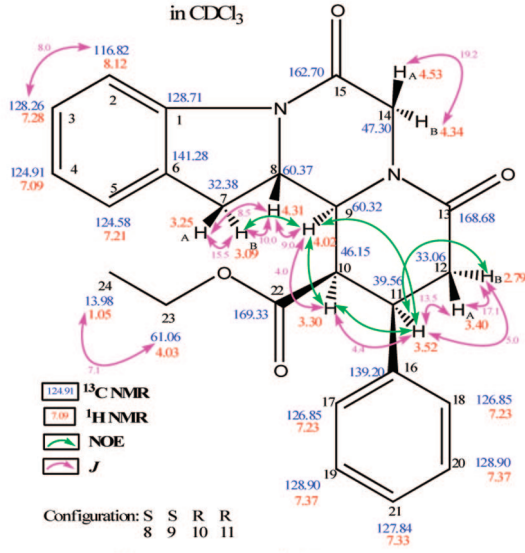
Small-scale solid-phase reactions (1−10 mg resin) were performed in 2 mL fritted polypropylene Bio-Spin chromatography columns. Medium-scale solid-phase reactions (10−200 mg) were performed in 10 mL polypropylene PD-10 columns. Agitation of solid-phase reaction mixtures was performed using a Barnstead-Thermolyne Labquake shaker. The linker cleavage reactions (<20 mg of beads) were carried out in 1.5 mL eppendorf tubes. Vacuum removal of solvents for the linker cleavage reactions was accomplished using Genevac HT-4 Atlas Evaporator. In cases where the products



Compound **5a**



Compound **5b**



Compound **5c**

Figure 2. Diagram showing the ^{13}C NMR, ^{1}H NMR, NOE, and *J* values corresponding to the structures of compounds **5a**−**5c**.

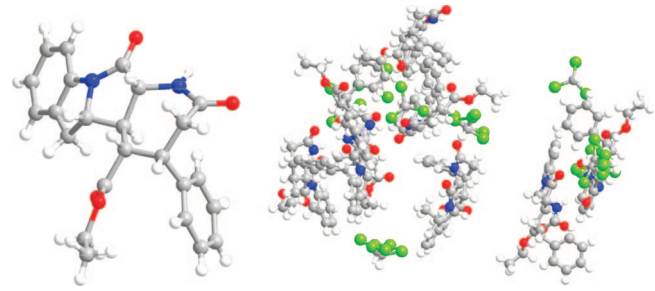


Figure 3. X-ray structure of compound **7** and the organization of compound **7** in the crystalline box.

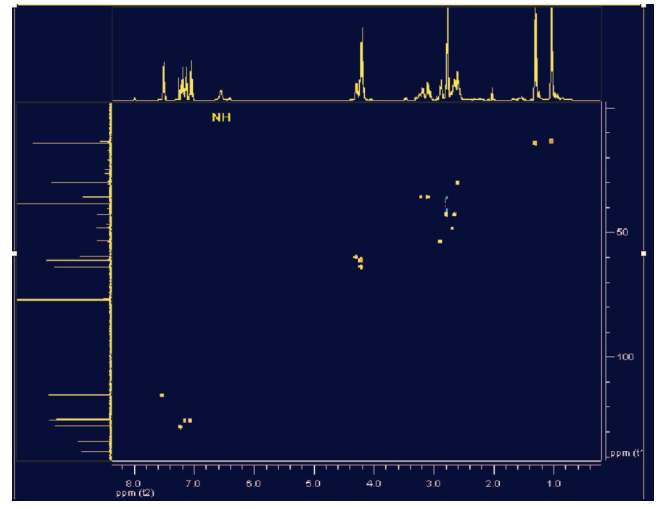
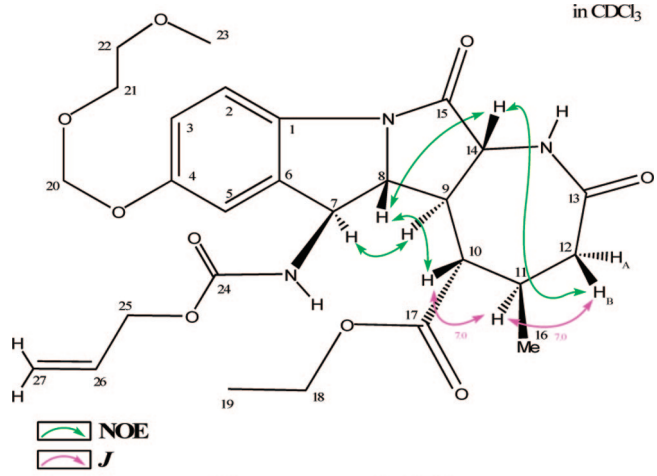


Figure 4. HSQC experiment showing the free NH within the 7-membered ring (no cross peak for −NH proton)

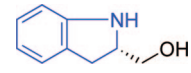


Compound **17b**

Figure 5. NOE and *J* values for the structure of compound **17b**.

from the solid phase were characterized by NMR, the reactions were carried out on a 15−20 mg resin scale.

Compound 1a, (*S*)-Indolin-2-ylmethanol.



To a solution of (*S*)-indoline-2-carboxylic acid (2.00 g, 12.19 mmol) in THF (50 mL) at −78 °C, was added $LiAlH_4$ (1 M solution in hexane, 24.38 mL, 24.38 mmol). The reaction mixture was stirred at −78 °C under N_2 for 3 h. The reaction

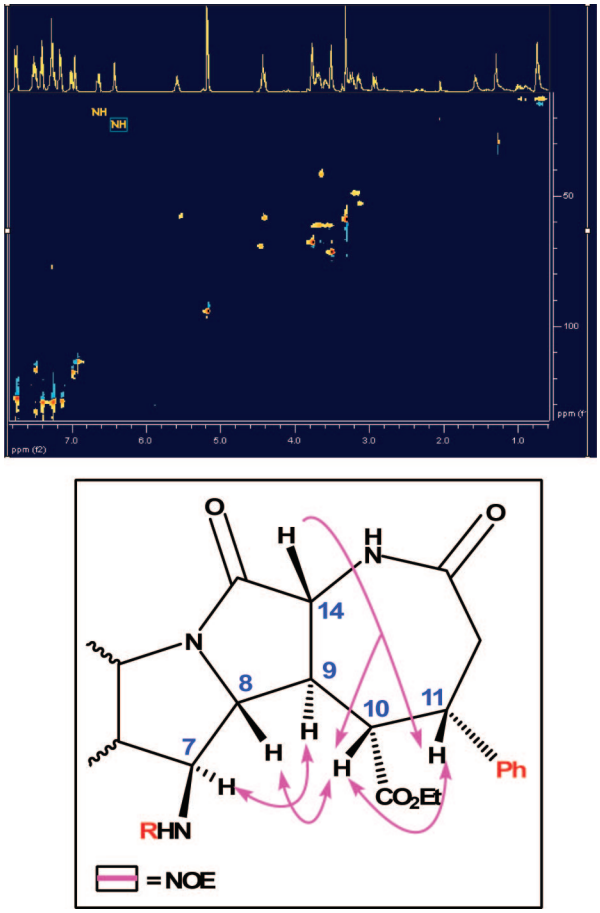
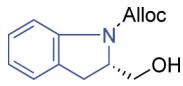


Figure 6. HSQC experiment showing the two free NH moieties from compound **18b**.

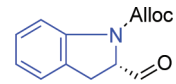
mixture was quenched with water and then extracted with dichloromethane. The combined organic layers were washed with brine then dried over magnesium sulfate, filtered, and purified by flash chromatography. Elution with hexane/ethyl acetate (3:2 v/v) gave 1.53 g (84%) of product as a light brown solid: MS (ES+) *m/z* (M + 1) 150.1; HRMS (FAB) *m/z* (M^+) calcd 149.08 for $C_9H_{11}NO$, obsd 149.09; mp = 65.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, J = 6.7 Hz, 1H), 7.07 (dd, J = 7.6, 7.6 Hz, 1H), 6.79 (dd, J = 7.5, 7.4 Hz, 1H), 6.73 (d, J = 7.8 Hz, 1H), 4.15−4.08 (m, 1H), 3.78 (dd, J = 11.0, 3.8 Hz, 1H), 3.64 (dd, J = 11.0, 6.3 Hz, 1H), 3.36 (br s, 2H), 3.15 (dd, J = 15.8, 9.2 Hz, 1H), 2.89 (dd, J = 15.8, 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 129.6, 127.9, 125.3, 120.3, 111.10, 65.4, 60.9, 32.3.

Compound 1b, (*S*)-Allyl 2-(hydroxymethyl)indoline-1-carboxylate.



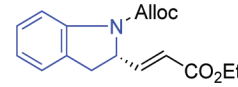
To a solution of the alcohol **2** (0.74 g, 4.90 mmol) in dichloromethane (69 mL) at −78 °C was added DIPEA (0.86 g, 1.15 mL, 4.90 mmol), followed by the addition of allylchloroformate (0.59 g, 0.52 mL, 4.90 mmol). The reaction mixture was stirred at −78 °C under N_2 for 2 h. The reaction mixture was quenched by addition of saturated ammonium chloride solution (25 mL), and then it was extracted with dichloromethane and ethyl acetate. The combined organic layers were washed with brine and dried over magnesium sulfate, filtered, and purified by flash chromatography. Elution with hexane/ethyl acetate (3:1 v/v) gave 1.14 g (99%) of product as a light yellow oil: MS (ES+) *m/z* (M + 1) 234.0; HRMS (FAB) *m/z* (M^+) calcd 233.11 for $C_{13}H_{15}NO_3$, obsd 233.113; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (br s, 1H), 7.22−7.18 (m, 2H), 7.01 (dd, J = 7.4, 7.3 Hz, 1H), 6.09−6.00 (m, 1H), 5.42 (d, J = 17.2 Hz, 1H), 5.32 (d, J = 10.4 Hz, 1H), 4.79 (d, J = 4.2 Hz, 2H), 4.66 (br s, 1H), 3.81 (dd, J = 11.1, 5.9 Hz, 1H), 3.75 (dd, J = 11.2, 5.0 Hz, 1H), 3.38 (dd, J = 16.4, 10.1 Hz, 1H), 2.93 (br s, 1H), 2.54 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 142.1, 132.7, 130.5, 127.9, 125.2, 123.5, 118.8, 116.1, 67.0, 65.8, 61.5, 31.7.

Compound 1c, (*S*)-Allyl 2-formylindoline-1-carboxylate.



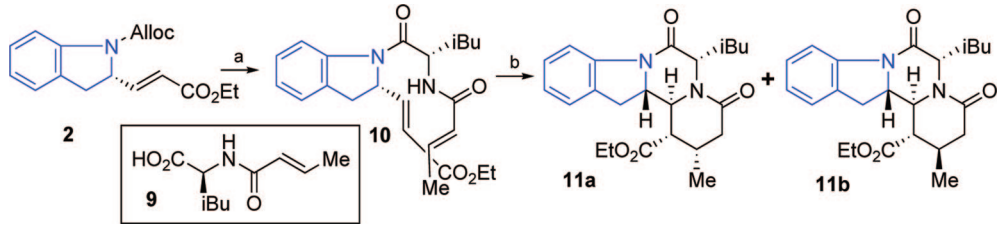
To a solution of the indoline alcohol **3** (3.80 g, 16.31 mmol) in dichloromethane (178 mL) was added DMSO (45 mL), followed by Et_3N (11.4 mL, 81.55 mmol) and then $SO_3 \cdot Py$ (10.38 g, 65.24 mmol), in that specific order. The reaction mixture was stirred at room temperature under N_2 for 3 h. The reaction mixture was quenched by addition of a saturated ammonium chloride solution, and then it was extracted with dichloromethane and ethyl acetate. The combined organic layers were washed with brine and dried over magnesium sulfate, filtered, and purified by flash chromatography. Elution with hexane/ethyl acetate (3:1 v/v) gave 3.18 g (84%) of product as a light yellow oil: MS (ES+) *m/z* (M + 1) 232.0; HRMS (FAB) *m/z* (M^+) calcd 232.10 for $C_{13}H_{13}NO_3$, obsd 232.0985; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (s, 1H), 7.96 (br s, 1H), 7.28−7.26 (m, 1H), 7.18 (d, J = 7.4 Hz, 1H), 7.02 (dd, J = 7.4, 7.3, 1H), 5.96 (br s, 1H), 5.44−5.30 (m, 2H), 4.87−4.75 (m, 3H), 3.46−3.44 (m, 1H), 3.22 (dd, J = 16.6, 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.2, 153.0, 142.5, 132.4, 130.5, 128.6, 125.1, 123.8, 119.1, 115.5, 66.9, 66.3, 30.3.

Compound 2, (*S,E*)-Allyl 2-(3-ethoxy-3-oxoprop-1-enyl)indoline-1-carboxylate.



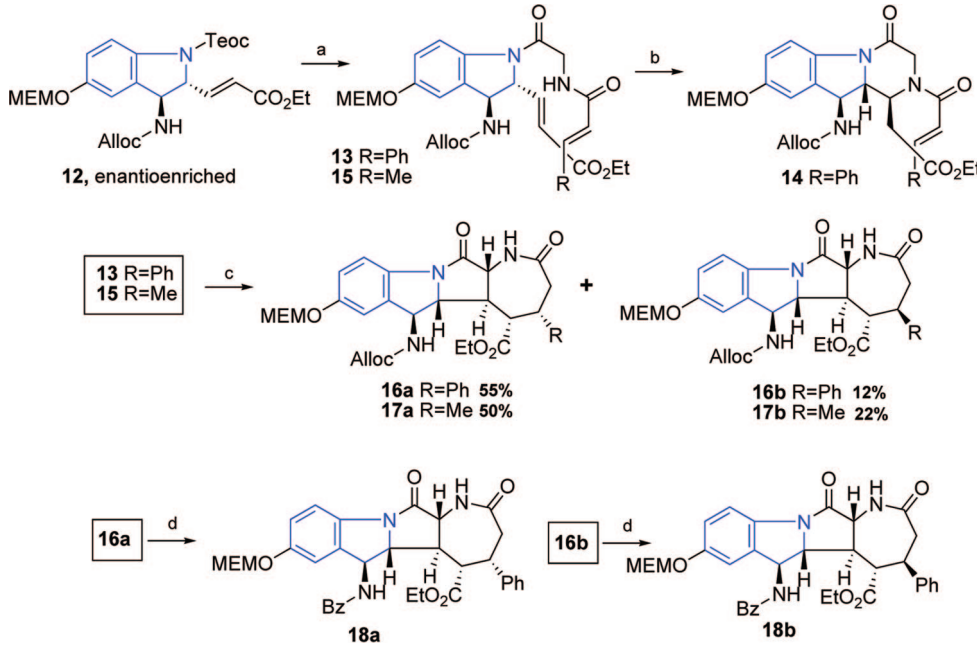
To a solution of the indoline aldehyde **4** (3.17 g, 13.71 mmol) in dichloromethane (102 mL) was added the Wittig reagent, (carbethoxymethylene) triphenylphosphorane (5.75 g, 16.51 mmol). The reaction mixture was stirred at RT, under N_2 for 2 h 20 min. The reaction mixture was quenched by adding brine, and then it was extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered, and purified by flash chromatography. Elution with hexane/ethyl acetate (9:1 v/v) gave 3.84 g (95%) of the trans product and 0.089 g of the cis product. The trans product **2** was a yellow oil: MS (ES+) *m/z* (M + 1) 302.2; HRMS

Scheme 3. Tandem Michael Reaction with the Substituted Amino Acid Derivative[a]



[a] Reagents and conditions: (a) (i) $Pd(Ph_3)_4$, morpholine, 90% (ii) **9**, PyBroP, DMAP, DIPEA, 52%; (b) TMSOTf, Et_3N, 37%.

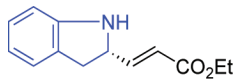
Scheme 4. Tandem Michael Reaction with an Aminoindoline Scaffold[a]



[a] Reagents and conditions: (a) (i) TBAF, 87% (ii) **3**, HATU, DIPEA, 58%; (b) TBSOTf, Et_3N, 76%; (c) TMSOTf, Et_3N, 67−72%; (d) (i) $Pd(Ph_3)_4$, morpholine (ii) BzCl, Et_3N, 67−70% for 2 steps.

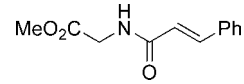
(FAB) *m/z* (M^+) calcd 301.13 for $C_{17}H_{19}NO_4$, obsd 301.14; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (br s, 1H), 7.23 (dd, J = 7.8, 7.5 Hz, 1H), 7.16 (d, J = 7.4 Hz, 1H), 7.00 (dd, J = 7.5, 7.4 Hz, 1H), 6.90 (dd, J = 15.6, 6.4 1H), 5.97 (br s, 1H), 5.91 (d, J = 15.6 Hz, 1H), 5.36 (d, J = 17.0 Hz 1H), 5.27 (d, J = 10.3 Hz, 1H), 5.12 (br s, 1H), 4.73 (br s, 2H), 4.17 (q, J = 7.1 Hz, 2 H), 3.50 (dd, J = 16.1, 10.4 Hz, 1H), 2.88 (dd, J = 16.2, 2.0 Hz, 1H), 1.27 (t, J = 7.1, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 153.0, 146.4, 142.5, 132.7, 129.2, 128.3, 125.4, 123.7, 121.5, 118.7, 115.8, 66.7, 60.9, 59.8, 34.6, 14.6.

Compound 2a, (*S*,*E*)-Ethyl 3-(indolin-2-yl)acrylate.



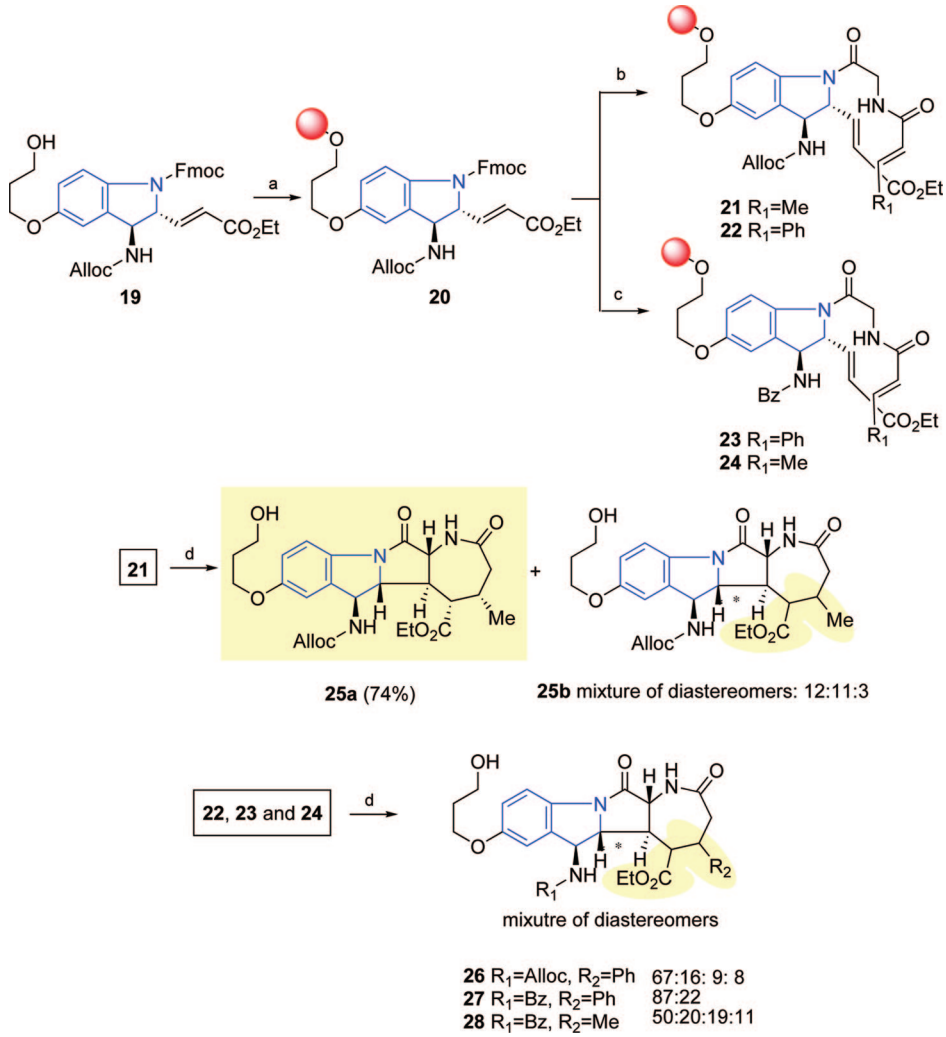
To a solution of the alloc indoline core **2** (1.03 g, 3.40 mmol) in dichloromethane (71 mL) at 0 °C was added $Pd(Ph_3)_4$ (0.39 g, 0.34 mmol), followed by morpholine (0.62 mL, 7.14 mmol). The reaction mixture was stirred from 0 °C to room temperature under N_2 for 4 h. The reaction solution was evaporated under vacuum pressure then purified by flash chromatography. Elution with hexane/ethyl acetate (9:1 v/v) gave 0.67 (90%) of product as a yellow oil: MS (ES+) *m/z* (M + 1) 218.1; HRMS (FAB) *m/z* (M^+) calcd 211.11 for $C_{13}H_{15}NO_2$, obsd 217.1116; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12−7.03 (m, 3H), 6.76 (dd, J = 7.4, 7.4 Hz, 1H), 6.67 (d, J = 7.8, Hz, 1H), 6.05 (d, J = 15.6 Hz, 1H), 4.54−4.48 (m, 1H), 4.23 (q, J = 7.2 Hz, 2H), 3.90 (br s, 1H), 3.31 (dd, J = 15.5, 9.2 Hz, 1H), 2.88 (dd, J = 15.5, 7.8 Hz, 1H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 150.5, 149.2, 134.9, 128.1, 125.1, 121.5, 119.6, 109.9, 60.9, 60.6, 36.5, 14.7.

Compound 3a, Methyl 2-cinnamamidoacetate.



To a solution of Gly−OMe HCl (1.31 g, 10.36 mmol) in dichloromethane (57 mL) was added DIPEA (3.51 mL, 20.72 mmol). The reaction mixture was stirred under N_2 for 15 min at room temperature. To this reaction mixture was added cinnamoyl-chloride (2.07 g, 12.43 mmol). The reaction mixture was stirred under N_2 for 1:25 h at RT. The reaction mixture was extracted with dichloromethane. The combined organic layers were washed with brine then dried over magnesium sulfate, filtered, and purified by flash chromatography. Elution with 3:10 ethyl acetate/hexane gave 1.75 g

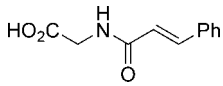
Scheme 5. Manual Solid-Phase Synthesis[a]



[a] Reagents and conditions: (a) alkylsilyl macrobeads (loading 0.99 mmol/g, 500−560μm), 95%; (b) (i) morpholine (ii) glycine acids, HATU, DIPEA; (c) (i) $Pd(PPh_3)_4$, PPh_3, 4-NMM, CH_3CO_2H, (ii) BzCl, 2,4,6-collidine, (iii) repeat b; (d) (i) TMSOTf, Et_3N (ii) HF-pyridine.

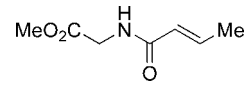
(77%) of product as a yellow oil: MS (ES+) *m/z* (M + 1) 220.1; HRMS (FAB) *m/z* (MH^+) calcd 220.10 for $C_{12}H_{14}NO_3$, obsd 220.1303; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 15.6 Hz, 1H), 7.55−7.52 (m, 2H), 7.38−7.41 (m, 3H), 6.49 (d, J = 15.6 Hz, 1H), 6.19 (br s, 1H), 4.22 (d, J = 5.1 Hz, 2H), 3.82 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 166.2, 142.3, 135.0, 130.3, 129.3, 128.3, 120.1, 52.9, 41.2.

Compound 3, 2-Cinnamamidoacetic Acid.



To a solution of the peptide ester (0.10 g, 0.47 mmol) in 8:2:1 THF/water/MeOH (10 mL) at 0 °C was added LiOH (0.039 g, 0.93 mmol). The reaction mixture was stirred at 0 °C to room temperature under N_2 for 3 h. The reaction mixture was neutralized with Amberlite H^+ resin to pH 6 and then evaporated by vacuum pressure to give 0.10 g (99%) of product as a white solid: MS (ES+) *m/z* (M + 1) 206.1; HRMS (FAB) *m/z* (MH^+) calcd 206.08 for $C_{11}H_{12}NO_3$, obsd 206.087; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.63−7.57 (m, 3H), 7.44−7.37 (m, 3H), 6.82 (d, J = 15.7 Hz, 1H), 4.11 (d, J = 5.0 Hz, 2H), 2.83 (br s, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 172.4, 167.3, 141.9, 137.1, 131.3, 130.7, 129.5, 123.2, 42.6.

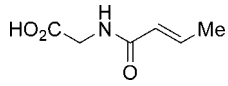
Compound 3b, (*E*)-Methyl 2-but-2-enamidoacetate.



To a solution of Gly-OMe HCl (4.01 g, 31.62 mmol) in dichloromethane (150 mL) was added DIPEA (11.00 mL, 63.24 mmol). The reaction mixture was stirred under N_2 for 15 min at room temperature. To this reaction mixture was added crotonyl chloride 90% (4.07 mL, 42.06 mmol). The reaction mixture was stirred under N_2 for 2 h at RT. The reaction was extracted with dichloromethane. The combined organic layers were washed with brine, then dried over magnesium sulfate, filtered, and purified by flash chroma-

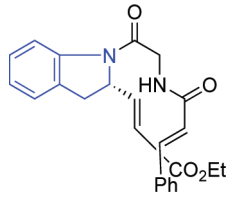
tography. Elution with 3:10 ethyl acetate/hexane gave 4.60 g (93%) of product as a yellow oil: MS (ES+) *m/z* (M + 1) 158.0; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (dq, J = 15.3, 7.0 Hz, 1H), 6.22 (br s, 1H), 5.86 (dq, J = 15.3, 1.8 Hz, 1H), 4.08 (d, J = 5.3 Hz, 2H), 3.74 (s, 3H), 1.84 (dd, J = 6.8, 1.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 166.0, 140.9, 124.2, 52.3, 41.1, 17.7.

Compound 3c, (*E*)-2-But-2-enamidoacetic Acid.



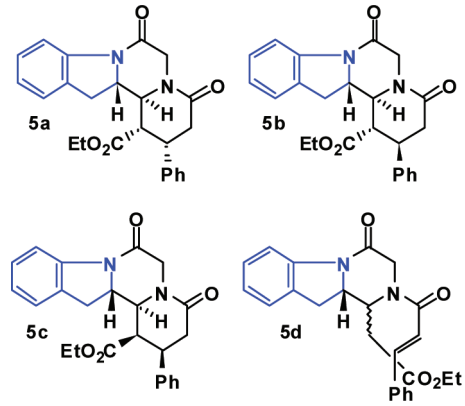
To a solution of the peptide ester (2.11 g, 13.41 mmol) in 8:2:1 THF/water/MeOH (125 mL) at 0 °C was added LiOH (1.15 g, 26.82 mmol). The reaction mixture was stirred at 0 °C to room temperature under N_2 for 3 h. The reaction was neutralized with Amberlite H^+ resin to pH 6 and then evaporated by vacuum pressure to give 1.78 g (90%) of product as an off-white solid: MS (ES+) *m/z* (M + 1) 144.0; ^{1}H NMR (400 MHz, DMSO) δ 12.54 (br s, 1H), 8.21(t, J = 5.5 Hz, 1H), 6.64 (dq, J = 15.3, 7.0 Hz, 1H), 5.97 (dq, J = 15.3, 1.8 Hz, 1H), 3.80 (d, J = 5.7 Hz, 2H), 1.80 (dd, J = 7.0, 1.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO) δ 171.3, 165.1, 138.3, 125.3, 40.5, 17.3.

Compound 4, (*E*)-Ethyl 3-((*S*)-1-(2-cinnamamidoacetyl)-indolin-2-yl)acrylate.



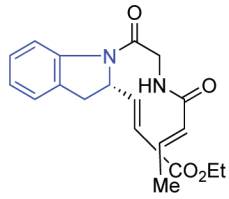
To a solution of the glycine-cinnamoyl acid (2.50 g, 12.21 mmol) in DMF (106 mL) was added HATU (4.64 g, 12.21 mmol), followed by the addition of DIPEA (2.13 mL, 12.21 mmol) and then the deprotected indoline core **2a** (0.53 g, 2.44 mmol). The reaction mixture was stirred at room temperature under N_2 for 48 h. The reaction mixture was condensed and washed with ammonium chloride then extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, and purified by flash chromatography. Elution with hexane/ethyl acetate (5:2 v/v) gave 0.79 g (81%) of product as a light orange solid: MS (ES+) *m/z* (M + 1) 405.1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 15.7 Hz, 1H), 7.55−7.49 (m, 2H), 7.43−7.33 (m, 3H), 7.32−7.24 (m, 1H), 7.21 (d, J = 7.3 Hz, 1H), 7.11 (t, J = 7.3 Hz, 1H), 6.92 (dd, J = 15.7, 5.9 Hz, 1H), 6.75 (br s, 1H), 6.52 (d, J = 15.7 Hz, 1H), 5.92 (d, J = 15.7 Hz, 1H), 5.14−5.06 (m, 1H), 4.47 (dd, J = 17.9, 4.4 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 4.07 (dd, J = 17.9, 3.2 Hz, 1H), 3.63 (dd, J = 15.9, 10.0 Hz, 1H), 2.95 (d, J = 15.9 Hz, 1H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 166.2, 165.9, 145.0, 142.0, 135.1, 130.3, 129.5, 129.3, 129.2, 128.5, 128.3, 125.54, 125.52, 122.2, 120.4, 117.9, 61.4, 59.4, 43.2, 35.8, 14.6.

Compounds 5a−5d.



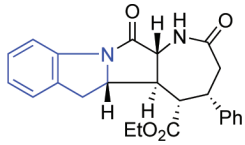
To a solution of the glycine−cinnamoyl-coupled indoline moiety (0.20 g, 0.49 mmol) in DCM (10 mL) at −78 °C was added Et_3N (0.076 mL, 0.54 mmol), followed by the addition of TBSOTf (0.23 mL, 0.99 mmol). The reaction mixture was allowed to warm to room temperature as it was stirred under an argon atmosphere for 24 h. The reaction mixture was quenched with a saturated solution of $NaHCO_3$ and then extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, and purified by flash chromatography. Elution with hexane/ethyl acetate (9:1 v/v) gave 25.6 (20%), 25.7 (20%), 10.3 (8%), and 25.6 mg (20%) of products **5a**−**5d**, respectively, as an off-white solid: MS (ES+) *m/z* (M + 1) 405.1; ^{1}H NMR (compound **5a**; 400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.0 Hz, 1H), 7.39−7.22 (m, 5H), 7.16−7.08 (m, 3H), 5.29 (d, J = 18.8 Hz, 1H), 4.48−4.39 (m, 1H), 4.11 (dd, J = 10.3, 4.0 Hz, 1H), 4.03 (q, J = 7.0 Hz, 2H), 3.84 (d, J = 18.8 Hz, 1H), 3.64−3.57 (m, 1H), 3.21−3.10 (m, 3H), 3.05 (dd, J = 15.1, 11.3 Hz, 1H), 2.81 (dd, J = 17.3, 5.0 Hz, 1H), 1.05 (t, J = 7.0 Hz, 3H); ^{13}C NMR (compound **5a**; 100 MHz, $CDCl_3$) δ 170.4, 167.6, 162.9, 141.8, 138.6, 128.9, 128.8, 128.1, 127.8, 127.2, 125.0, 124.5, 117.6, 64.0, 61.4, 58.2, 46.3, 46.2, 37.7, 34.0, 32.9, 13.8; ^{1}H NMR (compound **5b**; 400 MHz, C_6D_6) δ 8.55 (d, J = 8.0 Hz, 1H), 7.19−6.98 (m, 4H), 6.92−6.78 (m, 4H), 5.36 (d, J = 19.1 Hz, 1H), 3.68 (d, J = 19.1 Hz, 1H), 3.61−3.43 (m, 3H), 3.56 (dd, J = 10.0 Hz, J = 9.0 Hz, 1H), 3.60−3.53 (m, 2H), 3.13 (ddd, J = 12.5 Hz, J = 10.0 Hz, J = 8.0 Hz, 1H), 2.73 (td, J = 12.5 Hz, J = 3.0 Hz, 1H), 2.56 (dd, J = 15.1, 8.0 Hz, 1H), 2.50 (dd, J = 16.1, 3.0 Hz, 1H), 2.40 (dd, J = 15.1, J = 12.5 Hz, 1H), 2.32−2.21 (m, 2H), 0.52 (t, J = 7.0 Hz, 3H); ^{13}C NMR (compound **5b**; 100 MHz, C_6D_6) δ 171.2, 166.2, 162.3, 142.4, 139.9, 129.4, 128.7, 128.1, 127.9, 124.6, 124.3, 117.6, 64.9, 60.7, 59.0, 51.1, 46.2, 41.4, 38.7, 32.2, 13.5; ^{1}H NMR (compound **5c**; 400 MHz, $CDCl_3$) δ 8.12 (d, J = 8.0 Hz, 1H), 7.40−7.19 (m, 7H), 7.09 (t, J = 7.4 Hz, 1H), 4.53 (d, J = 19.2 Hz, 1H), 4.34 (d, J = 19.2 Hz, 1H), 4.35−4.26 (m, 1H), 4.07−3.98 (m, 3H), 3.55−3.47 (m, 1H), 3.39 (dd, J = 17.1, 13.6 Hz, 1H), 3.30 (dd, J = 4.0, 4.0 Hz, 1H), 3.25 (dd, J = 15.6, 8.5 Hz, 1H), 3.07 (dd, J = 15.5, 10.1 Hz, 1H), 2.79 (dd, J = 17.1, 5.2 Hz, 1H), 1.05 (t, J = 7.1 Hz, 3H); ^{13}C NMR (compound **5c**; 100 MHz, $CDCl_3$) δ 169.3, 168.7, 162.7, 141.3, 139.0, 128.9, 128.7, 128.3, 127.8, 126.9, 124.9, 124.6, 116.8, 61.1, 60.4, 60.3, 47.3, 46.1, 39.6, 33.1, 32.4, 14.0.

Compound 6, (*E*)-Ethyl 3-((*S*)-1-(2-(*E*)-but-2-enamidoacetyl)indolin-2-yl)acrylate.



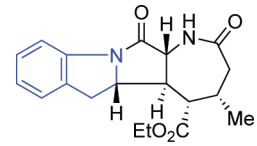
To a solution of the glycine-crotyl acid (0.54 g, 3.7421 mmol) in DMF (160 mL) was added HATU (1.42 g, 3.74 mmol), followed by the addition of DIPEA (0.65 mL, 3.74 mmol) and then the deprotected indoline core **2a** (0.16 g, 0.75 mmol). The reaction mixture was stirred at room temperature under N_2 for 24 h. The reaction mixture was condensed, washed with ammonium chloride, and then extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, and purified by flash chromatography. Elution with hexane/ethyl acetate (5:2 v/v) gave 0.21 g (83%) of product as a light yellow oil: MS (ES+) *m/z* (M + 1) 343.1; ^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.15 (d, J = 8.0 Hz, 1H), 7.26 (t, J = 8.0 Hz, 1H), 7.20 (d, J = 7.2 Hz, 1H), 7.10 (t, J = 7.3 Hz, 1H), 6.96−6.85 (m, 2H), 6.74 (br s, 1H), 5.94 (d, J = 15.1 Hz, 1H), 5.90 (d, J = 15.1 Hz, 1H), 5.09 (br t, 1H), 4.40 (d, J = 17.8 Hz, 1H), 4.12 (q, J = 7.0 Hz, 2H), 4.00 (d, J = 17.8 Hz, 1H), 3.61 (dd, J = 15.8, 10.0 Hz, 1H), 2.93 (d, J = 16.0 Hz, 1H), 1.88 (d, J = 6.8 Hz, 3H), 1.25 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 165.9, 165.4, 144.6, 141.5, 140.5, 128.7, 128.0, 125.0, 124.9, 124.4, 121.7, 117.4, 60.3, 58.9, 42.5, 35.3, 17.7, 14.1.

Compound 7.



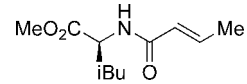
To a solution of the glycine−cinnamoyl-coupled indoline moiety **4** (0.11 g, 0.25 mmol) in DCM (5 mL) at −78 °C was added Et_3N (0.140 mL, 0.99mmol), followed by the addition of TMSOTf (0.18 mL, 0.99 mmol). The reaction mixture was allowed to warm to room temperature as it was stirred under an argon atmosphere for 4 h. The reaction mixture was quenched with brine and then extracted with DCM and ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, and purified by flash chromatography. Elution with hexane/ethyl acetate (4:1 v/v) gave 0.095 g (91%) of product as white needles. Stereochemistry was confirmed by crystal X-ray structure: MS (ES+) *m/z* (M + 1) 405.1; ^{1}H NMR: (400 MHz, acetone-d_6) δ 7.48 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 7.3 Hz, 2H), 7.30−7.20 (m, 5H), 7.06 (t, J = 7.5 Hz, 1H), 6.32 (br s, 1H), 4.78 (d, J = 10.8 Hz, 1H), 4.43 (q, J = 8.8 Hz, 1H), 3.98−3.87 (m, 2H) 3.84−3.77 (m, 1H), 3.43 (dd, J = 11.5, 5.5 Hz, 1H), 3.24 (ddd, J = 11.2, 11.1, 8.8 Hz, 1H), 3.18−2.94 (m, 4H), 1.04 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 173.7, 173.4, 169.2, 142.2, 140.8, 136.5, 130.9, 130.2, 129.2, 129.0, 127.4, 126.5, 116.7, 66.2, 62.2, 60.8, 55.2, 52.1, 44.3, 42.6, 37.2, 15.3; carbon displacements for 62.2, 42.6, and 37.2 are CH_2 carbons, determined by DEPT 135 analysis.

Compound 8.



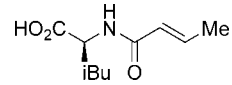
To a solution of the glycine−crotyl-coupled indoline moiety 6 (0.077 g, 0.23 mmol) in DCM (5 mL) at −78 °C was added Et_3N (0.16 mL, 1.17 mmol), followed by the addition of TMSOTf (0.22 mL, 1.17 mmol). The reaction mixture was allowed to warm to room temperature as it was stirred under argon atmosphere for 1 h. The reaction mixture was quenched with brine then extracted with DCM and ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, and purified by flash chromatography. Elution with hexane/ethyl acetate (4:1 v/v) gave 0.062 g (80%) of product as an off-white solid; MS (ES+) *m/z* (M + 1) 343.1; ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.51 (d, J = 7.9 Hz, 1H), 7.20 (t, J = 7.8 Hz, 1H), 7.14 (d, J = 7.3 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 6.54 (br s, 1H), 4.28 (dd, J = 10.5, 3.0 Hz, 1H), 4.24−4.15 (m, 3H) 3.21 (dd, J = 16.3, 9.3 Hz, 1H), 3.09 (dd, J = 16.3, 8.8 Hz, 1H), 2.89 (dd, J = 11.3, 3.0 Hz, 1H), 2.82−2.53 (m, 4H), 1.30 (t, J = 7.0 Hz, 3H), 1.03 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 172.0, 166.2, 137.9, 134.0, 127.7, 125.2, 125.1, 115.1, 63.8, 61.0, 59.8, 53.5, 48.1, 42.7, 35.8, 30.0, 14.2, 13.5.

Compound 9a, (*S*,*E*)-Methyl 2-but-2-enamido-4-methylpentanoate.



To a solution of Leu-OMe HCl (4.02 g, 22.01 mmol) in DCM (400 mL) was added DIPEA (7.67 mL, 44.03 mmol). The reaction mixture was stirred under N_2 for 15 min at room temperature. To this reaction mixture was added crotonyl chloride 90% (2.84 mL, 26.42 mmol). The reaction mixture was stirred under N_2 for 2 h at RT. The reaction mixture was extracted with DCM. The combined organic layers were washed with brine, then dried over magnesium sulfate, filtered, and purified by flash chromatography. Elution with 1:5 ethyl acetate/hexane gave 4.08 g (87%) of product as a clear oil: MS (ES+) *m/z* (M + 1) 214.2; ^{1}H NMR (400 MHz, C_6D_6) δ 6.99 (dq, J = 15.1, 7.0 Hz, 1H), 6.67 (d, J = 8.0 Hz, 1H), 5.75 (dq, J = 15.3, 1.5 Hz, 1H), 4.99 (ddd, J = 9.3, 8.3, 5.0 Hz, 1H), 3.31 (s, 3H), 1.76−1.51 (m, 3H), 1.48 (dd, J = 6.8, 1.5 Hz, 3H), 0.89 (d, J = 6.3 Hz, 3H), 0.85 (d, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 165.6, 140.0, 125.5, 51.7, 50.9, 41.8, 25.1, 23.0, 17.5.

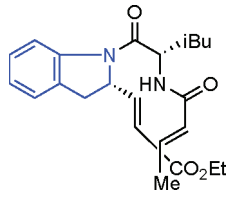
Compound 9, (*S*,*E*)-2-But-2-enamido-4-methylpentanoic Acid.



To a solution of the peptide ester (4.00 g, 18.76 mmol) in

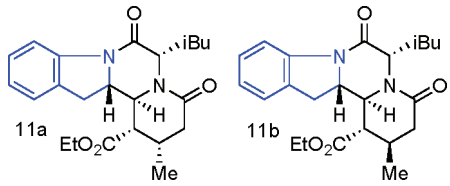
8:2:1 THF/water/MeOH (82 mL) at 0 °C, was added LiOH (1.57 g, 37.51 mmol). The reaction mixture was stirred at 0 °C to room temperature under N_2 for 3 h. The reaction was neutralized with Amberlite H^+ resin to pH 6 and then evaporated by vacuum pressure to give 3.84 g(quantitative yield) of the crude product as a very viscous clear oil solid: MS (ES+) *m/z* (M + 1) 200.3; ^{1}H NMR (400 MHz, DMSO) δ 7.63 (d, J = 7.8 Hz, 1H), 6.55 (dq, J = 15.3, 7.0 Hz, 1H), 5.99 (d, J = 15.3 Hz, 1H), 4.13−4.06 (m, 1H), 1.77 (d, J = 6.8 Hz, 3H), 1.63−1.35 (m, 3H), 0.84 (t, J = 6.3 Hz, 6H); ^{13}C NMR (100 MHz, DMSO) δ 175.4, 165.0, 137.9, 127.9, 127.3, 52.8, 42.7, 25.4, 24.1, 22.8, 17.3.

Compound 10, (*E*)-Ethyl 3-((*S*)-1-((*S*)-2-((*E*)-but-2-enamido)-4-methylpentanoyl)indolin-2-yl)acrylate.



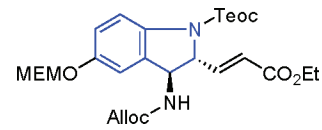
To a solution of the leucine−crotyl acid (0.92 g, 4.60 mmol) in DMF (25 mL) was added PyBrop (2.15 g, 4.60 mmol), followed by the addition of DMAP (0.56 g, 4.60 mmol), DIPEA (1.00 mL, 5.74 mmol), and then the deprotected indoline core **2a** (0.20 g, 0.92 mmol). The reaction mixture was stirred at room temperature under N_2 for 4.5 h. The reaction mixture was condensed, washed with ammonium chloride, and then extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, and purified by flash chromatography. Elution with hexane/ethyl acetate (5:2 v/v) gave 0.19 g (52%) of product as a clear viscous oil: MS (ES+) *m/z* (M + 1) 399.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 8.0 Hz, 1H), 7.25 (t, J = 8.3 Hz, 1H), 7.19 (d, J = 7.5 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 6.89 (dd, J = 15.8, 5.5 Hz, 1H), 6.80 (dq, J = 15.1, 7.0 Hz, 1H), 6.20 (d, J = 8.5 Hz, 1H), 5.86 (d, J = 15.8 Hz, 1H), 5.81 (d, J = 15.3 Hz, 1H), 5.08 (dd, J = 9.8, 5.5 Hz, 1H), 4.91 (ddd, J = 9.2, 9.1, 3.8 Hz, 1H), 4.16−4.05 (m, 2H), 3.59 (dd, J = 15.8, 9.8 Hz, 1H), 2.95 (d, J = 15.8 Hz, 1H) 1.83 (d, J = 6.8 Hz, 3H), 1.77−1.60 (m, 2H), 1.58−1.50 (m, 1H) 1.23 (t, J = 7.0 Hz, 3H) 1.04 (d, J = 6.3 Hz, 3H), 0.93 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 165.5, 164.9, 144.3, 141.7, 140.3, 129.1, 128.0, 125.0, 124.9, 124.8, 122.0, 117.8, 60.7, 59.4, 49.6, 44.0, 35.1, 24.8, 23.5, 22.1, 17.7, 14.1.

Compounds 11a and 11b.



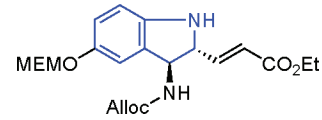
To a solution of the leucine−crotyl-coupled indoline moiety **10** (0.18 g, 0.46 mmol) in DCM (5 mL) at −78 °C was added Et_3N (0.51 mL, 3.65 mmol), followed by the addition of TMSOTf (0.66 mL, 3.65 mmol). The reaction mixture was allowed to warm to room temperature as it was stirred under argon atmosphere for 22 h. The reaction mixture was quenched with brine and then extracted with DCM and ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, and purified by flash chromatography. Elution with hexane/ethyl acetate (9:1 v/v) gave 0.048 (27%) and 0.018 g (10%) of products **11a** and **11b**, respectively, as off-white solids: MS (ES+) *m/z* (M + 1) 399.4; ^{1}H NMR (compound **11a**; 400 MHz, C_6D_6) δ 8.55 (d, J = 8.0 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 6.90 (t, J = 7.5 Hz, 1H), 6.85 (d, J = 7.5 Hz, 1H), 5.84 (dd, J = 10.0, 3.8 Hz, 1H), 3.85 (q, J = 7.0 Hz, 2H), 3.82 (dd, J = 10.5, 4.0 Hz, 1H), 3.12 (ddd, J = 11.0, 10.8, 8.0 Hz, 1H), 2.37 (dd, J = 17.1, 8.8 Hz, 1H), 2.23 (dd, J = 17.1, 5.0 Hz, 1H), 2.23−2.15 (m, 2H), 2.07 (dd, J = 9.8, 3.8 Hz, 1H), 2.10−1.94 (m, 3H), 1.80−1.71 (m, 1H), 1.70−1.61 (m, 1H), 1.23 (d, J = 6.3 Hz, 3H), 0.99 (d, J = 6.5 Hz, 3H) 0.89 (t, J = 7.0 Hz, 3H), 0.81 (d, J = 7.0 Hz, 3H); ^{13}C NMR (compound **11a**; 100 MHz, C_6D_6) δ 170.7, 166.5, 166.1, 143.3, 129.6, 128.1, 124.4, 124.3, 118.1, 64.2, 61.0, 54.1, 53.6, 45.1, 41.9, 37.6, 32.3, 27.0, 25.2, 23.7, 22.2, 17.2, 14.2 ppm; ^{1}H NMR (compound **11b**; 400 MHz, C_6D_6) δ 8.54 (d, J = 8.0 Hz, 1H), 7.13−7.06 (m, 1H), 6.90−6.82 (m, 2H), 5.82 (dd, J = 9.5, 4.8 Hz, 1H), 3.94 (dd, J = 9.5, 8.8 Hz, 1H), 3.84 (q, J = 7.0 Hz, 2H), 3.05−2.95 (m, 1H), 2.50 (dd, J = 14.7, 7.4 Hz, 1H), 2.38−2.28 (m, 2H), 2.07 (ddd, J = 13.8, 8.5, 5.0 Hz, 1H), 1.96−1.78 (m, 2H), 1.75−1.58 (m, 3H), 1.15 (d, J = 6.5 Hz, 3H), 1.02 (d, J = 6.5 Hz, 3H), 0.88 (t, J = 7.0 Hz, 3H), 0.61 (d J = 6.3 Hz, 3H); ^{13}C NMR (compound **11b**; 100 MHz, C_6D_6) δ 172.4, 167.0, 166.3, 143.0, 129.5, 128.1, 124.44, 124.38, 117.9, 66.0, 61.1, 55.7, 53.0, 51.2, 42.0, 39.7, 32.3, 30.1, 25.4, 23.5, 22.5, 18.6, 14.1.

Compound 12, (2*R*,3*S*)-2-(Trimethylsilyl)ethyl 3-(allyloxycarbonylamino)-2-((E)-3-ethoxy-3-oxoprop-1-enyl)-5-((2-methoxyethoxy)methoxy)indoline-1-carboxylate.



The synthetic procedure was already described:[4] yellow oil; MS (ES+) *m/z* (M + 1) 565.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (bs, 1H), 7.07−7.05 (m, 2H), 6.95 (dd, J = 15.6, 5.7 Hz, 1H), 5.98−5.89 (m, 2H), 5.33 (d, J = 17.2 Hz, 1H), 5.25 (d, J = 15.3 Hz, 1H), 5.23 (s, 2H), 5.06 (d, J = 6.7 Hz, 1H), 4.92 (bs, 1H), 4.84 (d, J = 6.7 Hz, 1H), 4.62 (bs, 2H), 4.30 (bs, 2H), 4.18 (q, J = 7.1 Hz, 2H), 3.83 (t, J = 4.6 Hz, 2H), 3.58 (t, J = 4.6 Hz, 2H), 3.39 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.07 (bs, 2H), 0.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 155.6, 154.2, 144.2, 132.8, 122.6, 119.3, 118.5, 117.0, 114.4, 94.5, 72.0, 68.3, 68.1, 66.4, 64.8, 61.0, 59.4, 57.2, 18.2, 14.6, −1.1.

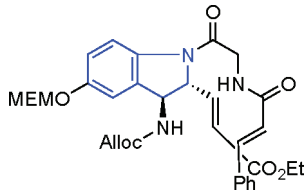
Compound 12a, (*E*)-Ethyl-3-((2*R*,3*S*)-3-(allyloxycarbonylamino)-5-((2-methoxyethoxy)methoxy)indolin-2-yl)acrylate.



The synthetic procedure was already described:[4] dark yellow oil; MS (ES+) *m/z* (M + 1) 421.3; ^{1}H NMR (400 MHz, $CDCl_3$)

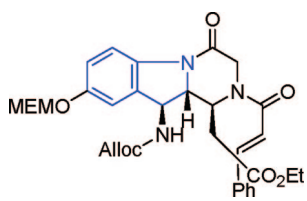
δ 6.98 (dd, J = 15.6, 6.7 Hz, 1H), 6.92 (d, J = 2.1 Hz, 1H), 6.85 (dd, J = 2.1, 8.5 Hz, 1H), 6.56 (d, J = 8.5 Hz, 1H), 6.05 (d, J = 15.6 Hz, 1H), 5.92 (m, 1H), 5.39 (d, J = 8.3 Hz, 1H), 5.31 (d, J = 15.6 Hz, 1H), 5.22 (d, J = 10.7 Hz, 1H), 5.14 (s, 2H), 4.98 (t, J = 6.8 Hz, 1H), 4.59 (d, J = 5.3 Hz, 1H), 4.20−4.14 (m, 3H), 3.81 (t, J = 4.6 Hz, 2 H), 3.56 (t, J = 4.6 Hz, 2H), 3.37 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 156.0, 151.7, 147.0, 145.1, 133.0, 128.3, 122.6, 119.0, 118.3, 114.5, 111.3, 95.1, 72.0, 68.5, 67.9, 66.2, 60.9, 59.5, 59.4, 14.6.

Compound 13, (*E*)-Ethyl-3-((2*R*,3*S*)-3-(allyloxycarbonylamino)-1-(2-cinnamamidoacetyl)-5-((2-methoxyethoxy)methoxy)indolin-2-yl)acrylate.



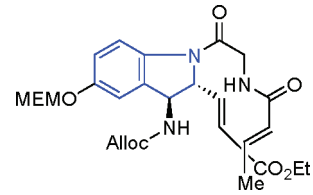
To a stirred solution of glycine cinnamic acid (255 mg, 1.24 mmol) in dry DMF (10 mL) was added HATU (473 mg, 1.24 mmol), followed by DIPEA (217 μL, 1.24 mmol). To the reaction mixture was added the above secondary amine (105 mg, 0.25 mmol), and the mixture was stirred for 72 h under argon atmosphere. The solution was condensed and dissolved in ethyl acetate, then washed with a saturated NH_4Cl solution, dried over sodium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography (1:5 ethyl acetate/hexanes) to give the coupled product (90.2 mg, 60%) as a dark yellow mousse: MS (ES+) m/z (M + 1) 608.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 9.3 Hz, 1H), 7.63 (d, J = 15.8 Hz, 1H), 7.54−7.49 (m, 2H), 7.41−7.34 (m, 3H), 7.13−7.06 (m, 2H), 6.97 (dd, J = 15.5, 4.5 Hz, 1H), 6.68 (br s, 1H), 6.51 (d, J = 15.6 Hz, 1H), 5.98 (d, J = 15.8 Hz, 1H), 5.98−5.87 (m, 1H), 5.38−5.20 (m, 5H), 4.96 (br d, J = 4.8, 0.0 Hz, 1H), 4.86 (br d, J = 5.8, 0.0 Hz, 1H), 4.67−4.58 (m, 2H), 4.45 (dd, J = 17.8, 4.3 Hz, 1H), 4.16 (q, J = 7.0 Hz, 2H), 3.98 (d, J = 17.8 Hz, 1H), 3.84−3.80 (m, 2H), 3.58−3.54 (m, 2H), 3.37 (s, 3 H), 1.26 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 165.9, 165.2, 164.3, 155.1, 142.4, 141.7, 136.7, 134.8, 134.6, 132.2, 129.8, 128.8, 127.9, 123.3, 119.9, 118.8, 118.7, 114.1, 113.7, 93.9, 71.5, 67.7, 67.5, 66.2, 60.9, 59.0, 57.8, 42.5, 14.1.

Compound 14, Ethyl-2-((1*S*,10*S*,10*aS*)-10-(allyloxycarbonylamino)-2-cinnamoyl-8-((2-methoxyethoxy)methoxy)-4-oxo-1,2,3,4,10,10*a*-hexahydropyrazino[1,2-*a*]indol-1-yl)acetate.



To a solution of the glycine−cinnamoyl-coupled indoline moiety (0.94 g, 0.15 mmol) in DCM (4 mL) at −78 °C was added Et_3N (0.22 mL, 1.55 mmol), followed by the addition of TBSOTf (0.36 mL, 1.55 mmol). The reaction mixture was allowed to warm to room temperature as it was stirred under an argon atmosphere for 4 h. The reaction mixture was quenched with a saturated solution of $NaHCO_3$ and then extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, and purified by flash chromatography. Elution with hexane/ethyl acetate (4:1 v/v) gave 55.0 mg (58%) of the tricyclic product as a beige mousse: MS (ES+) m/z (M + 1) 608.4; ^{1}H NMR (400 MHz, C_6D_6) δ 7.84 (d, J = 15.8 Hz, 1H), 7.69 (d, J = 8.5 Hz, 1H), 7.19−7.11 (m, 2H), 7.00−6.54 (m, 3H), 6.89 (br s, 1H), 6.63 (d, J = 15.6 Hz, 1H), 5.81−5.69 (m, 1H), 5.43 (t, J = 9.9 Hz, 1H), 5.17 (t, J = 6.8 Hz, 1H), 5.11 (d, J = 7.0 Hz, 1H), 5.01 (d, J = 10.5 Hz, 1H), 4.84−4.75 (m, 2H), 4.46 (d, J = 4.5 Hz, 2H), 4.05−3.95 (m, 2H), 3.68 (dd, J = 5.8, 3.8 Hz, 2H), 3.59 (dd, J = 8.5, 7.0 Hz, 1H), 3.32 (dd, J = 5.3, 4.3 Hz, 2H), 3.10 (s, 3H), 2.87 (dd, J = 16.3, 4.0 Hz, 1H), 2.81−2.61 (m, 2H), 1.03 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 169.8, 166.4, 155.9, 155.5, 141.7, 135.4, 133.4, 129.5, 128.8, 128.4, 128.2, 128.0, 121.1, 117.4, 117.3, 115.9, 114.2, 94.4, 72.0, 70.0, 68.2, 65.8, 60.7, 58.7, 58.6, 58.4, 47.3, 34.0, 14.3.

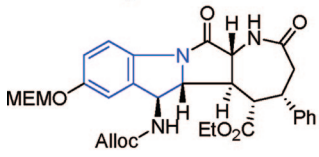
Compound 15, (*E*)-Ethyl-3-((2*R*,3*S*)-3-(allyloxycarbonylamino)-1-(2-(*E*)-but-2-enamidoacetyl)-5-((2-methoxyethoxy)methoxy)indolin-2-yl)acrylate.



To a stirred solution of glycine crotyl acid (170 mg, 1.19 mmol) in dry DMF (10 mL) was added HATU (452 mg, 1.19 mmol), followed by DIPEA (207 μL, 1.19 mmol). To the reaction mixture was added the above secondary amine (103 mg, 0.25 mmol), and the mixture was stirred for 24 h under argon atmosphere. The solution was condensed and dissolved in ethyl acetate, then washed with a saturated NH_4Cl solution, dried over sodium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography (1:4 ethyl acetate/hexanes) to give the coupled product (124 mg, 92%) as a dark yellow mousse: MS (ES+) m/z (M + 1) 546.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 9.5 Hz, 1H), 7.08 (d, J = 2.5 Hz, 1H), 7.06 (br s, 1H), 6.94 (dd, J = 15.8, 5.8 Hz, 1H), 6.85 (dq, J = 15.1, 6.8 Hz, 1H), 6.46 (br s, 1H), 5.95 (d, J = 15.8 Hz, 1H), 5.89 (dq, J = 15.3, 1.8 Hz, 1H), 5.34−5.24 (m, 3H), 5,22 (s, 2H), 4.92 (d, J = 5.0 Hz, 1H), 4.84 (d, J = 6.0 Hz, 1H), 4.70−4.57 (m, 2H), 4.37 (dd, J = 18.1, 4.8 Hz, 1H), 4.15 (q, J = 7.0 Hz, 2H), 3.89 (br d, J = 18.1 Hz, 1 H), 3.83−3.79 (m, 2H), 3.58−3.53 (m, 2H), 3.37 (s, 3H), 1.87 (dd, J = 6.8, 1.3 Hz, 3H), 1.25 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 166.0, 165.9, 165.2, 155.3, 155.0, 142.4, 140.8, 136.8, 132.2, 124.3, 123.2, 118.8, 118.6, 118.4, 113.7, 93.9, 71.5, 67.7, 66.2, 64.3, 60.4, 59.0, 57.8, 42.3, 17.7, 14.1.

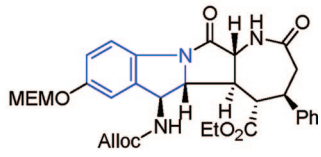
Compounds 16a and 16b.

major



16a

minor

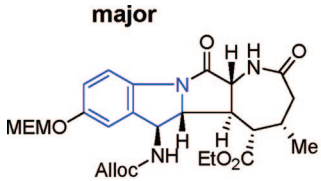


16b

To a stirred solution of glycine−cinnamoyl-coupled indoline (81 mg, 0.13 mmol) in dry DCM (10 mL) at −78 °C was added Et_3N (93 μL, 0.66 mmol), followed by TMSOTf (120 μL, 0.66 mmol). The reaction mixture was allowed to warm to room temperature and was stirred for 24 h under an argon atmosphere. The solution was washed with a saturated brine solution, dried over sodium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography (1:4 ethyl acetate/hexanes) and by PREP HPLC to give two diastereoisomers of the cyclized product (**16a** 44 mg, 55%; **16b** 10 mg, 12%) as a light yellow mousse: MS (ES+) *m/z* (M + 1) 608.4; ^{1}H NMR (compound **16a**; 400 MHz, C_6D_6) δ 7.70 (broad d, J = 8.3 Hz, 1H), 7.22 (s, 1H), 7.18−6.99 (m, H_{Ph}), 6.88 (broad s, 1H), 6.01 (broad s, 1H), 5.85−5.70 (broad m, 1H), 5.16 (d, J = 17.3 Hz, 1H), 5.08−4.87 (broad m, 4H), 4.64−4.41 (broad m, 2H), 3.97 (broad s, 1H), 3.84−3.66 (broad m, 3H), 3.63−3.55 (m, 2H), 3.36−3.22 (broad m, 3H), 3.08 (s, 3H), 2.85−2.65 (broad m, 3H), 1.43−1.10 (broad m, 3H); ^{13}C NMR (compound **16a**; 100 MHz, C_6D_6) δ 172.4, 171.4, 166.1, 155.9, 137.3, 133.0, 128.7, 128.6, 128.3, 128.1, 128.0, 127.9, 127.8, 117.4, 117.30, 117.25, 116.1, 113.6, 94.1, 71.9, 68.1, 65.6, 60.9, 58.6, 32.3, 30,2, 30.1, 29.8, 23.1, 14.4; ^{1}H NMR (compound **16b**; 400 MHz, $CDCl_3$ at 58 °C) δ 7.50 (d, J = 8.5 Hz, 1H), 7.32−7.22 (m, H_{Ph}), 7.20−7.15 (m, 2H), 7.00 (dd, J = 8.5 Hz, J = 2.0 Hz, 1H), 6.93 (d, J = 2.0 Hz, 1H), 6.40 (broad s, 1H), 5.91−5.77 (m, 1H), 5.24 (d, J = 17.6 Hz, 1H), 5.21−5.12 (m, 4H), 4.97 (broad m, 1H), 4.58−4.45 (m, 2H), 4.42 (dd, J = 10.5 Hz, J = 1.3 Hz, 1H), 4.27−4.19 (m, 1H), 3.94−3.84 (m, 2H), 3.81−3.76 (m, 2H), 3.73−3.67 (m, 1H), 3.56−3.51 (m, 2H), 3.36 (s, 3H), 3.22 (t, J = 10.8 Hz, 1H), 3.18 (d, J = 8.5 Hz, 1H), 3.13 (dd, J = 11.0 Hz, J = 5.5 Hz, 1H), 2.96 (broad d, J = 16.3 Hz, 1H), 1.00 (t, J = 7.0 Hz, 3H); ^{13}C NMR (compound **16b**; 100 MHz, C_6D_6) δ 173.4, 172.8, 169.4, 166.5, 156.1, 155.4, 150.0, 136.3, 133.9, 132.7, 132.3, 128.9, 127.1, 118.3, 118.1, 116.5, 112.8, 93.8, 71.5, 70.6, 67.7, 66.4, 60.9, 59.0, 55.9, 48.2, 38.6, 29.9, 29.7, 14.1.

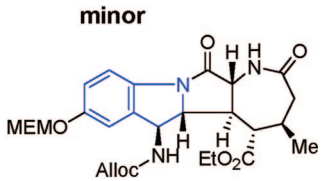
Compounds 17a and 17b.

major



17a

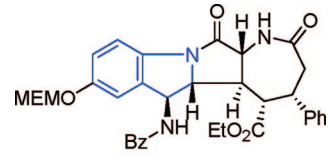
minor



17b

To a stirred solution of glycine−crotyl-coupled indoline (108 mg, 0.20 mmol) in dry DCM (10 mL) at −78 °C was added Et_3N (165 μL, 1.20 mmol), followed by TMSOTf (213 μL, 1.20 mmol). The reaction mixture was allowed to warm to room temperature and was stirred for 4 h under an argon atmosphere. The solution was washed with a saturated brine solution, dried over sodium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography (1:5 ethyl acetate/hexanes) and by preparative HPLC to give two diastereoisomers of the cyclized product (54 mg, 50% and 24 mg, 22%) as a light yellow mousse: MS (ES+) *m/z* (M + 1) 546.3; ^{1}H NMR (compound **17a**; 400 MHz, $CDCl_3$) δ 7.42 (broad d, J = 8.3 Hz, 1H), 7.02−6.86 (broad m, 2H), 6.42 (very broad s, 1H), 5.95−5.78 (broad m, 1H), 5.41 (broad s, 1H), 5.35−5.01 (broad m, 4H), 5.27 (d, J = 16.8 Hz, 1H), 4.52 (broad s, 2H), 4.33−4.06 (broad m, 4H), 3.79 (broad s, 2H), 3.57−3.50 (m, 2H), 3.36 (s, 3H), 2.96−2.44 (broad m, 5H), 1.27 (t, J = 7.0 Hz, 3H), 1.26 (d, J = 8.0 Hz, 3H); ^{13}C NMR (compound **17a**; 100 MHz, $CDCl_3$) δ 174.2, 173.6, 173.1, 166.3, 155.8, 136.2, 132.9, 132.4, 129.2, 126.7, 118.4, 117.3, 116.3, 113.1, 94.3, 71.9, 68.1, 66.2, 61.7, 59.4, 53.4, 50.7, 47.8, 43.0, 30.4, 14.6, 13.8; ^{1}H NMR (compound **17b**; 400 MHz, $CDCl_3$) δ 7.48 (d, J = 8.5 Hz, 1H), 7.05−7.00 (m, 2H), 6.18 (broad s, 1H), 5.96 (ddt, J = 17.1 Hz, J = 10.8 Hz, J = 5.8 Hz, 1H), 5.35 (dd, J = 17.1 Hz, J = 1.3 Hz, 1H), 5.27 (d, J = 10.8 Hz, 1H), 5.23 (s, 2H), 5.28−5.20 (m, 1H), 5.15 (dd, J = 11.0 Hz, J = 2.8 Hz, 1H), 4.68−4.63 (m 2H), 4.24−4,13 (m, 3H), 3.83−3.78 (m, 2H), 3.58−3.53 (m, 2H), 3.50 (s, 3H), 3.30 (dd, J = 7.0 Hz, J = 4.0 Hz, 1H), 3.01 (d, J = 14.6 Hz, 1H), 2.63 (td, J = 10.8 Hz, J = 4.3 Hz, 1H), 2.54 (t, J = 7.0 Hz, 1H), 2.42 (dd, J = 14.6 Hz, J = 7.0 Hz, 1H), 1.28 (t, J = 7.0 Hz, 3H), 1.26−1.22 (m, 3H); ^{13}C NMR (compound **17b**; 100 MHz, $CDCl_3$) δ 173.7, 173.5, 167.2, 164.3, 155.9, 155.4, 133.7, 133.0, 132.3, 118.3, 118.2, 116.6, 112.8, 93.8, 71.5, 67.7, 66.3, 60.8, 59.1, 55.9, 50.9, 47.8, 46.0, 39.4, 29.7, 17.7, 14.2.

Compound 18a.

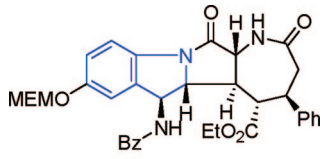


18a

To a stirred solution of the cyclized glycine cinnamoyl-functionalized indoline tetracycle (27 mg, 0.045 mmol) in dry DCM (2 mL) was added morpholine (8 μL, 0.090 mmol), followed by Pd(0)$(PPh_3)_4$ (5.2 mg, 0.0045 mmol). The reaction mixture was stirred for 30 min under argon atmosphere. To the reaction mixture was directly added Et_3N (64 μL, 0.45 mmol), followed by benzoyl chloride (32 μL, 0.27 mmol). The reaction mixture was stirred for an additional hour. The reaction mixture was washed with a saturated brine solution, dried over sodium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography (1:2 ethyl acetate/hexanes) to give the benzoylated compound (18 mg, 67%) as a light yellow mousse: MS (ES+) *m/z* (M + 1) 628.3; ^{1}H NMR (400 MHz, $CDCl_3$ at 58 °C) δ 7.73 (d, J = 7.3 Hz, 2H), 7.50 (d, J = 8.8 Hz, 1H), 7.48 (t, J = 7.5 Hz, 1H), 7.38 (t, J = 7.5 Hz, 2H), 7.29−7.20 (m, 3H), 7.14 (d, J = 6.8 Hz, 2H), 6.99 (d, J = 8.5 Hz, 1H), 6.94 (s, 1H), 6.62 (d,

J = 8.0 Hz, 1H), 6.41 (s, 1H), 5.57 (t, J = 7.5 Hz, 1H), 5.16 (s, 2H), 4.45−4.37 (m, 2H), 3.75 (t, J = 4.5 Hz, 2H), 3.71−3.62 (m, 2H), 3.61−3.52 (m, 1H), 3.49 (t, J = 4.5 Hz, 2H), 3.30 (s, 3H), 3.27−3.16 (m, 2H), 3.12 (dd, J = 10.8, 5.8 Hz, 1 H), 2.91 (d, J = 16.3 Hz, 1H), 0.72 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 171,6, 166.6, 165.9, 155.5, 141.9, 138.8, 135.7, 134.7, 133.4, 132.1, 128.75, 128.70, 128.1, 127.8, 126.9, 117.0, 116.1, 112.8, 93.8, 71.5, 69.3, 67.6, 61.3, 59.3, 59.0, 58.6, 58.2, 53.5, 49.1, 42.1, 40.0, 13.4.

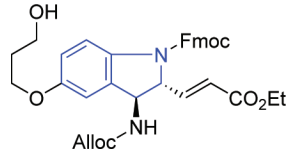
Compound 18b.



18b

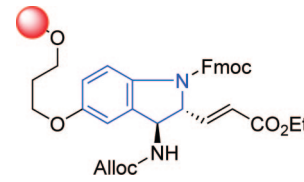
To a stirred solution of the cyclized glycine cinnamoyl-functionalized indoline tetracycle (14 mg, 0.023 mmol) in dry DCM (1 mL) was added morpholine (2 μL, 0.023 mmol), followed by Pd(0)$(PPh_3)_4$ (2.6 mg, 0.0023 mmol). The reaction mixture was stirred for 20 min under argon atmosphere. To the reaction mixture was directly added Et_3N (20 μL, 0.139 mmol), followed by benzoyl chloride (8 μL, 0.070 mmol). The reaction mixture was stirred for an additional hour. The reaction mixture was washed with a saturated brine solution, dried over sodium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography (1:2 ethyl acetate/hexanes) to give the benzoylated compound (12 mg, 67%) as a light yellow oil: MS (ES+) m/z (M + 1) 628.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 7.5 Hz, 2H), 7.59−7.43 (m, 7H), 7.36 (t, J = 7.5 Hz, 2H), 7.06 (d, J = 7.3 Hz, 1H), 7.05 (s, 1H), 6.96 (s, 1H), 6.56 (broad d, J = 7.8 Hz, 1H), 6.34 (s, 1H), 5.65 (t, J = 7.5 Hz, 1H), 5.27−5.20 (m, 2H), 5.11 (d, J = 10.5 Hz, 1H), 4.29−4.18 (broad m, 1H), 4.08−3.92 (broad m, 2H), 3.88 (s, 1H), 3.82−3.77 (m, 2H), 3.73 (t, J = 7.8 Hz, 1H), 3.57−3.50 (m, 2H), 3.34 (s, 3H), 3.16 (dd, J = 16.6, 8.8 Hz, 1H), 3.00 (d, J = 16.6 Hz, 1H), 2.50 (dt, J = 10.5, 7.5 Hz, 1H), 1.29 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 167,9, 155.5, 150.0, 136.2, 133.9, 133.4, 132.3, 129.8, 128.9 (2C), 128.83, 128.79 (2C), 128.6, 128.5, 127.21 (2C), 127.18, 127,0 (2C), 126.6, 126.3, 118,0, 116.7, 113.0, 93.9, 71.5, 70.8, 67.7, 60.8, 59.0, 57.3, 55.8, 48.3, 34.3, 30.0, 29.7, 13.9.

Compound 19, (2*R*,3*S*)-(9*H*-Fluoren-9-yl)methyl-3-(allyloxycarbonylamino)-2-((*E*)-3-ethoxy-3-oxoprop-1-enyl)-5-(3-hydroxypropoxy)indoline-1-carboxylate.



The synthetic procedure was already described:[4] viscous light yellow oil; MS (ES+) m/z (M + 1) 613.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (m, 3H), 7.57 (d, J = 6.2 Hz, 2H), 7.42 (t, J = 7.3 Hz, 2H), 7.30 (t, J = 7.3 Hz, 2H), 6.97−6.50 (m, 3H), 5.96 (m, 1H), 5.78 (m, 1H), 5.44− 5.18 (m, 2H), 4.95−4.50 (m, 6H), 4.28 (m, 1H), 4.18 (q, J = 7.1 Hz, 2H), 4.07 (m, 2H), 3.86 (t, J = 6.0 Hz, 2H), 2.03 (m, 2H), 1.78 (s, 1H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 156.0, 155.6, 152.9, 144.1, 141.9, 132.8, 128.2, 127.6, 125.3, 125.1, 122.6, 120.5, 120.4, 118.6, 117.2, 117.0, 112.1, 68.3, 67.8, 66.6, 66.4, 61.0, 60.7, 57.5, 47.6, 32.4, 14.6.

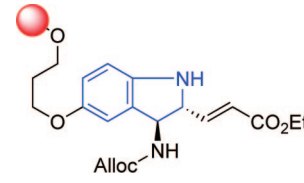
Compound 20, (2*R*,3*S*)-(9*H*-fluoren-9-yl)methyl-3-(allyloxycarbonylamino)-2-((*E*)-3-ethoxy-3-oxoprop-1-enyl)-5-(3-hydroxypropoxy)indoline-1-carboxylate.



The synthetic procedure was already described.[4] 3-[Diisopropyl-(*p*-methoxyphenyl) silyl] propyl-functionalized resin (420.4 mg, 0.4162 mmol) was swollen in dry DCM (2.5 mL) under argon for 30 min in a BIORAD tude. The solvent was then drained to add, by syringe, a solution of trifluoromethanesulfonate acid in dry DCM (4%, 5.61 mL). The resin was then gently agitated for 30 min under argon. The acidic solution was drained, and the activated resin was treated with 2,6-lutidine (364 μL, 3.36 mmol) for 15 min, followed by the addition of a solution of the compound to be loaded (515 mg, 0.841 mmol) in dry DCM (1 mL). The resin was gently shaken overnight. The resin was washed with DMF (3×), THF (3×), and DCM (3×) over a period of 90 min. The resin was then dried under vacuum overnight to give 598.4 mg of the loaded resin (>95%).

Cleavage. The loaded resin (three beads) in an Eppendorf tube was swelled in THF (0.5 mL) for 10 min and treated with HF−pyridine solution (15 μL). The reaction tube was shaken for 45 min; then the reaction was quenched with methoxytrimethylsilane (100 μL), and the tube was shaken for another 10 min. The solution was concentrated and submitted to MS and HPLC/MS analysis: MS and HPLC/MS (ES+) m/z (M + 1) 613.4; HPLC/MS purity >96%.

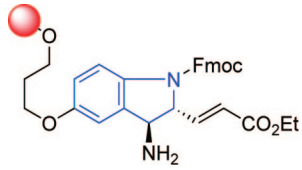
Compound 20a, (*E*)-Ethyl-3-((2R,3S)-3-(allyloxycarbonylamino)-5-(3-hydroxypropoxy) indolin-2-yl)acrylate.



The synthetic procedure was already described.[4] The Fmoc-protected resin (40.0 mg, 0.03960 mmol) was swelled in DMF (2.5 mL) for 30 min. Morpholine (1.0 mL) was added to the reaction mixture, and it was shaken for 30 min. The reaction mixture was drained and washed with DCM (3×), THF (3×), and DCM (3×) over a period of 90 min. The resin was then dried under vacuum overnight to give 32.7 mg of the resulting resin. A sample of the dried resin (three

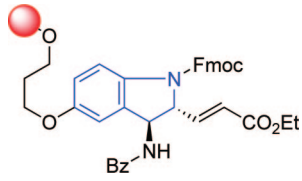
beads) was cleaved, and the resulting compound was analyzed by MS and HPLC/MS: MS (ES+) *m/z* (M + 1) 391.2; HPLC/MS purity >95%.

Compound 20b, (2*R*,3*S*)-(9*H*-Fluoren-9-yl)methyl-3-amino-2-((*E*)-3-ethoxy-3-oxoprop-1-enyl)-5-(3-hydroxypropoxy)indoline-1-carboxylate.



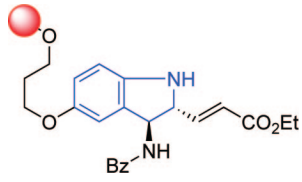
The Fmoc-protected resin (27.0 mg, 0.02673 mmol) was swelled in DCM (2.5 mL) for 30 min. The mixture was drained, and 2.5 mL of a solution of DCM (5 mL), *N*-methylmorpholine (0.32 mL), and acetic acid (0.66 mL) was added the swelled resin. To this mixture was added the ligand PPh_3 (90.3 mg, 0.3408 mmol) and the catalyst $Pd(0)(PPh_3)_4$ (83.0 mg, 0.07110 mmol). The reaction mixture was shaken for 18 h. The reaction mixture was drained and washed with DCM (3×), THF (3×), and DCM (3×) over a period of 90 min. The resin was then dried under vacuum overnight to give 24.5 mg of the resulting resin.

Compound 20c, (2*R*,3*S*)-(9*H*-Fluoren-9-yl)methyl-3-benzamido-2-((E)-3-ethoxy-3-oxoprop-1-enyl)-5-(3-hydroxypropoxy)indoline-1-carboxylate.



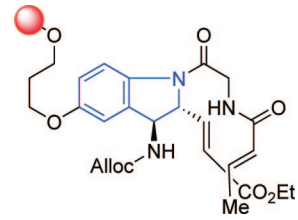
The above primary amine resin (24.5 mg, 0.02673 mmol) was swelled in DCM (2.5 mL) for 30 min. Collidine (0.032 μL, 0.2426 mmol) and benzoyl chloride (0.014 μL, 0.1213 mmol) were added to the reaction mixture, and it was shaken for 8 h. The reaction mixture was drained and washed with DCM (3×), THF (3×), and DCM (3×) over a period of 90 min. The resin was then dried under vacuum overnight to give 24.5 mg of the resulting resin. A sample of the dried resin (three beads) was cleaved, and the resulting compound was analyzed by MS and HPLC/MS: MS (ES+) *m/z* (M + 1) 633.3; HPLC/MS purity >73%.

Compound 20d, (*E*)-Ethyl-3-((2*R*,3*S*)-3-benzamido-5-(3-hydroxypropoxy)indolin-2-yl)acrylate.



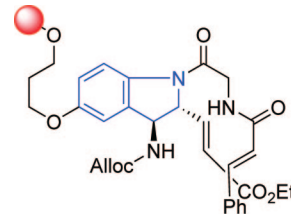
The Fmoc-protected resin (24.5 mg, 0.02673 mmol) was swelled in DMF (2.5 mL) for 30 min. Morpholine (1.0 mL) was added, and the reaction mixture was shaken for 30 min. The reaction mixture was drained and washed with DCM (3×), THF (3×), and DCM (3×) over a period of 90 min. The resin was then dried under vacuum overnight to give 18.0 mg of the resulting resin. A sample of the dried resin (three beads) was cleaved, and the resulting compound was analyzed by MS and HPLC/MS: MS (ES+) *m/z* (M + 1) 411.2.

Compound 21, (*E*)-Ethyl-3-((2*R*,3*S*)-3-(allyloxycarbonylamino)-1-(2-(*E*)-but-2-enamidoacetyl)-5-(3-hydroxypropoxy)indolin-2-yl)acrylate.



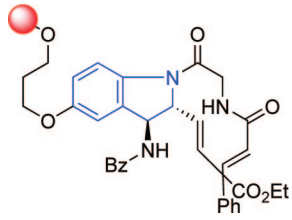
To a stirred solution of glycine crotyl acid (30.0 mg, 0.2093 mmol) in dry DMF (2.5 mL) was added HATU (79.6 mg, 0.2093 mmol), followed by DIPEA (36.5 μL, 0.2093 mmol). The reaction mixture was added to the above secondary amine resin (35.2 mg, 0.04288 mmol), which was swelled in DMF (2.5 mL) for 30 min. The reaction mixture was shaken for 48 h. The reaction mixture was then drained and washed with DCM (3×), THF (3×), and DCM (3×) over a period of 90 min. The resin was then dried under vacuum overnight to give 34.5 mg of the resulting resin. A sample of the dried resin (three beads) was cleaved, and the resulting compound was analyzed by MS and HPLC/MS: MS (ES+) *m/z* (M + 1) 516.2; HPLC/MS purity >94%.

Compound 22, (*E*)-Ethyl-3-((2*R*,3*S*)-3-(allyloxycarbonylamino)-1-(2-cinnamamidoacetyl)-5-(3-hydroxypropoxy)indolin-2-yl)acrylate.



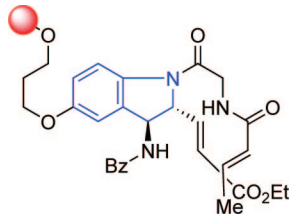
To a stirred solution of glycine cinnamic acid (26.0 mg, 0.1208 mmol) in dry DMF (2.5 mL) was added HATU (46.0 mg, 0.1208 mmol), followed by DIPEA (21.0 μL, 0.1208 mmol). The reaction mixture was added to the above secondary amine resin (24.4 mg, 0.02416 mmol), which was swelled in DMF (2.5 mL) for 30 min. The reaction mixture was shaken for 48 h. The reaction mixture was then drained and washed with DCM (3×), THF (3×), and DCM (3×) over a period of 90 min. The resin was then dried under vacuum overnight to give 26.4 mg of the resulting resin. A sample of the dried resin (three beads) was cleaved, and the resulting compound was analyzed by MS and HPLC/MS: MS (ES+) *m/z* (M + 1) 578.3; HPLC/MS purity >90%.

Compound 23, (*E*)-Ethyl-3-((2*R*,3*S*)-3-benzamido-1-(2-cinnamamidoacetyl)-5-(3-hydroxypropoxy) indolin-2-yl)acrylate.



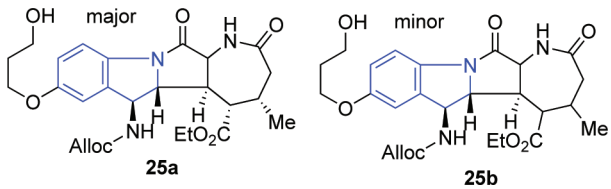
To a stirred solution of glycine cinnamic acid (19.0 mg, 0.08663 mmol) in dry DMF (2.5 mL) was added HATU (33.0 mg, 0.08663 mmol), followed by DIPEA (15.0 μL, 0.08663 mmol). The reaction mixture was added to the above secondary amine resin (18.0 mg, 0.02673 mmol), which was swelled in DMF (2.5 mL) for 30 min. The reaction mixture was shaken for 48 h. The reaction mixture was then drained and washed with DCM (3×), THF (3×), and DCM (3×) over a period of 90 min. The resin was then dried under vacuum overnight to give 18.6 mg of the resulting resin. A sample of the dried resin (three beads) was cleaved, and the resulting compound was analyzed by MS and HPLC/MS: MS (ES+) *m*/*z* (M + 1) 598.3.

Compound 24, (*E*)-Ethyl-3-((2*R*,3*S*)-3-benzamido-1-(2-(*E*)-but-2-enamidoacetyl)-5-(3-hydroxy propoxy)indolin-2-yl)acrylate.



To a stirred solution of glycine crotyl acid (79.0 mg, 0.5445 mmol) in dry DMF (2.5 mL) was added HATU (207.0 mg, 0.5445 mmol), followed by DIPEA (95.0 μL, 0.5445 mmol). The reaction mixture was added to the above secondary amine resin (0.1089 mmol), which was swelled in DMF (2.5 mL) for 30 min. The reaction mixture was shaken for 48 h. The reaction mixture was then drained and washed with DCM (3×), THF (3×), and DCM (3×) over a period of 90 min. The resin was then dried under vacuum overnight to give the resulting resin. A sample of the dried resin (three beads) was cleaved, and the resulting compound was analyzed by MS and HPLC/MS: MS (ES+) *m*/*z* (M + 1) 536.2.

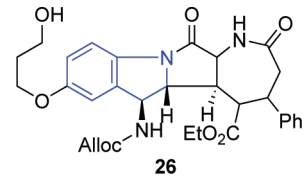
Compounds 25a and 25b.



25a **25b**

The glycine−crotyl-coupled indoline resin **21** (34 mg, 0.033 mmol) was swelled in DCM (2.5 mL) for 30 min. Triethylamine (19.0 μL, 0.132 mmol) and TMSOTf (25 μL, 0.132 mmol) were added to the swelled resin, and then the mixture was shaken for 20 h. The reaction mixture was drained and washed with DCM (3×), THF (3×), and DCM (3×) over a period of 90 min. The resin was then dried under vacuum overnight to give 30 mg of the resulting resin. All of the dried resin was cleaved, and the resulting crude compound (15 mg) was analyzed by MS and HPLC/MS: MS (ES+) *m*/*z* (M + 1) 516.2; HPLC/MS purity >98% showing 4 isomers 74%, 12%, 3%, and 11%. Analysis of the major product **25a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 8.3 Hz, 1H), 6.82 (d, J = 8.3 Hz, 1H), 6.81 (s, 1H), 6.24 (broad s, 1H), 5.95−5.81 (m, 1H), 5.30 (d, J = 8.0 Hz, 1H), 5.29 (d, J = 15.8 Hz, 1H), 5.22 (d, J = 10.5 Hz, 1H), 5.16 (t, J = 8.0 Hz, 1H), 4.61−4.48 (m, 2H), 4.28−4.14 (m, 4H), 4.13−4.03 (m, 2H), 3.85 (t, J = 6.0 Hz, 2H), 2.89 (dd, J = 11.3, 3.8 Hz, 1H), 2.84−2.72 (m, 2H), 2.71−2.68 (m, 1H), 2.61−2.51 (m, 1H), 2.02 (quint, J = 6.0 Hz, 2H), 1.29 (t, J = 7.0 Hz, 3H), 1.04 (d, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 165.6, 157.1, 154.9, 135.7, 134.8, 132.4, 131.1, 118.1, 115.9, 114.7, 110.8, 68.3, 66.1, 65.8, 61.4, 60.2, 59.18, 59.13, 53.3, 47.5, 42.8, 32.0, 30.1, 14.2, 13.4 (See the Supporting Information).

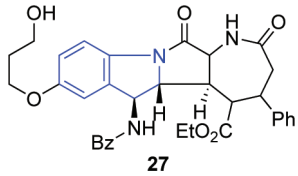
Compound 26 (Mixture of Diastereomers).



26

The glycine−cinnamoyl-coupled indoline resin **22** (26 mg, 0.026 mmol) was swelled in DCM (2.5 mL) for 30 min. Triethylamine (15 μL, 0.104 mmol) and TMSOTf (20 μL, 0.104 mmol) were added to the swelled resin, and then the mixture was shaken for 20 h. The reaction mixture was drained and washed with DCM (3×), THF (3×), and DCM (3×) over a period of 90 min. The resin was then dried under vacuum overnight to give 25 mg of the resulting resin. All of the dried resin was cleaved, and the resulting crude compound (16 mg) was analyzed by MS and HPLC/MS: MS (ES+) *m*/*z* (M + 1) 578.3; HPLC/MS purity >60% showing 4 isomers: 67%, 16%, 9%, and 8%. The major compound could be isolated after purification by preparative HPLC (6 mg, 60%): MS (ES+) *m*/*z* (M + 1) 578.5; HPLC/MS purity >95%. Analysis of the major product of **26**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 8.5 Hz, 1H), 7.40−7.22 (m, 3H), 7.17 (d, J = 6.5 Hz, 2H), 6.83 (dd, J = 8.0 Hz, J = 2.0 Hz, 1H), 6.78 (d, J = 2.0 Hz, 1H), 6.50 (broad s, 1H), 5.93−5.79 (m, 1H), 5.43−5.07 (m, 4H), 4.59−4.45 (m, 2H), 4.41 (d, J = 10.5 Hz, 1H), 4.25 (broad s, 1H), 4.13−4.01 (m, 2H), 3.93−3.79 (m, 3H), 3.76−3.59 (m, 5H), 3.23−3.08 (m, 2H), 2.95 (broad d, J = 15.8 Hz, 1H), 2.07−1.97 (m, 4H), 1.39−1.17 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 164.8, 156.5, 154.3, 142.2, 138.6, 135.1, 131.6, 130.3, 128.03 (2C), 128.02 (2C), 127.3, 127.1, 126.8, 117.4, 115.3, 114.1, 110.2, 69.8, 65.3, 65.2, 60.6, 59.4, 58.0, 31.2, 29.0, 21.9, 13.0 (see the Supporting Information).

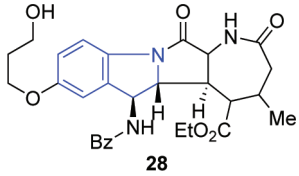
Compound 27 (Mixture of Diastereomers).



27

The glycine−cinnamoyl-coupled indoline resin **23** (18 mg, 0.020 mmol) was swelled in DCM (2.5 mL) for 30 min. Triethylamine (12 μL, 0.080 mmol) and TMSOTf (15 μL, 0.080 mmol) were added to the swelled resin, and then the mixtuer was shaken for 20 h. The reaction mixture was drained and washed with DCM (3×), THF (3×), and DCM (3×) over a period of 90 min. The resin was then dried under vacuum overnight to give the resulting resin (17 mg). All the dried resin was cleaved, and the resulting crude compound (20 mg) was analyzed by MS and HPLC/MS: MS (ES+) *m*/*z* (M + 1) 598.5; HPLC/MS purity >45% showing only 2 isomers 22% and 78%.The major compound could be isolated after purification by preparative HPLC (5 mg): MS (ES+) *m*/*z* (M + 1) 598.1; HPLC/MS purity >99%. Analysis of the major product of **27**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 7.8 Hz, 1H), 7.60−7.42 (m, 6H), 7.37 (d, J = 7.8 Hz, 2H), 6.95−6.87 (m, 2H), 6.62−6.46 (m, 1H), 5.67 (broad s, 1H), 5.11 (broad d, J = 10.8 Hz, 1H), 4.53 (t, J = 6.3 Hz, 1H), 4.23 (broad s, 1H), 4.17−3.93 (m, 5H), 3.92−3.81 (m, 2H), 3.78−3.64 (m, 2H), 3.17 (dd, J = 16.6 Hz, 8.8 Hz, 1H), 3.02 (broad d, J = 16.6 Hz, 1H), 2.99−2.86 (m, 1H), 2.28−2.15 (m, 2H), 1.96−1.73 (m, 1H), 1.34−1.19 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 168.9, 167.8, 157.2, 133.3, 132.3, 128.9 (2C), 128.8 (2C), 128.7, 128.5, 127.2 (2C), 127.0 (2C), 126.93, 126.90, 116.6, 115.4, 114.1, 111.3, 70.68, 70.65, 66.2, 60.8, 60.0, 55.8, 48.2, 43.1, 31.9, 29.7, 13.9 (see the Supporting Information).

Compound 28 (Mixture of Diastereomers).



28

The glycine−crotyl-coupled indoline resin **24** (75 mg, 0.073 mmol) was swelled in DCM (2.5 mL) for 30 min. Triethylamine (41.0 μL, 0.292 mmol) and TMSOTf (55 μL, 0.292 mmol) were added to the swelled resin, and then the mixture was shaken for 20 h. The reaction mixture was drained and washed with DCM (3×), THF (3×), and DCM (3×) over a period of 90 min. The resin was then dried under vacuum overnight to give the resulting resin (70 mg). All the dried resin was cleaved, and the resulting crude compound (60 mg) was analyzed by MS and HPLC/MS: MS (ES+) *m*/*z* (M + 1) 536.2; HPLC/MS purity >72% showing 4 isomers 20%, 50%, 19%, and 11% (see the Supporting Information).

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Supporting Information Available. Additional figures showing NMR, HPLC, and MS data of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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