NRC Publications Archive (NPArC)
Archives des publications du CNRC (NPArC)

Part 1. Modular Approach to Obtaining Diverse Tetrahydroquinoline-Derived Polycyclic Skeletons for Use in High-Throughput Generation of Natural-Product-like Chemical Probes

Prakesch, Michael; Sharma, Utpal; Sharma, Maya; Khadem, Shahriar; Leek, Donald; Arya, Prabhat

Web page / page Web
http://dx.doi.org/10.1021/cc060055i
http://nparc.cisti-icist.nrc-cnrc.gc.ca/npsi/ctrl?action=rtdoc&an=12328027&lang=en
http://nparc.cisti-icist.nrc-cnrc.gc.ca/npsi/ctrl?action=rtdoc&an=12328027&lang=fr

Part 1. Modular Approach to Obtaining Diverse Tetrahydroquinoline-Derived Polycyclic Skeletons for Use in High-Throughput Generation of Natural-Product-like Chemical Probes

Michael Prakesch,[†] Utpal Sharma,[†] Maya Sharma,[†] Shahriar Khadem,[†] Donald M. Leek,[†] and Prabhat Arya*,[†,‡,§]

Steacie Institute for Molecular Sciences, National Research Council of Canada, 100 Sussex Drive, Ottawa, Ontario, Canada K1A 0R6, Ottawa Institute of Systems Biology, University of Ottawa, 451 Smyth Road, Ottawa, Ontario, Canada K1H 8M5, and Department of Biochemistry, McGill University, 3655 Promenade Sir William Osler, Montreal, Quebec, Canada H3G 1Y6

A practical synthesis of a tetrahydroaminoquinoline scaffold (**12**) was developed that used a stereocontrolled aza Michael as the key reaction. Three tetrahydroquinoline alkaloid-like, tricyclic derivatives **16**, **18**, and **19** with different medium to macrocyclic ring skeletons were obtained, using this scaffold as the starting material, in a modular manner. The macrocyclic compounds with an isolated olefin and an electron-deficient olefin were obtained by ring-closing metathesis approaches. Compounds **16** and **18** are unique and contain bridged 10- and 12-membered functionalized rings. The NMR studies of these compounds revealed interesting information on the conformation of the bicyclic scaffolds that was dependent on the nature and the size of the macrocyclic rings. Finally, this modular methodology, using compound **21** anchored onto the solid support, successfully led to the generation of different macrocyclic derivatives, **23**, **25**, and **27** in solid-phase synthesis. The solid-phase synthesis approach outlined in this article has the potential to generate tetrahydroquinoline-based tricyclic compounds containing different medium to macrocyclic architectures.

Introduction

The use of small-molecule chemical probes to understand (and dissect) protein−protein interaction-based dynamic signaling pathways is of immense interest in the post-genomics age.[1] Small-molecule chemical probes have tremendous potential to function in a highly selective and reversible manner on proteins.[2] Although there are several advantages to developing small-molecule chemical probes, challenges such as developing synthetic methods leading to the high-throughput generation of structurally diverse and complex architectures are also associated.[3] As a result, this has met with little success to date.[4] Nevertheless, the demand for small-molecule chemical probes as dissectors of protein−protein interaction-based signaling pathways has coincided with the need for high-throughput generation of 3-dimensional (3-D) skeletally diverse natural-product-like compounds.[5,6] Several examples of bioactive natural products have been shown to be modulators of protein−protein interactions.[7]

To explore the natural product chemical space of alkaloid compounds, we anticipate that natural-product-like com-pounds synthesized containing diverse tetrahydroquinoline-derived polycyclic skeletons will likely compete for the same chemical territory that is currently being championed by bioactive natural products. Synthesis of novel natural-product-like (alkaloid-like) compounds would serve as useful chemical probes in the dissection of protein−protein interaction-based dynamic signaling networks.[8] Toward this objective, herein, we report a modular solid-phase methodology that uses an enantioenriched tetrahydroaminoquinoline scaffold as a common precursor for high-throughput generation of tetrahydroquinoline-derived, skeletally diverse, polycyclic compounds.[9] The tetrahydroquinoline is considered to be a highly privileged scaffold where several bioactive alkaloids (a few examples are shown in Figure 1, see **1**−**3**) contain this moiety.[10] The aim of this present study is to populate the 3-dimensional (3-D) chemical space around the tetrahydroquinoline scaffold (**4**, Scheme 1) to obtain stereoselective, complex architectures functioning as alkaloid-like (natural-product-like) small-molecule chemical probes.

Results and Discussion

The first milestone in this study was to develop a practical enantiocontrolled synthesis of the highly versatile tetrahydroquinoline scaffold **4**, containing orthogonal protecting functional groups. A facile practical synthesis of this scaffold was crucial to building a stereoselective, 3D, skeletally diverse program. This scaffold possesses several unique

* To whom correspondence should be addressed. Phone: (613) 993 7014. Fax: (613) 952 0068. E mail: prabhat.arya@nrc.ca.
† Steacie Institute for Molecular Sciences, National Research Council of Canada.
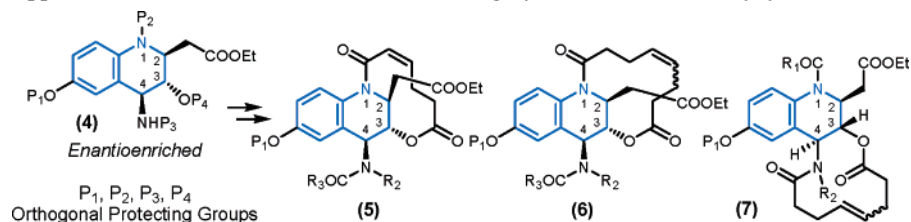‡ Ottawa Institute of Systems Biology, University of Ottawa.
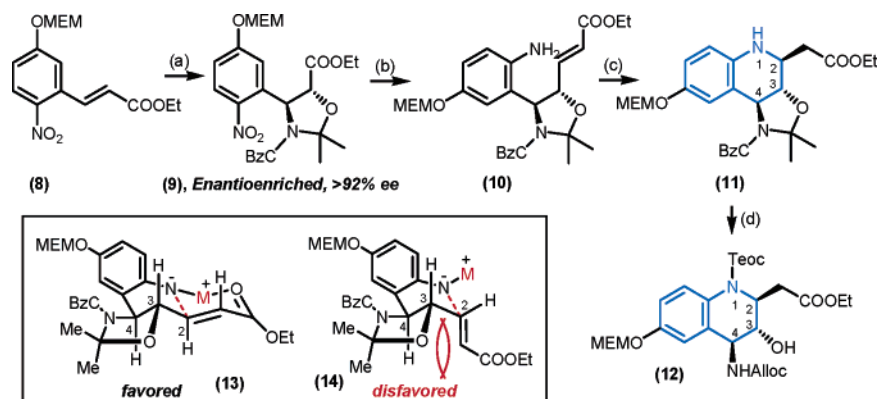§ Department of Biochemistry, McGill University.
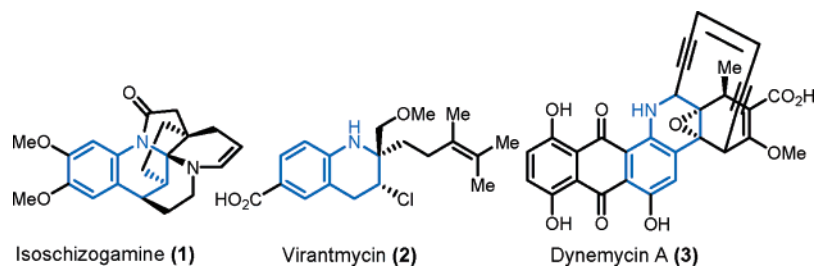
Figure 1. Few examples of bioactive alkaloids having a tetrahydroquinoline scaffold.

Scheme 1. Modular Approach to Obtain Diverse, Alkaloid-like, Highly Functionalized, Polycyclic Architectures

Scheme 2

^{a} (i) Sharpless aminohydroxylation, 75%, (ii) 2-methoxypropene, PPTS 86%. ^{b}(i) LiBH$_4$, (ii) SO$_3$ Py, (iii) Ph$_3$C=CHCOOEt, 65% for 2 steps, (iv) Zn/AcOH, 67%. ^{c}LDA, -78 °C to rt, 67%. ^{d}(i) TeocCl, pyridine, 77%, (ii) H$_2$, 10% Pd/C; SiO$_2$, 56%, (iii) AllocCl, DIPEA, 91%.

features and includes (i) the β- and δ-amino acid functionalities,[11] (ii) the 1,2-*trans*-amino alcohol moiety,[12] (iii) the 1,3-hydroxyl carboxylic ester,[13] and (iv) a phenolic hydroxyl group that could be utilized as an anchoring site in solid-phase synthesis. With compound **4** used as the starting material, the bridged tricyclic derivative **5** with an unsaturated enamide functional group could be obtained by a ring-closing metathesis reaction between the olefinic moiety at C$_3$ and the *N*-acryloyl functional group at N$_1$. In a similar manner, the replacement of the *N*-acryloyl group by the *N*-pentenoyl moiety would provide the bridged 12-membered ring derivative **6**, having the δ-amino acid functionality.

This approach could also be applied in a modular manner, in which, the introduction of the *N*-pentenoyl moiety at C$_3$ would result in a structurally different, tricyclic derivative having a trans-fused 12-membered ring derivative with β-amino acid functionality. Thus, with a common starting material, it is possible to develop a modular approach to obtain structurally different polycyclic compounds containing medium to macrocyclic rings. Compounds **5**−**7** could be further used in library generation. For example, compound **5** contains two diversity sites [R$_2$ and R$_3$, and the third diversity could be easily derived from the use of an enamide functional group (i.e., stereoselective conjugate addition,[9] Diels−Alder etc.)]. Similarly, with two diversity sites on

compound **6**, the use of the carboxyl group functionality could provide the third diversity in library generation. Compound **7** contains a functionalized trans-fused 12-membered ring which could easily be subjected to library generation. Thus, several polycyclic derivatives with a variation in their 3D architectures could be envisioned, by employing a common starting material, in the developement of a highly diverse combinatorial chemistry program.

Scheme 2 shows our approach to obtaining the enantioenriched, tetrahydroquinoline scaffold **12**. As an extension to our early finding related to an aza Michael approach,[9] this was the key reaction to obtain compound **11** from **10** in a stereocontrolled manner. Compound **10** was synthesized from **8** in several steps including (i) Sharpless enantioselective aminohydroxylation (>92% ee),[14] (ii) acetonide protection, and (iii) two carbon extension via a Wittig reaction. We were pleased to note that, as observed in a previous study from our group,[9] the aza Michael reaction was very clean and produced the cyclic β- and δ-amino acid derivative in high diastereomeric purity (NOE between C$_2$-H and C$_4$-H). In fact, there was no sign of any trace amounts of the other diastereomer, even when the reaction was carried out on a large scale ($\sim$10.0 g). A chairlike transition state (see, **13** and **14** in **Scheme 2** for both the favored and disfavored transition states) was proposed to explain the stereochemical

Scheme 3
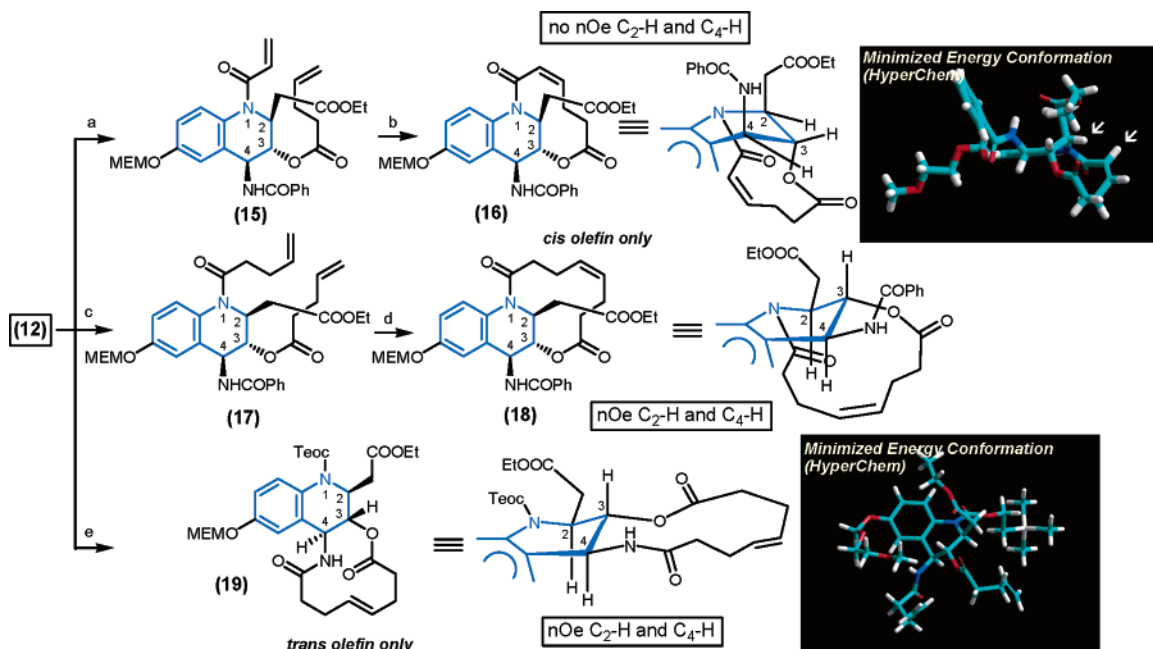
a (i) 4-Pentenoic acid, 4-DMAP, DIC, 85%, (ii) Pd(PPh₃)₄, morpholine, (iii) PhCOCl, NEt₃, 67% for 2 steps, (iv) TBAF, 87%, (v) acryloyl chloride, NEt₃, 73%. *b*Second-generation Grubbs' catalyst, 80%. *c*(i) Repeat steps i−iv from *a*, (ii) 4-pentenoyl chloride, NEt₃, 76%, *d*Second-generation Grubbs' catalyst, 72%, *e*(i) 4-pentenoic acid, DMAP, DIC, 85%, (ii) Pd(PPh₃)₄, morpholine, (iii) 4-pentenoyl chloride, NEt₃, 72% for 2 steps, (iv) second-generation Grubbs' catalyst, 98%.

outcome of this aza Michael reaction. This method is highly practical, and it allows a highly versatile, enantioenriched tetrahydroaminoquinoline scaffold to be obtained in large quantities. Finally, the desired compound, **12**, was easily obtained from **11** in simple high-yielding transformations.

The model studies to test the feasibility of our modular approach to obtain different macrocyclic derivatives are shown in Scheme 3. Compound **15**, a precursor for the bridged ring-closing metathesis containing the *N*-acryloyl moiety was obtained from **12** in several steps. We were pleased to note that, upon treatment with Grubbs' second-generation catalyst, ring-closing metathesis on **15** produced the desired tricyclic product, **16**, in an 80% yield. Compound **16** has a bridged 10-membered ring with an unsaturated enamide functional group. In addition to this, it also has a δ-amino acid functionality that could further be utilized in diversity generating reactions. Repeating the similar sequence, in which the *N*-acryloyl moiety is replaced by the *N*-pentenoyl moiety, provided the bridged 12-membered ring-derived polycyclic derivative **18**, having only a cis olefinic functionality. The ring-closing metathesis reaction was very fast and produced compound **18** in a high yield (80%) with complete stereocontrol. Finally, the successful synthesis of the trans-fused 12-membered ring-based polycyclic derivative was also achieved in a modular manner where the *N*-pentenoyl moiety was introduced at C₃.

The NMR studies of compounds **16**, **18**, and **19**, containing medium-sized macrocyclic rings, revealed interesting information about their conformations. For example, **15**, a precursor to compound **16**, showed a NOE between C₂-H and C₄-H. This indicated that the substituents at C-2, C-3, and C-5 occupy the pseudoequatorial positions. After formation of the macrocyclic ring containing the enamide functional group, there was no NOE observed between the

protons at C₂-H and C₄-H in compound **16**. The three substituents at C-2, C-3, and C-5 in the tricyclic derivative **16** occupy pseudoaxial positions. This information was helpful in the understanding of the shape of the 10-membered bridge macrocycle which appears to be perpendicular to the tetrahydroaminoquinoline ring architecture. In contrast to this observation, compound **18**, containing the 12-membered macrocycle, did show NOE between protons at C₂-H and C₄-H, indicating that all three substituents at C-2, C-3, and C-5 seem to occupy pseudoequatorial positions. Thus, extending the ring size (i.e., from compound **16** to **18**) seems to play an important role in forcing the tetrahydroamino-quinoline ring to adopt different ring conformations. Also, it was interesting to observe that, during the ring-closing metathesis reaction, only the cis olefin was produced in compound **18** containing a bridged 12-membered ring macrocycle. Finally, the third tricyclic derivative **19,** having a trans-fused 12-membered ring with the tetrahydroquinoline moiety, retained the NOE at C₂-H and C₄-H. As a result, this study helped in the prediction of the shape of the tetrahydroaminoquinoline scaffold in which the three substituents present at C-2, C-3, and C-4 occupy pseudoequatorial positions. The formation of the trans olefin-based macrocycle in compound **19** was another interesting feature of the ring-closing metathesis reaction.

The next goal of the project was to develop a modular solid-phase synthesis to obtain polycyclic derivatives **23**, **25**, and **27** (Scheme 5). For the solid-phase synthesis, compound **20**, containing a free hydroxyl group and a three carbon spacer, was obtained from **12** (Scheme 4). This was then immobilized onto the alkylsilyl macrobeads (500−560 μm, 1.29 mmol/g, courtesy of the Chemical Biology Program, Broad Institute),[15] where the loading was determined to be 76%, from the increase in weight containing the loaded

Scheme 4
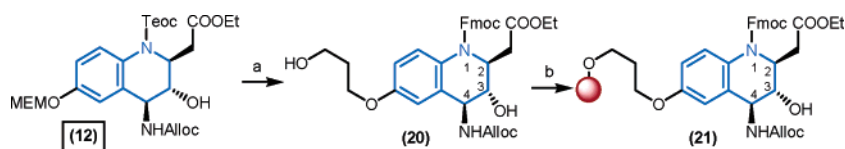
[a] See the Experimental Section. [b](i) (4-methoxyphenyl) diisopropylsilyl propyl polystyrene macrobeads (loading 1.29 mmol/g, 500−560 μm), 76% determined by an increase in the weight of the loaded alkylsilyl macrobeads.

Scheme 5
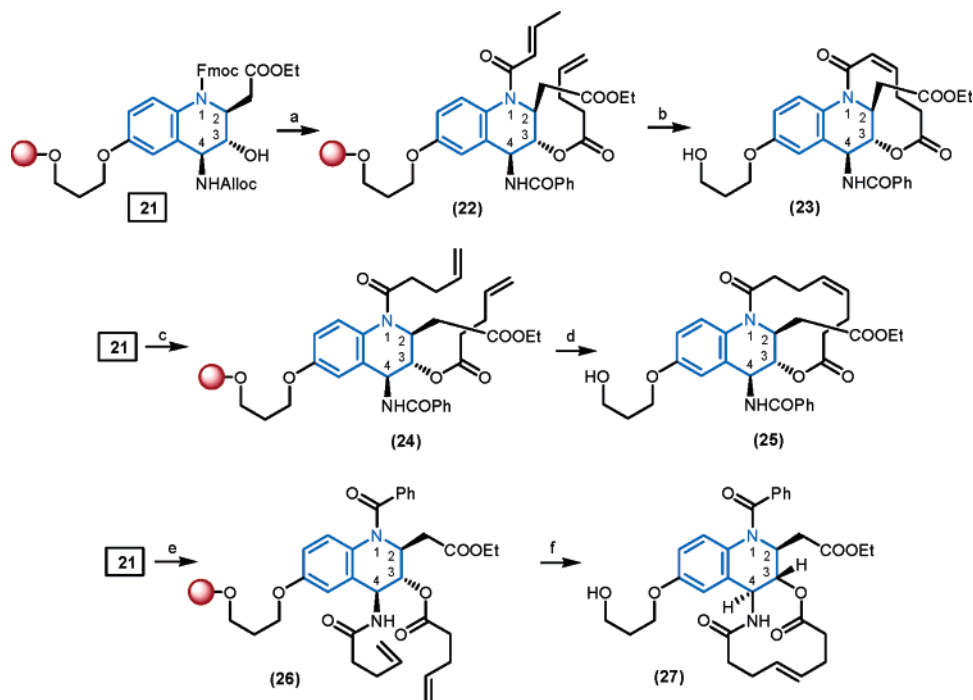
[a] (i) 4-Pentenoic acid, DMAP, DIC, (ii) piperidine, (iii) *trans*-crotonoyl chloride, 2,4,6-collidine, (iv) Pd(PPh₃)₄, PPh₃, 4-methyl morpholine, CH₃CO₂H, (v) PhCOCl, 2,4,6-collidine. [b](i) Second-generation Grubbs' catalyst, (ii) HF−pyridine. [c](i) 4-Pentenoic acid, DMAP, DIC, (ii) piperidine, (iii) 4-pentenoyl chloride, 2,4,6-collidine, (iv) Pd(PPh₃)₄, PPh₃, 4-methyl morpholine, CH₃CO₂H, (v) PhCOCl, 2,4,6-collidine. [d](i) Second-generation Grubbs' catalyst, (ii) HF−pyridine. [e](i) 4-Pentenoic acid, DMAP, DIC, (ii) piperidine, (iii) PhCOCl, 2,4,6-collidine, (iv) Pd(PPh₃)₄, PPh₃, 4-methyl morpholine, CH₃CO₂H, (v) 4-pentenoyl chloride, 2,4,6-collidine. [f](i) Second-generation Grubbs' catalyst, (ii) HF−pyridine.

product anchored onto the alkylsilyl macrobeads. With immobilized **21** in hand, the platform was set to explore different modular approaches using solid-phase synthesis, and these results are shown in Scheme 5.

Compound **21** was subjected to three parallel reactions: The first and the second sequence gave the bridged 10- and 12-membered rings **23** and **25**, respectively. These sequences involved (i) O-pentenoylation of the free hydroxyl group (HPLC yield 99%), (ii) N-Fmoc removal (HPLC yield 98%), (iii) N-acylation using *trans*-crotonoyl chloride for the first sequence on Scheme 5 or N-pentenoylation for the second sequence (HPLC yield 98% and 99%) (iv) N-Alloc removal (HPLC yield >85%), and (v) N-benzoylation (HPLC yield >80%, first diversity). These sequences gave compounds **22** and **24** which were independently subjected to RCM using Grubbs' second-generation catalyst (10−20 mol %). We were pleased to observe the formation of the bridged tricyclic products on solid support as observed in solution-phase synthesis. After they were cleaved from the solid support, products **23** and **25** were isolated and fully characterized. In both cases, the overall sequence was clean and the final products were obtained in 45 and 50% HPLC yields for 7 steps.

In the last series, the trans-fused 12-membered ring-based polycyclic derivative **27** was obtained from **21** in a similar manner. This modular sequence included (i) O-pentenoylation (HPLC yield 99%), (ii) N-Fmoc removal (HPLC yield 85%), (iii) N-amide formation (HPLC yield 78%, first diversity), (iii) N-Alloc removal (HPLC yield 71%), and (iv) N-pentenoylation (HPLC yield 81%). Subjection to RCM conditions, followed by cleavage of the product from solid support, produced the tricyclic derivative **27** containing a trans-fused 12-membered ring. As observed in previous examples, the sequence was very clean, and the final product, **27**, was obtained from **21** in 7 steps with an overall yield of 57%.

Conclusion

In summary, we have described a modular approach to obtain stereoselective and skeletally different alkaloid-like (i.e., natural-product-like) polycyclic derivatives containing medium to macrocyclic rings using solid-phase synthesis. For example, compounds **23** and **25** are unique and contain bridged 10- and 12-membered functionalized rings. Furthermore, from our developed methodology, work is in progress to develop a high-throughput library-generation program

that would enable rapid access to 3-D skeletally diverse, alkaloid-like, polycyclic compounds. Finally, the presence of a primary hydroxyl group attached to a three-carbon spacer makes these compounds well-suited for printing onto glass slides for the fabrication of small-molecule microarrays.[16] The incorporation of these chemical entities on a microarray will provide a unique screening chip where immobilized small molecules can be targeted with a diverse range of proteins.

Experimental Section

All reactions were carried out in flame-dried glassware under an atmosphere of nitrogen with magnetic stirring. Thin-layer chromatography (TLC) was done on EMD (Art. 5715-7) precoated silica gel 60 F$_{254}$ glass plates (layer thickness 0.25 mm). Visualization was affected with a UV lamp (254 nm) or by staining with vanillin, KMnO$_4$, or ammonium molybdate/ceric sulfate solution. Flash column chromatography was performed using silica gel 60 (40−63 μm, Silicycle) or a Biotage Horizon flash chromatography system. Solvents were purified as follows: trace amounts of water and oxygen from THF, DMF, and dichloromethane were removed using columns containing activated alumina and copper under N$_2$. Triethylamine, pyridine, ethyl ether, and toluene were obtained from commercial suppliers (EMD and Aldrich) and used without further purification. NMR spectra were recorded on a Bruker DRX 400 MHz spectrometer. All chemical shifts are reported in parts per million (δ). ^{1}H NMR (400 MHz) spectra were recorded at room temperature in CDCl$_3$ or C$_6$D$_6$ solutions and referenced to residual CHCl$_3$ (7.27 ppm) or C$_6$H$_6$ (7.16 ppm). Fully decoupled ^{13}C NMR (100 MHz) spectra were recorded in CDCl$_3$ or C$_6$D$_6$ solutions. The center peaks of CDCl$_3$ (77.0 ppm) and C$_6$D$_6$ (128.7 ppm) were used as the internal reference. Mass spectra were carried out on a VG Quattro I (Micromass) mass spectrometer equipped with a pneumatically assisted electrospray ionization source, operating in positive mode. HPLC were performed using a Hewlett-Packard (Agilent) 1100 Series equipped with a diode array detector and a NovaPack C18 (3.9 × 300 mm) column. The enantiomeric excess was determined by chiral HPLC, using a Hewlett-Packard (Agilent) 1090 Series II liquid chromatograph equipped with a diode array detector and a CHIRACEL-OD column. HPLC/MS were performed using Waters equipment: Waters micromass ZQ ESCI multimode ionization, Waters 996 photodiode array detector (254 nm), and Waters 2795 separation module with Phenomenex Spherisorb 3 ODS-2 column.
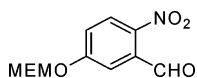

To a solution of commercially available 5-hydroxy-2-nitrobenzaldehyde (25.00 g, 146.6 mmol) in 500 mL of anhydrous CH$_2$Cl$_2$ was added the diisopropylethylamine (47 mL, 267.1 mmol) at −10 °C over a period of 10 min. During that time, the starting material dissolved completely. Then MEM chloride (25.00 g, 200.7 mmol) was slowly added over a period of 20 min at −10 °C. The reaction mixture was

allowed to warm to room temperature and was stirred for an additional 22 h. The reaction mixture was cooled to 0 °C, and a saturated solution of NaHCO$_3$ was slowly added (100 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 50 mL), and the organic layer was dried over MgSO$_4$. After filtration and concentration under vacuum, the crude product was chromatographed on silica gel (eluent = hexane/ethyl acetate, 7/3−1/1) to give the desired compound in a quantitative yield (37.42 g). Yellow solid. R_f: 0.43 (1/1, hexane/ethyl acetate). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 10.46 (s, 1H, C*H*O), 8.16 (d, J = 9.0 Hz, 1H, C*H*CNO$_2$), 7.48 (s, 1H, C*H*CCHO), 7.33 (d, J = 9.0 Hz, 1H, C*H*CCOMEM), 5.39 (s, 2H, OC*H$_2$*O), 3.83 (t, J = 4.3 Hz, 2H, OCH$_2$C*H$_2$*O), 3.55 (t, J = 4.3 Hz, 2H, OC*H$_2$*CH$_2$O), 3.36 (s, 3H, C*H$_3$*O). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 188.3, 161.6, 142.9, 134.2, 127.1, 119.8, 116.2, 93.5, 71.4, 68.5, 59.0. LRMS: MS (ES+) m/z = 270.1 (M + 1).


8
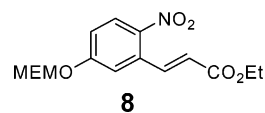
Triethyl phosphonate acetate (39.71 g, 194.4 mmol) was added to a suspension of sodium hydride (10.77 g, 269.2 mmol) in 760 mL of anhydrous THF at 0 °C over a period of 10 min. The reaction mixture was stirred vigorously for 50 min at 0 °C, before a solution of above compound (38.17 g, 149.6 mmol) in 100 mL of anhydrous THF was added over a period of 15 min via a syringe at 0 °C. Then, the reaction mixture was stirred for an additional 4 h at 0 °C and quenched by a reverse addition onto mixture of ice, a saturated solution of NH$_4$Cl, and solid NH$_4$Cl in a large beaker. The aqueous layer was extracted with ethyl acetate (3 × 150 mL), and the organic layer was dried over MgSO$_4$. After filtration and concentration under vacuum, the crude product was chromatographed on silica gel (eluent = hexane/ethyl acetate, 8/2−1/1) to give the title compound (46.22 g, 95%). Yellow oil. R_f: 0.45 (1/1 hexane/ethyl acetate). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.17 (d, J = 15.7 Hz, 1H, C*H*=CHCO$_2$Et), 8.09 (d, J = 9.0 Hz, 1H, C*H*CNO$_2$), 7.20 (s, 1H, C*H*CCHO), 7.14 (dd, J = 9.0 Hz, J = 1.8 Hz, 1H, C*H*CCOMEM), 6.30 (d, J = 15.7 Hz, 1H, CH=C*H*CO$_2$Et), 5.36 (s, 2H, OC*H$_2$*O), 4.28 (q, J = 7.0 Hz, 2H, CO$_2$C*H$_2$*-CH$_3$), 3.83 (t, J = 4.5 Hz, 2H, OCH$_2$C*H$_2$*O), 3.55 (t, J = 4.5 Hz, 2H, OC*H$_2$*CH$_2$O), 3.36 (s, 3H, C*H$_3$*O), 1.34 (t, J = 7.0 Hz, 3H, CO$_2$CH$_2$C*H$_3$*). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 165.7, 161.0, 141.9, 140.7, 133.5, 127.4, 123.3, 116.9, 116.1, 93.4, 71.4, 68.2, 60.8, 59.0, 14.2. LRMS: MS (ES+) m/z = 326.3 (M + 1).


8a
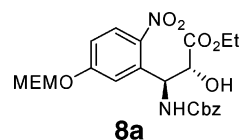
An aqueous solution of NaOH (3.87 g, 93.8 mmol) in 225 mL of water, *t*-butyl hypochlorite (10.76 mL, 93.8 mmol), and a solution of (DHQ)$_2$PHAL (1.26 g, 1.5 mmol) in 80 mL of *n*-propanol were added to a solution of benzyl carbamate (14.55 g, 95.3 mmol) in 120 mL of *n*-propanol at

0 °C with 5 min of stirring between each addition. The reaction mixture was left at room temperature for 15 min before being cooled to 0 °C. Then a solution of **8** (10 g, 30.7 mmol) in 10 mL of n-propanol and potassium osmate dehydrate (453 mg, 1.2 mmol) were added. After the mixture was stirred for 4 h at 0 °C, the temperature was slowly increased overnight; 200 mL of ethyl acetate was added, and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The organic layer was dried over MgSO$_4$. After filtration and concentration under vacuum, the crude product was chromatographed on silica gel (eluent = hexane/ethyl acetate, 7/3 to pure ethyl acetate) to give **8a** (11.35 g, 75%). Yellow oil. R_f: 0.20 (1/1 hexane/ethyl acetate), 0.44 (3/7 hexane/ethyl acetate). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.06 (d, $J = 9.0$ Hz, 1H, C*H*CNO$_2$), 7.32−7.20 (m, 5H, Ph), 7.19 (broad s, 1H, N*H*), 7.13 (d, $J = 2.5$ Hz, 1H, C*H*COMEM), 7.04 (dd, $J = 9.0$ Hz, $J = 2.5$ Hz, 1H, C*H*CHCNO$_2$), 6.02 (broad d, $J = 8.5$ Hz, 1H, C*H*NHCO), 5.88 (broad d, $J = 9.0$ Hz, 1H, C*H*OH), 5.26 (s, 2H, OC*H*$_2$O), 5.03 (dd, $J = 11.8$ Hz, $J = 2.0$ Hz, 1H, PhC*H*$_2$OCO), 4.96 (d, $J = 11.8$ Hz, 1H, PhC*H*$_2$OCO), 4.60 (broad s, 1H, O*H*), 4.33−4.17 (m, 2H, CO$_2$C*H*$_2$CH$_3$), 3.77−3.72 (m, 2H, OCH$_2$C*H*$_2$O), 3.49−3.45 (m, 2H, OCH$_2$C*H*$_2$O), 3.28 (s, 3H, C*H*$_3$O), 1.23 (t, $J = 7.3$ Hz, 3H, CO$_2$CH$_2$C*H*$_3$). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 172.6, 161.1, 155.2, 141.7, 138.0, 136.1, 128.5 (2C), 128.2, 128.1 (2C), 127.7, 116.9, 115.0, 93.3, 71.9, 71.4, 68.0, 67.1, 62.8, 58.9, 52.7, 14.0. LRMS: MS (ES+) m/z = 493.3 (M + 1).

9
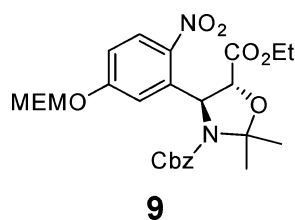
2-Methoxypropene (16.56 mL, 167.7 mmol) was added to a solution of **8a** (8.26 g, 16.8 mmol) in 400 mL of toluene, and the mixture was stirred for 15 min. Molecular sieves (4 Å, 400 mg) and pyridinium p-toluenesulfonate (215 mg, 0.84 mmol) were added to this reaction mixture. Then the mixture was warmed to 80 °C for 2 h. The reaction mixture was cooled, filtered, and concentrated under vacuum. The crude product was chromatographed on silica gel (eluent = hexane/ethyl acetate, 7/3−1/1) to give a mixture of **9** and **9-1** (7.70 g, 86%). Yellow oil. R_f: 0.68 (3/7 hexane/ethyl acetate using TLC silica plates neutralized with triethylamine).

9a   and   **9a-1** [M+41]
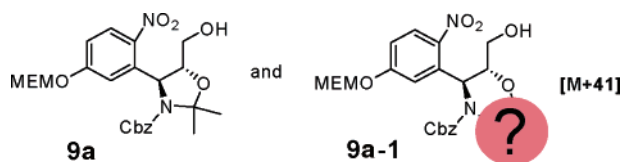
A 2 M lithium borohydride solution in THF (15.23 mL, 30.5 mmol) was added to a solution of the above mixture (5.06 g, 9.5 mmol) in 200 mL of anhydrous THF at room temperature, and the mixture was stirred for 24 h. The reaction mixture was quenched by reverse addition onto ice-cold saturated NH$_4$Cl solution. The aqueous layer was

extracted with Et$_2$O (3 × 100 mL), and the organic layer was dried over MgSO$_4$. After filtration and concentration under vacuum, the crude product was chromatographed on neutralized silica gel with hexane/triethylamine, 9/1 (eluent = hexane/ethyl acetate, 1/1) to give two compounds (**9a**, 1.83 g and **9a-1**, 2.42 g).
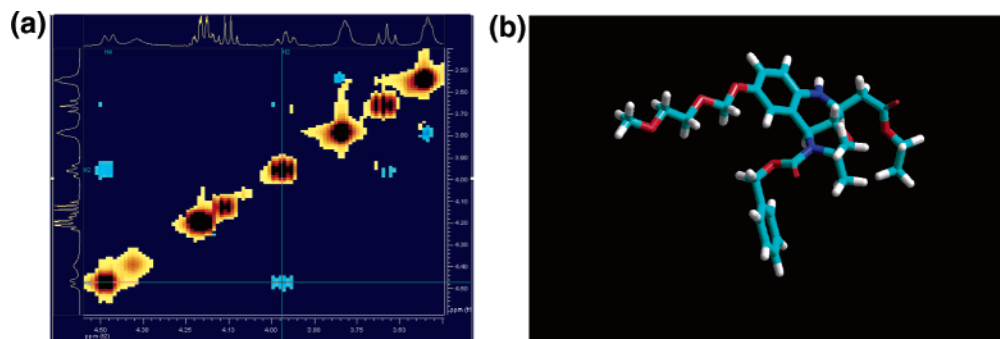
9a
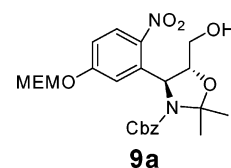
9a. Pale yellow oil. R_f: 0.41 (3/7 hexane/ethyl acetate), 0.26 (1/1 hexane/ethyl acetate). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.95 (d, $J = 9.0$ Hz, 1H, C*H*CNO$_2$), 7.40−7.33 (m, 6H, 5H$_{Ph}$ and C*H*COMEM), 7.11 (dd, $J = 9.0$ Hz, $J = 2.0$ Hz, 1H, C*H*CHCNO$_2$), 5.56 (broad s, 1H, C*H*NCO), 5.33 (broad s, 2H, OC*H*$_2$O), 5.23−5.17 (broad m, 2H, PhC*H*$_2$OCO), 4.10−3.99 (broad m, 2H, C*H*$_2$OH), 3.89−3.82 (m, 1H, C*H*OCMe$_2$), 3.83−3.79 (m, 2H, OCH$_2$C*H*$_2$O), 3.57−3.51 (m, 2H, OC*H*$_2$-CH$_2$O), 3.35 (s, 3H, C*H*$_3$O), 2.20 (broad s, 1H, OH), 1.69 (broad s, 3H, C(C*H*$_3$)$_2$), 1.60 (s, 3H, C(C*H*$_3$)$_2$). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 161.2, 151.7, 142.9, 139.0, 135.5, 128.1 (2C), 127.80 (2C), 127.75, 127.1, 115.2, 114.6, 95.6, 93.3, 83.7, 71.3, 68.0, 66.6, 62.4, 58.9, 57.7, 26.9, 26.0. LRMS: MS (ES+) m/z = 491.2 (M + 1).

9a-1
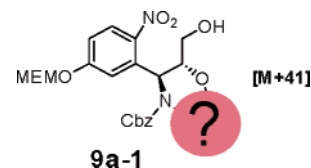
9a-1. Pale yellow oil. R_f: 0.54 (3/7 hexane/ethyl acetate), 0.33 (1/1 hexane/ethyl acetate). LRMS: MS (ES+) m/z = 531.2 (M + 41). Note: Compound **9a-1** was independently subjected to the same sequence of reactions as compound **9a** to give, after 6 steps, compound **11b** with similar yields at each step.

9b
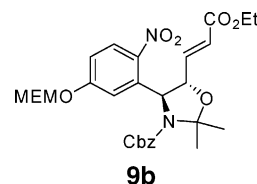
Triethylamine (2.30 mL, 16.5 mmol) and a solution of sulfur trioxide pyridine complex (2.67 g, 16,5 mmol) in 20 mL of DMSO were added to a solution of alcohol **9a** (2.69 g, 5.5 mmol) in 100 mL of anhydrous CH$_2$Cl$_2$ at 0 °C. The reaction mixture was warmed to room temperature and stirred for 4 h. Carbethoxymethylene triphenylphosphorane was then added (6.03 g, 16.5 mmol), and the reaction mixture was stirred overnight. The reaction mixture was diluted CH$_2$Cl$_2$ (100 mL) and then washed with 100 mL of a saturated solution of Na$_2$CO$_3$, followed by 200 mL of water. The organic layer was collected and then dried over MgSO$_4$. After filtration and concentration under vacuum, the crude product was chromatographed on neutralized silica gel with hexane/

Figure 2. (a) NOE between H_2 and H_4 and (b) the minimized energy structure of compound **11**.

triethylamine, 9/1 (eluent = hexane/ethyl acetate, 1/1) to give compound **9b** (1.98 g, 65%). Yellow oil. R_f: 0.41 (1/1 hexane/ethyl acetate), 0.64 (3/7 hexane/ethyl acetate), ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.96 (d, J = 8.3 Hz, 1H, C*H*CNO$_2$), 7.40−7.12 (m, 7H, 5H$_{Ph}$ and C*H*COMEM and C*H*=CHCO$_2$Et), 7.01 (d, J = 8.3 Hz, 1H, C*H*CHCNO$_2$), 6.14 (d, J = 15.8 Hz, 1H, CH=C*H*CO$_2$Et), 5.59 (broad d, J = 4.0 Hz, C*H*NCO), 5.24−5.11 (broad s, 2H, OC*H*$_2$O), 5.04 (broad d, J = 12.3 Hz, 1H, PhC*H*$_2$OCO), 4.73 (broad d, J = 12.3 Hz, 1H, PhC*H*$_2$OCO), 4.64 (t, J = 4.0 Hz, 1H, C*H*OCMe$_2$), 4.22 (q, J = 7.0 Hz, 2H, CO$_2$C*H*$_2$CH$_3$), 3.85−3.69 (m, 2H, OC*H*$_2$CH$_2$O), 3.56−3.45 (m, 2H, OC*H*$_2$CH$_2$O), 3.35 (s, 3H, C*H*$_3$O), 1.83 (s, 3H, C(C*H*$_3$)$_2$), 1.75 (s, 3H, C(C*H*$_3$)$_2$), 1.30 (t, J = 7.0 Hz, 3H, CO$_2$CH$_2$C*H*$_3$). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 165.7, 161.4, 151.7, 144.0, 142.2, 138.9, 135.6, 128.2 (2C), 127.8, 127.7 (2C), 127.5, 123.5, 115.3, 114.5, 96.5, 93.4, 82.0, 71.3, 68.1, 66.7, 61.1, 60.6, 58.9, 27.2, 26.2, 14.1. LRMS: MS (ES+) m/z = 558.58 (M + 1).
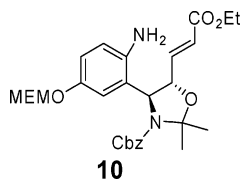
Zinc dust (2.25 g, 33.7 mmol) and glacial acetic acid (1.93 mL, 33.7 mmol) were added to a solution of **9b** (1.98 g, 3.5 mmol) in 30 mL of anhydrous ethanol at room temperature. The reaction mixture was stirred for 1 h and then filtered through celite. After concentration under vacuum to remove ethanol, a saturated solution of NaHCO$_3$ (30 mL) was added. The aqueous layer was extracted with Et$_2$O (3 × 50 mL), and the organic layer was dried over MgSO$_4$. After filtration and concentration under vacuum, the crude product was chromatographed on neutralized silica gel with hexane/triethylamine, 9/1 (eluent = hexane/ethyl acetate, 7/3−1/1) to give the title compound (1.26 g, 67%). Colorless oil. R_f: 0.46 (1/1 hexane/ethyl acetate). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.40−7.13 (m, 5H, H$_{Ph}$), 6.92 (dd, J = 15.8 Hz, J = 4.5 Hz, 1H, C*H*=CHCO$_2$Et), 6.91 (broad s, 1H, C*H*COMEM), 6.83 (dd, J = 8.5 Hz, J = 2.8 Hz, 1H, C*H*CHCNH$_2$), 6.55 (broad d, J = 8.5 Hz, 1H, C*H*CNH$_2$), 6.08 (d, J = 15.8 Hz, 1H, CH=C*H*CO$_2$Et), 5.08 (broad s, 2H, OC*H*$_2$O), 5.02 (broad d, J = 12.3 Hz, 1H, PhC*H*$_2$OCO), 4.85 (broad d, J = 12.3 Hz, 1H, PhC*H*$_2$OCO), 4.70 (broad

s, 2H, NH$_2$), 4.67 (d, J = 7.0 Hz, C*H*NCO), 4.15 (q, J = 7.0 Hz, 2H, CO$_2$C*H*$_2$CH$_3$), 3.77−3.72 (m, 2H, OC*H*$_2$CH$_2$O), 3.51−3.47 (m, 2H, OC*H*$_2$CH$_2$O), 3.49−3.45 (m, 1H, C*H*OC-Me$_2$), 3.32 (s, 3H, C*H*$_3$O), 1.74 (broad s, 3H, C(C*H*$_3$)$_2$), 1.68 (broad s, 3H, C(C*H*$_3$)$_2$), 1.23 (t, J = 7.0 Hz, 3H, CO$_2$-CH$_2$C*H*$_3$). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 165.6, 152.5, 150.8, 143.1, 135.6, 128.1 (2C), 127.7, 127.6 (2C), 124.5, 122.6, 118.4, 116.9, 115.4, 95.6, 94.2, 80.0, 71.4, 67.1, 66.9, 61.6, 60.3, 58.7, 26.3 (broad m for 2C), 14.0. LRMS: MS (ES+) m/z = 529.4 (M + 1).
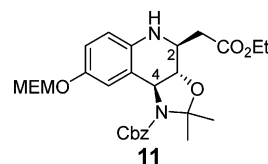

A 2 M solution of lithium diisopropylamide in heptane/THF/ethylbenzene (1.16 mL, 2.3 mmol) was added in one portion to a solution of amine **10** (1.23 g, 2.3 mmol) in 35 mL of anhydrous THF at −78 °C. The reaction mixture was stirred for 75 min at the same temperature and quenched via the addition of 20 mL of a saturated solution of NH$_4$Cl. The aqueous layer was extracted with ethyl acetate (3 × 30 mL), and the organic layer was dried over MgSO$_4$. After filtration and concentration under vacuum, the crude product was chromatographed on neutralized silica gel with hexane/triethylamine, 9/1 (eluent = hexane/ethyl acetate 1/1) to give **11** (642 mg, 67%) (Figure 2). Colorless oil. R_f: 0.54 (1/1 hexane/ethyl acetate). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.42−7.26 (m, 5H, Ph), 6.86 (broad s, 1H, MEMOC−C*H*=C), 6.78 (dd, J = 8.5 Hz, J = 2.3 Hz, 1H, C*H*−CH=C-N), 6.44 (d, J = 8.5 Hz, 1H, CH−C*H*=C−N), 5.29 (d, J = 12.3 Hz, 1H, PhC*H*$_2$OCO), 5.20 (d, J = 12.3 Hz, 1H, PhC*H*$_2$OCO), 5.06 (broad s, 2H, OMEM), 4.47 (d, J = 9.8 Hz, 1H, C*H*−NCO), 4.42 (broad s, 1H, N*H*), 4.16 (2q, J = 7.0 Hz, 2H, CO$_2$C*H*$_2$CH$_3$), 3.95 (td, J = 9.8 Hz, J = 2.5 Hz, 1H, C*H*CH$_2$-CO$_2$Et), 3.79−3.74 (m, 2H, OMEM), 3.66 (t, J = 9.8 Hz, 1H, C*H*OCMe$_2$), 3.54−3.49 (m, 2H, OMEM), 3.34 (s, 3H, OMEM), 2.84 (dd, J = 16.0 Hz, J = 2.5 Hz, 1H, CHC*H*$_2$-CO$_2$Et), 2.38 (dd, J = 16.0 Hz, J = 9.8 Hz, 1H, CHC*H*$_2$-CO$_2$Et), 1.66 (broad s, 3H, C*Me*$_2$), 1.56 (s, 3H, C*Me*$_2$), 1.25 (t, J = 7.0 Hz, 3H, CO$_2$CH$_2$C*H*$_3$). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 171.4, 154.6 (broad), 149.2, 137.0, 135.8, 128.2 (2C), 128.0 (2C), 127.9, 122.9 (broad), 115.7, 114.1 (broad), 113.8, 99.0 (broad), 94.4, 78.5 (broad), 71.4, 67.1, 66.9 (broad), 60.6, 60.1 (broad), 58.7, 52.2, 39.4, 26.1 (broad,

2C), 13.9. LRMS: MS (ES+) *m/z* = 529.4 (M + 1).

11a

(broad, 2C), 17.5, 13.7, −1.8 (3C). LRMS: MS (ES+) *m/z* = 673.5 (M + 1).

11b
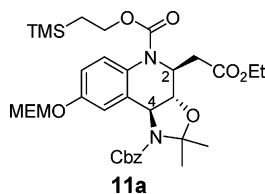
Triphosgene (192 mg, 0.63 mmol) was added to the round-bottom flask and cooled to −78 °C. This was then followed by a slow addition of 10 mL of anhydrous CH$_2$Cl$_2$, and the solution was vigorously stirred for 30 min. The 2-(trimethylsilyl) ethanol (265 μL, 1.84 mmol) was added in one portion to the reaction mixture at −78 °C, and it was then warmed to −10 °C. Then pyridine (150 μL, 1.84 mmol) was added dropwise to the reaction mixture and stirred for 2 h at −10 °C. The reaction mixture was cooled to −45 °C, and a solution of free amine **11** (485 mg, 0.92 mmol) and pyridine (225 μL, 2.75 mmol) in 3 mL of anhydrous CH$_2$Cl$_2$ was added via cannula over a period of 5 min. The mixture was stirred continuously for 1 h at −30 °C and for 15 min at 0 °C. When the TLC showed no starting material, the reaction mixture was quenched via the addition of 40 mL of a saturated solution of NaHCO$_3$, and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 30 mL). The organic layer was dried over MgSO$_4$, filtered, and concentrated under vacuum, and the crude product was chromatographed on neutralized silica gel with hexane/triethylamine, 9/1 (eluent = hexane/ethyl acetate 8/2) to give **11a** (470 mg, 77%) (Figure 3). Colorless oil. R_f: 0.59 (1/1 hexane/ethyl acetate). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.44−7.23 (m, 6H, 5H_{Ph} and CH−C*H*=C-N), 6.96 (dd, *J* = 8.8 Hz, *J* = 2.5 Hz, 1H, C*H*−CH=C-N), 6.82 (broad s, 1H, MEMOC−C*H*=C), 5.30−5.09 (m, 4H, 2H from OMEM and PhC*H$_2$*OCO), 4.56 (broad m, 1H, C*H*CH$_2$CO$_2$Et), 4.35−4.26 (m, 2H, TMSCH$_2$C*H$_2$*O), 4.29−4.19 (m, 1H, C*H*−NCO), 4.10−3.96 (m, 2H, CO$_2$C*H$_2$*-CH$_3$), 3.84−3.76 (m, 2H, OMEM), 3.71 (t, *J* = 9.5 Hz, 1H, C*H*OCMe$_2$), 3.57−3.51 (m, 2H, OMEM), 3.37 (s, 3H, OMEM), 2.81−2.71 (m, 2H, CHC*H$_2$*CO$_2$Et), 1.73 (broad s, 3H, C*Me$_2$*), 1.57 (s, 3H, C*Me$_2$*), 1.16 (t, *J* = 7.0 Hz, 3H, CO$_2$CH$_2$C*H$_3$*), 1.06 (broad s, 2H, TMSC*H$_2$*CH$_2$O), 0.03 (s, 9H, TMS). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 169.5, 154.8, 154.4, 153.7 (broad), 135.7, 132.6 (broad), 128.6, 128.3 (2C), 128.1 (2C), 127.9, 127.1 (broad), 113.8 (broad), 111.1 (broad), 99.5 (broad), 93.4, 80.4 (broad), 71.3, 67.4, 66.9 (broad), 64.3, 60.3, 59.5, 58.7, 54.3, 37.9 (broad), 25.8
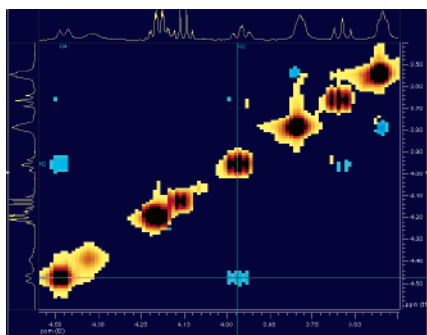

**Figure 3.** NOE between H$_2$ and H$_4$ for compound **11a**.
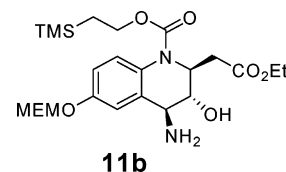
Palladium (10 wt %) on activated carbon (63 mg) was added to a solution of Teoc-protected amine (503 mg, 075 mmol) in 15 mL of anhydrous ethanol and stirred for 8.5 h under a hydrogen atmosphere. The reaction mixture was filtered through celite and concentrated under vacuum. The crude product was chromatographed on silica gel (eluent = CH$_2$-Cl$_2$/methanol 98/2) to give **11b** (210 mg, 56%). Colorless oil. R_f: 0.16 (98/2 CH$_2$Cl$_2$/methanol). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.26 (broad d, *J* = 8.5 Hz, 1H, CH−C*H*=C−N), 7.05 (d, *J* = 2.5 Hz, 1H, MEMOC−C*H*=C), 6.89 (dd, *J* = 8.5 Hz, *J* = 2.5 Hz, 1H, C*H*−CH=C−N), 5.24−5.19 (m, 2H, OMEM), 4.46−4.44 (m, 1H, C*H*CH$_2$CO$_2$Et), 4.28−4.12 (m, 2H, TMSCH$_2$C*H$_2$*O), 4.05−3.95 (m, 2H, CO$_2$C*H$_2$*CH$_3$), 3.80−3.75 (m, 2H, OMEM), 3.65 (t, *J* = 9.8 Hz, 1H, C*H*OH), 3.54−3.49 (m, 2H, OMEM), 3.33 (s, 3H, OMEM), 3.20 (ddd, *J* = 9.8 Hz, *J* = 6.0 Hz, *J* = 3.3 Hz, 1H, C*H*NH$_2$), 2.74−2.64 (m, 1H, O*H*), 2.71 (dd, *J* = 15.3 Hz, *J* = 4.5 Hz, 1H, CHC*H$_2$*CO$_2$Et), 2.52 (dd, *J* = 15.3 Hz, *J* = 8.5 Hz, 1H, CHC*H$_2$*CO$_2$Et), 2.01 (broad s, 2H, N*H$_2$*), 1.14 (t, *J* = 7.0 Hz, 3H, CO$_2$CH$_2$C*H$_3$*), 0.99 (t, *J* = 8.5 Hz, 2H, TMSC*H$_2$*-CH$_2$O), −0.03 (s, 9H, TMS). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 171.9, 155.0, 154.3, 135.1, 129.3, 126.3, 114.3, 111.1, 93.5, 78.8, 71.4, 67.4, 64.2, 60.7, 58.8, 57.4, 53.0, 38.7, 17.6, 13.9, −1.7 (3C). LRMS: MS (ES+) *m/z* = 499.4 (M + 1).


12
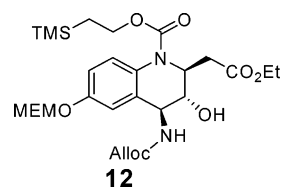
N,N-Diisopropylethylamine (135 μL, 0.77 mmol, one portion) and allylchloroformate (77 μL, 0.71 mmol, dropwise addition) were added to a solution of free amine **11b** (320 mg, 0.64 mmol) in 50 mL of anhydrous CH$_2$Cl$_2$ at −70 °C. The reaction mixture was slowly warmed to room temperature in 3 h, stirred for an additional 2.5 h, and quenched via the addition of 40 mL of a saturated solution of NH$_4$Cl. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 30 mL), and the organic layer was dried over MgSO$_4$. After filtration and concentration under vacuum, the crude product was chromatographed on silica gel (eluent = CH$_2$Cl$_2$/methanol 98/2) to give **12** (340 mg, 91%). Colorless oil. R_f: 0.19 (1/1 hexane/ethyl acetate). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.27 (broad d, *J* = 8.8 Hz, 1H, CH−C*H*=C−N), 6.94 (dd, *J* = 8.8 Hz, *J* = 2.5 Hz, 1H, C*H*−CH=C−N), 6.92 (broad s, 1H, MEMOC−C*H*=C), 6.00−5.87 (m, 1H, H$_2$C=C*H*−CH$_2$O), 5.36 (broad d, *J* = 7.5 Hz, 1H, NH), 5.33 (broad d, *J* = 17.1 Hz, 1H, *H$_2$*C=CH−CH$_2$O), 5.24−5.20 (m, 1H, *H$_2$*C=CH−CH$_2$O), 5.25−5.19 (m, 2H, OMEM), 4.70−4.62

(m, 1H, C*H*−NH), 4.62 (d, *J* = 5.5 Hz, 2H, H$_2$C=CH−C*H$_2$*O), 4.62−4.56 (m, 1H, C*H*CH$_2$CO$_2$Et), 4.32−4.16 (m, 2H, OC*H$_2$*CH$_2$TMS), 4.10−3.97 (m, 2H, CO$_2$C*H$_2$*CH$_3$), 3.93 (broad s, 1H, O*H*), 3.80 (dd, *J* = 6.0 Hz, *J* = 4.5 Hz, 2H, OMEM), 3.61−3.54 (m, 1H, C*H*−OH), 3.55 (dd, *J* = 6.0 Hz, *J* = 4.5 Hz, 2H, OMEM), 3.36 (s, 3H, OMEM), 2.73 (dd, *J* = 15.1 Hz, *J* = 4.8 Hz, 1H, CHC*H$_2$*CO$_2$Et), 2.54 (dd, *J* = 15.1 Hz, *J* = 8.3 Hz, 1H, CHC*H$_2$*CO$_2$Et), 1.17 (t, *J* = 7.0 Hz, 3H, CO$_2$CH$_2$C*H$_3$*), 1.03 (t, *J* = 8.5 Hz, 2H, OCH$_2$C*H$_2$*TMS), 0.01 (s, 9H, TMS). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 171.8, 156.7, 154.9, 154.4, 132.6, 131.8, 129.3, 126.7, 117.9, 114.9, 111.8, 93.6, 76.4, 71.5, 67.5, 66.0, 64.5, 60.9, 58.9, 57.1, 53.8, 38.4, 17.7, 13.9, −1.62 (3C). LRMS: MS (ES+) *m/z* = 583.4 (M + 1).

12a
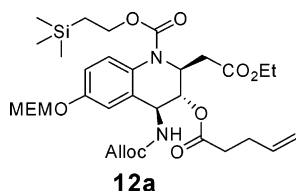
1,3-Diisopropylcarbodiimide (183 μL, 1.17 mmol), 4-pentenoic acid (92.1 μL, 0.88 mmol), and 4-(dimethylamino)-pyridine (7.2 mg, 0.06 mmol) were added at once to a solution of alcohol **12** (340 mg, 0.58 mmol) in 5 mL of anhydrous CH$_2$Cl$_2$ at room temperature. After the mixture was stirred for 3 h 40 min, a saturated solution of Na$_2$CO$_3$ (10 mL) was added, and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 20 mL); the organic layer was dried over MgSO$_4$. After filtration and concentration under vacuum, the crude product was chromatographed using the Biotage chromatograph system (A = hexane, B = ethyl acetate, CV=12 mL, vol fract. = 9 mL, flow = 6 mL/min, EQ-[5CV] 7%B, 1CV[1] 7%B, 10CV[2] 7%B to 50%B, 10CV-[3] 50%B) to give **12a** (330 mg, 85%). Colorless oil. *R$_f$*: 0.55 (1/1 hexane/ethyl acetate). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.34 (broad s, 1H, CH−C*H*=C−N), 7.00 (dd, *J* = 8.8 Hz, *J* = 2.3 Hz, 1H, C*H*−CH=C−N), 6.95 (s, 1H, MEMOC−C*H*=C), 5.95 (ddt, *J* = 16.1 Hz, *J* = 10.8 Hz, *J* = 5.0 Hz, 1H, H$_2$C=C*H*−CH$_2$O), 5.82 (ddt, *J* = 16.6 Hz, *J* = 10.0 Hz, *J* = 6.0 Hz, 1H, H$_2$C=C*H*−CH$_2$CH$_2$CO), 5.34 (broad d, *J* = 16.1 Hz, 1H$_{trans}$, H$_2$C=CH−CH$_2$O), 5.25 (broad d, *J* = 10.8 Hz, 1H$_{cis}$, H$_2$C=CH−CH$_2$O), 5.26 (s, 2H, OMEM), 5.14 (broad d, *J* = 8.3 Hz, 1H, N*H*), 5.07 (dd, *J* = 16.6 Hz, *J* = 1.3 Hz, 1H$_{trans}$, H$_2$C=CH−CH$_2$CH$_2$CO), 5.02 (dd, *J* = 10.0 Hz, *J* = 1.3 Hz, 1H$_{cis}$, H$_2$C=CH−CH$_2$-CH$_2$CO), 4.98 (dd, *J* = 8.3 Hz, *J* = 5.0 Hz, 1H, C*H*OC-OCH$_2$), 4.90 (dt, *J* = 5.0 Hz, *J* = 6.5 Hz, 1H, C*H*CH$_2$CO$_2$Et), 4.83 (t, *J* = 8.3 Hz, 1H, C*H*−NH), 4.62 (d, *J* = 5.0 Hz, 2H, H$_2$C=CH−C*H$_2$*O), 4.33−4.17 (m, 2H, OC*H$_2$*CH$_2$TMS), 4.02 (q, *J* = 7.3 Hz, 2H, CO$_2$C*H$_2$*CH$_3$), 3.84−3.80 (m, 2H, OMEM), 3.59−3.55 (m, 2H, OMEM), 3.39 (s, 3H, OMEM), 2.57 (dd, *J* = 14.6 Hz, *J* = 6.5 Hz, 1H, CHC*H$_2$*CO$_2$Et), 2.49−2.42 (m, 1H, CHC*H$_2$*CO$_2$Et), 2.46 (dt, *J* = 6.0 Hz, *J* = 6.3 Hz, 2H, H$_2$C=CH−C*H$_2$*CH$_2$CO), 2.39 (t, *J* = 6.3 Hz, 2H, H$_2$C=CH−CH$_2$C*H$_2$*CO), 1.18 (t, *J* = 7.3 Hz, 3H, CO$_2$-CH$_2$C*H$_3$*), 1.04 (t, *J* = 8.5 Hz, 2H, OCH$_2$C*H$_2$*TMS), 0.03 (s, 9H, TMS). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 172.8, 169.7, 155.9, 155.1, 154.4, 136.4, 136.2, 132.5, 129.4, 127.2, 118.0,

115.7, 115.6, 112.3, 93.6, 76.1, 71.5, 67.6, 66.0, 64.7, 60.8, 59.0, 54.1, 52.1, 37.6, 33.4, 28.5, 17.7, 14.0, −1.6 (3C). LRMS: MS (ES+) *m/z* = 665.4 (M + 1).

12b
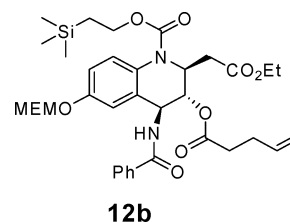
Redistilled morpholine (44 μL, 0.50 mmol) and a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (29 mg, 0.03 mmol) were added at once to a solution of alloc-protected amine **12a** (167 mg, 0.25 mmol) in 2.5 mL of anhydrous CH$_2$Cl$_2$ at room temperature. The alloc removal was followed on TLC and was completed after 20 min of stirring. Then, triethylamine (106 μL, 0.75 mmol) and benzoyl chloride (59 μL, 0.50 mmol) were slowly added to the reaction mixture. After the mixture was stirred for 25 min at room temperature, a saturated solution of Na$_2$CO$_3$ (5 mL) was added, and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 10 mL); the organic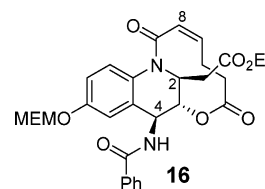 layer was dried over MgSO$_4$. After filtration and concentration under vacuum, the crude product was chromatographed using the Biotage chromatograph system (A = hexane, B = ethyl acetate, CV=12 mL, vol fract = 3 mL, flow = 7 mL/min, EQ[5CV] 5%B, 1CV[1] 5%B, 10CV[2] 5%B to 30%B, 10CV[3] 30%B) to give **12b** (116 mg, 67%). Colorless oil. *R$_f$*: 0.45 (1/1 hexane/ethyl acetate). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.83 (d, *J* = 7.5 Hz, 2H, Ph), 7.52 (t, *J* = 7.5 Hz, 1H, Ph), 7.44 (t, *J* = 7.5 Hz, 2H, Ph), 7.34 (broad d, *J* = 8.8 Hz, 1H, CH−C*H*=C−N), 6.99 (dd, *J* = 8.8 Hz, *J* = 2.5 Hz, 1H, C*H*−CH=C−N), 6.89 (d, *J* = 2.0 Hz, 1H, MEMOC−C*H*=C), 6.78 (broad d, *J* = 8.3 Hz, 1H, N*H*), 5.68 (ddt, *J* = 16.8 Hz, *J* = 10.3 Hz, *J* = 6.3 Hz, 1H, CH$_2$=C*H*−CH$_2$CH$_2$CO), 5.31 (t, *J* = 8.5 Hz, 1H, C*H*−NH), 5.20−5.15 (m, 2H, OMEM), 5.13 (dd, *J* = 8.8 Hz, *J* = 5.0 Hz, 1H, C*H*OCO), 4.98−4.91 (m, 1H, C*H*CH$_2$CO$_2$Et), 4.94 (dd, *J* = 17.1 Hz, *J* = 1.3 Hz, 1H$_{trans}$, H$_2$C=CH−CH$_2$CH$_2$CO), 4.85 (d, *J* = 10.3 Hz, 1H$_{cis}$, H$_2$C=CH−CH$_2$CH$_2$CO), 4.33−4.18 (m, 2H, OC*H$_2$*CH$_2$TMS), 4.04−3.95 (m, 2H, CO$_2$C*H$_2$*CH$_3$), 3.77−3.72 (m, 2H, OMEM), 3.50−3.46 (m, 2H, OMEM), 3.29 (s, 3H, OMEM), 2.58 (dd, *J* = 14.6 Hz, *J* = 7.3 Hz, 1H, CHC*H$_2$*CO$_2$Et), 2.51 (dd, *J* = 14.6 Hz, *J* = 6.5 Hz, 1H, CHC*H$_2$*CO$_2$Et), 2.41 (t, *J* = 7.0 Hz, 2H, H$_2$C=CH−CH$_2$C*H$_2$*-CO), 2.28 (dt, *J* = 6.8 Hz, *J* = 7.0 Hz, 2H, H$_2$C=CH-C*H$_2$*-CH$_2$CO), 1.16 (t, *J* = 7.0 Hz, 3H, CO$_2$CH$_2$C*H$_3$*), 1.04 (t, *J* = 8.8 Hz, 2H, OCH$_2$C*H$_2$*TMS), 0.02 (s, 9H, TMS). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 173.4, 169.8, 167.1, 155.0, 154.3, 136.0, 133.4, 131.8, 130.3, 129.5, 128.6 (2C), 128.2, 127.0 (2C), 115.6, 115.3, 112.6, 93.6, 75.8, 71.4, 67.5, 64.7, 60.8, 58.8, 53.9, 50.9, 37.7, 33.3, 28.4, 17.6, 13.9, −1.7 (3C). LRMS: MS (ES+) *m/z* = 685.5 (M + 1). TBAF (237 μL, 0.24 mmol) was added to a solution of Teoc-protected amine **12b** (108 mg, 0.16 mmol) in 5 mL of anhydrous THF at room temperature. The reaction mixture was stirred for 25 min, and a solution of brine (10 mL) was added. The aqueous layer was extracted with Et$_2$O (3 × 10 mL), and the organic
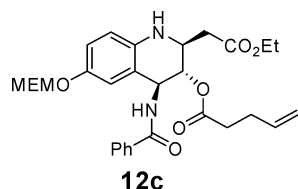
12c

layer was dried over MgSO$_4$. After filtration and concentration under vacuum, the crude product was chromatographed using the Biotage chromatograph system (A = hexane, B = ethyl acetate, CV = 12 mL, vol fract = 12 mL, flow = 6 mL/min, EQ[5CV] 10%B, 1CV[1] 105%B, 10CV[2] 10%B to 50%B, 10CV[3] 50%B) to give **12c** (74 mg, 87%). White solid. R_f: 0.29 (1/1 hexane/ethyl acetate). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.76 (dd, J = 7.5 Hz, J = 1.3 Hz, 2H, Ph), 7.51 (tt, J = 7.5 Hz, J = 1.3 Hz, 1H, Ph), 7.43 (t, J = 7.5 Hz, 2H, Ph), 6.87−6.82 (m, 2H, CH−CH=C−NH and MEMOC−CH=C), 6.53 (broad d, J = 9.5 Hz, 1H, NH), 6.44 (dd, J = 9.5 Hz, J = 7.0 Hz, 1H, CH−CH=C−NH), 5.68 (ddt, J = 16.8 Hz, J = 10.3 Hz, J = 6.3 Hz, 1H, CH$_2$=CH−CH$_2$CH$_2$CO), 5.64 (t, J = 9.5 Hz, 1H, CH−NH), 5.14 (dd, J = 9.5 Hz, J = 2.5 Hz, 1H, CHOCO), 5.12−5.06 (m, 2H, OMEM), 4.95 (dd, J = 16.8 Hz, J = 1.5 Hz, 1H$_{trans}$, H_2C=CH−CH$_2$CH$_2$CO), 4.86 (dd, J = 10.3 Hz, J = 1.3 Hz, 1H$_{cis}$, H_2C=CH−CH$_2$CH$_2$CO), 4.62 (broad s, 1H, NH), 4.19 (q, J = 7.0 Hz, 2H, CO$_2$CH_2CH$_3$), 3.90 (td, J = 9.8 Hz, J = 2.5 Hz, 1H, CH−CH$_2$CO$_2$Et), 3.76−3.73 (m, 2H, OMEM), 3.50−3.46 (m, 2H, OMEM), 3.30 (s, 3H, OMEM), 2.69 (ddd, J = 16.3 Hz, J = 3.5 Hz, J = 2.8 Hz, 1H, CHCH_2CO$_2$Et), 2.43 (dd, J = 16.3 Hz, J = 9.8 Hz, 1H, CHCH_2CO$_2$Et), 2.41 (t, J = 7.0 Hz, 2H, H_2C=CH−CH$_2$CH_2CO), 2.27 (dt, J = 6.5 Hz, J = 7.0 Hz, 2H, H_2C=CH−CH_2CH$_2$CO), 1.29 (t, J = 7.0 Hz, 3H, CO$_2$CH$_2$CH_3). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 173.1, 171.6, 167.9, 150.2, 138.6, 136.1, 134.0, 131.7, 128.6 (2C), 127.0 (2C), 121.3, 117.7, 116.3, 115.7, 115.6, 94.5, 72.9, 71.5, 67.4, 61.0, 58.9, 51.9, 51.8, 36.6, 33.3, 28.5, 14.1. LRMS: MS (ES+) m/z = 541.3 (M + 1).

15
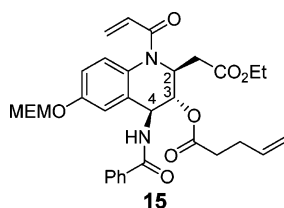
Triethylamine (27 μL, 0.19 mmol) and acryloyl chloride (11

μL, 0.13 mmol) were added slowly to a solution of free amine **12c** (34 mg, 0.06 mmol) in 1 mL of anhydrous CH$_2$Cl$_2$. After the mixture was stirred for 20 min at room temperature, a saturated solution of Na$_2$CO$_3$ (5 mL) was added, and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 10 mL); the organic layer was dried over MgSO$_4$. After filtration and concentration under vacuum, the crude product was chromatographed using the Biotage chromatograph system (A = hexane, B = ethyl acetate, CV = 12 mL, vol fract = 7 mL, flow = 6 mL/min, EQ[5CV] 10%B, 1CV[1] 10%B, 10CV[2] 10%B to 50%B, 10CV[3] 50%B) to give **15** (28 mg, 73%) (Figure 4). Colorless oil. R_f: 0.17 (1/1 hexane/ethyl acetate), 0.39 (3/7 hexane/ethyl acetate). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.85 (dd, J = 7.5 Hz, J = 1.5 Hz, 2H, Ph), 7.52 (tt, J = 7.5 Hz, J = 1.5 Hz, 1H, Ph), 7.44 (t, J = 7.5 Hz, 2H, Ph), 7.05−6.98 (m, 2H, CH−CH=C−N and CH−CH=C−N), 6.94 (d, J = 1.0 Hz, 1H, MEMOC−CH=C), 6.81 (broad d, J = 8.0 Hz, 1H, NH), 6.49 (dd, J = 16.8 Hz, J = 3.0 Hz, 1H$_{trans}$, H_2C=CHCO), 6.44 (d, J = 10.0 Hz, 1H$_{cis}$, H_2C=CHCO), 5.73 (dd, J = 16.6 Hz, J = 10.0 Hz, 1H, H$_2$C=CHCO), 5.69 (ddt, J = 16.8 Hz, J = 10.3 Hz, J = 6.3 Hz, 1H, CH$_2$=CH−CH$_2$CH$_2$CO), 5.28 (dd, J = 9.8 Hz, J = 8.0 Hz, 1H, CH−NH), 5.25−5.19 (m, 2H, OMEM), 5.22−5.17 (m, 1H, CHCH$_2$CO$_2$Et), 5.16 (dd, J = 9.8 Hz, J = 4.8 Hz, 1H, CHOCO), 4.96 (dd, J = 17.1 Hz, J = 1.5 Hz, 1H$_{trans}$, H_2C=CH−CH$_2$CH$_2$CO), 4.85 (dd, J = 10.3 Hz, J = 1.3 Hz, 1H$_{cis}$, H_2C=CH−CH$_2$CH$_2$CO), 4.01 (2q, J = 7.0 Hz, 2H, CO$_2$CH_2CH$_3$), 3.80−3.76 (m, 2H, OMEM), 3.54−3.50 (m, 2H, OMEM), 3.33 (s, 3H, OMEM), 2.61 (dd, J = 14.6 Hz, J = 5.8 Hz, 1H, CHCH_2CO$_2$Et), 2.55 (dd, J = 14.6 Hz, J = 7.3 Hz, 1H, CHCH_2CO$_2$Et), 2.47 (td, J = 7.0 Hz, J = 1.5 Hz, 2H, H_2C=CH−CH$_2$CH_2CO), 2.32 (dt, J = 6.3 Hz, J = 7.0 Hz, 2H, H_2C=CH−CH_2CH$_2$CO), 1.18 (t, J = 7.0 Hz, 3H, CO$_2$CH$_2$CH_3). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 174.2, 169,8, 167.3, 164.8, 156.3, 136.0, 133.3, 132.2, 132.1, 129.4, 129.2, 128.7 (2C), 128.1, 127.2, 127.1 (2C), 115.8, 115.1, 113.2, 93.6, 76.5, 71.5, 67.7, 60.8, 59.0, 53.5, 51.9, 37.9, 33.5, 28.5, 14.0. LRMS: MS (ES+) m/z = 595.3 (M + 1).

16

Second-generation Grubbs catalyst (2 mg, 0.002 mmol) was
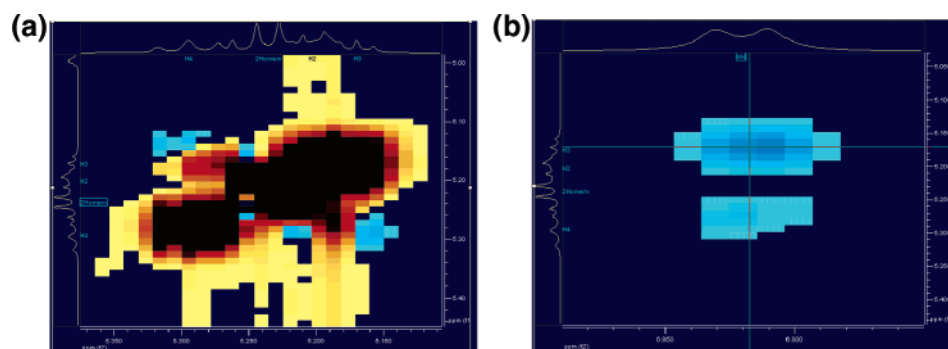
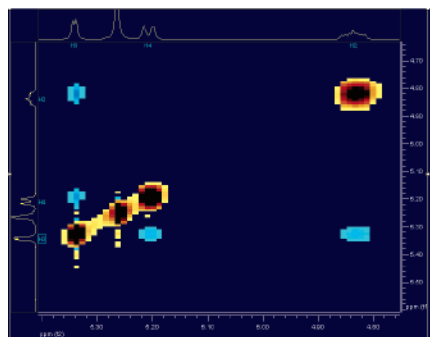**Figure 4.** (a) NOEs between H$_2$ and H$_4$ and (b) NH and H$_3$ for compound **15**.

Figure 5. Compound **16** has no NOE between H$_2$ and H$_4$.

added to a solution of compound **15** (13 mg, 0.022 mmol) in 13 mL of anhydrous CH$_2$Cl$_2$. The reaction was followed on TLC and was completed after 2 h of stirring at reflux. The reaction mixture was concentrated under vacuum and the crude product was chromatographed using the Biotage chromatograph system (A = hexane, B = ethyl acetate, CV = 12 mL, vol fract = 3 mL, flow = 8 mL/min, EQ[5CV] 17%B, 1CV[1] 17%B, 10CV[2] 17%B to 70%B, 10CV[3] 70%B) to give **16** (10 mg, 80%) (Figure 5). Colorless oil. R_f = 0.21 (3/7 hexane/ethyl acetate). ^{1}H NMR (C$_6$D$_6$/CDCl$_3$, 9/1, 400 MHz): δ 7.64 (d, J = 9.0 Hz, 1H, CH−CH=C−N), 7.59 (dd, J = 7.0 Hz, 2H, Ph), 7.20−7.14 (m, 2H, Ph), 7.10 (t, J = 7.0 Hz, 1H, Ph), 7.03 (d, J = 2.5 Hz, 1H, MEMOC−CH=C), 7.01 (dd, J = 9.0 Hz, J = 2.5 Hz, 1H, CH−CH=C−N), 6.40 (d, J = 12.6 Hz, 1H, N−CO−CH=CH), 6.17 (broad d, J = 6.5 Hz, 1H, NH), 5.49 (td, J = 12.6 Hz, J = 4.5 Hz, 1H, N−CO−CH=CH), 5.37 (d, J = 2.5 Hz, 1H, CHOCO), 5.27 (d, J = 6.5 Hz, 1H, CH−NH), 4.97−7.90 (m, 2H, OMEM), 4.78 (broad ddd, J = 10.0 Hz, J = 4.5 Hz, J = 2.5 Hz, 1H, CH−CH$_2$CO$_2$Et), 3.91−3.76 (m, 2H, CO$_2$CH_2CH$_3$), 3.56−3.45 (m, 2H, OMEM), 3.22−3.10 (m, 2H, OMEM), 3.28 (s, 3H, OMEM), 2.65 (qd, J = 12.6 Hz, J = 5.5 Hz, 1H, CH_2CH$_2$CO$_2$), 2.32 (dd, J = 16.1 Hz, J = 10.0 Hz, 1H, CHCH_2CO$_2$Et), 2.10 (broad ddd, J = 13.0 Hz, J = 12.6 Hz, J = 5.5 Hz, 1H, CH$_2$CH_2CO$_2$), 1.94 (dd, J = 16.1 Hz, J = 4.5 Hz, 1H, CHCH_2CO$_2$Et), 1.88 (td, J = 13.0 Hz, J = 5.0 Hz, 1H, CH$_2$CH_2CO$_2$), 1.74 (tdd, J = 12.6 Hz, J = 5.5 Hz, J = 4.5 Hz, 1H, CH_2CH$_2$CO$_2$), 0.91 (t, J = 7.0 Hz, 3H, CO$_2$CH$_2$CH_3). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 171.0, 169.5, 169.4, 166.7, 155.5, 133.9, 133.3, 132.2, 129.1, 128.8 (2C), 128.2, 127.8, 127.7, 127.1 (2C), 116.9, 115.5, 93.5, 72.2, 71.5, 67.6, 61.4, 58.9, 53.2, 48.0, 34.0, 33.0, 25.5, 14.1. LRMS: MS (ES+) m/z = 567.2 (M + 1).

Discussion on the Macrocyclic Ring Conformation. We could speculate if the ring would close "above" or "below" the molecule since it would be unable to flip between the two structures once the ring had closed. Molecular modeling using the quenched dynamics technique, which seems to search out a wide variety of conformations, was performed. The molecule was heated to 1000 degrees K, using the amber force field, for the starting material and the two forms of the macrocycles, and 250 structures were collected at 0.5 ps intervals. After all the structures were minimized and sorted according to energy, the two forms of the macrocycle are as shown in Figure 6.
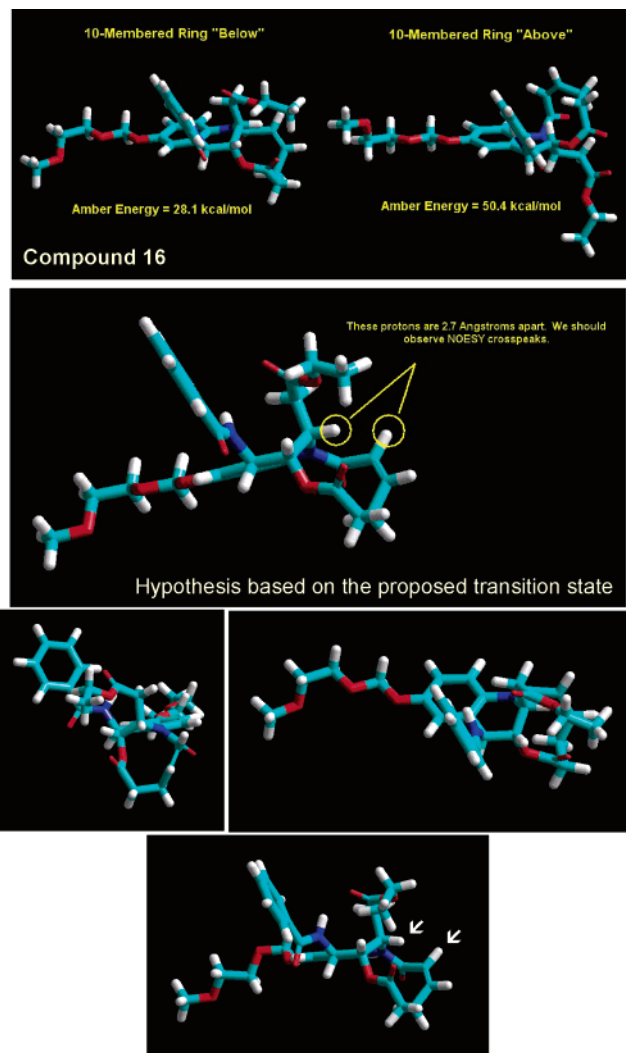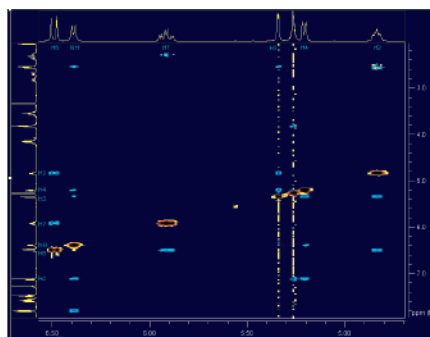

Figure 6. Compound **16**.

There is a strong NOE between H$_2$ and H$_8$ which confirmed the orientation of the 10-membered ring (Figure 7). As predicted, there was no NOE observed between H$_2$ and H$_4$. Triethylamine (6 μL, 0.044 mmol) and 4-pentenoyl chloride (13 μL, 0.118 mmol) were added slowly to a solution of free amine **12c** (8 mg, 0.015 mmol) in 1.35 mL of anhydrous CH$_2$Cl$_2$. After the mixture was stirred for 11.5 h at room temperature, a saturated solution of Na$_2$CO$_3$ (5 mL) was added; the aqueous layer was extracted with CH$_2$-Cl$_2$ (3 × 10 mL), and the organic layer was dried over MgSO$_4$. After filtration and concentration under vacuum, the crude product was chromatographed using the Biotage
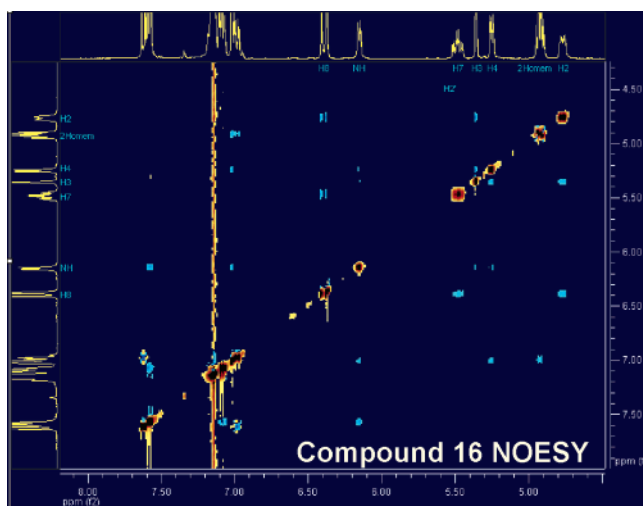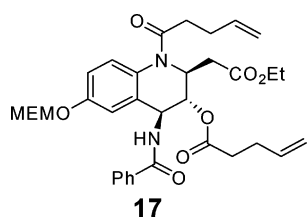
**Figure 7.** NOESY of compound **16**.

17

chromatograph system (A = hexane, B = ethyl acetate, CV = 12 mL, vol fract = 6 mL, flow = 7 mL/min, EQ[5CV] 10%B, 1CV[1] 10%B, 10CV[2] 10%B to 50%B, 10CV[3] 50%B) to give **17** (7.0 mg, 76%). Colorless oil. R_f: 0.21 (1/1 hexane/ethyl acetate). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.85 (d, J = 7.5 Hz, 2H, Ph), 7.58 (t, J = 7.5 Hz, 1H, Ph), 7.50 (t, J = 7.5 Hz, 2H, Ph), 7.09 (broad d, J = 8.5 Hz, 1H, CH−C*H*=C−N), 7.04 (dd, J = 8.5 Hz, J = 2.5 Hz, 1H, C*H*−CH=C−N), 6.93 (d, J = 1.5 Hz, 1H, MEMOC−C*H*=C), 6.78 (broad d, J = 8.0 Hz, 1H, N*H*), 5.85−5.75 (m, 1H, C*H*CH$_2$CO$_2$Et), 5.85 (ddt, J = 15.1 Hz, J = 10.0 Hz, J = 6.5 Hz, 1H, CH$_2$=C*H*−CH$_2$CH$_2$CON), 5.70 (ddt, J = 17.1 Hz, J = 10.0 Hz, J = 6.0 Hz, 1H, CH$_2$=C*H*−CH$_2$CH$_2$COO), 5.30−5.23 (m, 1H, C*H*−NH), 5.27−5.20 (m, 2H, OMEM), 5.08 (dd, J = 9.0 Hz, J = 5.5 Hz, 1H, C*H*OCO), 5.04 (d, J = 15.1 Hz, 1H$_{trans}$, *H*$_2$C=CH−CH$_2$CH$_2$CON), 5.02 (d, J = 10.0 Hz, 1H$_{cis}$, *H*$_2$C=CH−CH$_2$CH$_2$CON), 4.97 (dd, J = 17.1 Hz, J = 1.5 Hz, 1H$_{trans}$, *H*$_2$C=CH−CH$_2$CH$_2$COO), 4.85 (broad d, J = 10.0 Hz, 1H$_{cis}$, *H*$_2$C=CH−CH$_2$CH$_2$COO), 4.02 (q, J = 7.0 Hz, 2H, CO$_2$C*H*$_2$CH$_3$), 3.81−3.77 (m, 2H, OMEM), 3.54−3.51 (m, 2H, OMEM), 3.34 (s, 3H, OMEM), 2.57−2.50 (m, 2H, CHC*H*$_2$CO$_2$Et), 2.62−2.28 (m, 8H, *H*$_2$C=CH−C*H*$_2$C*H*$_2$COO and *H*$_2$C=CH−C*H*$_2$C*H*$_2$CON), 1.19 (t, J = 7.0 Hz, 3H, CO$_2$CH$_2$C*H*$_3$). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 174.3, 171.7, 169.8, 167.3, 156.4, 136.9, 136.0, 133.3, 132.8, 132.1, 130.0, 128.8 (2C), 127.1 (2C), 127.0, 115.9, 115.7, 115.2, 113.1, 93.6, 76.9, 71.5, 67.7, 60.8, 59.0, 53.1, 52.1, 38.2, 33.5, 33.1, 29.5, 28.5, 14.1. LRMS: MS (ES+) m/z = 623.4 (M + 1).

Second-generation Grubbs catalyst (2 mg, 0.003 mmol) was added to a solution of **17** (8.7 mg, 0.014 mmol) in 9 mL of anhydrous CH$_2$Cl$_2$. The reaction was followed on TLC and was completed after 20 min of stirring at reflux. The reaction mixture was concentrated under vacuum, and the crude product was chromatographed using the Biotage chro-

18
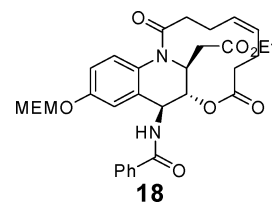
matograph system (A = hexane, B = ethyl acetate, CV = 12 mL, vol fract = 12 mL, flow = 7 mL/min, EQ[5CV] 17%B, 1CV[1] 17%B, 10CV[2] 17%B to 70%B, 10CV[3] 70%B) to give the cyclized compound **18** (6.0 mg, 72%). Colorless oil. R_f: 0.26 (3/7 hexane/ethyl acetate). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.64 (d, J = 9.0 Hz, 1H, CH−C*H*=C−N), 7.59 (dd, J = 7.0 Hz, 2H, Ph), 7.20−7.14 (m, 2H, Ph), 7.10 (t, J = 7.0 Hz, 1H, Ph), 7.03 (d, J = 2.5 Hz, 1H, MEMOC−C*H*=C), 7.01 (dd, J = 9.0 Hz, J = 2.5 Hz, 1H, C*H*−CH=C−N), 6.40 (d, J = 12.6 Hz, 1H, N−CO−C*H*=CH), 6.17 (broad d, J = 6.5 Hz, 1H, N*H*), 5.49 (td, J = 12.6 Hz, J = 4.5 Hz, 1H, N−CO−CH=C*H*), 5.37 (d, J = 2.5 Hz, 1H, C*H*OCO), 5.27 (d, J = 6.5 Hz, 1H, C*H*−NH), 4.97−7.90 (m, 2H, OMEM), 4.78 (broad ddd, J = 10.0 Hz, J = 4.5 Hz, J = 2.5 Hz, 1H, C*H*−CH$_2$CO$_2$Et), 3.91−3.76 (m, 2H, CO$_2$C*H*$_2$CH$_3$), 3.56−3.45 (m, 2H, OMEM), 3.22−3.10 (m, 2H, OMEM), 3.28 (s, 3H, OMEM), 2.65 (qd, J = 12.6 Hz, J = 5.5 Hz, 1H, C*H*$_2$CH$_2$CO$_2$), 2.32 (dd, J = 16.1 Hz, J = 10.0 Hz, 1H, CHC*H*$_2$CO$_2$Et), 2.10 (broad ddd, J = 13.0 Hz, J = 12.6 Hz, J = 5.5 Hz, 1H, CH$_2$C*H*$_2$CO$_2$), 1.94 (dd, J = 16.1 Hz, J = 4.5 Hz, 1H, CHC*H*$_2$CO$_2$Et), 1.88 (td, J = 13.0 Hz, J = 5.0 Hz, 1H, CH$_2$C*H*$_2$CO$_2$), 1.74 (tdd, J = 12.6 Hz, J = 5.5 Hz, J = 4.5 Hz, 1H, C*H*$_2$CH$_2$CO$_2$), 0.91 (t, J = 7.0 Hz, 3H, CO$_2$CH$_2$C*H*$_3$). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 172.6, 171.18, 171.15, 166.7, 155.2, 133.5, 131.9, 130.9, 129.3, 129.2, 129.1, 128.72, 128.65, 127.3, 127.1, 125.8, 116.9, 116.4, 93.8, 74.9, 71.5, 67.8, 61.7, 59.0, 48.6, 48.0, 35.7, 34.6, 34.0, 30.0, 27.0, 14.0. LRMS: MS (ES+) m/z = 595.3 (M + 1).


12d
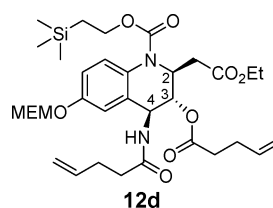
Redistilled morpholine (12 μL, 0.14 mmol) and a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (8 mg, 0.01 mmol) were added at once to a solution of alloc-protected amine **12** (47 mg, 0.07 mmol) in 1.5 mL of anhydrous CH$_2$Cl$_2$ at room temperature. The alloc removal was followed on TLC and was completed after 15 min of stirring. Then, triethylamine (30 μL, 0.21 mmol) and 4-pentenoyl chloride (16 μL, 0.14 mmol) were slowly added to the reaction mixture. After the mixture was stirred for 1 h at room temperature, a saturated solution of Na$_2$CO$_3$ (5 mL) was added; the aqueous layer was extracted with CH$_2$-Cl$_2$ (3 × 10 mL), and the organic layer was dried over MgSO$_4$. After filtration and concentration under vacuum, the crude product was chromatographed using the Biotage chromatograph system (A = hexane, B = ethyl acetate, CV
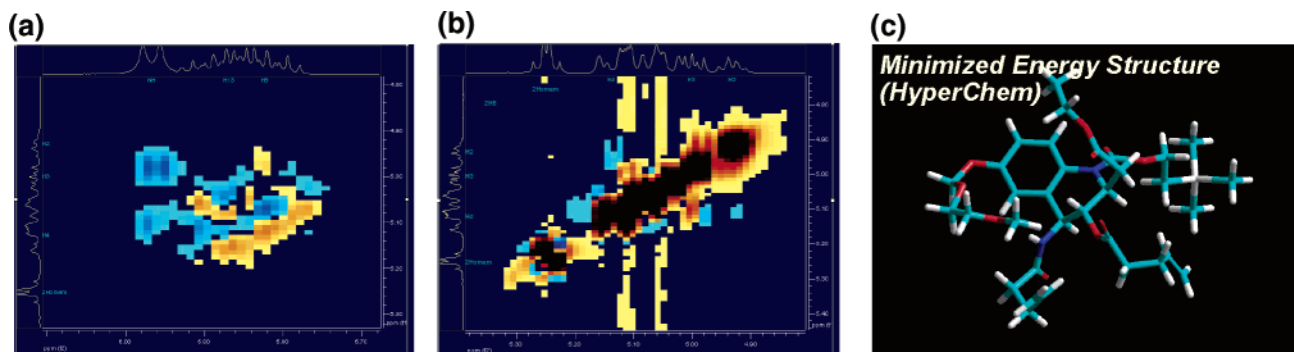
Figure 8. NOEs between (a) NH and H3 and (b) H2 and H4 and (c) the minimized energy structure (HyperChem) of compound **12d**.

= 12 mL, vol fract = 12 mL, flow = 5 mL/min, EQ[5CV] 10%B, 1CV[1] 10%B, 10CV[2] 10%B to 50%B, 10CV[3] 50%B) to give **12d** (33 mg, 72%) (Figure 8). Colorless oil. R_f: 0.34 (1/1 hexane/ethyl acetate), 0.60 (3/7 hexane/ethyl acetate). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.33 (broad d, J = 8.8 Hz, 1H, CH−CH=C−N), 6.99 (dd, J = 8.8 Hz, J = 2.5 Hz, 1H, CH−CH=C−N), 6.86 (d, J = 2.5 Hz, 1H, MEMOC−CH=C), 5.95 (broad d, J = 8.8 Hz, 1H, NH), 5.86 (ddt, J = 16.3 Hz, J = 10.3 Hz, J = 6.0 Hz, 1H, H$_2$C=CHCH$_2$CH$_2$CONH), 5.83 (ddt, J = 16.6 Hz, J = 10.3 Hz, J = 6.0 Hz, 1H, H$_2$C=CHCH$_2$CH$_2$COO), 5.27−5.21 (m, 2H, OMEM), 5.13 (dd, J = 17.1 Hz, J = 1.5 Hz, 1H$_{trans}$, H_2C=CHCH$_2$CH$_2$CONH), 5.07 (dd, J = 17.1 Hz, J = 1.5 Hz, 1H$_{trans}$, H_2C=CHCH$_2$CH$_2$COO), 5.06 (dd, J = 10.3 Hz, J = 1.5 Hz, 1H$_{cis}$, H_2C=CHCH$_2$CH$_2$CONH), 5.03 (dd, J = 10.3 Hz, J = 1.5 Hz, 1H$_{cis}$, H_2C=CHCH$_2$CH$_2$COO), 5.11 (dd, J = 8.8 Hz, J = 8.3 Hz, 1H, CH−NH), 4.99 (dd, J = 8.3 Hz, J = 4.8 Hz, 1H, CHOCO), 4.92 (ddd, J = 5.0 Hz, J = 7.0 Hz, J = 6.0 Hz, 1H, CHCH$_2$CO$_2$Et), 4.32−4.17 (m, 2H, OCH_2CH$_2$TMS), 4.03 (2q, J = 7.3 Hz, 2H, CO$_2$CH$_2$-CH$_3$), 3.83−3.80 (m, 2H, OMEM), 3.59−3.55 (m, 2H, OMEM), 3.38 (s, 3H, OMEM), 2.54 (dd, J = 14.3 Hz, J = 7.0 Hz, 1H, CHCH_2CO$_2$Et), 2.49 (dd, J = 14.3 Hz, J = 6.0 Hz, 1H, CHCH_2CO$_2$Et), 2.49−2.42 (m, 4H, H$_2$C=CHCH$_2$CH_2-COO and H$_2$C=CHCH_2CH$_2$CONH), 2.42−2.35 (m, 4H, H$_2$C=CHCH_2CH$_2$COO and H$_2$C=CHCH$_2$CH_2CONH), 1.19 (t, J = 7.3 Hz, 3H, CO$_2$CH$_2$CH_3), 1.04 (t, J = 8.5 Hz, 2H, OCH$_2$CH_2TMS), 0.03 (s, 9H, TMS). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 173.1, 172.2, 169.9, 155.1, 154.4, 136.8, 136.2, 130.2, 129.5, 127.1, 115.9, 115.8, 115.5, 112.5, 93.7, 75.8, 71.6, 67.6, 64.8, 60.9, 59.0, 53.8, 50.2, 37.7, 35.8, 33.4, 29.4, 28.6, 17.7, 14.0, −1.6 (3C). LRMS: MS (ES+) m/z = 663.6 (M + 1).

19
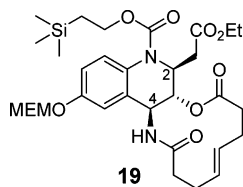
Second-generation Grubbs catalyst (4 mg, 0.003 mmol) was added to a solution of compound **12d** (21 mg, 0.032 mmol) in 25 mL of anhydrous CH$_2$Cl$_2$. The reaction was followed on TLC and was completed after 1 h of stirring at reflux. The reaction mixture was concentrated under vacuum, and the crude product was chromatographed using the Biotage
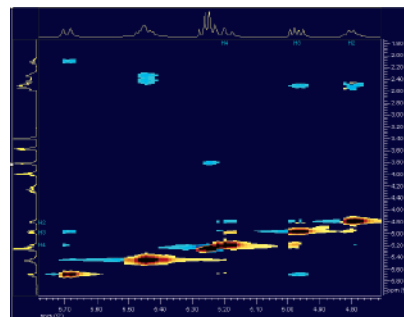

Figure 9. NOE between H2 and H4 for compound **19**.

chromatograph system (A = hexane, B = ethyl acetate, CV = 12 mL, vol fract = 12 mL, flow = 5 mL/min, EQ[5CV] 17%B, 1CV[1] 17%B, 10CV[2] 17%B to 70%B, 10CV[3] 70%B) to give compound **19** (20 mg, 98%) (Figure 9). Colorless oil. R_f: 0.24 (3/7 hexane/ethyl acetate). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.29 (broad d, J = 8.8 Hz, 1H, CH−CH=C−N), 6.99 (dd, J = 8.8 Hz, J = 2.5 Hz, 1H, CH−CH=C−N), 6.85 (d, J = 2.5 Hz, 1H, MEMOC−CH=C), 5.68 (broad d, J = 9.5 Hz, 1H, NH), 5.51−5.36 (m, J = 15.3 Hz can be read, 2H, CH$_2$CH=CHCH$_2$), 5.27−5.21 (m, 2H, OMEM), 5.19 (dd, J = 10.8 Hz, J = 9.5 Hz, 1H, CH−NH), 4.96 (dd, J = 10.8 Hz, J = 5.8 Hz, 1H, CHOCO), 4.79 (broad q, J = 6.0 Hz, 1H, CHCH$_2$CO$_2$Et), 4.32−4.16 (m, 2H, OCH_2CH$_2$TMS), 3.99 (q, J = 7.0 Hz, 2H, CO$_2$CH$_2$-CH$_3$), 3.83−3.79 (m, 2H, OMEM), 3.69−3.54 (m, 2H, OMEM), 3.39 (s, 3H, OMEM), 2.59−2.26 (m, 9H, 7H from NHCOCH_2CH_2CH=CHCH_2CH_2 and 2H from CHCH_2CO$_2$-Et), 2.10 (td, J = 12.8 Hz, J = 3.0 Hz, 1H, NHCOCH_2), 1.16 (t, J = 7.0 Hz, 3H, CO$_2$CH$_2$CH_3), 1.04 (t, J = 8.8 Hz, 2H, OCH$_2$CH_2TMS), 0.03 (s, 9H, TMS). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 173.4, 172.7, 169.8, 155.2, 154.2, 131.3, 130.6, 129.9, 129.8, 127.1, 115.0, 111.4, 93.5, 75.6, 71.6, 67.6, 64.8, 60.7, 59.0, 55.1, 50.3, 38.7, 37.8, 34.4, 29.4, 28.6, 17.7, 14.0, −1.6 (3C). LRMS: MS (ES+) m/z = 635.3 (M + 1).

Compound 19: Stereochemistry of the Double Bond.

19
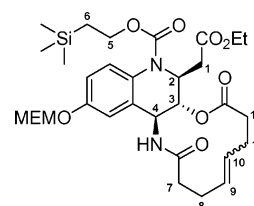
It is difficult to make this determination from the NMR because the olefinic protons have almost identical chemical
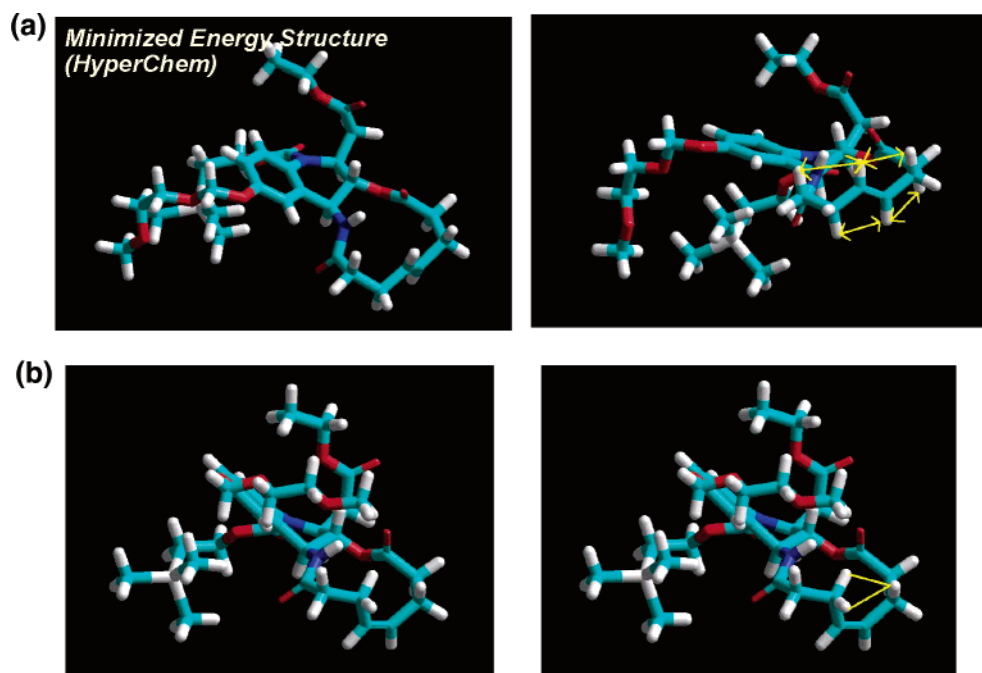
Figure 10. (a) Lowest-energy conformation of 800 minimized structures with a trans olefinic moiety and (b) the lowest-energy conformation of 800 minimized structures with a cis olefinic moiety for compound **19**.

shifts, resulting in strong second-order effects (Figures 10 and 11).


12e
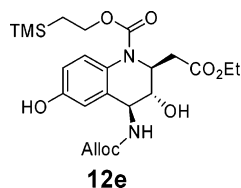
p-Toluenesulfonic acid monohydrate (69 mg, 0.35 mmol) was added to a solution of MEM-protected compound **12** (412 mg, 0.71 mmol) in 5 mL of anhydrous ethanol at room temperature. The reaction mixture was stirred for 24 h at room temperature and then at 50 °C for 7 h. An additional batch of *p*-toluenesulfonic acid monohydrate (69 mg, 0.35 mmol) was added, and the solution was stirred for an additional 20 h at 50 °C. After it was cooled to room temperature, the reaction mixture was concentrated under vacuum to remove the ethanol, and a saturated solution of NH$_4$Cl (20 mL) was added. The aqueous layer was extracted with Et$_2$O (3 × 40 mL), and the organic layer was dried over MgSO$_4$. After filtration and concentration under vacuum, the crude product was chromatographed using the Biotage chromatograph system (A = hexane, B = ethyl acetate, CV = 12 mL, vol fract = 6 mL, flow = 6 mL/min, EQ[5CV] 10%B, 1CV[1] 10%B, 10CV[2] 10%B to 50%B, 10CV[3] 50%B) to give **12e** (200 mg, 57%). White solid. R_f: 0.25 (1/1 hexane/ethyl acetate). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.41−7.29 (broad s, 1H, PhO*H*), 7.15 (broad d, J = 8.0 Hz, 1H, CH−C*H*=C−N), 6.74−6.56 (broad m, 2H, C*H*−CH= C−N and MEMOC−C*H*=C), 5.95−5.73 (m, 2H, H$_2$C= C*H*−CH$_2$O and NH), 5.27 (broad d, J = 17.3 Hz, 1H, *H$_2$*C= CH−CH$_2$O), 5.16 (broad d, J = 10.0 Hz, 1H, *H$_2$*C=CH− CH$_2$O), 4.65−4.50 (broad m, 2H, C*H*−NH and CHC*H$_2$*CO$_2$Et), 4.54 (broad d, J = 5.3 Hz, 2H, H$_2$C=CH-C*H$_2$*O), 4.29 (broad

s, 1H, O*H*), 4.30−4.15 (broad m, 2H, OC*H$_2$*CH$_2$TMS), 4.07−3.94 (m, 2H, CO$_2$C*H$_2$*CH$_3$), 3.60−3.47 (m, 1H, C*H*− OH), 2.67 (broad dd, J = 14.6 Hz, J = 5.0 Hz, 1H, CHC*H$_2$*- CO$_2$Et), 2.56 (broad dd, J = 14.6 Hz, J = 6.5 Hz, 1H, CHC*H$_2$*CO$_2$Et), 1.16 (t, J = 7.0 Hz, 3H, CO$_2$CH$_2$C*H$_3$*), 1.02 (broad t, J = 8.0 Hz, 2H, OCH$_2$C*H$_2$*TMS), 0.00 (s, 9H, TMS). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 171.9, 157.1, 154.8, 154.0, 132.4, 131.6, 127.3, 126.7, 118.0, 114.5, 110.7, 76.0, 66.1, 64.7, 61.1, 57.1, 53.8, 38.2, 17.6, 13.9, −1.6 (3C). LRMS: MS (ES+) m/z = 495.2 (M + 1).


12f
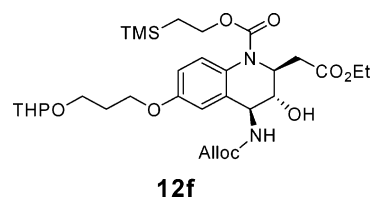
3-(Tetrahydro-2H-pyran-2-yloxy)propyl 4-methylbenzene-sulfonate (116 mg, 0.37 mmol) and **12e** (130 mg, 0.26 mmol) were added at room temperature via canula (1 mL of anhydrous DMF was used to wash the round-bottom flasks) to a solution of cesium carbonate (122 mg, 0.37 mmol) in 3 mL of anhydrous DMF. The reaction mixture was stirred for 40 h at room temperature, and then the DMF was removed under vacuum. A solution of brine (10 mL) was then added, and the aqueous layer was extracted with Et$_2$O (3 × 30 mL) and CH$_2$Cl$_2$ (1 × 30 mL). The organic layer was dried over MgSO$_4$, filtered, and concentration under vacuum. The crude product was chromatographed using the Biotage chromatograph system (A = hexane, B = ethyl acetate, CV = 12 mL, vol fract = 12 mL, flow = 7 mL/ min, EQ[5CV] 10%B, 1CV[1] 10%B, 10CV[2] 10%B to 50%B, 10CV[3] 50%B) to give **12f** (129 mg, 77%, a mixture diastereomers). Colorless oil. R_f: 0.29 (1/1 hexane/ethyl acetate). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.26 (broad d, J =
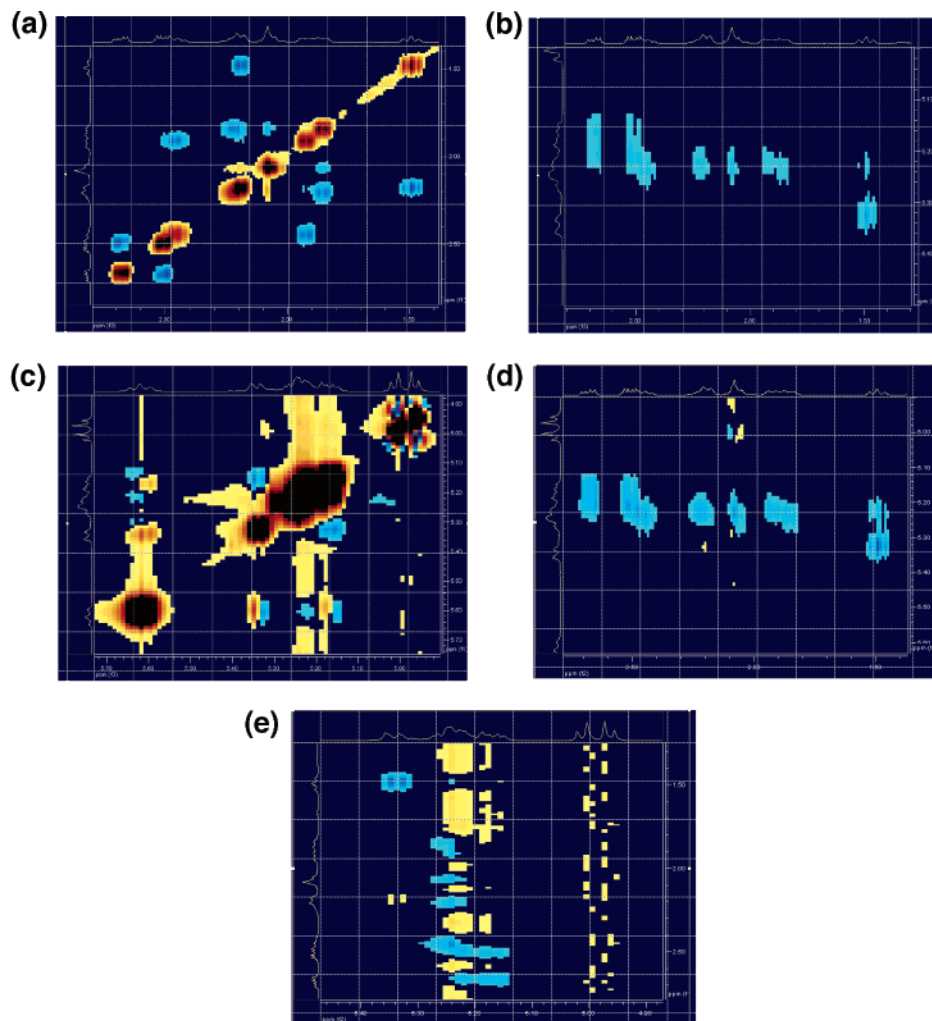
Figure 11. NOEs between (a) H_1 and H_8, (b) H_1 and H_3/H_7 and NH, (c) NH and H_3/H_4 and H_4 and H_2, (d) H_7 and H_9/H_{10} and H_8 and H_9/H_{10}, and (e) H_9/H_{10} and H_{11} for the NOESY of compound **19**.

8.8 Hz, 1H, CH−CH=C−N), 6.79 (s, 1H, MEMOC−CH=C), 6.77 (dd, $J = 8.8$ Hz, $J = 2.8$ Hz, 1H, CH−CH=C−N), 6.02−5.85 (m, 1H, H$_2$C=CH−CH$_2$O), 5.34 (d, $J = 17.1$ Hz, 1H$_{trans}$, H_2C=CH−CH$_2$O), 5.32−5.24 (m, 1H, NH), 5.23 (d, $J = 11.1$ Hz, 1H$_{cis}$, H_2C=CH−CH$_2$O), 4.70−4.60 (broad m, 1H, OCHO), 4.63 (broad d, $J = 5.5$ Hz, 2H, H$_2$C=CH−CH_2O), 4.61−4.56 (broad m, 2H, CH−NH and CHCHCH$_2$CO$_2$-Et), 4.31−4.16 (broad m, 2H, OCH_2CH$_2$TMS), 4.09−4.00 (m, 4H, CO$_2$CH_2CH$_3$ and CH_2OPh), 3.95−3.80 (m, 3H, CH_2-OCHO and OH), 3.60−3.53 (m, 2H, CH_2CH$_2$CH$_2$OPh), 3.53−3.46 (m, 1H, CH−OH), 2.75 (dd, $J = 15.3$ Hz, $J = 5.0$ Hz, 1H, CHCHCO$_2$Et), 2.52 (dd, $J = 15.3$ Hz, $J = 8.5$ Hz, 1H, CHCHCO$_2$Et), 2.05 (quint, $J = 6.0$ Hz, 2H, CH$_2$CH_2CH$_2$OPh), 1.81 (qd, $J = 8.8$ Hz, $J = 3.5$ Hz, 1H, CH_2CHO), 1.72 (dt, $J = 12.6$ Hz, $J = 3.0$ Hz, 1H, CH_2-CH$_2$CHO), 1.61−1.47 (m, 4H, 1H from CH_2CHO, 1H from CH_2CH$_2$CHO and 2H from CH_2CH$_2$O), 1.18 (t, $J = 7.3$ Hz, 3H, CO$_2$CH$_2$CH_3), 1.03 (broad t, $J = 8.8$ Hz, 2H, OCH$_2$CH_2-TMS), 0.01 (s, 9H, TMS). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 171.9, 156.7, 154.4 (2C), 132.6, 131.83 and 131.82 (2 diastereomers), 128.1, 126.6, 117.9, 113.04 and 112.95 (2 diastereomers), 109.98 and 109.88 (2 diastereomers), 99.02 and 98.95 (2 diastereomers), 76.6, 66.0, 65.16 and 65.12 (2 diastereomers), 64.5, 63.94 and 63.92 (2 diastereomers),

62.39 and 62.34 (2 diastereomers), 61.0, 57.2, 53.8, 38.4, 30.6, 29.64 and 29.61 (2 diastereomers), 25.36 and 25.35 (2 diastereomers), 19.60 and 19.57 (2 diastereomers), 17.7, 14.0, −1.6 (3C). LRMS: MS (ES+) $m/z = 637.3$ (M + 1).

12g
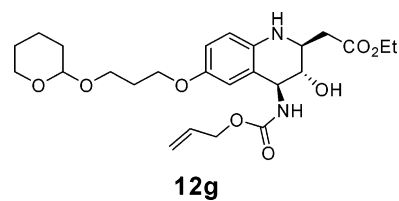
A molar solution of TBAF (405 μL, 0.40 mmol) at room temperature was added to a solution of Teoc-protected compound **12f** (129 mg, 0.20 mmol) in 10 mL of anhydrous THF. The reaction mixture was stirred for 25 min at room temperature and then concentrated under vacuum. The crude product was chromatographed using the Biotage chromatograph system (A = hexane, B = ethyl acetate, CV = 12 mL, vol fract = 9 mL, flow = 7 mL/min, EQ[5CV] 10%B, 1CV[1] 10%B, 10CV[2] 10%B to 50%B, 10CV[3] 50%B) to give **12g** (84 mg, 84%). White solid. R_f: 0.27 (1/1 hexane/ethyl acetate), 0.56 (3/7 hexane/ethyl acetate). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 6.74 (d, $J = 2.0$ Hz, 1H, MEMOC−

C*H*=C), 6.69 (dd, *J* = 8.8 Hz, *J* = 2.8 Hz, 2H, C*H*−CH=
C−N), 6.51 (d, *J* = 8.8 Hz, 1H, CH−C*H*=C−N), 5.95 (ddt,
J = 17.1 Hz, *J* = 10.5 Hz, *J* = 5.8 Hz, 1H, H₂C=C*H*−
CH₂O), 5.35 (dd, *J* = 17.1 Hz, *J* = 1.3 Hz, 1H$_{trans}$, H₂C=
CH−CH₂O), 5.25 (d, *J* = 10.5 Hz, 1H$_{cis}$, H₂C=CH−CH₂O),
5.28−5.21 (broad m, 1H, NH), 4.87 (broad t, *J* = 7.3 Hz,
1H, OC*H*O), 4.64 (d, *J* = 5.5 Hz, 2H, H₂C=CH−C*H₂*O),
4.61−4.56 (broad m, 1H, C*H*−NH), 4.44 (broad s, 1H, NH),
4.17 (2q, *J* = 7.0 Hz, 2H, CO₂C*H₂*CH₃), 3.98 (t, *J* = 6.0
Hz, 2H, C*H₂*OPh), 3.93−3.80 (m, 3H, C*H₂*OCHO and O*H*),
3.59−3.46 (m, 4H, C*H₂*CH₂CH₂OPh and C*H*CH₂CO₂Et and
C*H*−OH), 3.11 (broad d, *J* = 16.3 Hz, 1H, CHC*H₂*CO₂Et),
2.39 (dm, *J* = 16.3 Hz, 1H, CHC*H₂*CO₂Et), 2.02 (quint, *J*
= 6.3 Hz, 2H, CH₂C*H₂*CH₂OPh), 1.81 (qd, *J* = 8.3 Hz, *J* =
3.5 Hz, 1H, C*H₂*CHO), 1.71 (dt, *J* = 12.8 Hz, *J* = 3.0 Hz,
1H, C*H₂*CH₂CHO), 1.61−1.46 (m, 4H, 1H from C*H₂*CHO,
1H from C*H₂*CH₂CHO and 2H from C*H₂*CH₂O), 1.29 (t, *J*
= 7.0 Hz, 3H, CO₂CH₂C*H₃*). ¹³C NMR (CDCl₃, 100 MHz):
δ 172.7, 158.4, 152.1, 138.4, 132.3, 120.7, 118.3, 116, 115.84
and 115.82 (1, 2 diastereomers), 113.5 and 113.4 (2
diastereomers), 98.9, 75.2, 66.3, 65.68 and 65.65 (2 diaster-
eomers), 64.0, 62.30 and 62.28 (2 diastereomers), 60.7, 56.2,
54.0, 36.4, 30.6, 29.7, 25.4, 19.57 and 19.55 (2 diastereo-
mers), 14.2. LRMS: MS (ES+) *m/z* = 493.2 (M + 1).

12h
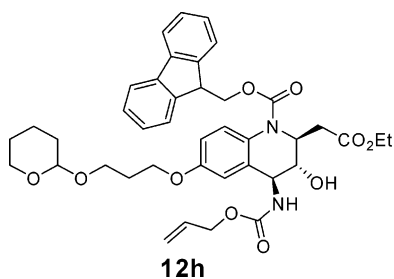
Anhydrous sodium bicarbonate (200 mg, 2.37 mmol) and
9-fluorenylmethyl chloroformate (75 mg, 0.28 mmol) were
added to a solution of free amine **12g** (84 mg, 0.17 mmol)
in 5 mL of ethyl acetate at room temperature. The reaction
mixture was stirred for 16 h at room temperature, and 3 mL
of water was added. The reaction mixture was stirred for an
additional 3 h, and 9-fluorenylmethyl chloroformate (68 mg,
0.25 mmol) was again added at room temperature and stirred
for 1 h. Then, 5 mL of water was added, and the aqueous
layer was extracted with AcOEt (3 × 10 mL). The organic
layer was dried over MgSO₄. After filtration and concentra-
tion under vacuum, the crude product was chromatographed
using the Biotage chromatograph system (A = hexane, B =
ethyl acetate, CV = 12 mL, vol fract = 12 mL, flow = 7
mL/min, EQ[5CV] 10%B, 1CV[1] 10%B, 10CV[2] 10%B
to 50%B, 10CV[3] 50%B) to give **12h** (107 mg, 88%).
Colorless oil. *R$_f$*: 0.55 (3/7 hexane/ethyl acetate). ¹H NMR
(CDCl₃, 400 MHz): δ 7.75 (t, *J* = 6.8 Hz, 2H, Ph), 7.49
(broad s, 2H, Ph), 7.39 (q, *J* = 7.0 Hz, 2H, Ph), 7.28 (q, *J*
= 7.0 Hz, 2H, Ph), 6.98 (broad s, 1H, CH−C*H*=C−N), 6.80
(s, 1H, MEMOC−C*H*=C), 6.67 (broad d, *J* = 7.3 Hz, 1H,
C*H*−CH=C−N), 6.03−5.89 (m, 1H, H₂C=C*H*−CH₂O),
5.36 (d, *J* = 17.3 Hz, 1H$_{trans}$, H₂C=CH−CH₂O), 5.25 (d, *J*
= 10.0 Hz, 1H$_{cis}$, H₂C=CH−CH₂O), 5.13 (dd, *J* = 11.3 Hz,
J = 8.5 Hz, 1H, OC*H*O), 4.65 (broad d, *J* = 5.5 Hz, 2H,
H₂C=CH−C*H₂*O), 4.65−4.54 (broad m, 4H, C*H*−NH and

CHC*H₂*CO₂Et and NCOOC*H₂*), 4.51 (broad s, 1H, NH), 4.22
(broad t, *J* = 5.8 Hz, 1H, NCOOCH₂C*H*), 4.10−4.00 (m,
4H, CO₂C*H₂*CH₃ and C*H₂*OPh), 3.97−3.83 (m, 2H, C*H₂*-
OCHO), 3.75 (broad s, 1H, OH), 3.63−3.56 (m, 1H, C*H*−
OH), 3.54−3.48 (m, 2H, C*H₂*CH₂CH₂OPh), 2.63 (broad d,
J = 14.6 Hz, 1H, CHC*H₂*CO₂Et), 2.40 (broad dd, *J* = 14.6
Hz, *J* = 8.5 Hz, 1H, CHC*H₂*CO₂Et), 2.07 (quint, *J* = 6.0
Hz, 2H, CH₂C*H₂*CH₂OPh), 1.83 (qd, *J* = 8.8 Hz, *J* = 3.8
Hz, 1H, C*H₂*CHO), 1.74 (dt, *J* = 12.5 Hz, *J* = 3.0 Hz, 1H,
C*H₂*CH₂CHO), 1.64−1.49 (m, 4H, 1H from C*H₂*CHO, 1H
from C*H₂*CH₂CHO and 2H from C*H₂*CH₂O), 1.19 (t, *J* =
7.3 Hz, 3H, CO₂CH₂C*H₃*). ¹³C NMR (CDCl₃, 100 MHz): δ
171.8, 156.9, 156.7, 154.1, 143.66, 143.62, 141.34, 141.31,
132.6, 131.9, 127.69, 127.65 (2C), 127.13, 127.05, 126.7,
124.96, 124.92, 119.90, 119.88, 118.0, 113.04 and 112.94
(2 diastereomers), 110.04 and 109.94 (2 diastereomers), 99.07
and 99.00 (2 diastereomers), 76.7, 67.5, 66.1, 65.22 and 65.18
(2 diastereomers), 63.9, 62.45 and 62.40 (2 diastereomers),
61.0, 57.2, 53.7, 47.2, 38.2, 30.7, 29.67 and 29.63 (2
diastereomers), 25.40 and 25.38 (2 diastereomers), 19.66 and
19.62 (2 diastereomers), 14.0. LRMS: MS (ES+) *m/z* =
715.4 (M + 1).

20
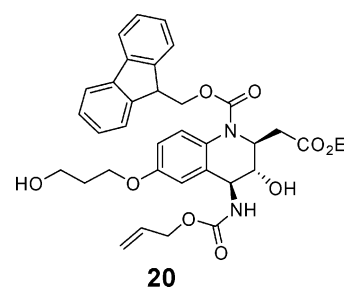
Pyridinium *p*-toluenesulfonate (16 mg, 0.06 mmol) was
added to a solution of THP-protected compound **12g** (45 mg,
0.06 mmol) in 8 mL of anhydrous ethanol at room temper-
ature. The reaction mixture was stirred for 2 h at 50 °C.
After it was cooled to room temperature, the reaction mixture
was concentrated under vacuum to remove the ethanol, and
the crude product was chromatographed using the Biotage
chromatograph system (A = hexane, B = ethyl acetate, CV
= 12 mL, vol fract = 15 mL, flow = 8 mL/min, EQ[5CV]
20%B, 1CV[1] 20%B, 10CV[2] 20%B to 70%B, 10CV[3]
70%B) to give **20** (34 mg, 86%). White solid. *R$_f$*: 0.28 (3/7
hexane/ethyl acetate). ¹H NMR (CDCl₃, 400 MHz): δ 7.75
(t, *J* = 7.0 Hz, 2H, Ph), 7.49 (broad s, 2H, Ph), 7.39 (q, *J* =
7.0 Hz, 2H, Ph), 7.29 (q, *J* = 7.0 Hz, 2H, Ph), 6.97 (broad
s, 1H, CH−C*H*=C−N), 6.80 (s, 1H, MEMOC−C*H*=C),
6.67 (broad d, *J* = 7.5 Hz, 1H, C*H*−CH=C−N), 6.02−5.88
(m, 1H, H₂C=C*H*−CH₂O), 5.35 (d, *J* = 17.1 Hz, 1H$_{trans}$,
H₂C=CH−CH₂O), 5.24 (d, *J* = 10.0 Hz, 1H$_{cis}$, H₂C=CH−
CH₂O), 5.25 (broad s, 1H, OH), 4.64 (broad d, *J* = 5.5 Hz,
2H, H₂C=CH−C*H₂*O), 4.65−4.52 (broad m, 4H, C*H*−NH
and CHC*H₂*CO₂Et and NCOOC*H₂*), 4.50 (broad s, 1H, NH),
4.25−4.18 (broad m, 1H, NCOOCH₂C*H*), 4.09 (broad t, *J*
= 5.5 Hz, 2H, HOCH₂CH₂C*H₂*O), 4.09−3.99 (m, 2H,
CO₂C*H₂*CH₃), 3.85 (broad t, *J* = 5.5 Hz, 2H, HOC*H₂*CH₂-
CH₂O), 3.56−3.48 (broad m, 1H, C*H*-OH), 3.54−3.48 (m,
2H, C*H₂*CH₂CH₂OPh), 2.60 (broad d, *J* = 14.3 Hz, 1H,
CHC*H₂*CO₂Et), 2.39 (broad dd, *J* = 14.3 Hz, *J* = 8.3 Hz,

1H, CHCH_2CO$_2$Et), 2.03 (quint, $J = 5.5$ Hz, 2H, HOCH$_2$CH_2-CH_2O), 1.18 (t, $J = 7.3$ Hz, 3H, CO$_2$CH$_2$CH_3). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 171.8, 156.71, 156.65, 154.1, 143.64, 143.62, 141.33, 141.31, 132.6, 131.9, 127.8, 127.71, 127.67, 127.13, 127.06, 126.7, 124.96, 124.90, 119.91, 119.89, 118.0, 113.2, 110.0, 76.4, 67.5, 66.1, 65.8, 61.0, 60.1, 57.2, 53.7, 47.2, 38.1, 31.9, 14.0. LRMS: MS (ES+) $m/z = 631.3$ (M + 1).

Solid-Phase Synthesis.

21
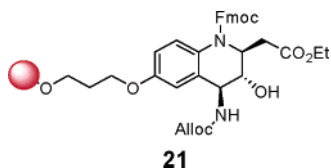
The resin (49.6 mg, 0.064 mmol) and compound **20** (80.8 mg, 0.1281 mmol) were dried on a freeze dryer for 24 h hours. The beads were placed in a vial, and 1 mL of anhydrous CH$_2$Cl$_2$ was added at room temperature to allow the bead to swell. The solution containing the beads was gently shaken for 30 min. The CH$_2$Cl$_2$ was then removed, and a 0.45 M of trifluoromethanesulfonate solution (0.85 mL, 0.3843 mmol) was added to the resin and kept for 20 min (shaking gently). The beads and the solution became an orange-red color. The trifluoromethanesulfonate solution was removed completely, and the resin was washed with anhydrous CH$_2$Cl$_2$ twice (3 mL). Then 1 mL of anhydrous CH$_2$-Cl$_2$ was added to the resin, followed by the 2,6-lutidine (60 μL, 0.5124 mmol). The beads became colorless and stood for 10 min. The compound was dissolved in a minimum of solvent (0.5 mL of anhydrous CH$_2$Cl$_2$) and added to the resin. The resulting mixture was gently shaken for 1 h. Then the vial was capped and kept on tumble shaker for 12 h. The vial was removed from the tumble shaker, and the mixture was washed with DCM (5 mL) 3 times, THF 3 times, and DCM, again, 3 times. Finally, the resin was dried on a vacuum pump for 6 h and in the freeze dryer for 12 h (62.7 mg, 76%). Rf: 0.36 (1/9 hexane/ethyl acetate). LRMS: MS (ES+) $m/z = 631.2$ (M + 1). HPLC: 14.005 min.
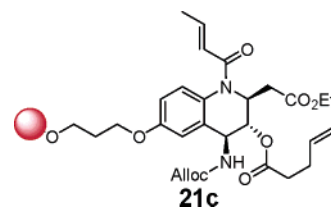

21a
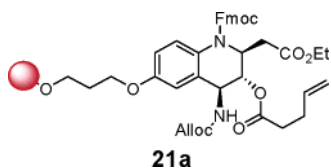
The compound loaded onto resin **21** (43.2 mg, 0.0361 mmol) was swelled in 3 mL of anhydrous CH$_2$Cl$_2$ for 30 min. The solvent was removed and replaced with 1 mL of anhydrous CH$_2$Cl$_2$. 1,3-Diisopropylcarbodiimide (34 μL, 0.217 mmol), 4-pentenoic acid (15.2 μL, 0.144 mmol), and 4-(dimethyl-amino)-pyridine (4.4 mg, 0.0361 mmol) were added at once to the beads at room temperature. The mixture was shaken with a tumble shaker for 23 h. The mixture was filtered; the resin was washed with CH$_2$Cl$_2$ (3 × 5 mL), THF (3 × 5 mL), and CH$_2$Cl$_2$ (3 × 5 mL) and dried under vacuum overnight. The compound was obtained after the cleavage

of 3 beads. R_f: 0.67 (1/9 hexane/ethyl acetate). LRMS: MS (ES+) $m/z = 713.1$ (M + 1). HPLC: 15.771 min. HPLC yield: 99%.

21b
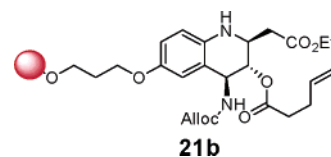
Resin **21a** (21 mg, 0.0181 mmol) was swelled in 3 mL of anhydrous DMF for 30 min. The solvent was removed and replaced with 1 mL of anhydrous DMF. Piperidine (100 μL, 1.0 mmol) was added to the beads at room temperature. The mixture was shaken with a tumble shaker for 17 h. The mixture was filtered; the resin was washed with THF (3 × 5 mL), CH$_2$Cl$_2$ (3 × 5 mL), THF (3 × 5 mL), and CH$_2$Cl$_2$ (3 × 5 mL) and dried under vacuum overnight. The compound was obtained after cleavage of 3 beads. R_f: 0.62 (1/9 hexane/ethyl acetate). LRMS: MS (ES+) $m/z = 491.2$ (M + 1). HPLC: 11.125 min. HPLC yield: 85%.
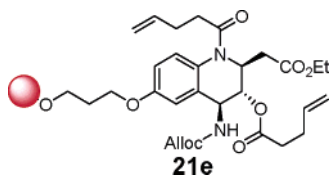

21c

Resin **21b** (38.7 mg, 0.0487 mmol) was swelled in 3 mL of anhydrous CH$_2$Cl$_2$ for 30 min. The solvent was removed and replaced with 1 mL of anhydrous CH$_2$Cl$_2$. 2,4,6-Collidine (65 μL, 0.487 mmol) and crotonyl chloride (26.2 μL, 0.243 mmol) were added to the beads at 0 °C. The mixture was shaken with a tumble shaker for 19 h. The mixture was filtered; the resin was washed with CH$_2$Cl$_2$ (3 × 5 mL), THF (3 × 5 mL), and CH$_2$Cl$_2$ (3 × 5 mL) and dried under vacuum overnight. The compound was obtained after cleavage of 2 beads. R_f: 0.54 (1/9, hexane/ethyl acetate). LRMS: MS (ES+) $m/z = 559.3$ (M + 1). HPLC: 9.86 min. HPLC yield: 99%.
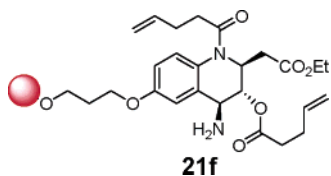

21d
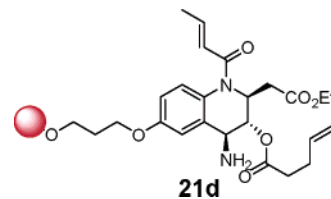
Resin **21c** (40 mg, 0.0487 mmol) was swelled in 3 mL of anhydrous THF for 30 min. The solvent was removed and replaced with 1 mL of a mixture of anhydrous CH$_2$Cl$_2$ (5 mL), 4-methyl morpholine (0.32 mL), and acetic acid (0.66 mL). Triphenylphosphine (165 mg, 0.621 mmol) and tetrakis-(triphenylphosphine) palladium (151 mg, 0.130 mmol) were added to the beads at room temperature. The mixture was shaken with a tumble shaker for 4 h. The mixture was filtered; the resin was washed with CH$_2$Cl$_2$ (3 × 5 mL), THF (3 × 5 mL), and CH$_2$Cl$_2$ (3 × 5 mL) and dried under vacuum overnight. The compound was obtained after cleavage of 3 beads. R_f: 0.12 (1/9 hexane/ethyl acetate). LRMS: MS
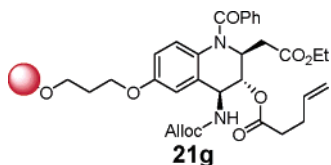
(ES+) *m/z* = 475.3 (M + 1). HPLC: 7.79 min. HPLC yield: 98%.

21e

Resin **21b** (38 mg, 0.0425 mmol) was swelled in 3 mL of anhydrous CH₂Cl₂ for 30 min. The solvent was removed and replaced with 1 mL of anhydrous CH₂Cl₂. 2,4,6-Collidine (58.6 μL, 0.425 mmol) and 4-pentenoyl chloride (24 μL, 0.213 mmol) were added to the beads at 0 °C. The mixture was shaken with a tumble shaker for 14 h. The mixture was filtered; the resin was washed with CH₂Cl₂ (3 × 5 mL), THF (3 × 5 mL), and CH₂Cl₂ (3 × 5 mL) and dried under vacuum overnight. The compound was obtained after cleavage of 2 beads. R_f: 0.54 (1/9 hexane/ethyl acetate). LRMS: MS (ES+) *m/z* = 573.4 (M + 1). HPLC: 10.15 min. HPLC yield: 99%.
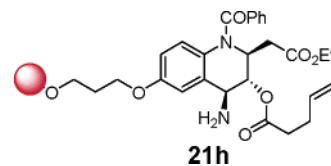

21f

Resin **21e** (40 mg, 0.0425 mmol) was swelled in 3 mL of anhydrous THF for 30 min. The solvent was removed and replaced with 1 mL of a mixture of anhydrous CH₂Cl₂ (5 mL), 4-methyl morpholine (0.32 mL), and acetic acid (0.66 mL). Triphenylphosphine (144 mg, 0.542 mmol) and tetrakis-(triphenylphosphine) palladium (132 mg, 0.113 mmol) were added to the beads at room temperature. The mixture was shaken with a tumble shaker for 14 h. The mixture was filtered; the resin was washed with CH₂Cl₂ (3 × 5 mL), THF (3 × 5 mL), and CH₂Cl₂ (3 × 5 mL) and dried under vacuum overnight. The compound was obtained after cleavage of 3 beads. R_f: 0.18 (1/9 hexane/ethyl acetate). LRMS: MS (ES+) *m/z* = 489.2 (M + 1), 506.3 (M + 18). HPLC: 8.12 min. HPLC yield: 80%.

21g
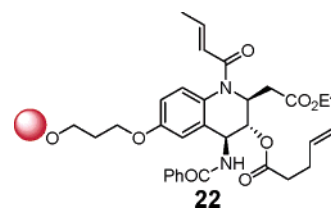
Resin **21b** (18.6 mg, 0.0181 mmol) was swelled in 3 mL of anhydrous CH₂Cl₂ for 30 min. The solvent was removed and replaced with 1 mL of anhydrous CH₂Cl₂. 2,4,6-Collidine (24.1 μL, 0.181 mmol) and benzoyl chloride (10.6 μL, 0.0903 mmol) were added to the beads at room temperature. The mixture was shaken with a tumble shaker for 16 h. The mixture was filtered; the resin was washed with CH₂Cl₂ (3 × 5 mL), THF (3 × 5 mL), and CH₂Cl₂ (3 × 5 mL) and dried under vacuum overnight. The compound was obtained after cleavage of 2 beads. R_f: 0.58 (1/9 hexane/ethyl acetate).

LRMS: MS (ES+) *m/z* = 595.2 (M + 1). HPLC: 13.649 min. HPLC yield: 78%.

21h

Resin **21g** (19.1 mg, 0.0181 mmol) was swelled in 3 mL of anhydrous THF for 30 min. The solvent was removed and replaced with 1 mL of a mixture of anhydrous CH₂Cl₂ (5 mL), 4-methyl morpholine (0.32 mL), and acetic acid (0.66 mL). Triphenylphosphine (61 mg, 0.230 mmol) and tetrakis-(triphenylphosphine) palladium (56 mg, 0.048 mmol) were added to the beads at room temperature. The mixture was shaken with a tumble shaker for 4 h. The mixture was filtered; the resin was washed with CH₂Cl₂ (3 × 5 mL), THF (3 × 5 mL), and CH₂Cl₂ (3 × 5 mL) and dried under vacuum overnight. The compound was obtained after cleavage of 3 beads. R_f: 0.10 (1/9 hexane/ethyl acetate). LRMS: MS (ES+) *m/z* = 511.2 (M + 1). HPLC: 2.854 min. HPLC yield: 71%.
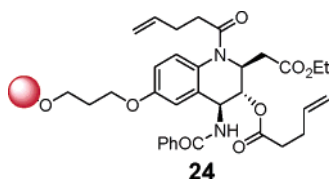

22

Resin **21d** (36 mg, 0.0487 mmol) was swelled in 3 mL of anhydrous CH₂Cl₂ for 30 min. The solvent was removed and replaced with 1 mL of anhydrous CH₂Cl₂. 2,4,6-Collidine (65 μL, 0.487 mmol) and benzoyl chloride (28.5 μL, 0.243 mmol) were added to the beads at room temperature. The mixture was shaken with a tumble shaker for 19 h. The mixture was filtered; the resin was washed with CH₂Cl₂ (3 × 5 mL), THF (3 × 5 mL), and CH₂Cl₂ (3 × 5 mL) and dried under vacuum overnight. The compound was obtained after cleavage of 2 beads. R_f: 0.48 (1/9 hexane/ethyl acetate). LRMS: MS (ES+) *m/z* = 579.2 (M + 1). HPLC: 9.88 min. HPLC yield: 90%.
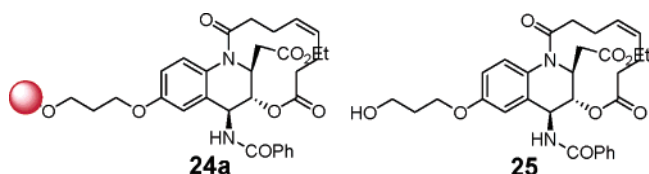

22a   **23**
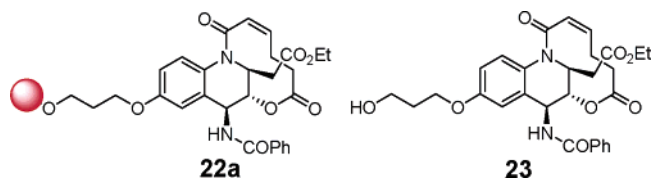
Resin **22** (38 mg, 0.487 mmol) was swelled in 2 mL of anhydrous CH₂Cl₂ for 30 min. Second-generation Grubbs' catalyst (41 mg, 0.0487 mmol) was added to the beads at room temperature. The mixture was heated to reflux for 19 h. After it was cooled, the mixture was filtered, and the resin was washed with THF (3 × 5 mL), CH₂Cl₂ (3 × 5 mL), THF (3 × 5 mL), and CH₂Cl₂ (3 × 5 mL) and dried under vacuum overnight. The compound was obtained after cleavage of 3 beads. R_f: 0.14 (1/9 hexane/ethyl acetate). LRMS: MS (ES+) *m/z* = 537.3 (M + 1). HPLC: 8.71 min. After

cleavage of all resin **22a**, the crude product was chromatographed on silica gel (eluent = hexane/ethyl acetate, 1/9 to pure ethyl acetate) to give the title compound as a white solid.

24

Resin **21f** (35 mg, 0.0425 mmol) was swelled in 3 mL of anhydrous CH$_2$Cl$_2$ for 30 min. The solvent was removed and replaced with 1 mL of anhydrous CH$_2$Cl$_2$. 2,4,6-Collidine (57 μL, 0.425 mmol) and benzoyl chloride (25 μL, 0.213 mmol) were added to the beads at room temperature. The mixture was shaken with a tumble shaker for 19 h. The mixture was filtered, and the resin was washed with CH$_2$Cl$_2$ (3 × 5 mL), THF (3 × 5 mL), and CH$_2$Cl$_2$ (3 × 5 mL) and dried under vacuum overnight. The compound was obtained after cleavage of 2 beads. R_f: 0.53 (1/9 hexane/ethyl acetate). LRMS: MS (ES+) m/z = 593.3 (M + 1), 610.4 (M + 18). HPLC: 10.12 min. HPLC yield: 90%.
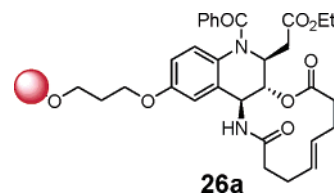
24a   **25**

Resin **24** (38 mg, 0.425 mmol) was swelled in 2 mL of anhydrous CH$_2$Cl$_2$ for 30 min. Second-generation Grubbs catalyst (36 mg, 0.0425 mmol) was added to the beads at room temperature. The mixture was heated to reflux for 17 h. After it was cooled, the mixture was filtered, and the resin was washed with THF (3 × 5 mL), CH$_2$Cl$_2$ (3 × 5 mL), THF (3 × 5 mL), and CH$_2$Cl$_2$ (3 × 5 mL) and dried under vacuum overnight. The compound was obtained after cleavage of 3 beads. R_f: 0.10 (1/9 hexane/ethyl acetate). LRMS: MS (ES+) m/z = 565.2 (M + 1), 582.3 (M + 18). HPLC: 9.17 min. After cleavage of all resin **24a**, the crude product was chromatographed on silica gel (eluent = hexane/ethyl acetate, 1/9 to pure ethyl acetate) to give the title compound as a white solid.

26
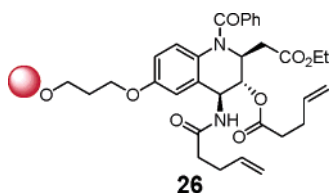
Resin **21h** (16.4 mg, 0.0181 mmol) was swelled in 3 mL of anhydrous CH$_2$Cl$_2$ for 30 min. The solvent was removed and replaced with 1 mL of anhydrous CH$_2$Cl$_2$. 2,4,6-Collidine (24.1 μL, 0.181 mmol) and 4-pentenoyl choloride (10.2 μL, 0.0903 mmol) were added to the beads at room temperature. The mixture was shaken with a tumble shaker for 2 days. The mixture was filtered, and the resin was washed with CH$_2$Cl$_2$ (3 × 5 mL), THF (3 × 5 mL) and CH$_2$Cl$_2$ (3 × 5

mL) and dried under vacuum overnight. The compound was obtained after cleavage of 3 beads. R_f: 0.49 (1/9 hexane/ethyl acetate). LRMS: MS (ES+) m/z = 593.3 (M + 1). HPLC: 11.971 min. HPLC yield: 81%.

26a

Resin **26** (17.9 mg, 0.0181 mmol) was swelled in 2 mL of anhydrous CH$_2$Cl$_2$ for 30 min. Second-generation Grubbs catalyst (3 mg, 0.0036 mmol) was added to the beads at room temperature. The mixture was heated to reflux for 19 h. After it was cooled, the mixture was filtered, and the resin was washed with THF (3 × 5 mL), CH$_2Cl_2$ (3 × 5 mL), THF (3 × 5 mL), and CH$_2$Cl$_2$ (3 × 5 mL) and dried under vacuum overnight. The compound was obtained after cleavage of 3 beads. R_f: 0.16 (1/9 hexane/ethyl acetate). LRMS: MS (ES+) m/z = 565.2 (M + 1). HPLC: 3.883 min.

27
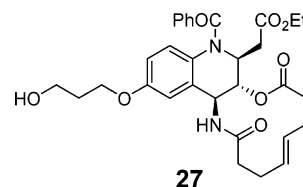
After cleavage of all resin **26a**, the crude product was purified using the Biotage chromatograph system (A = hexane, B = ethyl acetate, CV = 12 mL, vol fract = 12 mL, flow = 4 mL/min, EQ[5CV] 23%B, 1CV[1] 23%B, 10CV[2] 230%B to 90%B, 10CV[3] 90%B) to give the title compound (5.8 mg, 57%) (Figure 12). White solid. R_f: 0.16 (1/9, hexane/ethyl acetate). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.36−7.20 (m, 5H, H$_{Ph}$), 6.80 (broad d, J = 2.0 Hz, 1H, MEMOC−CH=C), 6.48 (dd, J = 8.5 Hz, J = 2.0 Hz, 1H, CH−CH=C−N), 6.41 (d, J = 8.5 Hz, 1H, CH−CH=C−N), 5.79 (d, J = 9.0 Hz, 1H, NH), 5.54−5.42 (m, 2H, CH$_2$CH=CHCH$_2$), 5.38 (dd, J = 10.0 Hz, J = 9.0 Hz, 1H, CH−NH), 5.16−5.10 (m, 1H, CHCH$_2$CO$_2$Et), 5.09 (dd, J = 10.5 Hz, J = 4.5 Hz, 1H, CHOCO), 4.07−3.98 (m, 4H, CH$_2$CH$_2$O and CO$_2$CH_2CH$_3$), 3.84 (t, J = 6.0 Hz, 1H, CH_2OH), 2.70−2.31 (m, 9H, 7H from NHCOCH_2CH_2CH=CHCH_2CH_2 and 2H from CHCH_2CO$_2$Et), 2.16 (td, J = 12.0 Hz, J = 2.5 Hz,
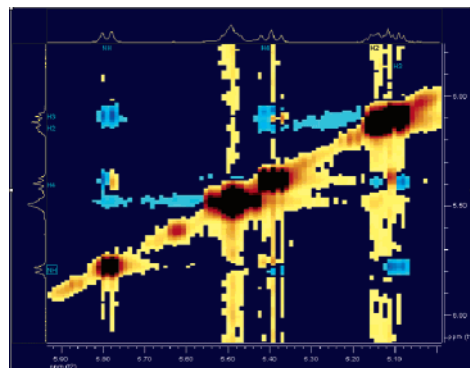
Figure 12. NOESY of compound **27** showing NOEs between H$_2$ and H$_4$ and NH and H$_4$.

1H, NHCOCH_2), 2.01 (quint, $J = 6.0$ Hz, 2H, CH_2CH$_2$O), 1.21 (t, $J = 7.0$ Hz, 3H, CO$_2$CH$_2$CH_3). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 173.5, 173.0, 169.8, 169.0, 157.3, 134.5, 131.4, 130.7, 130.6, 130.4, 130.1, 128.9 (2C), 128.1 (2C), 127.6, 112.8, 110.6, 76.3, 65.7, 60.9, 60.1, 54.7, 50.9, 38.3, 37.9, 34.4, 31.9, 29.5, 28.6, 14.1. LRMS: MS (ES+) $m/z = 565.3$ (M + 1). HPLC: 3.883 min.

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

References and Notes

(1) (a) Arya, P.; Roth, H.-J. *Curr. Opin. Chem. Biol.* **2005**, *9*, 229−231. (b) Reayi, A.; Arya, P. *Curr. Opin. Chem. Biol.* **2005**, *9*, 240−247.

(2) (a) Schreiber, S. L. *Nature Chem. Biol.* **2005**, *1*, 64−66. (b) Schreiber, S. L. *Chem. Eng. News* **2003**, *81*, 51−61. (c) Gura, T. *Nature* **2000**, *407*, 282−284. (d) Hinterding, K.; Alonso-Diaz, D.; Waldmann, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 688−749.

(3) (a) Burke, M. D.; Berger, E. M.; Schreiber, S. L. *Science* **2003**, *302*, 613−618. (b) Burke, M. D.; Berger, E. M.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 14095−14104.

(4) For a recent example of building structurally complex and skeletally different architectures on a solid phase, see: Mitchell, J. T.; Shaw, J. T. *Angew. Chem., Int. Ed.* **2006**, *45*, 1722−1726.

(5) (a) Austin, C. J.; Brady, L. S.; Insel, T. R.; Collins, F. S. *Science* **2004**, *306*, 1138−1139. (b) Strausberg, R. L.; Schreiber, S. L. *Science* **2003**, *300*, 294−295.

(6) (a) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46−58. (b) Arya, P.; Joseph, R.; Gan, Z.; Rakic, B. *Chem. Biol.* **2005**, *12*, 163−180. (c) Borman, S. *Chem. Eng. News* **2004**, *82*, 32−40.

(7) For a few examples of bioactive natural products as inhibitors of protein-protein interactions, see: Boger, D. L.; Desharnais, J.; Capps, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 4138−4176. For general review articles on protein−protein interactions, see: (a) Arkin, M. R. *Curr. Opin. Chem. Biol.* **2005**, *9*, 317−324. (b) Arkin, M. R.; Wells, J. A. *Nat. Rev. Drug Discovery* **2004**, *3*, 301−317. (c) Berg, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 2462−2481.

(8) For a few examples of bioactive natural products as chemical dissectors of complex protein−protein interactions, see (a) Jordan, A.; Hadfield, J. A.; Lawrence, N. J.; McGown, A. T. *Med. Res. Rev.* **1998**, *18*, 259−296. (b) Nicolaou, K. C.; Hepworth, D.; King, N. P.; Finlay, M. R. V. *Pure Appl. Chem.* **1999**, *71*, 989−997. (c) Ravelli, R. B. G.; Gigant, B.; Curmi, P. A.; Jourdain, I.; Lachkar, S.; Sobel, A.; Knossow, M. *Nature* **2004**, *428*, 198−202. (d) Usui, T.; Watanabe, H.; Nakayama, H.; Tada, Y.; Kanoh, N.; Kondoh, M.; Asao, T.; Takio, K.; Watanabe, H.; Nishikawa, K.; Kitahara, T.; Osada, H. *Chem. Biol.* **2004**, *11*, 799−806.

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

(10) For a review on the synthesis of tetrahydroquinolines, see: Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031−15070.

(11) (a) Seebach, D.; Beck, A. K.; Bierbaum, D. J. *Chem. Biodiversity* **2004**, *1*, 1111−1239. (b) Eusebio Juaristi, Ed. *Enantioselective Synthesis of β-Amino Acids*; VCH: New York, 1997.

(12) (a) Hoffman, R. V.; Maslouh, N.; Cervantes-Lee, F. *J. Org. Chem.* **2002**, *67*, 1045−1056. (b) Wee, A. G. H.; Tang, F. *Can. J. Chem.* **1998**, *76*, 1070−1081.

(13) Several bioactive natural products contain a 1,3-hydroxy carboxyl ester functional moiety.

(14) Li, G. G.; Angert, H. H.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1996**, *35*, 2813−2817.

(15) (a) Tallarico, J. A.; Depew, K. M.; Pelish, H. E.; Westwood, N. J.; Lindsley, C. W.; Shair, M. D.; Schreiber, S. L.; Foley, M. A. *J. Comb. Chem.* **2001**, *3*, 312−318. (b) Mazitschek, R. Chemical Biology Program, Broad Institute of Harvard University and MIT, Boston, MA.

(16) For a few examples on small molecule microarrays, see: (a) Uttamchandani, M.; Walsh, D. P.; Yao, S. Q.; Chang, Y.-T. *Curr. Opin. Chem. Biol.* **2005**, *9*, 4−13. (b) Seeman, D. B.; Park, S. B.; Koehler, A. N.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 2376−2379. (c) Koehler, A. N.; Shamji, A. F.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 8420−8421. (d) Bradner, J. E.; McPherson, O. M.; Mazitschek, R.; Barnes-Seeman, D.; Shen, J. P.; Dhaliwal, J.; Stevenson, K. E.; Duffner, J. L.; Park, S. B.; Neuberg, D. S.; Nghiem, P. T.; Schreiber, S. L.; Koehler, A. N. *Chem. Biol.* **2006**, *13*, 493−504.

CC060055I