JOURNAL OF combinatorial CHEMISTRY

Subscriber access provided by American Chemical Society

Article

Solution- and Solid-Phase Synthesis of Natural Product-Like Tetrahydroquinoline-Based Polycyclics Having a Medium Size Ring

Prabhat Arya, Samuel Couve-Bonnaire, Patricia Durieux, Daisy Laforce, Rohtash Kumar, and Donald M. Leek

J. Comb. Chem., **2004**, 6 (5), 735-745• DOI: 10.1021/cc049935s • Publication Date (Web): 23 July 2004

Downloaded from http://pubs.acs.org on March 20, 2009

More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

ACS Publications
High quality. High impact.

Journal of Combinatorial Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Solution- and Solid-Phase Synthesis of Natural Product-Like Tetrahydroquinoline-Based Polycyclics Having a Medium Size Ring

Prabhat Arya,* Samuel Couve-Bonnaire, Patricia Durieux, Daisy Laforce, Rohtash Kumar, and Donald M. Leek

Chemical Biology Program, Steacie Institute for Molecular Sciences, National Research Council of Canada, 100 Sussex Drive, Ottawa, Ontario, Canada K1A 0R6

Received March 17, 2004

A solid-phase synthesis of tetrahydroquinoline-derived polycyclic **4**, having a medium size ring with an enamide functionality, was achieved from tetrahydroquinoline derivative **3** in five steps with overall 40−45% yield. An enantiopure, tetrahydroquinoline-derived β-amino ester, **1**, was converted into compound **2** that has a free phenolic hydroxyl group as an anchoring site for solid-phase synthesis. The solid-phase worked well for this sequence, in which the synthesis of the unsaturated eight-membered enamide lactam was obtained by a ring-closing metathesis approach. Compound **4** is a novel, natural product-like polycyclic derivative that could further be utilized in library generation for developing small molecule chemical probes.

Introduction

Due to the growing interest in having small molecules that could help in understanding protein−protein interactions-based signal transduction, the demand for the generation of small molecule libraries that are inspired by bioactive natural products has grown significantly.[1] Many of these pathways are highly complex and present tremendous challenges with the use of classical tools.[2] Rapid access to natural product-like small molecules having structural complexity and diversity is crucial for systematically dissecting the functions of complex protein networking and for understanding cell-signaling pathways.[3] There are several examples in the literature in which complex natural products are shown to be specific modulators of protein functions and protein−protein interactions.[4] The complex nature, the three-dimensional architecture, and the number of protein-binding functional groups presented in three-dimensional arrays are some of the unique features that are embedded in natural products.[5] Some of these features make them highly attractive small molecule chemical probes for understanding protein functions.

Synthesis Plan

With the goal of obtaining rapid access to natural product-like tetrahydroquinoline-based complex polycyclic derivatives, we developed a practical, enantioselective solution synthesis of tetrahydroquinoline chiral scaffold **1** (Scheme 1). This scaffold was further utilized to obtain complex polycyclics leading to library generation by partial solid-phase synthesis.[6] Due to the wide range of bioactive natural products having a tetrahydroquinoline moiety[7] and the presence of medium to large size rings,[8] this type of scaffold was selected for our studies and to map the three-dimensional space around this scaffold toward the synthesis of functionalized medium size rings. The library generation of polycyclics having functionalized medium to large ring derivatives is still in its infancy and presents tremendous challenges from the design strategies.[9]

Herein, we outline our solid-phase library approach to the synthesis of tetrahydroquinoline-based polycyclics having a functionalized eight-membered ring including the enamide functional group (**3**). This derivative can then be subjected to a ring-conformation-controlled, stereoselective Michael-type reaction followed by hydroxyl group derivatization giving three sites for introducing diversity as shown in **4**. The plan is to utilize the enantiopure β-amino acid derivative, **1**, and then modify the side chain to incorporate the allylic hydroxyl group to obtain compound **2**. The synthesis of an eight-membered ring having an enamide functional group can be obtained by a ring-closing metathesis (RCM) as the key reaction in our approach. To our knowledge, there are no examples in the literature that utilize the scope of the RCM (solution and solid-phase synthesis) to obtain an eight-membered ring having an enamide functional group.[10]

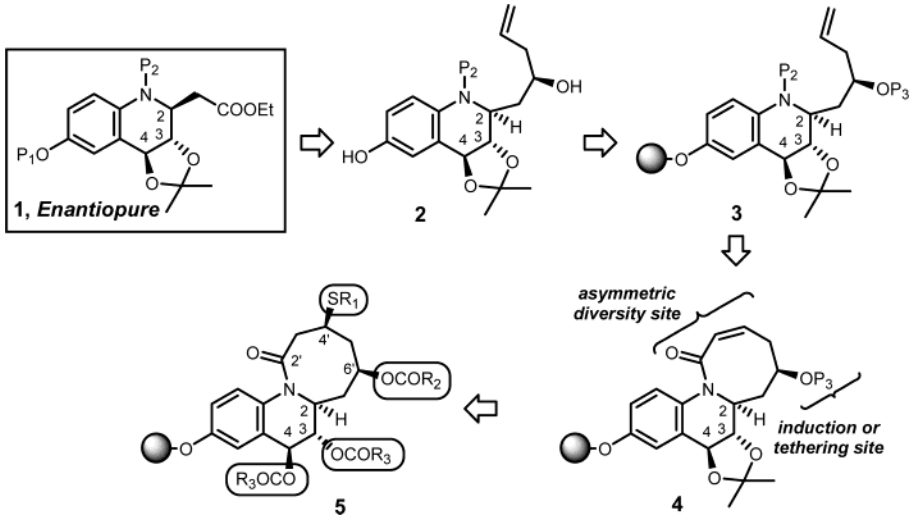
Results and Discussion

To test the feasibility of this strategy, our model solution-phase studies are shown in Scheme 2. An enantiopure, tetrahydroquinoline-based β-amino acid derivative, **6**, was utilized in our study.[6] The N-alloc protected β-amino aldehyde was prepared and then subjected to a Lewis-acid-mediated Grignard reaction giving the corresponding hydroxyl derivatives, **8a** and **8b**. Both isomers **8a** and **8b** were obtained in near equal yields and then utilized further to explore the scope of the ring-closing metathesis reaction. For example, compound **8a** was subjected to N-alloc removal and acryloylation (**9**) and was then subjected to RCM. To

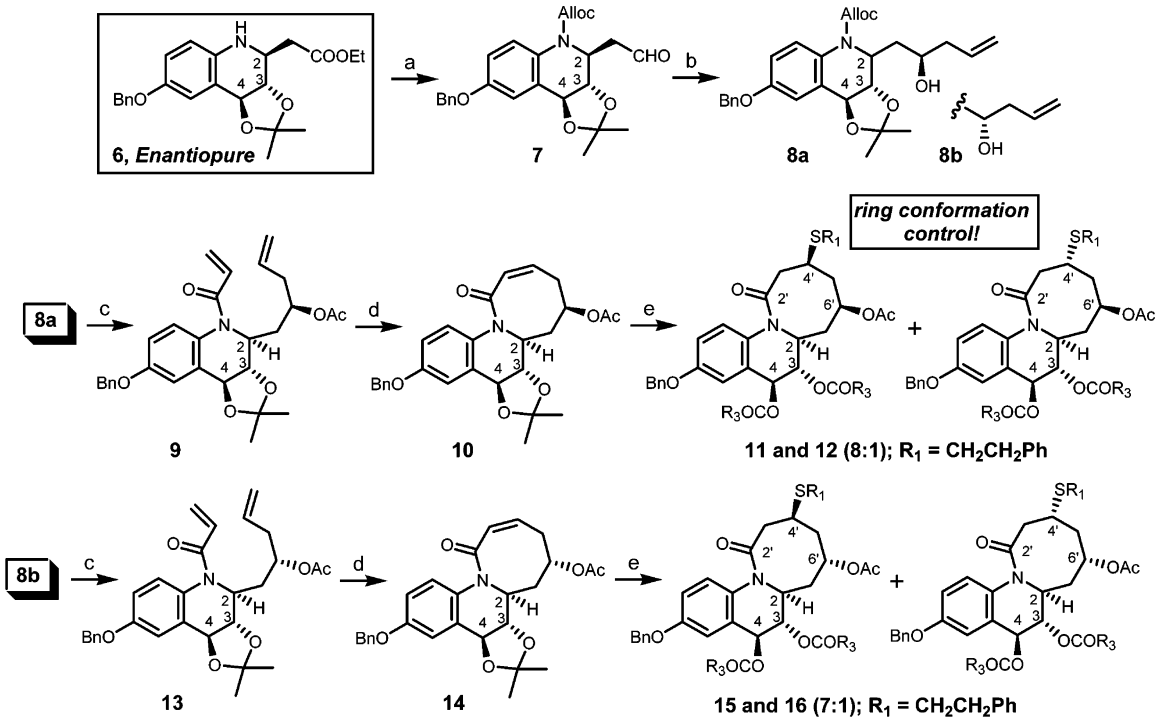
* Author to whom correspondence should be addressed. Phone: (613) 993-7014. Fax: (613) 952-0068. E-mail: Prabhat.Arya@nrc.ca.

10.1021/cc049935s CCC: $27.50 Published 2004 by the American Chemical Society
Published on Web 07/23/2004

Scheme 1. Natural Product-Like, Tetrahydroquinoline-Derived Polycyclics Having a Functionalized Eight-Membered Ring



Scheme 2



(a) (i) $LiBH_4$, 95%; (ii) allyl chloroformate, pyridine, 89%; (iii) DMSO, SO_3−pyridine complex, Et_3N, 95%. (b) $ZnCl_2$, allylMgBr, 89%. (c) (i) Ac_2O, DMAP, 83−88%; (ii) $Pd(PPh_3)_4$, morpholine, room temp, 98%; (ii) acryloyl chloride, pyridine, 0 °C, 55−60%. (d) 20 mol % second-generation Grubbs' catalyst, dichloromethane, reflux, 1 h, 83% (**10**) and 88% (**14**). (e) (i) $PhCH_2CH_2SH$, BuLi, 76−84%; (ii) *p*-TSA; (iii) BzCl, pyridine, 83−88% for two steps.

our pleasant surprise, this reaction was very clean, thus giving the desired eight-membered ring derivative, **10**, having an enamide functional group in 83% yield. The product was well characterized by 2D NMR studies. To our knowledge, the use of this approach to obtain medium size rings having an enamide functional group has not been utilized before. The novelty of this approach lies in the formation of a functionalized ring skeleton that can further be utilized in asymmetric diversity-oriented reactions. Under similar conditions, the other allylic alcohol derivative **8b** gave the expected cyclic enamide product in very high yield (88%). In both cases, the stereochemistry of the −OAc group in the eight-membered ring was assigned by NOE studies (see Figure 1 for the NOESY spectrum). Further, model studies with a hetero Michael reaction were carried out on eight-membered rings having enamide functional groups. Compounds **10** and **14** were independently subjected to thiol addition. To our surprise, in both cases the major product was influenced by the ring conformation, and the nucleophilic attack was independent from the stereochemistry of the −OAc group in the eight-membered ring. In both cases, the two isomers were found to be in a ratio of 7−8:1 and the major isomer resulted from an attack from the β-face. One could explain this reaction as the ring conformation control, and it has very little influence from the chiral group present on the midsize ring system. This conformation-controlled hetero Michael reaction opens an attractive approach for introducing an asymmetric diversity site in a solid-phase synthesis. To

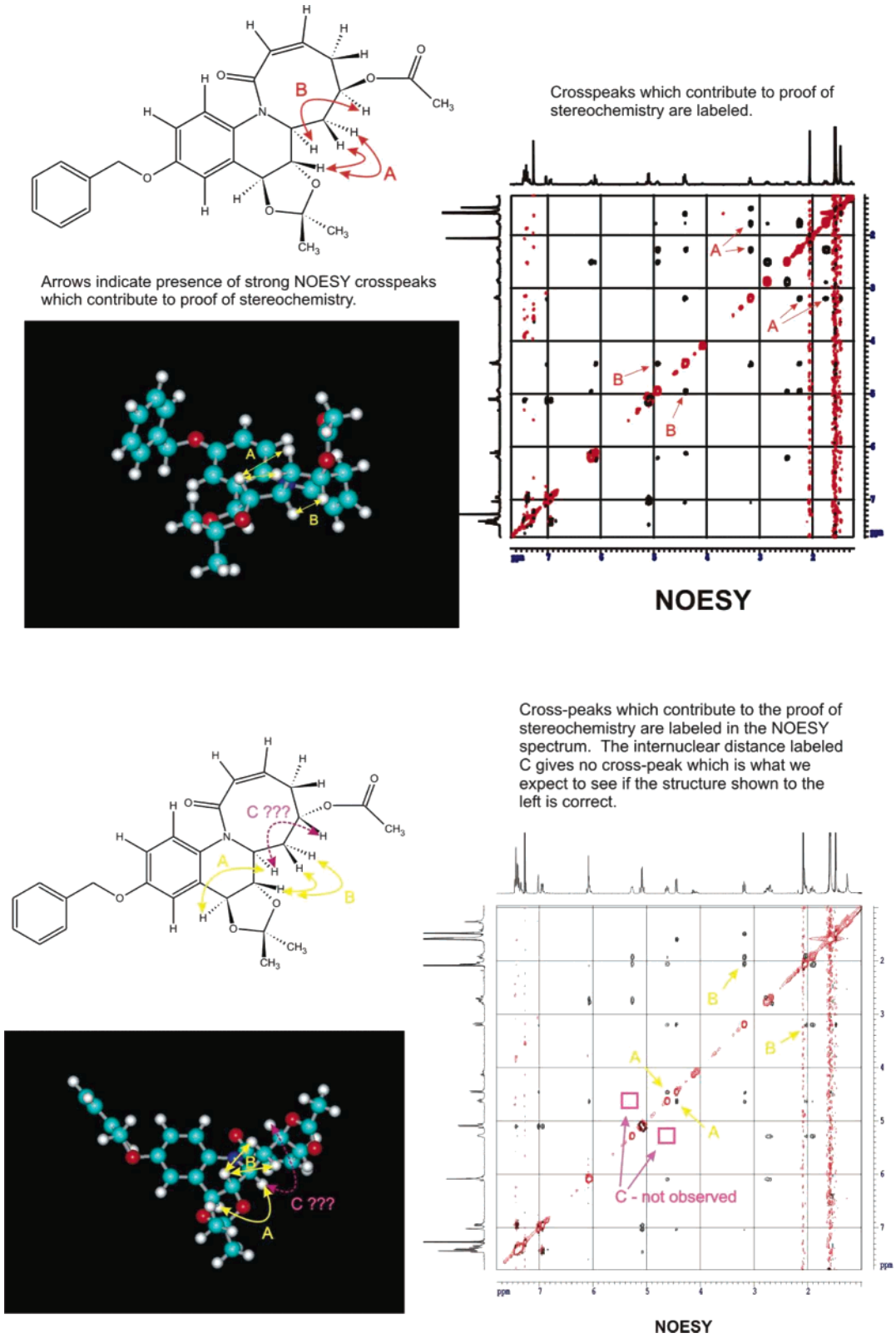
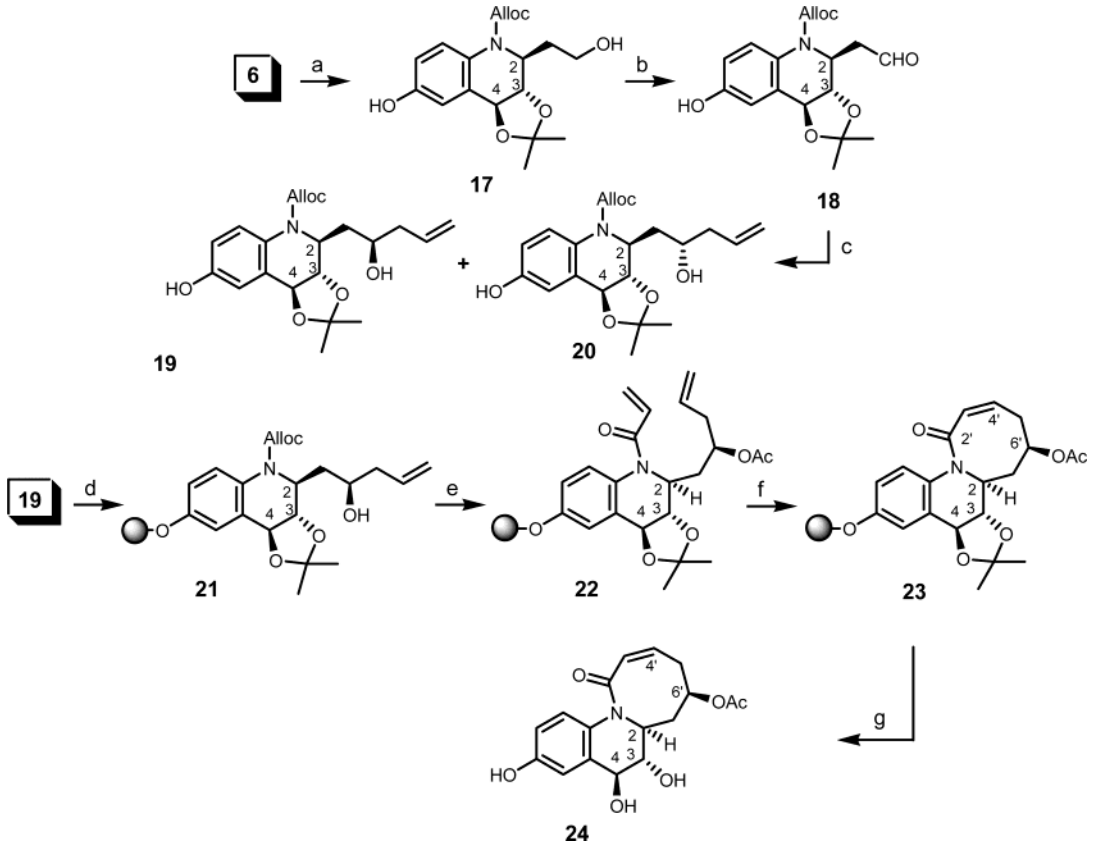


Figure 1. NOESY of compounds **10** and **14**.

complete the sequence, in both cases the hetero Michael products were then subjected to acetonide removal and acylation giving the expected compounds (**11** and **12** from **10**; **15** and **16** from **14**). Following the success with the solution synthesis, manual solid-phase synthesis was then undertaken, and it is shown in Scheme 3. Compound **18** was prepared from **6** in a number of steps as described before and then subjected to a Grignard reaction giving two diastereomers, **19** and **20**. Both these products were separated and fully characterized. Following this, compound **19** was immobilized onto the solid support using a bromoWang resin (loading ~91%, determined after cleavage from the support with 5% TFA). To continue further, this compound **21** was then subjected to N-alloc removal, followed by acryloylation giving product **22**. It was then subjected to ring-closing metathesis that successfully gave the cyclic product on the

Scheme 3



(a) (i) $LiBH_4$, 95%; (ii) H_2, 10% Pd/C, 88%; (iii) allyl chloroformate, pyridine, 70%; (b) DMSO, SO_3−pyridine complex, Et_3N, 84%. (c) $ZnCl_2$, allylMgBr, 72%. (d) BromoWang resin, NaI, Cs_2CO_3. (e) (i) Ac_2O, DMAP; (ii) $Pd(PPh_3)_4$, *N*-methylmorpholine, AcOH; (iii) acryloyl chloride, pyridine. (f) Second-generation Grubbs' catalyst, dichloromethane, reflux. (g) 5% TFA (40−45% for five steps).

solid phase. Thus, compound **24** (see Figure 2 for the NOESY spectrum) was obtained after cleavage from the support (5% TFA) with an overall 40−45% yield for the five steps from **21**. Further work is in progress to complete the sequence on the solid phase that involves (i) thiol addition, (ii) acteonide removal (PPTS), (iii) acylation of the hydroxyl groups, and (iv) cleavage from the support (5%TFA). The solid-phase synthesis method developed in our system can easily be utilized in library generation by exploring three diversity sites, and this will be reported in due course.

Summary

A solid-phase synthesis of a tetrahydroquinoline-derived polycyclic compound having a medium size ring with an enamide functional group has been achieved that can further be utilized in library generation. A key step in our approach was the ring-closing metathesis reaction to obtain an eight-membered ring having an enamide functionality. This approach worked very nicely on the solid phase, and the final product obtained was well characterized by extensive NMR studies. With the use of the solid-phase synthesis method discussed herein, further work is ongoing for library generation by an IRORI split and mix type approach, and it will be reported in due time.

Experimental Section

General Methods. The materials were obtained from commercial suppliers and used without purification. THF and CH_2Cl_2 were distilled under N_2 over sodium/benzophenone and CaH_2, respectively. All NMR experiments were recorded on a Bruker DRX-400. Unless otherwise noted, proton and carbon chemical shifts are reported in ppm using residual $CHCl_3$ as an internal standard at 7.26 and 77.0 ppm, respectively. Analysis by mass spectrometry was performed on a VG Quattro I (Micromass) mass spectrometer equipped with a pneumatically assisted electrospray ionization source, operating in positive mode. The enantiomeric excess was determined by chiral HPLC, using a Hewlett-Packard (Agilent) 1090 LC equipped with a diode array detector and a CHIRACEL-OD column.

Solution-Phase Synthesis. Compound 6a. To a solution of the carboxyl ester **6** (1.10 g, 2.77 mmol) in THF (25 mL) was added lithium borohydride (2.0 M in THF, 2.77 mL, 5.54 mmol) slowly at 0 °C. The reaction mixture was stirred at room temperature overnight. The reaction was quenched with saturated NH_4Cl, extracted with dichloromethane (3 × 10 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography on silica gel (3:1, hexane/ethyl acetate) afforded the product **6a** (934 mg, 95%) as a yellow oil. R_f: 0.20 (2:1, hexane/ethyl acetate). ^1H NMR: (400 MHz, $CDCl_3$) δ = 7.43−7.26 (m, 5H), 6.89 (d, J = 2.05 Hz, 1H), 6.71 (dd, J = 2.74 Hz, 8.60 Hz, 1H), 6.43 (d, J = 8.66 Hz, 1H), 4.99 (d, J = 4.3 Hz, 2H), 4.71 (d, J = 8.89 Hz, 2H), 3.89−3.83 (m, 2H), 3.71 (m, 1H), 3.63 (t, J = 9.35 Hz, 1H), 1.94−1.86 (m, 1H), 1.57 (m, 1H), 1.55 (s, 3H), 1.51 (s, 3H) ppm. ^{13}C NMR: (100 MHz,

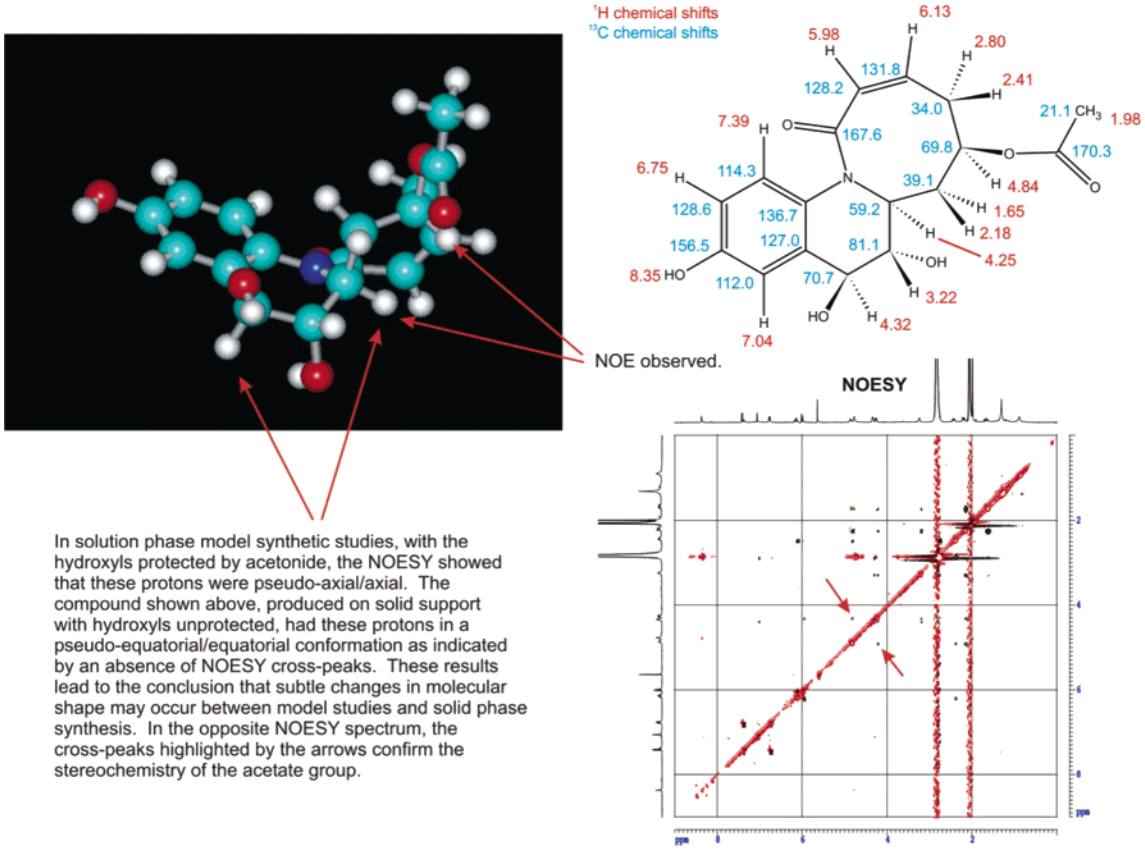
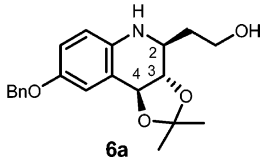


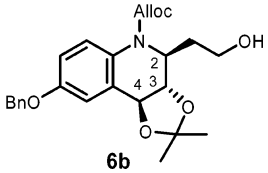
Figure 2. NOESY of compound **24** prepared by solid-phase synthesis.

$CDCl_3$) δ = 151.40, 137.93, 136.79, 128.92, 128.16, 127.90, 121.23, 116.07, 114.17, 113.83, 110.69, 80.30, 77.87, 73.07, 61.12, 56.06, 38.36, 27.53, 27.43 ppm. LRMS: MS (ES^+) m/z = 356.3 (M + 1).



6a

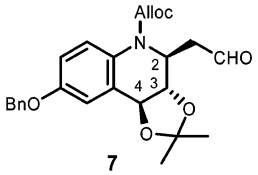
Compound 6b. To a solution of **6a** (480 mg, 1.35 mmol) in dichloromethane (20 mL), at 0 °C, under N_2, was added pyridine (120 μL, 1.48 mmol) and allyl chloroformate (144 μL, 1.35 mmol). After keeping the reaction mixture for 2 h at 0 °C under N_2, it was quenched with a saturated solution of ammonium chloride. The aqueous layer was washed 3 times with dichloromethane, and then the combined organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (1:1, hexane/ethyl acetate) giving compound **6b** (530 mg, 89%) as a colorless oil. R_f: 0.56 (1:1, hexane/ethyl acetate). LRMS: MS (ES^+) m/z = 440.2 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.45−7.33 (m, 5H), 7.26 (m, 1H), 6.98 (d, J = 2.43 Hz, 1H), 6.87 (dd, J = 2.72, 8.71 Hz, 1H), 5.90 (m, 1H), 5.28−5.20 (m, 2H), 5.07 (dd, J = 7.32, 11.50 Hz, 2H), 4.69 (dd, J = 5.27, 13.42 Hz, 1H), 4.60 (m, 1H), 4.51 (d, J = 9.34 Hz, 1H), 4.45 (m, 1H), 3.74 (m, 2H), 3.31 (t, J = 8.82 Hz, 1H), 2.04 (m, 2H), 1.58 (s, 3H), 1.49 (s, 3H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ = 137.10, 132.55, 128.99, 128.47, 128.12, 127.97, 118.36, 114.59, 113.87, 107.78, 101.03, 76.61, 70.73, 67.29, 59.46, 39.94, 38.64, 27.49, 27.43 ppm.



6b

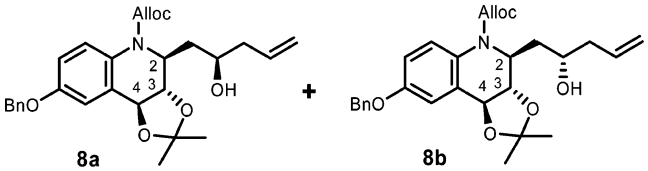
Compound 7. To a solution of **6b** (500 mg, 1.136 mmol) in dichloromethane (15 mL) at 0 °C, under N_2, was added triethylamine (475 mL, 3 equiv), DMSO (3.39 mL, 47.73 mmol), and sulfur trioxide−pyridine complex (543 mg, 3.41 mmol). After 1 h at 0 °C, the reaction was quenched with a solution of saturated ammonium chloride. The organic layer was extracted and dried with magnesium sulfate. After filtration and evaporation of the solvent, the crude product was purified by column chromatography on silica gel (3:1 hexane/ethyl acetate) to afford compound **7** as a colorless oil (473 mg, 95%). R_f: 0.82 (1:1, hexane/ethyl acetate), 0.47 (2:1, hexane/ethyl acetate). LRMS: MS (ES^+) m/z = 438.3 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 9.83 (s, 1H), 7.47−7.34 (m, 6H), 7.00 (d, J = 2.29 Hz, 1H), 6.90 (dd, J = 2.82, 8.82 Hz, 1H), 5.94 (m, 1H), 5.30 (d, J = 17.31 Hz, 1H), 5.25 (d, J = 10.52 Hz, 1H), 5.12 (d, J = 11.50 Hz, 1H), 5.07 (d, J = 11.50 Hz, 1H), 4.70 (m, 2H), 4.63 (m, 1H), 4.55 (d, J = 9.23 Hz, 1H), 3.38 (t, J = 9.15 Hz, 1H), 2.87 (ddd, J = 1.90, 5.38, 15.53 Hz, 1H), 2.77 (ddd, J = 3.62, 5.94, 15.48 Hz, 1H), 1.61 (s, 3H), 1.50 (s, 3H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ = 199.23, 157.30, 137.09, 132.54, 132.38, 129.00, 128.47, 127.96, 127.72, 127.10,

114.83, 113.99, 107.94, 83.21, 76.55, 70.72, 67.44, 53.84, 48.82, 27.48, 27.43 ppm.



7

Compounds 8a and 8b. To a solution of zinc chloride (4.12 mL of a 1.0 M solution in ether, 4.12 mmol) in anhydrous ether (15 mL) was added a solution of aldehyde 7 (450 mg, 1.03 mmol), in anhydrous ether (8 mL) at −78 °C. After 30 min of stirring at −78 °C, allylmagnesium bromide (6.18 mL of a 1.0 M solution in ether, 6.18 mmol) was added, and the mixture was stirred at −78 °C for 2 h. The reaction mixture was then allowed to warm at room temperature and was further stirred for 1 h. The reaction was quenched at 0 °C with a solution of saturated ammonium chloride. The organic layer was collected and washed with a saturated solution of ammonium chloride. It was dried over sodium sulfate and then evaporated. Purification of the crude product by column chromatography on silica gel (1:3, ethyl acetate/hexane) gave a mixture two diastereomers, **8a** and **8b** (**8a** = 243 mg and **8b** = 200 mg). The overall yield of the reaction was 89%.

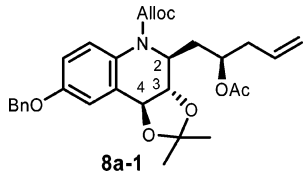


8a **8b**

8a: R_f: 0.50 (3:1, hexane/ethyl acetate). LRMS: MS (ES^+) m/z = 480.4 (M + 1). ^1H NMR: (400 MHz, $CDCl_3$) δ = 7.47−7.36 (m, 5H), 7.27 (s, 1H), 7.00 (d, J = 2.58 Hz, 1H), 6.89 (dd, J = 2.58, 8.74 Hz, 1H), 5.91 (m, 2H), 5.24 (m, 2H), 5.11 (m, 4H), 4.71 (dd, J = 5.28, 13.40 Hz, 1H), 4.60 (m, 1H), 4.53 (d, J = 9.12 Hz, 1H), 4.46 (m, 1H), 3.86 (m, 1H), 3.31 (t, J = 9.04 Hz, 1H), 2.30 (m, 2H), 1.72 (m, 2H), 1.59 (s, 3H), 1.51 (s, 3H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ = 171.56, 157.54, 137.08, 135.60, 133.32, 132.49, 129.00, 128.47, 128.24, 127.96, 126.99, 118.33, 117.41, 114.63, 113.86, 107.77, 84.85, 77.63, 70.73, 67.36, 60.80, 43.57, 41.79, 31.33, 27.46, 27.40, 21.45, 14.60 ppm.

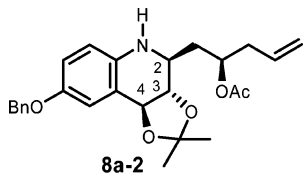
8b: R_f: 0.28 (3:1, hexane/ethyl acetate). LRMS: MS (ES^+) m/z = 480.4 (M + 1). ^1H NMR: (400 MHz, $CDCl_3$) δ = 7.47−7.31 (m, 6H), 7.00 (d, J = 2.69 Hz, 1H), 6.89 (dd, J = 2.69, 8.74 Hz, 1H), 5.93 (m, 1H), 5.86 (m, 1H), 5.32 (m, 1H), 5.24 (d, J = 10.27 Hz, 1H), 5.10 (m, 4H), 4.72 (dd, J = 5.18, 13.10 Hz, 1H), 4.65 (m, 1H), 4.54 (d, J = 9.02 Hz, 1H), 4.50 (m, 1H), 3.90 (m, 1H), 3.38 (t, J = 8.98 Hz, 1H), 2.30 (t, J = 6.61 Hz, 2H), 2.19 (m, 1H), 1.66 (m, 1H), 1.60 (s, 3H), 1.52 (s, 3H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ = 171.50, 157.00, 136.97, 134.96, 132.73, 132.49, 128.79, 128.24, 127.75, 127.62, 127.23, 118.14, 117.85, 114.40, 113.65, 107.58, 84.07, 76.44, 70.53, 66.95, 60.61, 42.22, 41.96, 31.13, 27.31, 21.26, 14.41 ppm.

Compound 8a-1. To a solution of **8a** (243 mg, 0.507 mmol) in dichloromethane (5 mL) was added acetic anhydride (96 μL, 1.014 mmol) and DMAP (71 mg, 0.58 mmol). The reaction mixture was stirred for 3 h at room temperature and then quenched with aqueous ammonium chloride. After an extraction with dichloromethane, the organic layer was dried over sodium sulfate and then evaporated to dryness. The crude product obtained after evaporation of the solvent was purified by column chromatography on silica gel (3:1 hexane/ethyl acetate) giving compound **8a-1** as a colorless oil (83% yield, 220 mg). R_f: 0.53 (3:1, hexane/ethyl acetate). LRMS: MS (ES^+) m/z = 522.4 (M + 1). ^1H NMR: (400 MHz, $CDCl_3$) δ = 7.47−7.35 (m, 5H), 7.28 (m, 1H), 6.99 (d, J = 2.10 Hz, 1H), 6.87 (dd, J = 2.10, 6.10 Hz, 1H), 5.95 (m, 1H), 5.80 (m, 1H), 5.24 (m, 2H), 5.09 (m, 5H), 4.71 (dd, J = 5.36, 13.32 Hz, 1H), 4.62 (m, 1H), 4.48 (d, J = 9.06 Hz, 1H), 4.35 (m, 1H), 3.36 (t, J = 8.98 Hz, 1H), 2.40 (m, 1H), 2.02 (s, 3H), 1.84 (m, 1H), 1.58 (s, 3H), 1.51 (s, 3H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ = 171.12, 170.87, 157.30, 154.93, 137.18, 133.66, 133.09, 132.70, 128.99, 128.80, 128.43, 127.95, 127.62, 118.48, 114.29, 113.83, 107.73, 84.30, 77.62, 76.57, 70.72, 70.69, 67.15, 55.18, 39.15, 38.76, 27.50, 21.80 ppm.



8a-1

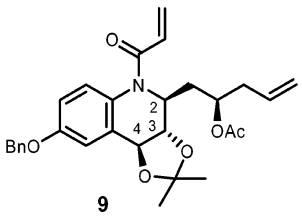
Compound 8a-2. To a solution of **8a-1** (220 mg, 0.42 mmol) in dichloromethane (2 mL) under N_2 at room temperature was added morpholine (74 μL, 0.84 mmol) and 10% of tetrakis(triphenylphosphine) palladium (0) catalyst (49 mg, 0.042 mmol). The reaction mixture was covered with tin foil and then stirred for 1 h. The reaction was quenched with aqueous ammonium chloride and extracted several times with dichloromethane. The combined organic layer was dried with magnesium sulfate, filtered, and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (1:3, ethyl acetate/hexane) to give **8a-2** as a yellow oil in 98% yield. R_f: 0.56 (3:1, hexane/ethyl acetate). LRMS: MS (ES^+) m/z = 438.3 (M + 1). ^1H NMR: (400 MHz, $CDCl_3$) δ = 7.45−7.29 (m, 5H), 6.89 (d, J = 2.50 Hz, 1H), 6.75 (dd, J = 2.50, 8.69 Hz, 1H), 6.51 (d, J = 8.69 Hz, 1H), 5.81 (m, 1H), 5.19 (m, 4H), 5.01 (m, 2H), 4.70 (d, J = 8.24 Hz, 1H), 3.60 (m, 1H), 2.41 (m, 2H), 2.11 (s, 3H), 2.08 (m, 1H), 1.73 (m, 1H), 1.58 (s, 3H), 1.54 (s, 3H) ppm. ^{13}C NMR: (100 MHz, CDCl3) δ = 171.61, 151.7, 137.9, 136.8, 133.6, 128.3, 128.1, 127.9, 121.9, 118.7, 116.1, 115.1, 113.5, 110.7, 109.2, 82.4, 80.3, 71.24, 71.00, 69.9, 52.1, 39.6, 39.4, 27.5, 27.5, 21.6 ppm.



8a-2

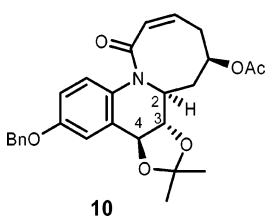
Compound 9. To a solution of **8a-2** (180 mg, 0.412 mmol) in dichloromethane (4.0 mL) was added pyridine (83 μL, 1.030 mmol). The mixture was cooled to 0 °C and then

acryloyl chloride (67 μL, 0.824 mmol) was added. The reaction was allowed to stir at room temperature for 2.5 h. The reaction was quenched with aqueous ammonium chloride and extracted with dichloromethane, and the organic phases were dried over magnesium sulfate, filtered, and then concentrated. The crude product was purified by column chromatography on silica gel (1:3, ethyl acetate/hexane) to afford compound **9** as a pale yellow oil (55%, 100 mg). R_f: 0.35 (3:1, hexane/ethyl acetate). LRMS: MS (ES^+) m/z = 492.4 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.48−7.36 (m, 5H), 7.07 (d, J = 2.60 Hz, 1H), 6.99 (d, J = 8.56 Hz, 1H), 6.87 (dd, J = 2.63, 8.57 Hz, 1H), 6.44 (dd, J = 1.80, 16.81 Hz, 1H), 6.32 (dd, J = 10.10, 16.79 Hz, 1H), 5.84 (m, 1H), 5.64 (dd, J = 1.90, 10.08 Hz, 1H), 5.11 (m, 5H), 4.60 (m, 1H), 4.43 (d, J = 9.01 Hz, 1H), 3.38 (t, J = 8.95 Hz, 1H), 2.51 (m, 1H), 2.41 (m, 1H), 2.26 (m, 1H), 2.02 (s, 3H), 1.71 (m, 1H), 1.57 (s, 3H), 1.51 (s, 3H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ = 170.92, 165.63, 158.35, 136.90, 134.52, 133.76, 129.06, 128.90, 128.90, 128.75, 128.57, 127.99, 127.96, 127.30, 118.42, 114.55, 113.68, 108.59, 84.96, 76.60, 70.95, 70.83, 53.92, 38.72, 38.63, 27.48, 21.80 ppm.



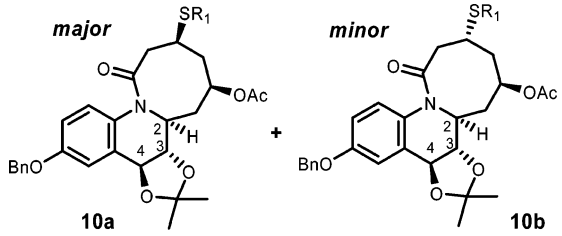
9

Compound 10. To a solution of compound **9** (90 mg, 0.183 mmol) in dichloromethane (9 mL) was added 20 mol % of second-generation Grubbs' catalyst (31 mg, 0.0366 mmol). The solution was stirred for 45 min under reflux. It was then allowed to warm at room temperature and concentrated under vacuum, and the crude product was purified by column chromatography on silica gel (ethyl acetate/hexane 1:3 to 1:1). The eight-membered ring derivative, **10**, was obtained as a white solid (70 mg, 83%). R_f: 0.29 (1:1, hexane/ethyl acetate). LRMS: MS (ES^+) m/z = 464.4 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.47−7.36 (m, 6H), 7.05 (d, J = 2.58 Hz, 1H), 6.97 (dd, J = 2.61, 8.67 Hz, 1H), 6.21 (m, 1H), 6.11 (d, J = 11.79 Hz, 1H), 5.14 (d, J = 11.53 Hz, 1H), 5.09 (d, J = 11.49 Hz, 1H), 4.94 (m, 1H), 4.42 (m, 2H), 3.19 (t, J = 8.97 Hz, 1H), 2.88 (m, 1H), 2.50 (dd, J = 7.30, 13.40 Hz, 1H), 2.27 (dd, J = 5.24, 14.33 Hz, 1H), 2.07 (s, 3H), 1.76 (m, 1H), 1.58 (s, 3H), 1.49 (s, 3H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ = 170.44, 168.48, 158.33, 137.08, 134.10, 132.14, 129.56, 129.01, 128.47, 127.95, 127.06, 126.03, 114.53, 113.94, 108.24, 86.35, 76.04, 70.76, 68.61, 55.38, 40.50, 33.99, 30.10, 27.46, 27.37, 21.62 ppm.



10

Compounds 10a and 10b. To a solution of benzene ethanethiol (224 μL, 1.6 mmol) in THF (4.0 mL) was added *n*-butyllithium (608 μL, 1.52 mmol (2.5 M in hexane) at 78 °C. The reaction mixture was stirred overnight and was allowed to warm at room temperature. Following this, a solution of compound **10** (10 mg, 0.0216 mmol) in THF (1.0 mL) was added at 0 °C to 0.5 mL of the lithium salt (9 equiv). After 30 min, the solvent was evaporated, and the crude product was separated by column chromatography on silica gel (1:2 ethyl acetate/hexane). The overall yield for the reaction was 98% giving two diastereomers **10a** and **10b** (in a ratio of 8:1).



10a **10b**

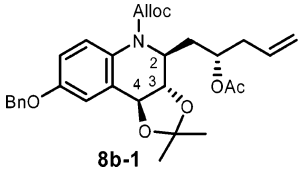
10a:10b (8:1, R_1 = CH_2CH_2Ph)

Compound 10a (R_1 = CH_2CH_2Ph). R_f: 0.36 (2:1, hexane/ethyl acetate). LRMS: MS (ES^+) m/z = 602.5 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.45−7.21 (m, 11H), 7.00 (d, J = 2.66 Hz, 1H), 6.91 (dd, J = 2.74, 8.78 Hz, 1H), 5.12 (d, J = 11.52 Hz, 1H), 5.07 (d, J = 11.51 Hz, 1H), 4.93 (m, 1H), 4.50 (d, J = 9.04 Hz, 1H), 4.21 (dd, J = 8.24, 11.10 Hz, 1H), 3.45 (m, 1H), 3.32 (dd, J = 5.48, 13.66 Hz, 1H), 3.22 (t, J = 8.98 Hz, 1H), 3.02−2.90 (m, 4H), 2.66 (d, J = 13.64 Hz, 1H), 2.25 (m, 2H), 2.08 (m, 1H), 2.06 (s, 3H), 1.74 (m, 1H), 1.59 (s, 3H), 1.49 (s, 3H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ = 170.41, 169.65, 157.74, 140.94, 140.44, 137.13, 133.30, 129.61, 129.02, 128.98, 128.93, 128.90, 128.43, 127.97, 126.81, 126.79, 126.28, 114.61, 113.82, 107.79, 85.18, 76.10, 72.47, 70.72, 56.58, 42.05, 40.62, 36.53, 36.13, 33.44, 27.45, 27.44, 21.58 ppm.

Compound 10b (R_1 = CH_2CH_2Ph). R_f: 0.61 (2:1, hexane/ethyl acetate). LRMS: MS (ES^+) m/z = 602.5 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.47−7.22 (m, 11H), 7.02 (d, J = 2.76 Hz, 1H), 6.93 (dd, J = 2.81, 8.85 Hz, 1H), 5.35 (m, 1H), 5.13 (d, J = 11.53 Hz, 1H), 5.08 (d, J = 11.53 Hz, 1H), 4.51 (d, J = 9.25 Hz, 1H), 4.33 (dd, J = 8.04, 11.10 Hz, 1H), 3.50 (m, 1H), 3.18 (dd, J = 7.96, 9.15 Hz, 1H), 3.04−2.75 (m, 6H), 2.47 (m, 1H), 2.34 (m, 1H), 2.12 (m, 1H), 2.09 (s, 3H), 1.72 (m, 1H), 1.58 (s, 3H), 1.49 (s, 3H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ = 170.87, 169.84, 157.79, 140.62, 140.44, 137.09, 133.55, 129.02, 128.96, 128.93, 128.90, 128.88, 128.46, 127.94, 126.90, 126.82, 125.96, 114.74, 113.64, 107.95, 85.22, 76.09, 70.73, 69.58, 56.33, 42.62, 41.07, 39.20, 37.86, 36.54, 33.27, 27.47, 27.42, 21.67 ppm.

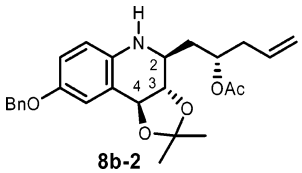
Compound 8b-1. (83% yield, 220 mg.) R_f: 0.53 (hexane/ethyl acetate 3:1). LRMS: MS (ES^+) m/z = 522.4 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.46−7.35 (m, 6H), 6.99 (d, J = 2.55 Hz, 1H), 6.88 (dd, J = 2.65, 8.72 Hz, 1H), 5.95 (m, 1H), 5.76 (m,1H), 5.30 (m, 1H), 5.24 (d, J = 10.12 Hz, 1H), 5.09 (m, 4H), 4.98 (m, 1H), 4.72 (dd, J = 5.1, 13.3 Hz, 1H), 4.65 (m, 1H), 4.48 (d, J = 9.12 Hz, 1H), 4.42

(m, 1H), 3.34 (t, J = 8.95 Hz, 1H), 2.41 (m, 2H), 2.25 (m, 1H), 1.90 (s, 3H), 1.81 (m, 1H), 1.56 (s, 3 H), 1.49 (s, 3H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ = 170.68, 157.17, 154.98, 137.17, 133.56, 132.99, 132.72, 128.98, 128.43, 127.94, 127.43, 118.53, 118.17, 114.29, 113.79, 107.73, 83.78, 76.61, 77.62, 70.71, 70.69, 67.09, 54.99, 39.28, 37.79, 27.47, 27.36, 21.46 ppm.



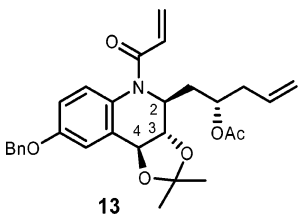
8b-1

Compound 8b-2. (93% yield.) R_f: 0.56 (3:1, hexane/ethyl acetate). LRMS: MS (ES^+) m/z = 438.3 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.45−7.32 (m, 5H), 6.89 (d, J = 2.52 Hz, 1H), 6.73 (dd, J = 2.58, 8.61 Hz, 1H), 6.45 (d, J = 8.64 Hz, 1H), 5.80 (m, 1H), 5.16−5.12 (m, 3H), 5.00 (m, 2H), 4.67 (d, 1H, J = 9.28 Hz), 3.69 (m, 1H), 3.54 (t, J = 9.34 Hz, 1H), 2.43 (m, 2H), 2.14 (m, 1H), 2.11 (s, 3H), 1.73 (m, 1 H), 1.56 (s, 3H), 1.52 (s, 3H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ = 171.57, 151.43, 136.75, 135.45, 133.41, 128.91, 128.15, 127.91, 121.47, 118.78, 116.52, 116.01, 114.09, 113.72, 110.64, 80.23, 77.61, 72.68, 71.29, 70.99, 54.29, 39.56, 39.34, 27.50, 27.43, 21.45 ppm.



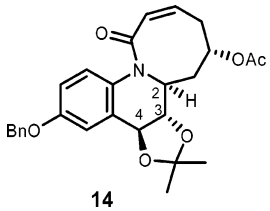
8b-2

Compound 13. (60% yield.) R_f: 0.36 (3:1, hexane/ethyl acetate). LRMS: MS (ES^+) m/z = 492.4 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.48−7.35 (m, 5H), 7.06 (d, J = 2.58 Hz, 1H), 7.03 (d, J = 8.58 Hz, 1H), 6.89 (dd, J = 2.62, 8.60 Hz, 1H), 6.45 (d, J = 16.79 Hz, 1H), 6.33 (dd, J = 10.10, 16.74 Hz, 1H), 5.77 (m, 1H), 5.65 (d, J = 10.08 Hz, 1H), 5.20−5.06 (m, 4H), 4.95 (m, 1H), 4.69 (m, 1H), 4.43 (d, J = 9.09 Hz, 1H), 3.33 (t, J = 8.89 Hz, 1H), 2.44 (m, 2H), 2.31 (m, 1H), 1.92 (s, 3H), 1.75 (m, 1H), 1.55 (s, 3H), 1.49 (s, 3H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ = 170.80, 165.87, 158.25, 136.89, 134.47, 133.68, 129.05, 128.95, 128.74, 128.57, 128.19, 127.95, 127.45, 118.45, 114.54, 113.62, 108.60, 84.39, 76.62, 70.90, 70.79, 53.66, 39.16, 37.58, 27.45, 27.32, 21.50 ppm.



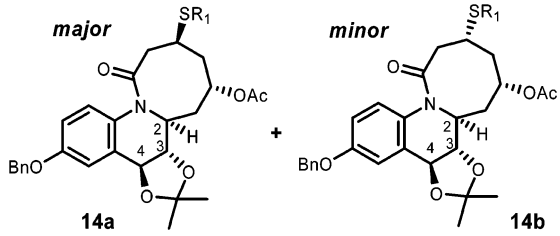
13

Compound 14. (88% yield.) R_f: 0.32 (1:1, hexane/ethyl acetate). LRMS: MS (ES^+) m/z = 464.4 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.47−7.34 (m, 6H), 7.04 (d, J = 2.53 Hz, 1H), 6.96 (dd, J = 2.69, 8.69 Hz, 1H), 6.09 (m, 2H), 5.29 (m, 1H), 5.12 (d, J = 11.57 Hz, 1H), 5.08 (d, J = 11.54 Hz, 1H), 4.63 (m, 1H), 4.46 (d, J = 9.28 Hz, 1H), 3.20 (t, J = 9.17 Hz, 1H), 2.82−2.67 (m, 2H), 2.10 (s, 3H), 2.04 (m, 1H), 1.92 (m, 1H), 1.60 (s, 3H), 1.49 (s, 3H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ = 170.47, 168.30, 158.24, 137.11, 133.81, 133.28, 129.49, 129.00, 128.44, 127.94, 125.98, 125.91, 114.55, 113.86, 108.26, 86.29, 76.18, 70.73, 68.10, 53.93, 41.34, 33.16, 30.10, 27.50, 27.38, 21.54 ppm.



14

Compound 14a. LRMS: MS (ES^+) m/z = 602.5 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.46−7.25 (m, 11H), 7.00 (d, J = 2.69 Hz, 1H), 6.92 (dd, J = 2.72, 8.75 Hz, 1H), 5.32 (m, 1H), 5.11 (d, J = 11.55 Hz, 1H), 5.07 (d, J = 11.58 Hz, 1H), 4.49 (d, J = 9.21 Hz, 1H), 4.36 (m, 1H), 3.49 (dd, J = 4.67, 13.54 Hz, 1H), 3.21 (dd, J = 7.63, 9.18 Hz, 2H), 2.93 (m, 4H), 2.72 (dd, J = 3.26, 13.65 Hz, 1H), 2.63 (m, 1H), 2.16 (m, 1H), 2.13 (s, 3H), 2.05 (m, 1H), 1.80 (m, 1H), 1.61 (s, 3H), 1.49 (s, 3H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ = 170.19, 169.97, 157.81, 140.98, 137.16, 133.24, 129.63, 128.98, 128.96, 128.88, 128.41, 127.95, 126.77, 126.31, 114.53, 113.78, 107.86, 85.63, 76.22, 70.71, 68.84, 54.77, 41.83, 40.22, 38.03, 36.46, 35.77, 33.48, 27.52, 27.41, 21.53 ppm.



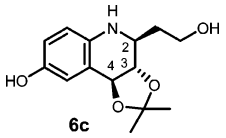
14a **14b**

14a:14b (7:1, R_1 = CH_2CH_2Ph)

Compound 14b. LRMS: MS (ES^+) m/z = 601.2 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.56 (d, J = 8.75 Hz, 1H), 7.47−7.25 (m, 10 H), 7.01 (d, J = 2.79 Hz, 1H), 6.93 (dd, J = 2.81, 8.75 Hz, 1H), 5.12 (d, J = 11.60 Hz, 1H), 5.07 (d, J = 11.60 Hz, 1H), 4.98 (m,1H), 4.51 (d, J = 9.31 Hz, 1H), 4.46 (m, 1H), 3.43 (m, 1H), 3.24 (dd, J = 6.98, 9.29 Hz, 1H), 3.14 (t, J = 12.56 Hz, 1H), 2.95−2.86 (m, 5H), 2.29 (dd, J = 3.91, 14.72 Hz, 1H), 2.21 (m, 1H), 2.12 (m, 1H), 2.07 (s, 3H), 1.86 (m, 1H), 1.62 (s, 3H), 1.51 (s, 3H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ = 170.54, 170.53, 157.83, 140.63, 137.12, 133.10, 128.98, 128.97, 128.94, 128.90, 128.43, 127.92, 126.83, 126.04, 114.79, 113.55, 108.07, 85.84, 76.35, 70.70, 70.53, 54.45, 42.63, 42.09, 42.01,40.21, 36.37, 33.86, 27.48, 27.41, 21.78 ppm.

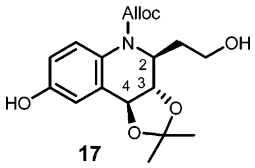
Solid-Phase Synthesis. Compound 6c. To a solution of **6a** (1.53 g, 4.31 mmol) in ethanol (40 mL) was added 20 wt % of palladium on carbon (306 mg). This was stirred under hydrogen at room temperature for 1 day. The catalyst was removed by filtration over Celite, and then the solvent was

evaporated. The residue was purified by flash chromatography on silica gel (1:2, hexane/ethyl acetate) to give product **6c** as a yellow solid (1 g, 88%). R_f: 0.25 (1:1, hexane/ethyl acetate). LRMS: MS (ES^+) m/z = 266.3 (M + 1). ^{1}H NMR: (400 MHz, DMSO-d_6) δ = 8.43 (s, 1H), 6.42−6.39 (m, 3H), 5.08 (s, 1H), 4.57 (d, J = 8.93 Hz, 2H), 3.63−3.55 (m, 3H), 3.41 (t, J = 9.49 Hz, 1H), 1.83−1.78 (m, 1H), 1.63−1.57 (m, 1H), 1.45 (s, 3H), 1.41 (s, 3H) ppm. ^{13}C NMR: (100 MHz, DMSO-d_6) δ = 148.62, 136.58, 121.15, 115.41, 114.37, 113.04, 110.89, 81.03, 77.81, 58.52, 53.12, 38.25, 27.87 ppm.



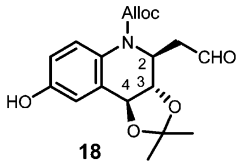
6c

Compound 17. To a solution of **6c** (900 mg, 3.39 mmol) in dichloromethane/acetonitrile (35:5 mL) at 0 °C, under N_2, was added pyridine (302 μL, 3.73 mmol) and allyl chloroformate (360 μL, 3.39 mmol). After 3 h of reaction at 0 °C, the reaction was quenched with a saturated solution of ammonium chloride. The aqueous layer was washed 3 times with dichloromethane, and then the combined organic layer was dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (1:1, hexane/ethyl acetate) to give compound **17** as a white solid (826 mg, 70%). R_f: 0.49 (1:2, hexane/ethyl acetate), 0.25 (1:1. hexane/ethyl acetate). LRMS: MS (ES^+) m/z = 350.3 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.21 (m, 1H), 6.82 (m, 1H), 6.73 (dd, J = 2.75, 8.63 Hz, 1H), 5.93 (m, 1H), 5.22∼5.30 (m, 2H), 4.71 (dd, J = 5.31, 13.48 Hz, 1H), 4.61 (m, 1H), 4.50 (d, J = 9.30 Hz, 1H), 4.42 (m, 1H), 3.77 (m,2H), 3.31 (t, J = 8.69 Hz, 1H), 1.90 (s, 2H), 1.59 (s, 3H), 1.50 (s, 3H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ = 154.22, 132.52, 128.28, 118.35, 114.61, 114.02 108.86, 84.64, 77.62, 76.47, 67.31, 59.83, 59.47, 38.58, 27.47, 27.41 ppm.



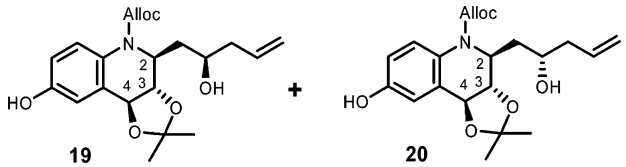
17

Compound 18. To a solution of **17** (826 mg, 2.365 mmol) in dichloromethane (30 mL), under N_2 at 0 °C, was added triethylamine (1.0 mL, 7.095 mmol) and a mixture of DMSO (7 mL, 99.319 mmol) and sulfur trioxide−pyridine complex (1.13 g, 7.095 mmol). After 1 h at 0 °C, the reaction was quenched by a solution of saturated ammonium chloride. The organic phase was extracted and dried with $MgSO_4$ and then filtered. After evaporation, the residue obtained was purified by flash chromatography on silica gel with 2:1 hexane/ethyl acetate to provide compound **18** as a pale yellow solid (690 mg, 84%). R_f: 0.59 (1:1, hexane/ethyl acetate). LRMS: MS (ES^+) m/z = 348.3 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 9.80 (s, 1H), 7.22 (m, 1H), 6.80 (d, J = 2.31 Hz, 1H), 6.71 (dd, J = 2.76, 8.69 Hz, 1H), 5.89 (m, 1H), 5.30−5.21 (m, 2H), 4.71−4.58 (m, 3H), 4.50 (d, J = 9.27 Hz, 1H), 3.34 (t, J = 9.15 Hz, 1H), 2.88−2.82 (ddd, J = 1.73, 7.00, 15.53 Hz, 1H), 2.77−2.71 (ddd, J = 3.73, 5.73, 9.46 Hz, 1H), 1.57 (s, 3H), 1.47 (s, 3H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ = 199.91, 154.28, 136.85, 132.82, 132.34, 127.87, 126.87, 114.84, 114.26, 108.95, 83.16, 76.43, 67.46, 60.85, 53.81, 48.77, 27.46, 27.41 ppm.



18

Compound 19. (36% yield.) R_f: 0.36 (3:2, hexane/ethyl acetate). LRMS: MS (ES^+) m/z = 390.4 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.19 (m, 1H), 6.83 (d, J = 2.52 Hz, 1H), 6.74 (dd, J = 2.56, 8.6 Hz, 1H), 5.89 (m, 2H), 5.28 (m, 3H), 5.10 (m, 2H), 4.70 (dd, J = 5.20, 13.53 Hz, 1H), 4.61 (m, 1H), 4.50 (d, J = 9.04 Hz, 1H), 4.43 (m, 1H), 3.87 (m, 1H), 3.30 (t, J = 8.97 Hz, 1H), 2.28 (m, 2H), 1.76 (m, 2H), 1.58 (s, 3H), 1.49 (s, 3H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ = 171.71, 154.44, 135.53, 133.68, 132.46, 128.39, 126.79, 118.33, 117.48, 114.64, 114.02, 108.86, 84.81, 77.61, 76.43, 67.37, 55.35, 43.49, 41.75, 27.44, 27.38 ppm.

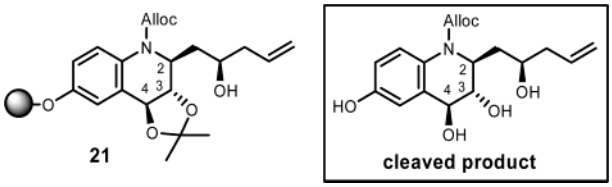


19 **20**

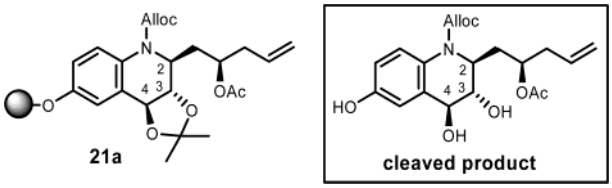
Compound 20. (36% yield.) R_f: 0.26 (3:2, hexane/ethyl acetate). LRMS: MS (ES^+) m/z = 390.4 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.28 (m, 1H), 6.80 (s, 1H), 6.73 (dd, J = 2.78, 8.61 Hz, 1H), 5.87 (m, 2H), 5.30 (m, 3H), 5.10 (m, 2H), 4.70 (m, 2H), 4.50 (m, 2H), 3.89 (m, 1H), 3.36 (t, J = 8.95 Hz, 1H), 2.30 (m, 2H), 2.17 (m, 1H), 1.65 (m, 1H), 1.59 (s, 3H), 1.51 (s, 3H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ = 171.51, 154.10, 135.09, 133.19, 132.64, 127.96, 127.17, 118.36, 118.10, 114.60, 114.06, 108.78, 83.16, 77.61, 76.51, 67.18, 55.30, 42.39, 42.11, 27.49 ppm.

Compound 21. BromoWang resin (1.40 mmol/g) was first washed several times with dichloromethane and DMF and then suspended for 30 min in DMF. To this resin in DMF (5 mL) was added a solution of compound **19** (288 mg, 0.74 mmol) in DMF (5.0 mL), sodium iodide (111 mg, 0.74 mmol), and cesium carbonate (241 mg, 0.74 mmol). Both reagents were dried in the oven overnight prior to use. The mixture was bubbled vigorously with nitrogen for 40 h. The resin was successively washed with MeOH (2×), DMF (2×), water (2×), MeOH (2×), and dichloromethane (3×) and then dried under vacuum for a few hours. The filtrate containing the starting material was evaporated, and the residue was dissolved in DCM. The organic layer was washed with water and brine, dried over sodium sulfate, filtered, and then evaporated. The residue was purified by flash chromatography on silica gel (1:2, hexane/ethyl acetate). The loading

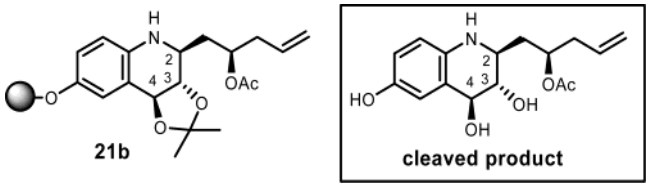
was determined to be 85% upon cleavage of the product from the solid support.



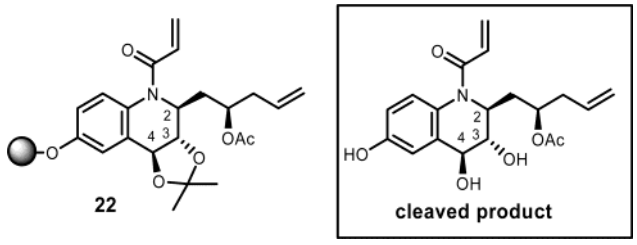
Compound 21a. To the resin **21** (265 mg) in dichloromethane (10 mL) was added pyridine (240 μL, 2.96 mmol), acetic anhydride (140 μL, 1.48 mmol), and 4-(dimethylamino)-pyridine (14 mg, 0.111 mmol). The mixture was shaken overnight. The mixture was filtered, and the resin washed with MeOH (2×), DMF (2×), water (2×), MeOH (2×), and dichloromethane (3×) and then dried under vacuum for a few hours.



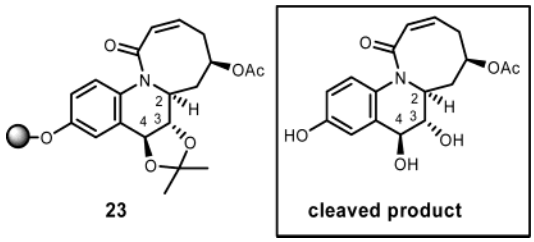
Compound 21b. To the above resin **21a** (265 mg, 0.371 mmol) in dichloromethane (15 mL) was successively added tetrakis(triphenylphosphine) palladium (214 mg, 0.185 mmol), *N*-methylmorpholine (0.4 mL, 3.64 mmol), and acetic acid (0.8 mL, 13.97 mmol). The mixture was mechanically stirred overnight. It was washed with MeOH (2×), DMF (2×), water (2×), MeOH (2×), and dichloromethane (3×) and then dried under vacuum for a few hours.



Compound 22. To the above resin (265 mg, 0.371 mmol) in dichloromethane (10 mL) was successively added triethylamine (1.4 mL, 10 mmol) and acryloyl chloride (0.6 mL, 7.4 mmol). The mixture was mechanically stirred overnight. Then the solution was washed with MeOH (2×), DMF (2×), water (1×), MeOH (2×), and dichloromethane (4×) and then dried under vacuum for a few hours.



Compound 23. To the above resin (265 mg, 0.371 mmol) in dichloromethane (20 mL) was added second-generation Grubbs catalyst (189 mg, 0.222 mmol) under a nitrogen atmosphere. The mixture was refluxed for 14 h. It was washed with MeOH (2×), DMF (2×), water (1×), MeOH (2×), and dichloromethane (4×) and then dried under vacuum for a few hours. The 30 mg of resin was submitted to cleavage with 5% TFA in dichloromethane for 1 h. The resin was then filtered and washed several times with dichloromethane. The filtrate was evaporated and dried under vacuum. The cleaved product was purified over column chromatography giving the pure cleaved compound (40% yield for six steps). R_f: 0.18 (ethyl acetate). LRMS: MS (ES^+) $m/z = 334.3$ (M + 1). ^{1}H NMR: (400 MHz, acetone-d_6) $\delta = 8.36$ (s, 1H), 7.41 (d, $J = 8.61$ Hz, 1H), 7.06 (d, $J = 2.61$ Hz, 1H), 6.77 (dd, $J = 2.65$, 8.60 Hz, 1H), 6.15 (m, 1H), 6.00 (d, $J = 11.58$ Hz, 1H), 5.64 (s, 1H), 4.86 (m, 1H), 4.77 (s, 1H), 4.34 (d, $J = 7.81$ Hz, 1H), 4.27 (dd, $J = 5.50$, 10.90 Hz, 1H), 3.24 (m, 1H), 2.83 (m, 1H), 2.43 (dd, $J = 7.38$, 13.18 Hz, 1H), 2.20 (m, 1H), 1.99 (s, 3H), 1.67 (m, 1H) ppm.



Acknowledgment. We thank the NRC Genomics Program, Special VP-Research NRC Funds for Chemical Biology, National Cancer Institute of Canada for financial support. Ayub Reayi is thanked for providing the analytical information on two compounds (**11** and **15**) obtained from the thiol addition shown in Scheme 2.

Supporting Information Available. Analysis of the 1D and 2D NMR spectra for compounds **10**, **11**, **14**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) For a review on solution and solid-phase synthesis leading to the library generation based upon natural products and natural product-like compounds, see: (a) Hall, D. G.; Manku, S.; Wang, F. *J. Comb. Chem.* **2001**, *3*, 125−150. (b) Wessjohann, L. A. *Curr. Opin. Chem. Biol*. **2000**, *4*, 303−309. (c) Weber, L. *Curr. Opin. Chem. Biol*. **2000**, *4*, 295−302. (d) Arya, P.; Joseph, R.; Chou, D. T. H. *Chem. Biol*. **2002**, *9*, 145−156.

(2) (a) Berg, T. *Angew. Chem., Int. Ed*. **2003**, *42*, 2462−2481. (b) Boger, D. L.; Desharnais, J.; Capps, K. *Angew. Chem., Int. Ed*. **2003**, *42*, 4138−4176. (c) Breimbaur, R.; Vetter, I. R.; Waldmann, H. *Angew. Chem., Int. Ed*. **2002**, *41*, 2878−2890. (d) Hinterding, K.; Alonso-Diaz, D.; Waldmann, H. *Angew. Chem., Int. Ed*. **1998**, *37*, 688−749. (e) Huwe, A.; Mazitschek, R.; Giannis, A. *Angew. Chem., Int. Ed*. **2003**, *42*, 2122−2138. (f) Klabunde, T.; Hessler, G. *ChemBioChem.* **2002**, *3*, 928−944.

(3) (a) Schreiber, S. L. *Chemical and Engineering News*, March 3, 2003, pp 51−61. (b) Gura, T. *Nature* **2000**, *407*, 282−284. (c) Strausberg, R. L.; Schreiber S. L. *Science* **2003**, *300*, 294−295. (d) Burke, M. D.; Berger, E. M.; Schreiber, S. L. *Science* **2003**, *302*, 613−618.

(4) (a) Crews, C. M.; Mohan, R. *Curr. Opin. Chem. Biol*. **2000**, *4*, 47−53. (b) Crews, C. M.; Splittgerber, U. *Trends Biochem. Sci*. **1999**, *24*, 317−320. (c) Stockwell, B. R. *TIBTECH* **2000**,

18, 449−455. (d) Stockwell, B.R. *Nat. Rev. Genet.* **2000**, *1*, 116. (e) Mayer, T. U. *Trends Cell Biol.* **2003**, *13*, 270−277. (f) Peterson, J. R.; Mitchison, T. J. *Chem. Biol.* **2002**, *9*, 1275−1285.

(5) (a) Newmann, D. J.; Cragg, G. M.; Snader, K. M. *Nat. Prod. Rep.* **2000**, *17*, 215−234. (b) Faulkner, D. J. *Nat. Prod. Rep.* **2001**, *18*, 1−49. (c) Faulkner, D. J. *Nat. Prod. Rep.* **1999**, *16*, 155−198.

(6) Arya, P.; Durieux, P.; Chen, Z.-X.; Joseph, R.; Leek, D. M. *J. Comb. Chem.* **2004**, *6*, 54−64.

(7) Dewick P. M. In *Medicinal Natural Products—A Biosynthetic Approach*; Wiley-Interscience: New York, 2002; Chapter 6.

(8) (a) Bieraugel, H.; Jansen, T. P.; Schoemaker, H. E.; Hiemstra, H.; van Maarseveen, J. H. *Org. Lett.* **2002**, *4*, 2673−2674. (b) Yet, L. *Chem. Rev.* **2000**, *100*, 2963−3007. (c) Evans, P. A.; Holmes, A. B. *Tetrahedron* **1991**, *47*, 9131−9166. (d) Nubbemeyer, U. *Top. Curr. Chem.* **2001**, *216*, 125−196.

(9) (a) Spring, D. R.; Krishnan, S.; Schreiber, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 5656−5657. (b) Lee, D. S.; Sello, J. K.; Schreiber S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10648−10649. (c) Spring, D. R.; Krishnan, S.; Blackwell, H. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1354−1363. (d) Sello, J. K.; Andreana, P. R.; Lee, D.; Schreiber, S. L. *Org. Lett.* **2003**, *5*, 4125−4127.

(10) (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res*. **2001**, *34*, 18−29. (b) Phillips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75−90. (c) Bieraugel, H.; Jansen, T. P.; Schoemaker, H. E.; Hiemstra, H.; van Maarseveen, J. H. *Org. Lett.* **2002**, *4*, 2673−2674. (d) Rutjes, F. P. J. T.; Schoemaker, H. E. *Tetrahedron Lett.* **1997**, *38*, 677−680. (e) Schuster, M.; Pernerstorfer, J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1979−1980.

CC049935S