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Solution- and Solid-Phase, Modular Approaches for Obtaining Different Natural Product-Like Polycyclic Architectures from an Aminoindoline Scaffold for Combinatorial Chemistry

P. Thirupathi Reddy,[†] S. Quevillon,[†] Zhonghong Gan,[†] Nauzer Forbes,[†] Donald M. Leek,[†] and Prabhat Arya*[,†,‡]

Steacie Institute for Molecular Sciences, National Research Council of Canada, 100 Sussex Drive, Ottawa, Ontario, Canada, K1A 0R6, and Ottawa Institute of Systems Biology, University of Ottawa, 451 Smyth Road, Ottawa, Ontario, Canada, K1H 8M5

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With the goal of developing a modular approach leading to different indoline alkaloid natural-product-like tricyclic derivatives having an unsaturated lactam (see compounds **13**, **14**, and **16**), an aminoindoline-based bicyclic scaffold **10** was obtained from **9**. The selective deprotection of the indoline *N*Teoc or benzylic *N*HAlloc in compound **10**, followed by N-acryloylation and then subjection to a ring-closing metathesis reaction, successfully led to obtaining two different architectures (**13**/**14** and **16**) having an unsaturated lactam functionality. This modular solution-phase methodology was then developed on solid phase. To achieve this objective, the aminoindoline bicyclic scaffold having an additional hydroxyl group could be immobilized onto the solid support using alkylsilyl linker-based polystyrene macrobeads, giving **18**. By applying a ring-closing metathesis approach, **20** (tricyclic derivative with seven-membered-ring unsaturated lactam) and **23** (tricyclic derivative with eight-membered-ring unsaturated lactam) were then obtained from **18** in a number of steps.

Introduction

There is a growing interest in the use of small-molecule chemical probes as chemical dissectors of macromolecular (i.e., protein−protein, DNA/RNA−protein) interactions.[1] Because these interactions involve multiple dynamic and complex relationships, the reversible effect of small molecules and their ability to modulate highly specific domains of a given protein offer them several advantages over classical biochemical tools.[2] To move forward with this approach, easy access to a wide variety of small-molecule chemical probes is necessary. In this arena, small molecules (i.e., natural-product-like compounds)[3] that are inspired by bioactive natural products are much in demand. Unlike most bioactive natural products that are hard to obtain readily and in sufficient quantities, diversity-oriented synthesis (DOS) is aimed at rapidly accessing different, natural-product-like architectures.[4] It is hoped that the compounds produced by DOS would occupy a chemical space similar to that currently taken by natural products.[5]

Results and Discussion

With the goal of accessing indoline-derived, complex, natural-product-like compounds, a few years ago, we embarked on a research program that was aimed at developing a practical synthesis of a highly functionalized, aminoindoline scaffold in an enantioselective manner.[6] Using this bicyclic aminoindoline derivative, the plans were to develop a DOS program to obtain several different polycyclic architectures in a high-throughput manner. Due to the wide variety of bioactive indoline alkaloids (two examples are shown in Figure 1: vindoline, **1**, and tabersonine, **2**),[7] we decided to develop a DOS program on the aminoindoline substructure. For example, in one study, we report the solid-phase synthesis and subsequent library generation of tricyclic derivatives that utilized a stereocontrolled aza-Michael reaction.[6] A major challenge in DOS is to develop modular approaches leading to structurally complex and architecturally diverse skeletons. With few exceptions, this has previously met with only little success.[8] Utilizing the aminoindoline scaffold, we herein report our results reaching this objective.

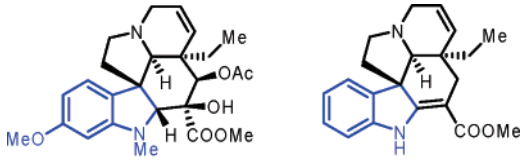

Figure 1. Two examples of bioactive, indoline alkaloid natural products.

The aminoindoline scaffold **3** is unique, highly functionalized, and could be easily modified to obtain compound **4** as a diastereomeric mixture having an allyl moiety and two orthogonally protected amines. The selective N-acryloylation followed by the ring-closing metathesis reaction could lead to skeletally different architectures, **5/6** and **7/8**, having unsaturated lactam functional groups. Thus, in addition to

* Phone: (613) 993 7014. Fax: (613) 952 0068. E-mail: prabhat.arya@nrc.ca.
[†] National Research Council of Canada.
[‡] University of Ottawa.

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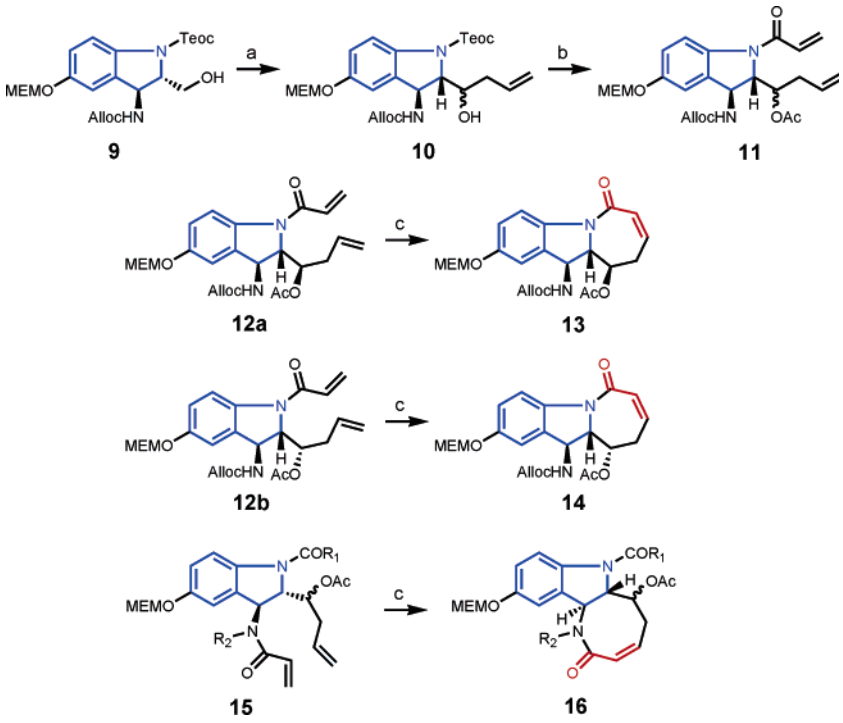
Scheme 1



(a) (i) Dess−Martin periodinane, $NaHCO_3$, DCM; (ii) $ZnCl_2$, allylmagnesium bromide, −78 °C, THF; (b) (i) Ac_2O, 4-DMAP, DCM; (ii) TBAF, THF; (iii) acryloyl chloride, pyridine, °C; (c) second generation Grubbs' catalyst (20 mol %), DCM.

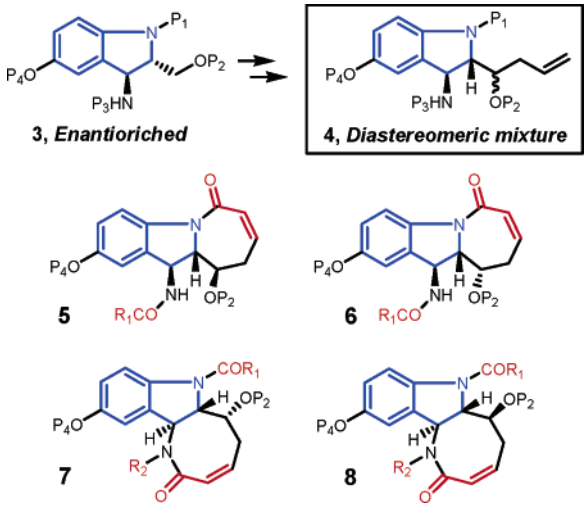


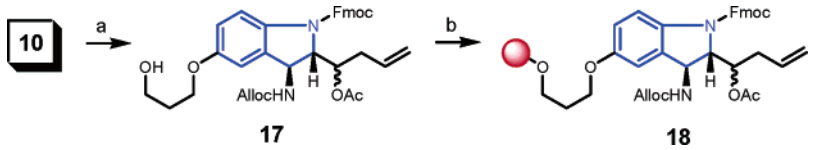
Figure 2. A modular approach to obtaining different indoline alkaloid-like polycyclic architectures.

having the benzylic amine and the hydroxyl moiety for diversification, the tricyclic derivative **5** has an unsaturated lactam functional group that could further be used as the third diversity site. In a related study, we have shown that nucleophilic thiol attack occurred in a stereocontrolled manner and that the nucleophile approached the unsaturated lactam giving the relative 1,3-*trans* substituted product (not shown in Figure 2).[9] In a similar manner, the use of the benzylic nitrogen in N-acryloylation could provide the aminoindoline-based tricyclic derivative having an eight-membered ring with an unsaturated lactam moiety. To our knowledge, there are very few examples of generating different indoline-based, polycyclic architectures in a modular manner. The successful outcome of our approach would provide an entry to a few complex aminoindoline-derived polycyclic compounds that could further be subjected to diversification in library synthesis planning. It is interesting to note that the modular formation of the third, medium-sized ring is not usually readily accessible.

The *enantioenriched* aminoindoline derivative **9** (Scheme 1) was obtained as reported earlier[6] and further subjected to oxidation to produce the corresponding aldehyde. Upon treatment with the Grignard reagent in the presence of the Lewis acid, it gave compound **10** as a mixture of diastereomers (diastereomeric ratio 1:3). The mixture was not separable at this stage, and it was directly utilized in further studies. In one study, compound **10** was subjected to *N*-Teoc removal followed by N-acryloylation. The diastereomeric mixture of *N*-acryloyl derivative **11** could be separated at this stage, providing compounds **12a** and **12b** as two diastereomers. Both compounds were then independently subjected to ring-closing metathesis reaction[10] using 10−20 mol % second-generation Grubbs' catalyst. We were pleased to note that in both cases, the formation of the seven-membered ring having an unsaturated lactam functional group occurred very easily (i.e., reaction at room temperature), giving products **13** and **14**. Interestingly, in both cases, there were no side products arising from the participation of the *N*-Alloc group in the ring-closing metathesis reaction. The aminoindoline-derived tricyclic products, **13** and **14**, were then thoroughly characterized by MS and NMR studies (see the Experimental Section).

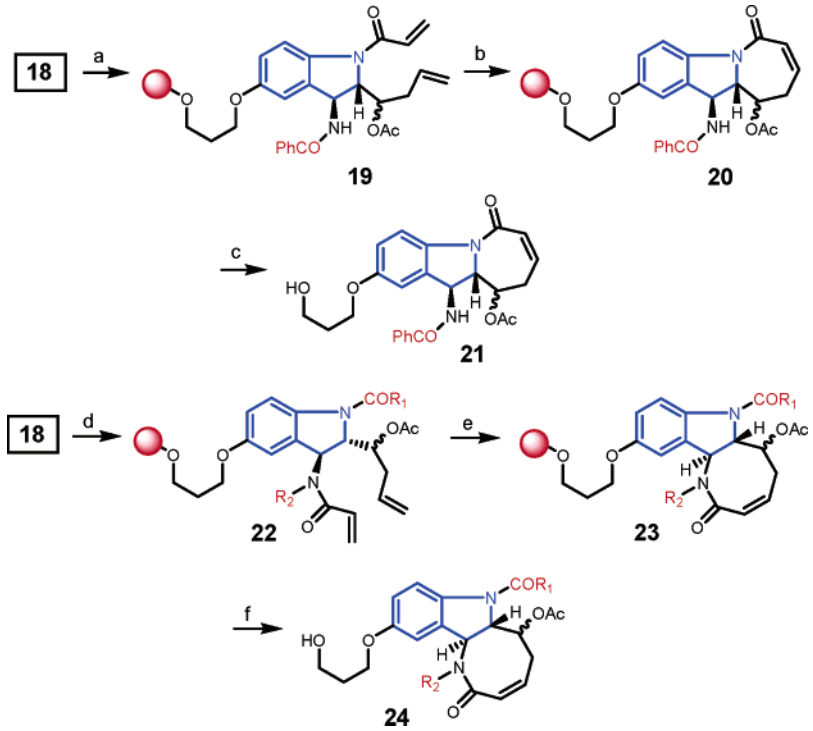
In another experiment, with the goal of examining the scope of the modular approach for obtaining aminoindoline-derived tricyclic compounds having eight-membered rings, the following sequence of reactions was attempted. As a diastereomeric mixture, compound **10** was subjected to

Scheme 2



(a) (i) *p*-TSA, EtOH, 50 °C, 24 h; (ii) 3-(tetrahydro-2*H*-pyran-2-yloxy)propyl 4-methylbenzenesulfonate, $CsCO_3$, DMF; (iii) Ac_2O, 4-DMAP, DCM; (iv) TBAF, THF; (v) Fmoc-Cl, aq $NaHCO_3$, EtOAc; (vi) PPTS, EtOH, 55 °C, 48 h; (b) (4-methoxyphenyl)diisopropylsilylpropyl polystyrene macrobeads (500−560 μm, loading 1.29 mmol/g), TFA, 2,6-lutidine, DCM.

Scheme 3



(a) (i) Pd (0), PPh_3, *N*-methylmorpholine, AcOH, DCM; (ii) benzoyl chloride, 2,6-collidine, DCM; (iii) 20% piperidine, DMF; (iv) acryloyl chloride, 2,6-collidine, DCM; (b) second generation Grubbs' catalyst (40−50 mol %), DCM, 40 °C; (c) Hf−pyridine, THFf; (d) (i) 20% piperidine, DMF; (ii) isobutyroyl chloride, 2,6-collidine, DCM; (iii) Pd (0), PPh_3, *N*-methylmorpholine, AcOH, DCM; (iv) isobutyraldehyde, $NaCNBH_3$, MeOH, AcOH, TMOF; (v) acryloyl chloride, 2,6-collidine, (e) second generation Grubbs' catalyst (40−50 mol %), 40 °C DCM; (f) Hf−pyridine, THF.

(i) *N*-Teoc removal and (ii) *N*-amide formation (test of first diversity). Following the *N*-Alloc removal, the free benzylic amines were then reductively alkylated (test of second diversity). The resulting secondary amine derivatives were then reacted with the acryloyl chloride to produce the *N*-acryloyl derivatives **15** as mixtures of inseparable isomers. To our pleasant surprise, when subjected independently to the ring-closing metathesis reaction using 10−20 mol % second-generation Grubbs' catalyst, the compounds (**15**) produced the eight-membered rings having unsaturated lactam functionality. The reaction is very clean and high-yielding, and the product **16** was well-characterized by MS and NMR studies. This successful method development is an interesting example of the formation of medium-sized rings containing unsaturated lactam functionality through ring-closing metathesis. In comparison to ring-closing metathesis reactions that produce the isolated olefins, the generation of an unsaturated lactam has an advantage in that it can be further subjected to a wide variety of diversity-oriented transformations. To our knowledge, there are not many examples of ring-closing metathesis approaches that produce aminoindoline-based tricyclic compounds having unsymmetrical medium-sized rings.[11] Thus, using aminoindoline scaffold **10**, we successfully demonstrated that it is possible to develop a modular ring-closing metathesis approach that can be used to generate aminoindoline-derived, different tricyclic architectures having functionalized medium-sized rings. At present, there are very few examples in DOS literature that are capable of providing natural-product-like, structurally different architectures to be utilized in library generation. The ease of our modular, synthesis-based, ring-closing metathesis approach therefore prompted us to develop this strategy on solid phase. These results are shown in Schemes 2 and 3.

For the solid-phase synthesis, the required compound **17** (Scheme 2) was easily obtained from aminoindoline scaffold **10** in the following steps: (i) *O*-MEM removal; (ii) introduction of three-carbon spacer with the *O*-THP-protected hydroxyl group; (iii) *N*-Teoc removal; (iv) *N*-Fmoc; and finally, (v) *O*-THP deprotection. As in our previous study,[6] for the solid-phase synthesis, we decided to introduce a three-carbon spacer between the phenolic hydroxyl and the primary hydroxyl group available for the loading. The introduction of the spacer serves two useful purposes: (i) to keep the

organic moiety away from the resin polystyrene backbone and (ii) to utilize a primary hydroxyl group for immobilization. The use of a spacer would also be advantageous in printing the small-molecule library onto glass slides and in conducting protein-binding studies with small-molecule microarrays.[12] Having compound **17** as a diastereomeric mixture in hand, the stage was now set for the solid-phase synthesis. Following the Broad Institute loading synthesis protocol and with the use of alkylsilyl linker-based polystyrene macrobeads (loading 1.29 mmol/g, 500−560 μm), we were pleased to note that the loading worked very well, giving product **18** (88.5%) upon cleavage from the macrobead support).[13] The macrobeads are easy to handle, and simple cleavage of two to three beads provides enough product for analytical (i.e., TLC, HPLC, and MS) purposes.

Compound **18**, having orthogonal protected amines (i.e., *N*-Fmoc and *N*-Alloc), offers the advantage of developing a modular approach to DOS in which one pathway (i.e., the use of *N*-Fmoc site in an RCM reaction) would lead to a seven-membered ring, whereas simply altering the site (i.e., the use of *N*-Alloc site in an RCM reaction) would result in the synthesis of an eight-membered ring containing an unsaturated lactam functional group. To test this approach, compound **18** was loaded onto the resin and was then subjected to parallel sequences. In one study, following *N*-Alloc removal, the benzylic amine was derivatized as an amide group (a test of the first diversity). The resin was then subjected to *N*-Fmoc removal and then coupled with acryloyl chloride giving *N*-acryloyl group, **19**. We were delighted to note that when subjected to the ring-closing metathesis reaction, compound **19** on-resin produced the seven-membered ring having an unsaturated lactam functional group (see compound **20**). The final product **21** was thoroughly characterized by MS and NMR studies (see the Experimental Section) as a diastereomeric mixture after cleavage from the support. Although the reaction was very easy and high-yielding in solution, the RCM was observed to be a slow reaction and required nearly 40 mol % of the second-generation Grubbs' catalyst in the solid-phase reaction.

In another series of experiment, compound **18** was loaded onto the resin and subjected to *N*-Fmoc removal, then amide coupling (test of first diversity). Following the *N*-Alloc removal, the benzylic amine then reductively alkylated to give the secondary amine (test of second diversity). The secondary amine was then reacted with acryloyl chloride to produce **22**, a precursor for the ring-closing metathesis reaction. As observed in our previous series with the solid-phase synthesis of the seven-membered ring, the ring-closing metathesis reaction successfully produced the eight-membered ring **23** having an unsaturated lactam functional group. After cleavage of the product from the solid support, compound **24** was thoroughly characterized by MS and NMR studies.

Conclusions

To summarize, in this article, we report successful, modular, solution- and solid-phase approaches toward obtaining aminoindoline-based polycyclic architectures. The production of either seven- or eight-membered ring derivatives is highly attractive for exploring the use of this approach in the diversity planning of library generation.

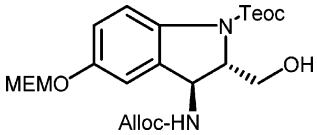
Experimental Section

General Methods. The materials were obtained from commercial suppliers and were used without purification. THF, CH_2Cl_2, and DMF were passed through the activated alumina columns to remove impurities prior to use. 2,6-Lutidine was distilled from CaH_2 under N_2. Column chromatography was performed using Silicycle Ultra Pure Silica Gel (230−400 mesh). Reactions were monitored by thin-layer chromatography (TLC) using Merck 60 F_{254} 0.25-mm silica gel plates.

Small-scale solid-phase reactions (1−50 mg of resin) were performed in 2-mL fritted polypropylene Bio-Spin chromatography columns. Medium-scale solid-phase reactions (20−200 mg) were performed in 10-mL polypropylene PD-10 columns. Agitation of solid-phase reactions was performed using a Barnstead-Thermolyne Labquake shaker. The linker cleavage reactions (<50 mg of beads) were carried out in 1.5-mL Eppendorf tubes. Vacuum removal of solvents for the linker cleavage reactions was accomplished using a Genevac HT-4 Atlas Evaporator.

All NMR experiments were recorded on an AC-Bruker instrument (400 MHz). Unless otherwise noted, proton and carbon chemical shifts are reported in parts per million using residual $CHCl_3$ as an internal standard at 7.26 and 77.0 ppm, respectively. Analysis by mass spectrometry was performed on a VG Quattro I (Micromass) mass spectrometer equipped with a pneumatically assisted electrospray ionization source operating in positive mode. The enantiomeric excess (ee%) was determined by chiral HPLC using a Hewlett-Packard (Agilent) 1090 LC equipped ilent 1100 Series HPLC system.

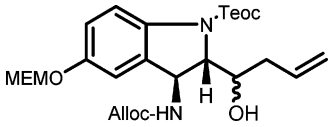
Compound 9.



To a solution of 3-allyloxycarbonylamino-2-benzoyloxymehtyl-5- (2-methoxyethoxymethoxy)-2,3-dihydroindole carboxylic acid 2-trimethylsilanylethyl ester (2.40 g, 4.20 mmol) in methanol (50 mL) was added potassium carbonate (580 mg, 4.20 mmol). The mixture was stirred at room temperature. After 3 h, TLC showed the completion of the reaction. The reaction was neutralized with Amberlite H^+ resin to a pH of 7. The mixture was then filtered. The filtrate was concentrated under reduced pressure. The crude product was diluted with ethyl acetate and washed with brine. The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (1:1, ethyl acetate/hexanes) to give the product **9** (1.80 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (bs, 1H), 7.06 (d, J = 2.4 Hz, 1H), 7.03 (dd, J = 8.8, 2.4 Hz, 1H), 5.94 (m, 1H), 5.34 (d, J = 17.2 Hz, 1H), 5.27−5.23 (m, 3H), 4.99 (d, J = 5.6 Hz, 1H), 4.63 (d, J = 4.6 Hz, 1H), 4.38−4.30 (m, 2H), 3.98 (bs, 1H), 3.83 (t, J = 4.6 Hz, 2H), 3.70 (bs, 1H), 3.58 (t, J = 4.6 Hz, 2H),

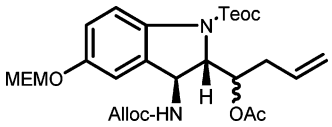
3.39 (s, 3H), 3.13 (bs, 1H), 1.13 (t, J = 8.6 Hz, 2H), 0.08 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 154.1, 132.7, 118.9, 118.7, 117.0, 113.9, 94.5, 72.0, 69.9, 68.0, 66.6, 64.8, 63.8, 59.4, 55.2, 18.4, −1.1; MS (ES+) m/z 497.4 (M + 1).

Compound 10.



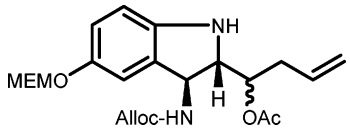
The Dess−Martin periodinane (2.17 g, 5.13 mmol) was added to a solution of compound **9** (1.69 g, 3.42 mmol) and sodium bicarbonate (1.72 g, 20.52 mmol) in dichloromethane (75 mL). The resulting suspension was stirred for 2 h at 0 °C and 1 h at room temperature. TLC showed complete conversion to the aldehyde after 3 h. The mixture was then washed with 10% sodium thiosulfate solution and brine sequentially. The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was dried on the high-vacuum pump for 1 h. The resulting aldehyde was dissolved in dry THF (20 mL) and cooled to −78 °C, and after it was stirred for 30 min, a solution of $ZnCl_2$ (17.0 mL, 17.0 mmol) was added. After 30 min, a solution of allylmagnesium bromide (13.68 mL, 13.68 mmol) was added, and the reaction mixture was stirred for 1 h at −78 °C. TLC showed completion of the reaction. The mixture was quenched with saturated NH_4Cl solution, diluted with ethyl acetate, and washed with water and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (1:1, ethyl acetate/hexanes) to give the product **10** as a diastereomeric mixture (1.29 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.00 (m, 3H), 6.00−5.86 (m, 2H), 5.34 (d, J = 17.2 Hz, 1H), 5.26 (s, 2H), 5.24−5.02 (m, 3H), 4.62 (d, J = 6.7 Hz, 2H), 4.30 (m, 2H), 4.08 (bs, 1H), 3.84 (m, 2H), 3.58 (t, J = 4.6 Hz, 2H), 3.42 (s, 3H), 2.42 (m, 2H), 1.26 (t, J = 7.2, 2H), 0.09 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 155.6, 152.4, 135.2, 134.1, 133.2, 119.2, 118.8, 118.3, 117.5, 116.8, 114.1, 96.4, 72.3, 71.6, 69.2, 67.9, 66.5, 59.7, 52.8, 36.1, 21.4, 20.2, 18.4, −1.1; MS (ES$^+$) m/z 537.4 (M + 1).

Cmpound 10a.



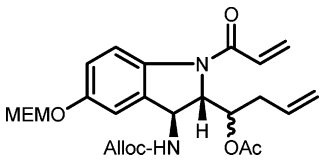
To a solution of **10** (1.20 g, 2.23 mmol) and DMAP (326 mg, 2.67 mmol) in dry CH_2Cl_2 (25 mL) was added acetic anhydride (420μL, 4.46 mmol). The mixture was stirred at room temperature overnight. The reaction was quenched with saturated NH_4Cl solution and washed with water and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (1:1, ethyl acetate/hexanes) to give the product as a mixture of two diastereomers **10a** (1.18 g, 91.5%) as a colorless syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (bs, 1H), 7.05 (d, J = 2.1 Hz, 1H), 7.02 (d, J = 9.0 Hz, 1H), 5.99−5.87 (m, 1H), 5.82−5.72 (m, 1H), 5.34 (d, J = 6.5 Hz, 1H), 5.31−5.18 (m, 4H), 5.11 (d, J = 10.0 Hz, 1H), 5.05−5.01 (m, 2H), 4.67−4.52 (m, 2H), 4.39−4.30 (m, 2H), 3.84 (t, J = 5.5 Hz, 2 H), 3.60 (t, J = 5.5 Hz, 2H), 3.39 (s, 3H), 2.66−2.46 (m, 2H), 2.29−2.07 (m, 2H), 1.55 (s, 3H), 1.16 (m, 2H), 0.07 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 155.1, 154.2, 153.9, 153.5, 133.7, 133.4, 132.9, 118.8, 118.4, 118.1, 116.2, 94.5, 71.9, 69.8, 68.0, 66.7, 66.2, 64.8, 59.4, 53.4, 35.1, 21.2, 20.6, 18.1, −1.1; MS (ES$^+$) m/z 578.3 (M + 1).

Compound 10b.



TBAF solution (1 M, 1.71 mL, 1.71 mmol) was added to the solution of compound **10a** (495 mg, 0.85 mmol) in THF (20 mL) at 0 °C. The solution was stirred at room temperature for 2 h. The solution was washed with saturated NH_4Cl solution, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (2:3, ethyl acetate/hexanes) to give the product **10b** (340 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.2 Hz, 1H), 7.10 (d, J = 2.1 Hz, 1H), 7.04 (dd, J = 8.2,1.5 Hz, 1H), 5.95 (m, 1H), 5.80 (m, 1H), 5.56 (bs, 1H), 5.34−5.15 (m, 7H), 4.65 (m, 1H), 4.65 (m, 2H), 4.13 (d, J = 5.7 Hz, 1H), 3.83 (m, 2H), 3.57 (m, 2 H), 3.39 (s, 3H), 2.73−2.56 (m, 2H), 1.94 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 155.7, 149.2, 143.7, 137.4, 133.7, 124.9, 116.8, 115.4, 114.6, 112.8, 112.1, 76.3, 72.8, 67.0, 64.7, 60.3, 59.2, 57.4, 34.1, 21.6; MS (ES$^+$) m/z 435.3 (M + 1).

Compound 11.



To a solution of **10b** (150 mg, 0.34 mmol) and pyridine (0.550 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C was added a solution of acryloyl chloride (42 μL, 0.51 mmol), and the mixture was stirred for 2 h. The reaction was quenched with saturated NH_4Cl solution and washed with water and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (1:1, ethyl acetate/hexanes) to give compound **11** as a mixture of two diastereomers (0.155 g, 92%). The two isomers were separated as **12a** (100 mg, 65%; major isomer) and **12b** (54 mg, 27%; minor isomer).

12a (Major Isomer). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (bs, 1H), 7.10 (s, 1H), 7.01 (d, J = 8.0 Hz, 1H), 6.64−6.43 (m, 2H), 6.00−5.90 (m, 1H), 5.75 (d, J = 11.5 Hz, 1H), 5.82−5.73 (m, 1H), 5.39−5.10 (m, 9H), 4.72 (d, J = 4.0 Hz, 2H), 4.56 (bs, 1H), 3.85 (t, J = 5.0 Hz, 2H), 3.57 (t, J = 5.0 Hz, 2H), 3.39 (s, 3H), 2.75−2.66 (m, 1H), 2.59−2.51 (m, 1H), 1.52 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 164.3, 155.2, 155.1, 133.1, 132.7, 130.4, 128.6, 118.9, 118.8,

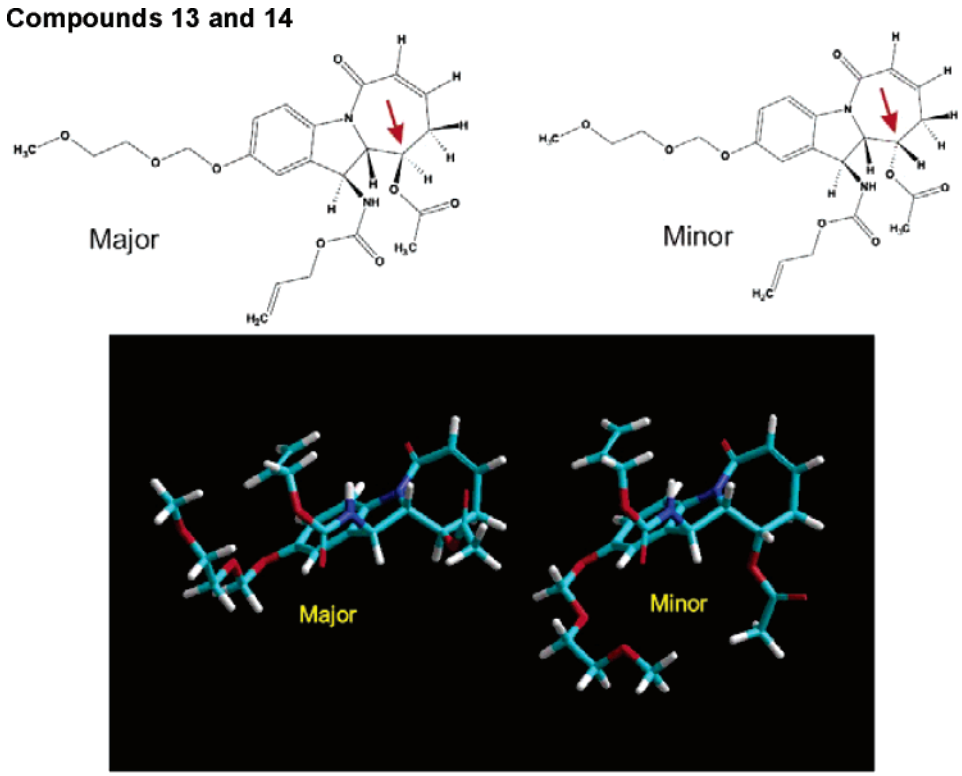
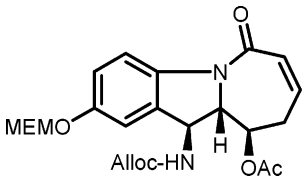


Figure 3.

118.4, 113.4, 94.3, 78.7, 72.4, 71.9, 68.1, 66.3, 59.4, 53.6, 33.0, 21.3; MS (ES^+) *m*/*z* 489.2 (M + 1).

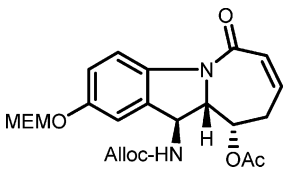
12b (Minor Isomer). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 7.7 Hz, 1H), 7.08 (d, J = 7.7 Hz, 1H), 7.06 (d, J = 2.2 Hz, 1H), 6.87 (dd, J = 16.5, 10.0 Hz, 1H), 6.60 (d, J = 15.8 Hz, 1H), 5.97−5.92 (m, 1H), 5.87 (dd, J = 11.7, 1.5 Hz, 1H), 5.71−5.60 (m, 1H), 5.31 (d, J = 16.5 Hz, 1H), 5.26 (m, 4H), 5.05−5.01 (m, 3H), 4.95−4.92 (m, 2H), 4.64−4.55 (m, 3H), 3.85 (m, 2H), 3.60 (t, J = 5.5 Hz, 2H), 3.40 (s, 3H), 2.28−2.20 (m, 2H), 2.19 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 164.3, 155.2, 155.1, 133.1, 132.7, 130.4, 128.6, 118.9, 118.8, 118.4, 113.4, 94.3, 78.7, 72.4, 71.9, 68.1, 66.3, 59.4, 53.6, 33.0, 21.3; MS (ES^+) *m*/*z* 489.2 (M + 1).

Compound 13.



To a solution of compound **12a** (90 mg, 0.184 mmol) in dichloromethane (10 mL) was added 20 mol % of second-generation Grubbs' catalyst (31 mg, 0.036 mmol). The reaction mixture was stirred for 3 h at room temperature. It was then concentrated under vacuum, and the crude product was purified by column chromatography (1:3 to 2:3, ethyl acetate/hexanes). (See Figures 3−6.) The seven-member ring derivative **13** was obtained as a colorless syrup (70.5 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.5 Hz, 1H), 7.06 (d, J = 3.0 Hz, 1H), 7.03 (d, J = 8.5 Hz, 1H), 6.42 (m, 1H), 6.18 (dd, J = 12.5, 1.5 Hz, 1H), 5.92 (m, 1H), 5.37−5.28 (m, 2H), 5.27−5.16 (m, 4H), 5.12 (d, J = 8.0 Hz, 1H), 4.59 (d, J = 5.5 Hz, 1H), 4.14 (d, J = 9.7 Hz, 1H), 3.83 (dd, J = 4.7, 1.5 Hz, 2H), 3.58 (t, J = 4.7 Hz, 2H), 3.39 (s, 3H), 2.75−2.65 (m, 1H), 2.48 −2.40 (dd, J = 16.5, 8.0 Hz, 1H), 2.20 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 165.8, 155.2, 155.1, 136.7, 135.9, 132.9, 130.6, 129.7, 118.9, 118.6, 118.3, 114.1, 94.3, 75.4, 71.9, 70.7, 68.1, 66.2, 59.4, 55.5, 31.8, 21.6; LRMS: MS (ES^+) *m*/*z* 461.3 (M + 1).

Compound 14.



To a solution of compound **12b** (50 mg, 0.082 mmol) in dichloromethane (5.0 mL) was added 20 mol % of second-generation Grubbs' catalyst (31 mg, 0.016 mmol). The reaction mixture was stirred for 3 h at room temperature. It was concentrated under vacuum, and the crude product was purified by column chromatography (1:3 to 2:3, ethyl acetate/hexanes). The seven-member ring derivative **14** was obtained as a colorless syrup (30 mg, 80%). ^{1}H NMR (400 MHz,

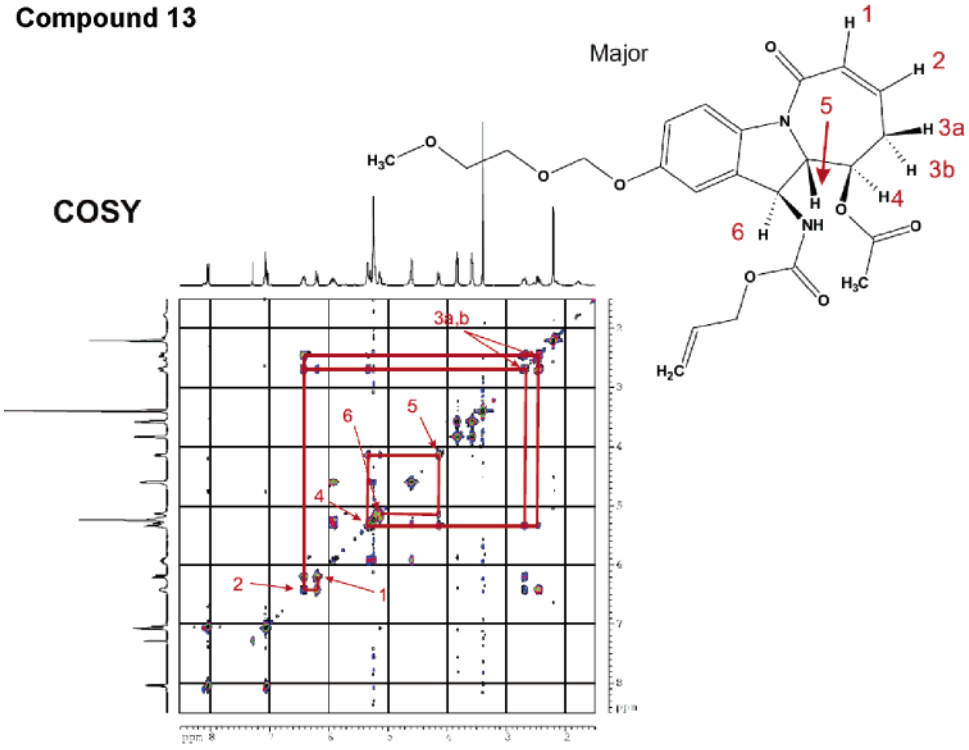


Figure 4.

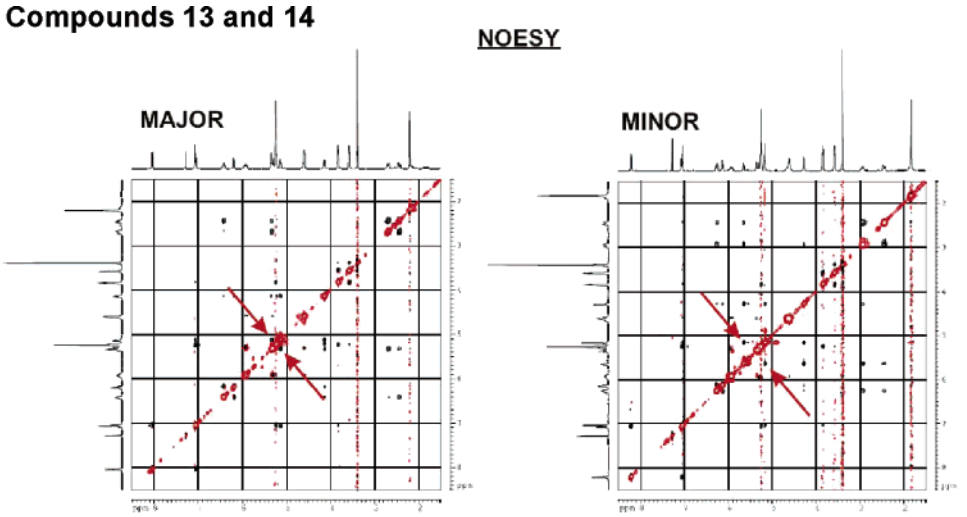
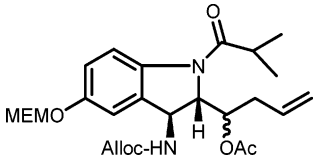


Figure 5.

$CDCl_3$) δ 8.21 (d, J = 9.0 Hz, 1H), 7.06 (dd, J = 8.5, 2.5 Hz, 1H), 7.03 (d, J = 1.5 Hz, 1H), 6.26 (m, 1H), 6.13 (d, J = 12.0 Hz, 1H), 5.94 (m, 1H), 5.65 (t, J = 5.5 Hz, 1H), 5.33 (d, J = 16.5 Hz, 1H), 5.28−5.23 (m, 3H), 5.17 (s, 2H), 4.66−4.57 (m, 2H), 4.28 (d, J = 1.1 Hz, 1H), 3.83 (t, J = 5.5 Hz, 2H), 3.58 (t, J = 5.5 Hz, 2H), 3.39 (s, 3H), 2.99−2.89 (dt, J = 17.0, 6.5 Hz, 1H), 2.46−2.42 (dt, J = 17.0, 4.5 Hz 1H), 1.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 165.1, 155.6, 155.1, 136.1, 135.7, 135.9, 132.4, 130.6, 129.1, 118.6, 118.2, 117.9, 114.1, 93.8, 75.1, 71.8, 70.4, 68.3, 66.7, 59.6, 55.1, 32.1, 21.8; LRMS: MS (ES^+) m/z 461.3 (M + 1).

Compound 10c.



To a solution of **10b** (100 mg, 0.230 mmol) and pyridine (37 μL, 0.460 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C was added isobutyryl chloride (36 μL, 0.345 mmol), and the mixture was stirred for 1 h. The mixture was then stirred at

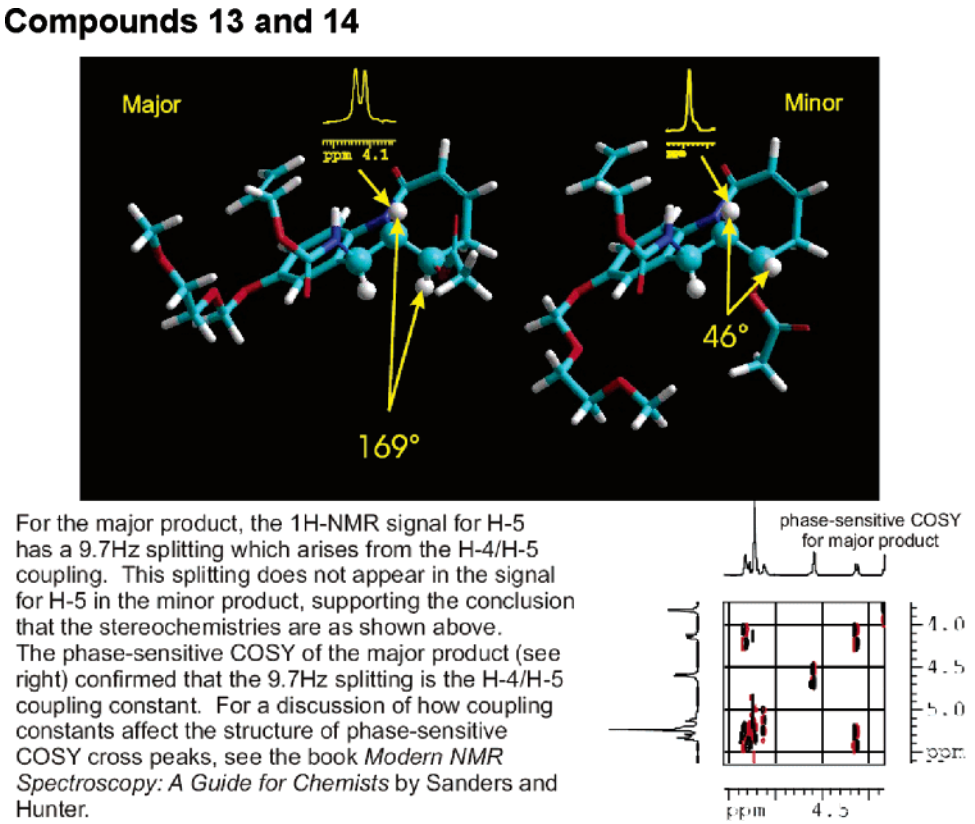


Figure 6.

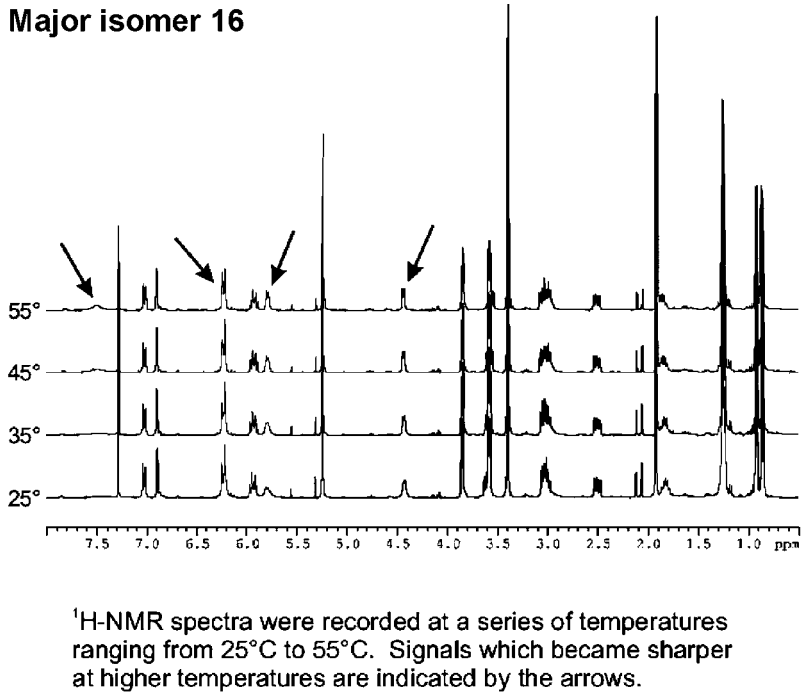
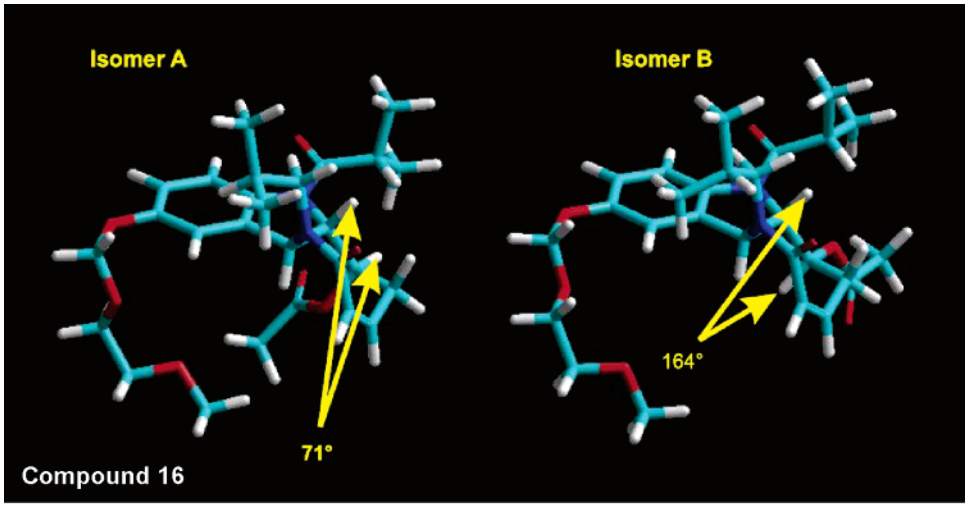


Figure 7.

room temperature for4 h. The reaction was quenched with saturated NH_4Cl solution and washed with water and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (1:1 ethyl acetate/hexanes) to give the product **10c** as a mixture of two diastereomers (106.5 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 8.0 Hz, 1H), 7.07 (d, J = 2.1 Hz, 1H), 7.00 (dd, J = 8.0, 2.2 Hz, 1H), 5.92 (m, 1H), 5.7 (m, 1H), 5.36−5.21 (m, 5H), 5.15 (m, 1H), 5.05 (d, J = 8.0 Hz, 1H), 5.00 (d, J = 7.0 Hz, 1H), 4.96−4.87 (m, 1H), 4.66−4.58 (m, 2H), 3.83 (m, 2 H), 3.57 (m, 2H), 3.39 (s, 3H), 3.07 (m, 1H), 2.69 (m, 1H), 2.56 (m, 1H), 1.52 (s, 3H), 1.28 (d, J = 7.0 Hz, 3H), 1.21 (d, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 171.3, 155.4, 154.8, 138.4, 133.2, 132.8, 131.7, 119.1,

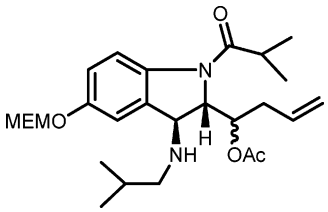


A conformational search was performed using the quenched dynamics technique. A total of 600 minimized structures were obtained for each isomer and the lowest energy structures are shown above. The H-4/H-5 dihedral angles are shown for each isomer. From the Karplus equation, we would expect an angle of 71° to give a coupling constant of around 2Hz and an angle of 164° to give a coupling constant of around 10Hz. The experimental value was 1.7Hz which supports Isomer A. Also, the NOESY showed no H-4/H-6 cross peak which is consistent with Isomer A.

Figure 8.

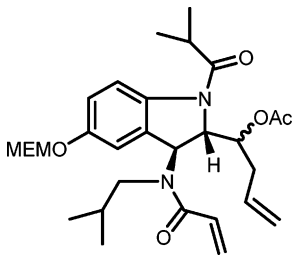
118.4, 114.9, 113.5, 113.0, 97.8, 72.3, 71.9, 69.7, 68.0, 66.3, 59.4, 53.7, 35.2, 32.8, 20.8, 20.4; MS (ES^+) *m*/*z* 505.3 (M + 1).

Compound 10d.



To a solution of **10c** (80 mg, 0.158 mmol) in dry CH_2Cl_2 (5 mL) under N_2 atmosphere at 0 °C, was added morpholine (27.6 μL, 0.317 mmol) and tetrakis(triphenylphosphine) palladium (0) catalyst (18.2 mg, 0.0158 mmol). The round-bottom flask containing the mixture was covered with aluminum foil and stirred for 1 h. TLC showed the completion of the reaction. The reaction was quenched with saturated NH_4Cl solution and washed with water and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was then dissolved in triethyl orthoformate (4.0 mL), and a solution of $NaCNBH_4$ (14.9 mg, 0.237 mmol) in TMOF/MeOH/ACOH (1.0 mL/200 μL/20 μL) and isobutaraldehyde (16 μL, 0.173 mmol) was added to the mixture at room temperature. The reaction mixture was stirred for 4 h. The reaction was quenched with saturated NH_4Cl solution and washed with water and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1:1 ethyl acetate/hexanes) to give the product **10d** (52.2 mg, 70%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.7 Hz, 1H), 7.16−7.02 (m, 1H), 5.80 (m, 1H), 5.44 (m, 1H), 5.31−5.23 (m, 3H), 5.04 (m, 1H), 4.81 (m, 1H), 3.84 (m, 2H), 3.58 (m, 2H), 3.39 (s, 3H), 3.15 (m, 1H), 2.52 (m, 2H), 2.25−2.12 (m, 2H), 1.65 (s, 3H), 1.70 (m, 2H), 1.60−1.41 (m, 6), 1.36−1.30 (m, 3H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.70 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 170.9, 162.4, 156.9, 137.2, 135.9, 132.7, 131.8, 129.3, 122.7, 112.5, 112.1, 93.6, 74.1, 72.1, 59.7, 56.7, 54.6, 52.1, 33.6, 26.4, 20.3, 2016; LRMS: MS (ES^+) *m*/*z* 477.3 (M + 1).

Compound 15.



To a solution of **10d** (50 mg, 0.105 mmol) and pyridine (17 μL, 0.210 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C, was added acryloyl chloride (13 μL, 0.157 mmol) and stirred for 2 h. The reaction was quenched with saturated NH_4Cl solution and washed with water and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (2:3 ethyl acetate/hexanes) to give the product **15** as a mixture of two diastereomers (52.4 mg, 94%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 7.2 Hz, 1H), 7.07−6.94 (m, 2H), 6.66−6.54 (m, 1H), 6.50−6.38 (m, 1H), 5.80−5.71 (m, 2H), 5.47 (m, 1H), 5.35 (m, 1H), 5.29−5.21 (m, 2H), 5.17−5.11 (m, 1H), 5.09−5.01 (m, 1H), 3.82 (m, 2H), 3.587 (m, 2 H), 3.39 (s, 3H), 3.19−3.12 (m, 1H), 3.01−2.82 (m, 2H), 2.65−2.50 (m, 2H), 2.29−2.17 (m, 1H), 2.12 (s, 3H), 1.69 (m, 1H), 1.36−1.30 (m, 3H), 1.25−1.18 (m,

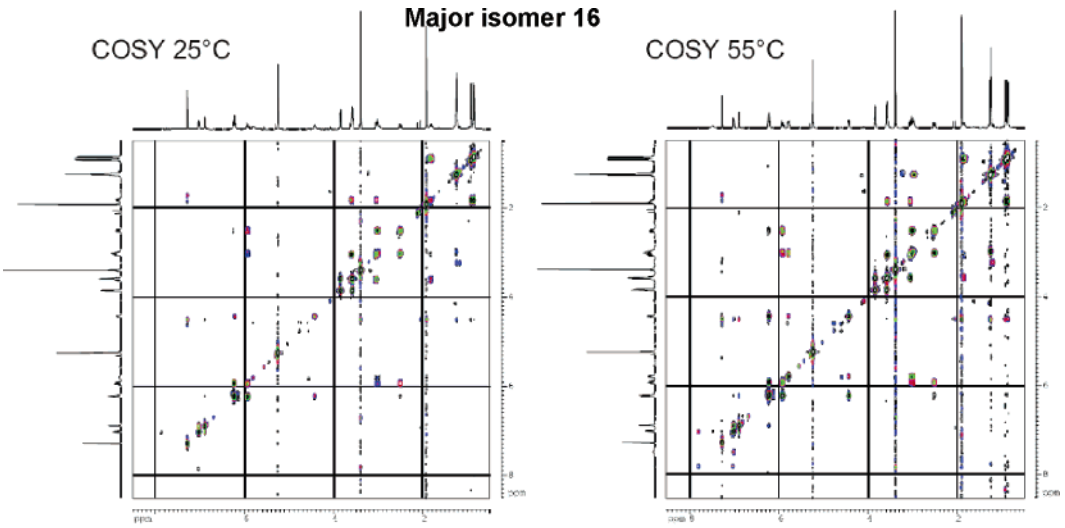


Figure 9.

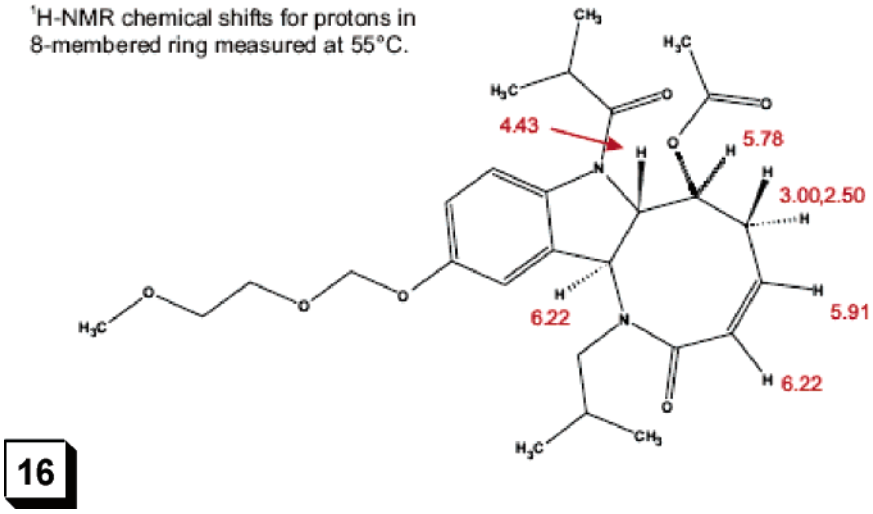
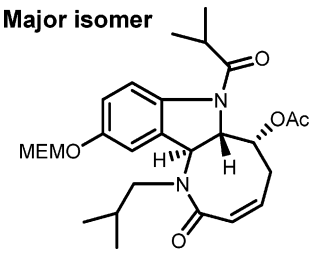


Figure 10.

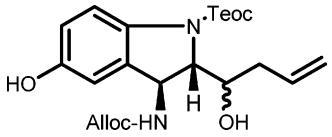
3H), 0.75−0.68 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 170.9, 162.4, 156.9, 137.2, 135.9, 132.7, 131.8, 129.3, 122.7, 112.5, 112.1, 93.6, 74.1, 72.1, 59.6, 56.7, 54.6, 52.1, 33.6, 26.4, 20.6, 20.3; LRMS;: MS (ES^+) *m*/*z* 531.3 (M + 1).

Compound 16.



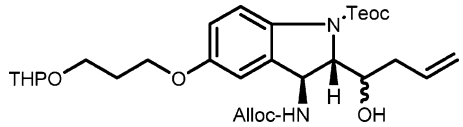
To the solution of compound **15** (45 mg, 0.085 mmol) in dichloromethane (5 mL) was added 20 mol % of second-generation Grubbs' catalyst (31 mg, 0.0169 mmol). The reaction mixture was stirred for 16 h at room temperature. It was then concentrated under vacuum, and the crude product was purified by column chromatography on silica gel (ethyl acetate/hexanes 1:1 to 3:1). (See Figures 7−10.) The eight-member ring derivative **16** was obtained as a diasteoreomeric mixture (35.1 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) on the major isomer δ 7.50 (bs, 1H), 7.02 (dd, J = 9.0, 1.7 Hz, 1H), 6.89 (d, J = 1.5 Hz, 1H), 6.22 (d, J = 10.3 Hz, 2H), 5.91 (m, 1H), 5.78 (d, J = 7.5 Hz, 1H), 5.24 (s, 2H), 4.43 (d, J = 5.7 Hz, 1H), 3.85 (t, J = 5.0 Hz, 2H), 3.53 (m, 3H), 3.39 (s, 3H), 3.09−2.93 (m, 2H), 2.50 (dd, J = 14.5, 7.7 Hz, 1H), 1.90 (s, 3H), 1.85 (m, 1H), 1.25 (t, J = 6.0 Hz, 6H), 0.92 (d, J = 6.2 Hz, 3H), 0.85 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 170.2, 169.8, 154.0, 129.3, 118.3, 97.8, 94.5, 71.9, 68.9, 68.2, 59.4, 49.9, 33.6, 29.0, 28.0, 21.2, 21.0, 20.9, 20.3; LRMS: MS (ES^+) *m*/*z* 503.3 (M + 1).

Compound 10c.



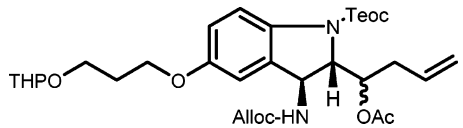
To a solution of compound **10** (2.50 g, 4.66 mmol) in EtOH (50 mL) was added *p*-TSA (888 mg, 4.46 mmol). The solution was stirred at 50 °C for 24 h. The solvent was removed under vacuum, and the residue was diluted with ethyl acetate (50 mL) and washed with sodium bicarbonate solution and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (1:1 ethyl acetate/hexanes) to give the product **10c** (1.92 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (bs, 1H), 6.81 (d, J = 8.7 Hz, 1H), 6.77 (d, J = 2.5 Hz, 1H), 6.00−5.76 (m, 2H), 5.33 (d, J = 16.8 Hz, 1H), 5.25 (d, J = 10.0 Hz, 1H), 5.21−4.99 (m, 3H), 4.61 (d, J = 4.7 Hz, 2H), 4.33 (t, J = 7.7 Hz, 2H), 4.08 (t J = 6.5 Hz, 1H), 2.41 (bs, 1H), 2.20 (m, 1H), 2.05 (m, 1H), 0.08 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 154.8, 153.9, 137.8, 133.7, 133.4, 133.1, 132.3, 122.4, 117.0, 116.2, 114.1, 113.2, 71.0, 65.3, 64.6, 61.2, 55.8, 17.3, −1.1; MS (ES$^+$) m/z 449.3 (M + 1).

Compound 10d.



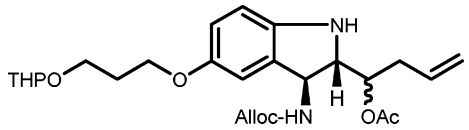
Compound **10c** (1.91 g, 4.26 mmol), 3-(tetrahydro-*2H*-pyran-2-yloxy)propyl 4-methylbenzenesulfonate (1.60 g, 5.11 mmol), and cesium carbonate (1.80 g, 5. 53 mmol) were added to DMF (30 mL). The mixture was stirred at room temperature for 12 h, then the DMF was removed under reduced pressure. The mixture was diluted with ethyl acetate (50 mL) and washed with brine. The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (1:2 ethyl acetate/hexanes) to give the product **10d** (2.13 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (bs, 1H), 6.91−6.84 (m, 2H), 6.00−5.80 (m, 2H), 5.33 (d, J = 17.0 Hz, 1H), 5.25 (d, J = 10.0 Hz, 1H), 5.16 (d, J = 16.0 Hz, 1H), 5.13 (d, J = 10.0 Hz, 1H), 5.03 (d, J = 8.5 Hz, 1H), 4.61 (m, 3H), 4.33 (m, 2H), 4.12−4.02 (m, 3H), 3.97−3.83 (m, 2H), 3.62−3.48 (m, 2H), 2.41 (bs, 1H), 2.11−2.02 (m, 2H), 1.89−1.76 (m, 2H), 1.74−1.66 (m, 2H), 1.62−1.48 (m, 5H), 1.20−1.09 (m, 2H), 0.09 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 152.8, 140.9, 137.8, 132.4, 130.7, 121.1, 115.3, 114.7, 113.9, 112.1, 100.6, 71.5, 68.3, 67.6, 63.9, 60.8, 60.1, 59.3, 51.8, 37.4, 33.6, 31.8, 28.2, 19.3, 16.7, −1.1; MS (ES$^+$) m/z 591.5 (M + 1).

Compound 10e.



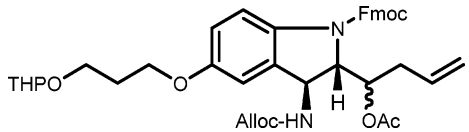
To a solution of **10d** (2.10 g, 3.55 mmol) and DMAP (0.52 g, 4.27 mmol) in dry CH_2Cl_2 (50 mL) was added acetic anhydride (670 μL, 7.10 mmol). The mixture was stirred at room temperature for 4 h. The reaction was quenched with saturated NH_4Cl solution and washed with water and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (1:1 ethyl acetate/hexanes) to give the product **10e** as a mixture of two diastereomers (1.97 g, 88%) as colorless syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (bs, 1H), 6.91−6.84 (m, 2H), 5.99−5.81 (m, 2H), 5.35 (d, J = 16.5 Hz, 1H), 5.27 (d, J = 9.4 Hz, 1H), 5.18−5.04 (m, 3H), 4.66 (m, 3H), 4.36 (m, 2H), 4.16−4.07 (m, 3H), 3.92−3.82 (m, 2H), 3.67−3.51 (m, 2H), 2.38−2.14 (m, 2H), 1.87 (s, 3H), 1.85−1.78 (m, 4H), 1.69−1.51 (m, 5H), 1.29−1.10 (m, 2H), 0.09 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 155.7, 154.2, 152.3, 137.8, 133.7, 132.8, 131.9, 121.6, 117.1, 115.8, 112.7, 111.5, 106.8, 73.9, 66.1, 65.0, 64.9, 62.8, 60.1, 57.3, 55.6, 37.4, 34.1, 30.8, 29.4, 25.3, 21.6, 16.7, −1.1; MS (ES$^+$) m/z 633.3 (M + 1).

Compound 10f.



TBAF solution (1 M, 6.16 mL, 6.16 mmol) was added to the solution of compound **10e** (1.95 g, 3.08 mmol) in THF (50 mL). The solution was stirred at room temperature for 1 h. The organic solution was washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (3:2 ethyl acetate/hexanes) to give the product **10f** (1.36 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90−6.88 (m, 2H), 6.79 (d, J = 8.5 Hz, 1H), 5.95 (m, 1H), 5.86−5.75 (m, 1H), 5.43−5.35 (m, 2H), 5.33−5.23 (m, 2H), 5.18−5.09 (m, 2H), 4.65−4.58 (m, 3H), 4.03 (m, 2H), 3.97−3.83 (m, 3H), 3.61−3.49 (m, 2H), 2.56 (m, 2H), 2.06 (m, 2H), 1.92 (s, 3H), 1.87−1.79 (m, 1H), 1.77−1.69 (m, 1H), 1.65 (m, 1H), 1.63−1.48 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 157.3, 147.2, 140.2, 137.7, 135.1, 124.0, 114.8, 113.1, 112.2, 100.6, 76.1, 68.9, 67.4, 63.8, 60.4, 55.1, 33.5, 32.6, 31.8, 27.9, 19.2, 18.8; MS (ES$^+$) m/z 489.3 (M + 1).

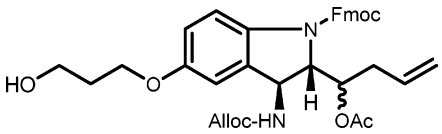
Compound 10g.



To a solution of the compound **10f** (1.35 g, 2.76 mmol) in ethyl acetate (25 mL) was added 5% aqueous sodium bicarbonate solution (25 mL) and Fmoc-chloride (1.06 g, 4.14 mmol). The mixture was stirred at room temperature for 1.5 h and then separated. The organic phase was washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (1:2 ethyl acetate/hexanes) to give the product **10g** (1.85 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 7.2 Hz, 2H), 7.70−7.58 (m, 3H),

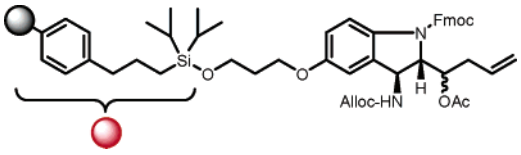
7.42 (t, J = 7.2 Hz, 2H), 7.34 (t, J = 7.2 Hz, 2H), 6.85 (m, 2H), 5.95 (m, 1H), 5.39−5.23 (m, 2H), 5.16 (d, J = 8.2 Hz, 1H), 4.98 (m, 1H), 4.87−4.79 (m, 2H), 4.75−4.59 (m, 3H), 4.35 (m, 2H), 4.08 (t, J = 5.5 Hz, 2H), 3.97−3.83 (m, 2H), 3.62−3.49 (m, 2H), 2.56−2.45 (m, 1H), 2.11−2.02 (m, 4H), 1.93−1.79 (m, 1H), 1.72 (m, 1H), 1.64−1.46 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 157.1, 154.7, 152.9, 142.3, 140.1, 137.6, 135.3, 132.1, 129.8, 128.5, 128.2, 127.2, 121.0, 114.8, 114.1, 111.9, 101.3, 73.6, 68.3, 67.5, 63.8, 60.1, 57.9, 51.2, 38.4, 33.6, 32.4, 31.8, 21.0, 19.9; MS (ES$^+$) m/z 711.3 (M + 1).

Compound 17.



PPTS (650 mg, 2.59 mmol) was added to a solution of compound **10g** (1.84 g, 2.59 mmol) in ethanol (50 mL). The solution was stirred at 55 °C for 48 h, then it was diluted with ethyl acetate (60 mL), washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (1:1 ethyl acetate/hexanes) to give the product **17** (1.50 g, 92.5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (m, 2H), 7.70−7.59 (m, 3H), 7.42 (t, J = 7.2 Hz, 2H), 7.30 (t, J = 7.2 Hz, 2H), 6.85 (m, 2H), 5.88 (m, 1H), 5.68−5.54 (m, 1H), 5.33 (d, J = 16.2 Hz, 1H), 5.26 (d, J = 8.2 Hz, 1H), 5.11 (d, J = 7.2 Hz, 1H), 5.00−4.93 (m, 2H), 4.89 (m, 1H), 4.81 (m, 1H), 4.69−4.58 (m, 3H), 4.30 (t, J = 5.2 Hz, 1H), 4.07 (t, J = 5.7 Hz, 2H), 3.87 (t, J = 5.7 Hz, 2H), 2.59−2.40 (m, 1H), 2.33−2.15 (m, 1H), 2.04 (s, 3H), 1.71 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 154.5, 152.8, 155.7, 143.9, 142.1, 137.9, 133.8, 132.2, 131.3, 128.5, 128.3, 128.0, 126.3, 122.4, 116.7, 115.3, 112.5, 111.7, 73.4, 68.3, 67.8, 64.6, 61.0, 55.3, 55.0, 34.1, 31.8, 21.2; LRMS: MS (ES$^+$) m/z 627.4 (M + 1).

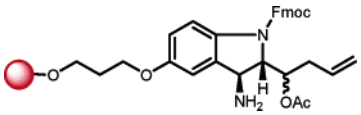
Solid-Phase Synthesis. Compound 18. (1) Loading.



3-[Diisopropyl(*p*-methoxyphenyl)silyl]propyl functionalized resin (150 mg, 0.193 mmol) was swollen in CH_2Cl_2 (3.0 mL) under N_2 for 30 min. The solvent was then drained under positive N_2 pressure. A solution of trifluoromethanesulfonic acid in CH_2Cl_2 (4%, 2.55 mL, 1.16 mmol) was added by syringe. The resin was then gently agitated for 15 min under N_2. The acid solvent was drained under positive N_2 pressure and washed once with dry CH_2Cl_2 (3.0 mL). The activated resin in 1 mL of CH_2Cl_2 was treated with 2,6-lutidine (150 μL, 1.54 mmol) for 15 min, followed by addition of a solution of compound **17** (242 mg, 0.387 mmol) in CH_2Cl_2 (1.5 mL). The resin was gently shaken overnight. The resin was washed with CH_2Cl_2 (3×), THF (3×), and CH_2Cl_2 (3×). The resin was then dried under vacuum overnight to give 236 mg of the loaded resin **18**.

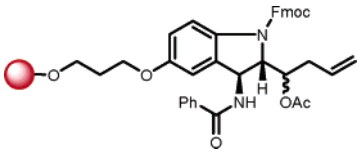
(2) Cleavage. The loaded resin (20 mg) in an Eppendorf tube was swelled in THF (0.5 mL) for 30 min and treated with HF−pyridine solution (15.0 μL). The reaction tube was shaken for 2 h. Methoxytrimethylsilane (150 μL) was added, and the tube was shaken for another 30 min. The solution was removed, and the resin was washed with THF. All solvents were combined and concentrated. The crude sample was purified by column chromatography (1:1 ethyl acetate/hexanes) to give the product **17** (8.5 mg, 88.5% loading).

Compound 18a.



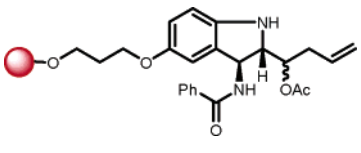
Resin **18** (100 mg) was swelled in CH_2Cl_2 (3.0 mL) for 30 min. A stock solution of DCM, *N*-methylmorpholine, acetic acid (5/0.32/0.66, 3.0 mL), triphenylphosphine (528 mg, 1.60 mmol), and tetrakis(triphenylphosphine)palladium (0) (392 mg, 0.340 mmol) were added the mixture. The mixture was shaken for 3 h. The resin was washed with CH_2Cl_2 (3×), THF (3×), and CH_2Cl_2 (3×) and vacuum-dried overnight to give 89 mg of the resin **18a**. The dried resin (5.0 mg) was cleaved by the above method using HF−pyridine solution. The resulting compound was checked by MS. LRMS (MS ES$^+$) calcd for $C_{32}H_{34}N_2O_6$, 543.2 m/z (M + 1)$^+$; observed, 543.4.

Compound 18b.



Resin **18a** (84 mg) was swelled in CH_2Cl_2 (2.5 mL) under N_2 for 30 min. Collidine (132 μL, 1.0 mmol) and benzoylchloride (60 μL, 0.250 mmol) were added to the mixture, and the mixture was shaken for 24 h. The resin was washed with CH_2Cl_2 (3×), THF (3×), and CH_2Cl_2 (3×). The resin was then dried under vacuum overnight to give 90 mg of the resin **18b.** The dried resin (5.0 mg) was cleaved by the above method using HF−pyridine solution. The resulting compound was checked by MS. LRMS (MS ES$^+$) calcd for $C_{39}H_{38}N_2O_7$, 647.2 m/z (M + 1)$^+$; observed, 647.2.

Compound 18c.



Resin (84 mg) **18b** was swelled in DMF (5.0 mL) for 30 min. Piperidine (0.5 mL) was added to the mixture, and the mixture was shaken for 1h. The resin was washed with DMF (3×), THF (3×), and CH_2Cl_2 (3×). The resin was then dried under vacuum overnight to give 72.5 mg of the resin **18c**. The dried resin (5 mg) was cleaved by the above method using HF−pyridine solution. The resulting compound was checked by MS. LRMS (MS ES$^+$) calcd for $C_{24}H_{25}N_2O_5$, 425.2 m/z (M + 1)$^+$; observed, 425.3.

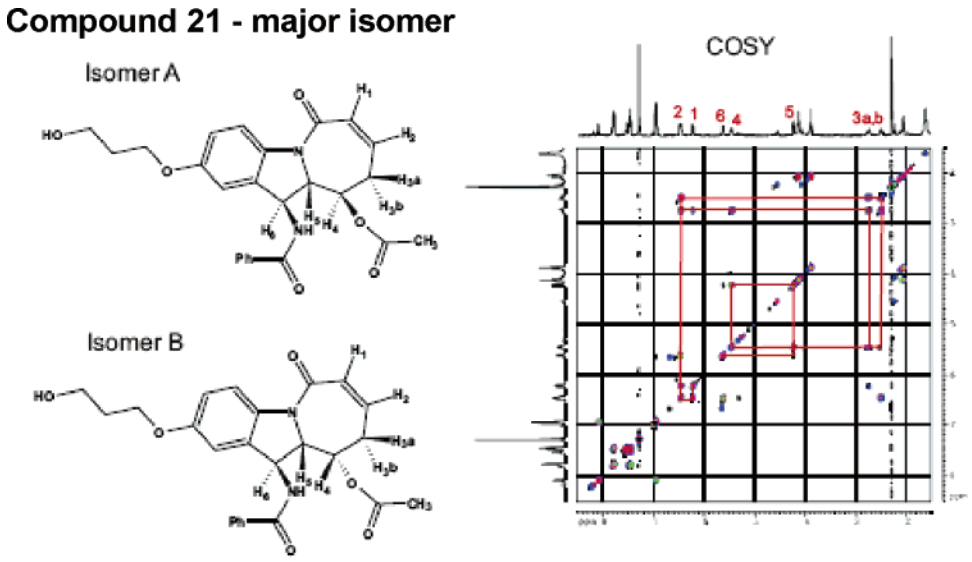


Figure 11.

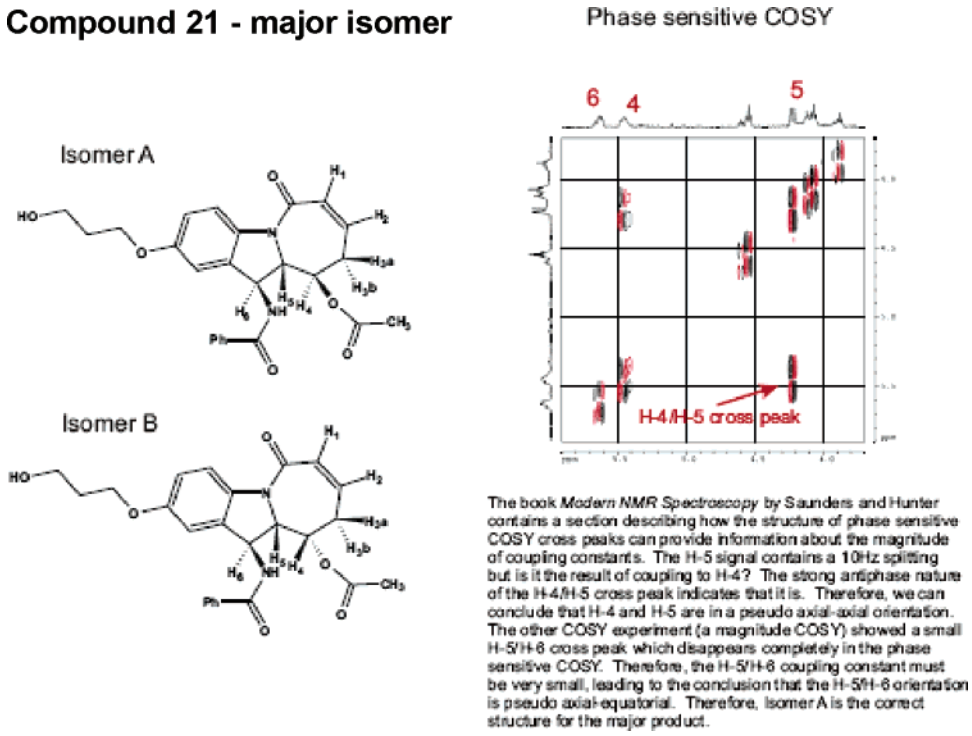
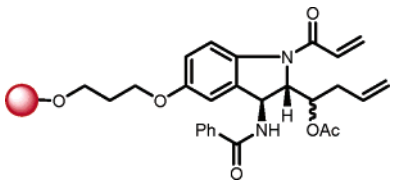


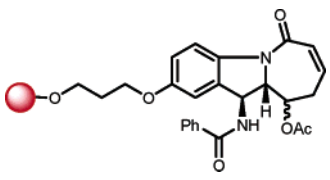
Figure 12.

Compound 19.



Resin **18c** (65 mg) was swelled in CH_2Cl_2 (5.0 mL) under N_2 for 30 min. The resin-containing vial was cooled to 0 °C, and collidine (260 μL, 1.20 mmol) and acryloyl chloride (μL, 1.20 mmol) were added to the mixture. The mixture was shaken for 24 h at room temperature. The resin was washed with CH_2Cl_2 (3×), THF (3×), and CH_2Cl_2 (3×). The resin was vacuum-dried overnight to give 70 mg of the resin **19**. The dried resin (5.0 mg) was cleaved by the above method using HF−pyridine solution. The resulting compound was checked by MS. LRMS (MS ES^+) calcd for $C_{27}H_{30}N_2O_6$, 479.2 *m*/*z* $(M + 1)^+$; observed, 479.3.

Compound 20.



Resin **19** (65 mg) was swelled in THF (10.0 mL) under N_2 for 30 min. Grubbs'-II catalyst (50 mol %) was added to the mixture, and the mixture was shaken for 24 h at 40 °C.

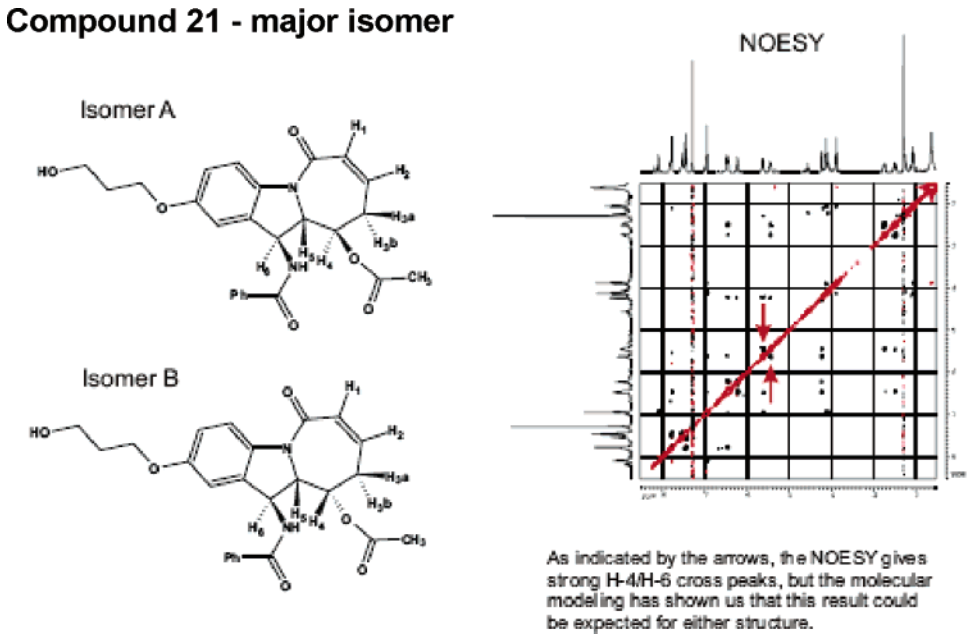


Figure 13.

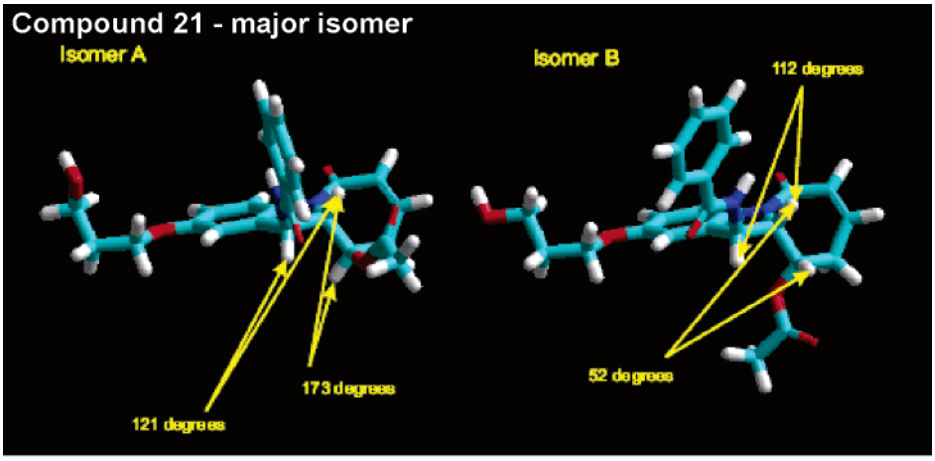
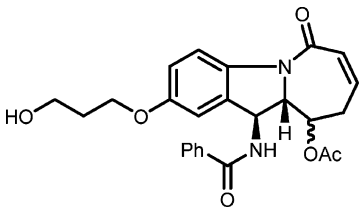


Figure 14.

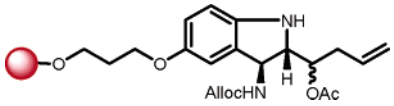
The resin was washed with DMF (3×), THF (3×), and CH_2Cl_2 (3×). The resin was vacuum-dried overnight to give 58 mg of resin **20**.

Compound 21.



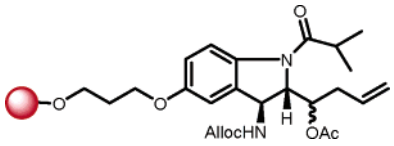
The loaded resin **20** (20 mg) in an Eppendorf tube was swelled in THF (0.5 mL) for 30 min and treated with HF−pyridine solution (15.0 μL). The reaction tube was shaken for 2 h. Methoxytrimethylsilane (150 μL) was added, and the tube was shaken for another 30 min. The solution was removed, and the resin was washed with THF. All solvents were combined and concentrated. The crude sample was purified by column chromatography (1:1 ethyl acetate/hexanes) to give the product **21**. (See Figures 11−14.) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 7.5 Hz, 1H), 7.77 (d, J = 7.5 Hz, 1H), 7.45 (t, J = 7.5 Hz, 3H), 6.94 (d, J = 8.0 Hz, 2H), 6.45 (m, 1H), 6.22 (d, J = 11.5 Hz, 1H), 5.61 (d, J = 8.0 Hz, 1H), 4.45 (t, J = 8.0 Hz, 1H), 4.22 (d, J = 10.0 Hz, 1H), 4.14 (t, J = 6.0 Hz, 2H), 3.88 (t, J = 5.5 Hz, 2H), 2.79−2.68 (m, 1H), 3.08−2.98 (m, 2H), 2.51−2.45 (dd, J = 14.5, 7.5 Hz, 1H), 2.28 (s, 3H), 2.02 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 165.8, 156.9, 136.1, 132.3, 129.7, 18.7, 116.9, 112.0, 77.1, 75.3, 70.7, 66.6, 60.6, 54.1, 32.3, 32.0, 21.7; LRMS (MS ES$^+$) calcd for $C_{25}H_{26}N_2O_6$, 451.1 m/z (M + 1)$^+$; observed, 451.2.

Compound 18d.



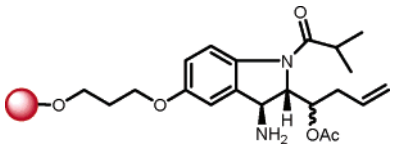
Resin (100 mg) **18** was swelled in DMF (5.0 mL) for 30 min. Piperidine (0.5 mL) was added to the mixture, and the mixture was shaken for 1 h. The resin was washed with DMF (3×), THF (3×), and CH_2Cl_2 (3×). The resin was then dried under vacuum overnight to give 82 mg of the resin **18d**. The dried resin (5.0 mg) was cleaved by the above method using HF−pyridine solution. The resulting compound was checked by MS. LRMS (MS ES$^+$) calcd for $C_{21}H_{28}N_2O_6$, 405.2 *m*/*z* (M + 1)$^+$; observed, 405.3.

Compound 18e. Resin **18d**



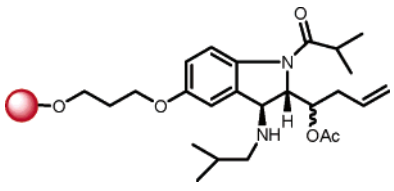
(80 mg) was swelled in CH_2Cl_2 (2.5 mL) under N_2 for 30 min. Collidine (240 μL, 1.80 mmol) and isobutyryl chloride (128 μL, 1.20 mmol) were added to the mixture, and the mixture was shaken for 24 h. The resin was washed with CH_2Cl_2 (3×), THF (3×), and CH_2Cl_2 (3×). The resin was then dried under vacuum overnight to give 88 mg of the resin **18e.** The dried resin (5.0 mg) was cleaved by the above method using HF−pyridine solution. The resulting compound was checked by MS. LRMS (MS ES$^+$) calcd for $C_{25}H_{34}N_2O_7$, 475.2 *m*/*z* (M + 1)$^+$; observed, 475.3.

Compound 18f.



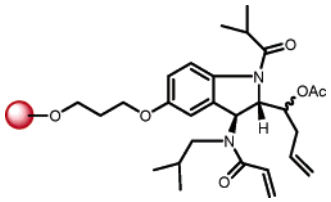
Resin **18e** (80 mg) was swelled in CH_2Cl_2 (4.0 mL) for 30 min. A stock solution of DCM, *N*-methylmorpholine, acetic acid (5/0.32/0.66, 3.0 mL), triphenylphosphine (247.6 mg, 1.10 mmol), and tetrakis(triphenylphosphine) palladium (0) (266 mg, 0.220 mmol) were added the mixture, and the mixture was shaken for 3 h. The resin was washed with CH_2Cl_2 (3×), THF (3×), and CH_2Cl_2 (3×). The resin was vacuum-dried overnight to give 65 mg of the resin **18f**. The dried resin (5.0 mg) was cleaved by the above method using HF−pyridine solution. The resulting compound was checked by MS. LRMS (MS ES$^+$) calcd for $C_{21}H_{30}N_2O_5$, 391.2 *m*/*z* (M + 1)$^+$; observed, 391.3

Compound 18g.



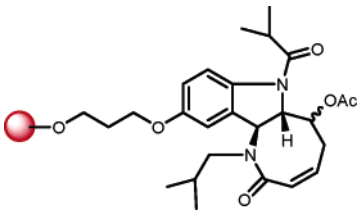
Resin **18f** (60 mg) was swelled in triethylorthoformate (1.0 mL) for 30 min. A solution of $NaCNBH_3$ (2.5 mmol) in TMOF/MeOH/ACOH (1.5 mL/200 μL/20 μL) and isobutaraldehyde (180 μL, 1 mmol) were added to the mixture. The mixture was shaken for 24 h. The resin was washed with CH_2Cl_2 (3×), THF (3×), and CH_2Cl_2 (3×). The resin was then dried under vacuum overnight to give 65 mg of the resin **18g**. The dried resin (5.0 mg) was cleaved by the above method using HF−pyridine solution. The resulting compound was checked by MS. LRMS (MS ES$^+$) calcd for $C_{25}H_{38}N_2O_5$, 447.3 *m*/*z* (M + 1)$^+$; observed, 447.4.

Compound 22.



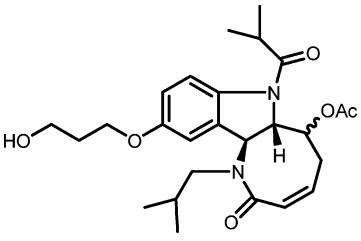
Resin **18g** (60 mg) was swelled in CH_2Cl_2 (4.0 mL) for 30 min. Collidine (160 μL, 1.80 mmol) and acryloyl chloride (67 μL, 0.60 mmol) were added to the mixture. The mixture was shaken for 24 h. The resin was washed with CH_2Cl_2 (3×), THF (3×), and CH_2Cl_2 (3×). The resin was then dried under vacuum overnight to give 68 mg of the resin **22**. The dried resin was cleaved by the above method using HF−pyridine solution. The resulting compound was checked by MS. LRMS (MS ES$^+$) calcd for $C_{28}H_{40}N_2O_6$, 501.3 *m*/*z* (M + 1)$^+$; observed, 501.4.

Compound 23.



The resin **22** (60 mg) was swelled in THF (5.0 mL) for 30 min, and G-II catalyst (50 mol %) was added to the reaction mixture. The mixture was shaken for 24 h at 40 °C. The resin was washed with CH_2Cl_2 (3×), THF (3×), and CH_2Cl_2 (3×). The resin was then dried under vacuum overnight to give 54 mg of the resin **23**.

Compound 24.



Resin **23** (20 mg) in an Eppendorf tube was swelled in THF (0.5 mL) for 30 min and treated with HF−pyridine solution (15.0 μL). The reaction tube was shaken for 2 h. Methoxytrimethylsilane (150 μL) was added, and the tube was shaken for another 30 min. The solution was removed, and the resin was washed with THF. All solvents were combined

and concentrated. The crude sample was purified by column chromatography (1:1 ethyl acetate/hexanes) to give the product **24**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (bs, 1H), 6.88 (dd, J = 8.8, 2.0 Hz, 1H), 6.72 (d, J = 1.5 Hz, 1H), 6.24 (d, J = 12.0 Hz, 2H), 5.98−5.91 (m, 1H), 5.80 (d, J = 8.0 Hz, 1H), 4.43 (dd, J = 7.0, 2.0 Hz, 1H), 4.11 (m, 3H), 3.89 (t, J = 5.0 Hz, 2H), 3.65 (dd, J = 14.0, 8.5 Hz, 1H), 3.08−2.98 (m, 2H), 2.51 (dd, J = 14.0, 8.0 Hz, 1H), 2.10−2.04 (m, 3H), 1.91 (s, 3H), 1.24 (m, 6H), 0.93 (d, J = 7.0 Hz, 3H), 0.86 (d, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 170.2, 169.8, 129.3, 118.5, 116.2, 116.1, 111.9, 69.0, 68.9, 66.5, 64.5, 60.7, 60.6, 49.9, 33.6, 32.3, 30.1, 29.0, 28.7, 28.0, 21.1, 21.0, 20.8, 20.3; LRMS (MS ES$^+$) calcd for $C_{26}H_{36}N_2O_6$, 473.2 m/z $(M + 1)^+$; observed, 473.2

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