

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

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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

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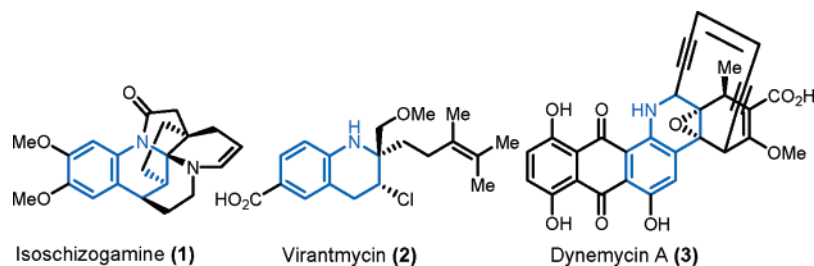
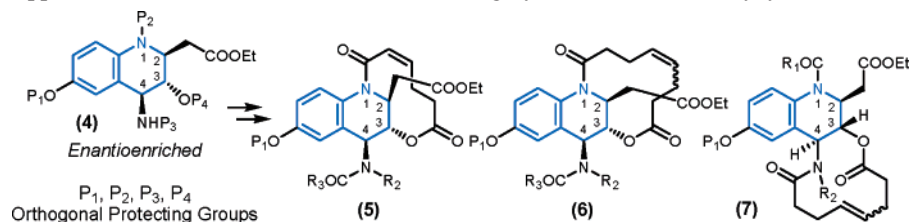
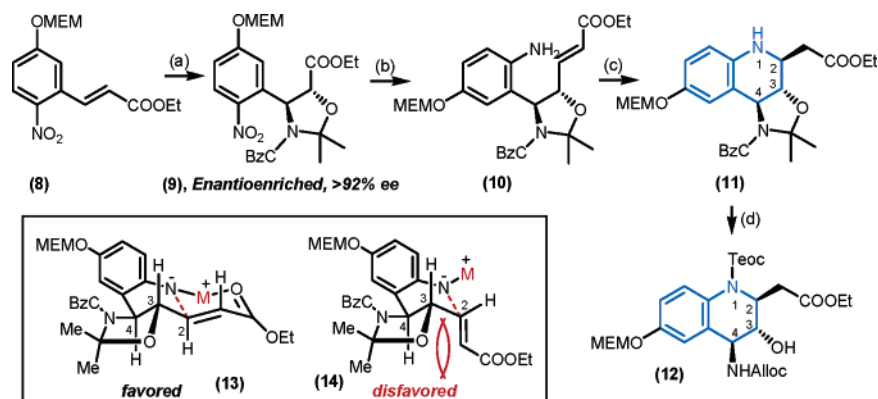


Figure 1. Few examples of bioactive alkaloids having a tetrahydroquinoline scaffold.

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) LiBH₄, (ii) SO₃ Py, (iii) Ph₃C=CHCOOEt, 65% for 2 steps, (iv) Zn/AcOH, 67%. ^cLDA, -78 °C to rt, 67%. ^d(i) TeocCl, pyridine, 77%, (ii) H₂, 10% Pd/C; SiO₂, 56%, (iii) AllocCl, DIPEA, 91%.

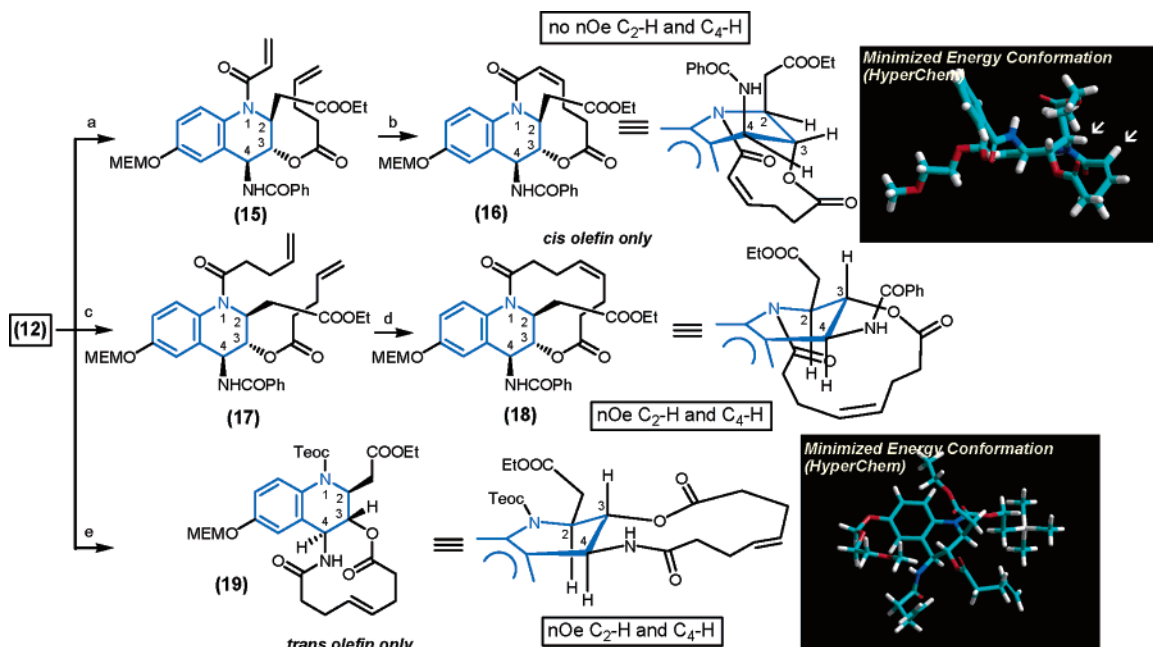
features and includes (i) the β - and δ -amino acid functionalities,¹¹ (ii) the 1,2-*trans*-amino alcohol moiety,¹² (iii) the 1,3-hydroxyl carboxylic ester,¹³ and (iv) a phenolic hydroxyl group that could be utilized as an anchoring site in solid-phase synthesis. With compound **4** used as the starting 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 C₃ and the *N*-acryloyl functional group at N₁. 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 C₃ 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 [R₂ and R₃, 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 development 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 C₂-H and C₄-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 (~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.

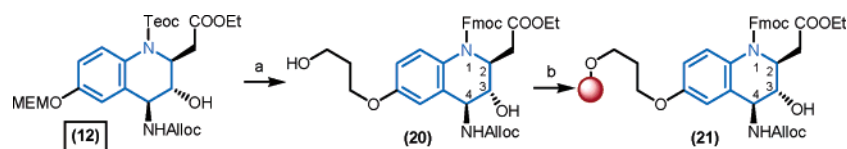
The model studies to test the feasibility of our modular approach to obtain different macrocyclic derivatives are shown in Scheme 3. Compound **15**, a precursor for the bridged ring-closing metathesis containing the *N*-acryloyl moiety was obtained from **12** in several steps. We were pleased to note 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 tetrahydroaminoquinoline 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.

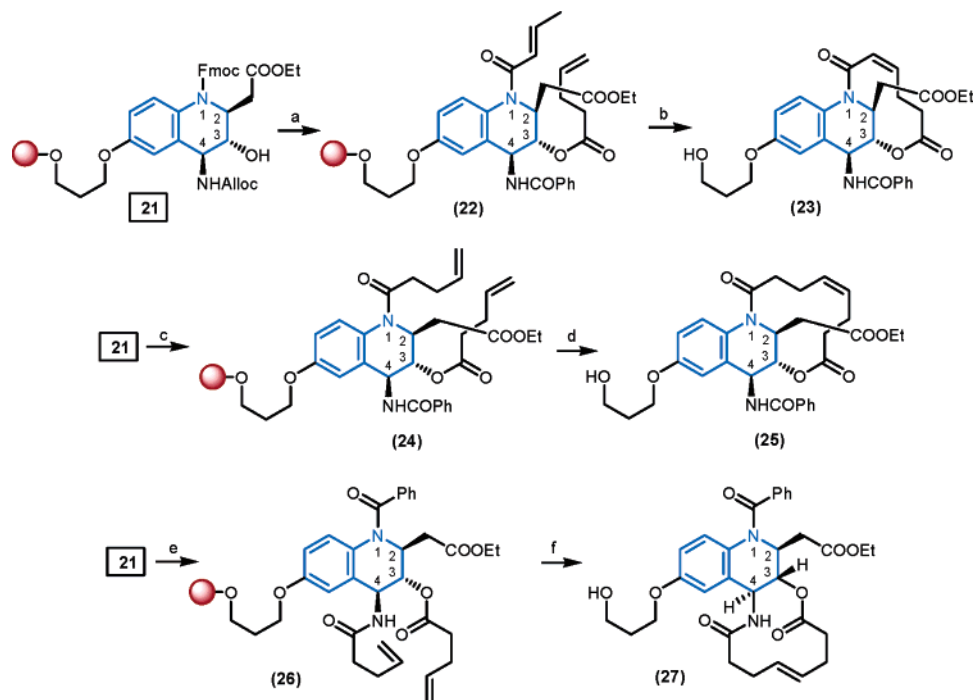
The next goal of the project was to develop a modular solid-phase synthesis to obtain polycyclic derivatives **23**, **25**, and **27** (Scheme 5). For the solid-phase synthesis, compound **20**, containing a free hydroxyl group and a three carbon spacer, was obtained from **12** (Scheme 4). This was then immobilized onto the alkylsilyl macrobeads (500–560 μ m, 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), (iv) *N*-Alloc removal (HPLC yield 71%), and (v) *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%.

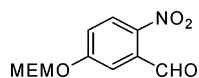
Conclusion

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.

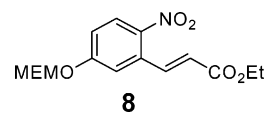
Experimental Section

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 F₂₅₄ glass plates (layer thickness 0.25 mm). Visualization was affected with a UV lamp (254 nm) or by staining with vanillin, KMnO₄, 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 N₂. 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). ¹H NMR (400 MHz) spectra were recorded at room temperature in CDCl₃ or C₆D₆ solutions and referenced to residual CHCl₃ (7.27 ppm) or C₆H₆ (7.16 ppm). Fully decoupled ¹³C NMR (100 MHz) spectra were recorded in CDCl₃ or C₆D₆ solutions. The center peaks of CDCl₃ (77.0 ppm) and C₆D₆ (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.

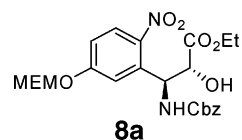


To a solution of commercially available 5-hydroxy-2-nitrobenzaldehyde (25.00 g, 146.6 mmol) in 500 mL of anhydrous CH₂Cl₂ was added the diisopropylethylamine (47 mL, 267.1 mmol) at –10 °C over a period of 10 min. During that time, the starting material dissolved completely. Then MEM chloride (25.00 g, 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 NaHCO₃ was slowly added (100 mL). The aqueous layer was extracted with CH₂Cl₂ (3 × 50 mL), and the organic layer was dried over MgSO₄. 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). ¹H NMR (CDCl₃, 400 MHz): δ 10.46 (s, 1H, CHO), 8.16 (d, *J* = 9.0 Hz, 1H, CHCNO₂), 7.48 (s, 1H, CHCCHO), 7.33 (d, *J* = 9.0 Hz, 1H, CHCCOMEM), 5.39 (s, 2H, OCH₂O), 3.83 (t, *J* = 4.3 Hz, 2H, OCH₂CH₂O), 3.55 (t, *J* = 4.3 Hz, 2H, OCH₂CH₂O), 3.36 (s, 3H, CH₃O). ¹³C NMR (CDCl₃, 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).

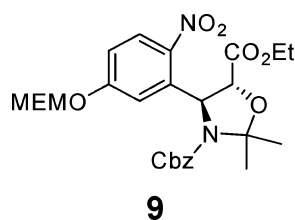


Triethyl phosphonate acetate (39.71 g, 194.4 mmol) was added to a suspension of sodium hydride (10.77 g, 269.2 mmol) in 760 mL of anhydrous THF at 0 °C over a period of 10 min. The reaction mixture was stirred vigorously for 50 min at 0 °C, before a solution of above compound (38.17 g, 149.6 mmol) in 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 NH₄Cl, and solid NH₄Cl in a large beaker. The aqueous layer was extracted with ethyl acetate (3 × 150 mL), and the organic layer was dried over MgSO₄. 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). ¹H NMR (CDCl₃, 400 MHz): δ 8.17 (d, *J* = 15.7 Hz, 1H, CH=CHCO₂Et), 8.09 (d, *J* = 9.0 Hz, 1H, CHCNO₂), 7.20 (s, 1H, CHCCHO), 7.14 (dd, *J* = 9.0 Hz, *J* = 1.8 Hz, 1H, CHCCOMEM), 6.30 (d, *J* = 15.7 Hz, 1H, CH=CHCO₂Et), 5.36 (s, 2H, OCH₂O), 4.28 (q, *J* = 7.0 Hz, 2H, CO₂CH₂CH₃), 3.83 (t, *J* = 4.5 Hz, 2H, OCH₂CH₂O), 3.55 (t, *J* = 4.5 Hz, 2H, OCH₂CH₂O), 3.36 (s, 3H, CH₃O), 1.34 (t, *J* = 7.0 Hz, 3H, CO₂CH₂CH₃). ¹³C NMR (CDCl₃, 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).

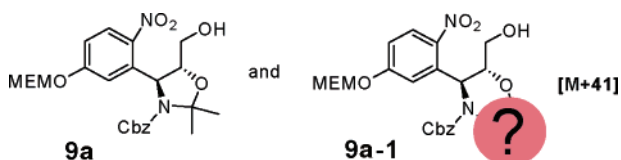


An aqueous solution of NaOH (3.87 g, 93.8 mmol) in 225 mL of water, *t*-butyl hypochlorite (10.76 mL, 93.8 mmol), and a solution of (DHQ)₂PHAL (1.26 g, 1.5 mmol) in 80 mL of *n*-propanol were added to a solution of benzyl carbamate (14.55 g, 95.3 mmol) in 120 mL of *n*-propanol at

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 MgSO₄. 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). ¹H NMR (CDCl₃, 400 MHz): δ 8.06 (d, *J* = 9.0 Hz, 1H, *CHCNO*₂), 7.32–7.20 (m, 5H, Ph), 7.19 (broad s, 1H, *NH*), 7.13 (d, *J* = 2.5 Hz, 1H, *CHCOMEM*), 7.04 (dd, *J* = 9.0 Hz, *J* = 2.5 Hz, 1H, *CHCHCNO*₂), 6.02 (broad d, *J* = 8.5 Hz, 1H, *CHNHCO*), 5.88 (broad d, *J* = 9.0 Hz, 1H, *CHOH*), 5.26 (s, 2H, *OCH*₂O), 5.03 (dd, *J* = 11.8 Hz, *J* = 2.0 Hz, 1H, *PhCH*₂OCO), 4.96 (d, *J* = 11.8 Hz, 1H, *PhCH*₂OCO), 4.60 (broad s, 1H, *OH*), 4.33–4.17 (m, 2H, *CO*₂*CH*₂*CH*₃), 3.77–3.72 (m, 2H, *OCH*₂*CH*₂O), 3.49–3.45 (m, 2H, *OCH*₂*CH*₂O), 3.28 (s, 3H, *CH*₃O), 1.23 (t, *J* = 7.3 Hz, 3H, *CO*₂*CH*₂*CH*₃). ¹³C NMR (CDCl₃, 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).

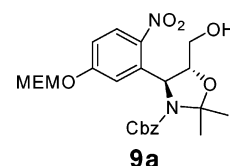


2-Methoxypropene (16.56 mL, 167.7 mmol) was added to a solution of **8a** (8.26 g, 16.8 mmol) in 400 mL of toluene, and the mixture was stirred for 15 min. Molecular sieves (4 Å, 400 mg) and pyridinium *p*-toluenesulfonate (215 mg, 0.84 mmol) were added to this reaction mixture. Then the mixture was 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).

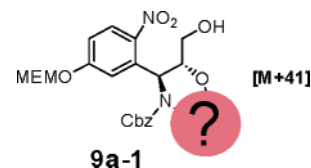


A 2 M lithium borohydride solution in THF (15.23 mL, 30.5 mmol) was added to a solution of the above mixture (5.06 g, 9.5 mmol) in 200 mL of anhydrous THF at room temperature, and the mixture was stirred for 24 h. The reaction mixture was quenched by reverse addition onto ice-cold saturated NH₄Cl solution. The aqueous layer was

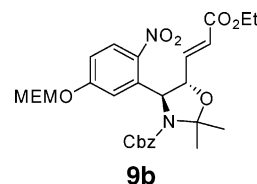
extracted with Et₂O (3 × 100 mL), and the organic layer was dried over MgSO₄. After filtration and concentration under vacuum, the crude product was chromatographed on neutralized silica gel with hexane/triethylamine, 9/1 (eluent = hexane/ethyl acetate, 1/1) to give two compounds (**9a**, 1.83 g and **9a-1**, 2.42 g).



9a. Pale yellow oil. *R_f*: 0.41 (3/7 hexane/ethyl acetate), 0.26 (1/1 hexane/ethyl acetate). ¹H NMR (CDCl₃, 400 MHz): δ 7.95 (d, *J* = 9.0 Hz, 1H, *CHCNO*₂), 7.40–7.33 (m, 6H, 5H_{Ph} and *CHCOMEM*), 7.11 (dd, *J* = 9.0 Hz, *J* = 2.0 Hz, 1H, *CHCHCNO*₂), 5.56 (broad s, 1H, *CHNCO*), 5.33 (broad s, 2H, *OCH*₂O), 5.23–5.17 (broad m, 2H, *PhCH*₂OCO), 4.10–3.99 (broad m, 2H, *CH*₂OH), 3.89–3.82 (m, 1H, *CHOCMe*₂), 3.83–3.79 (m, 2H, *OCH*₂*CH*₂O), 3.57–3.51 (m, 2H, *OCH*₂*CH*₂O), 3.35 (s, 3H, *CH*₃O), 2.20 (broad s, 1H, OH), 1.69 (broad s, 3H, *C(CH*₃)₂), 1.60 (s, 3H, *C(CH*₃)₂). ¹³C NMR (CDCl₃, 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. 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.



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 CH₂Cl₂ at 0 °C. The reaction mixture was warmed to room temperature and stirred for 4 h. Carboethoxymethylene triphenylphosphorane was then added (6.03 g, 16.5 mmol), and the reaction mixture was stirred overnight. The reaction mixture was diluted CH₂Cl₂ (100 mL) and then washed with 100 mL of a saturated solution of Na₂CO₃, followed by 200 mL of water. The organic layer was collected and then dried over MgSO₄. After filtration and concentration under vacuum, the crude product was chromatographed on neutralized silica gel with hexane/

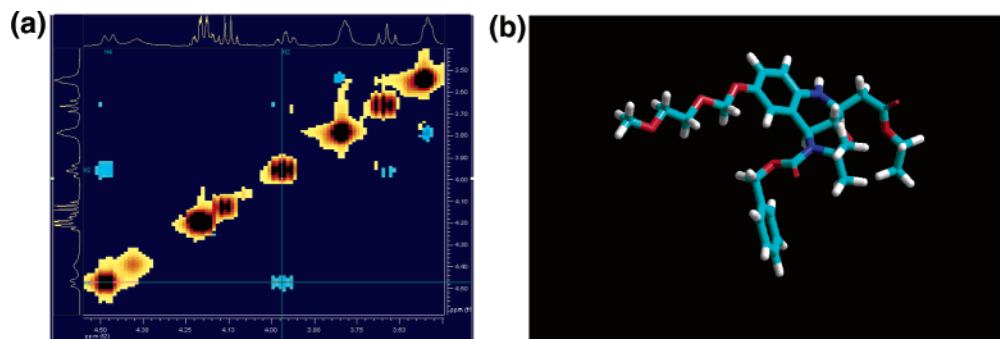
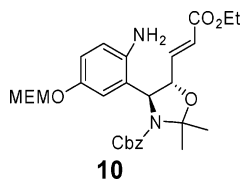


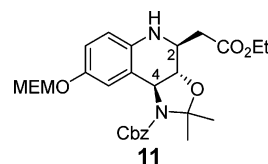
Figure 2. (a) NOE between H₂ and H₄ and (b) the minimized energy structure of compound **11**.

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), ¹H NMR (CDCl₃, 400 MHz): δ 7.96 (d, *J* = 8.3 Hz, 1H, CHCNO₂), 7.40–7.12 (m, 7H, 5H_{Ph} and CHCOMEM and CH=CHCO₂Et), 7.01 (d, *J* = 8.3 Hz, 1H, CHCHCNO₂), 6.14 (d, *J* = 15.8 Hz, 1H, CH=CHCO₂Et), 5.59 (broad d, *J* = 4.0 Hz, CHNCO), 5.24–5.11 (broad s, 2H, OCH₂O), 5.04 (broad d, *J* = 12.3 Hz, 1H, PhCH₂OCO), 4.73 (broad d, *J* = 12.3 Hz, 1H, PhCH₂OCO), 4.64 (t, *J* = 4.0 Hz, 1H, CHOCMe₂), 4.22 (q, *J* = 7.0 Hz, 2H, CO₂CH₂CH₃), 3.85–3.69 (m, 2H, OCH₂CH₂O), 3.56–3.45 (m, 2H, OCH₂CH₂O), 3.35 (s, 3H, CH₃O), 1.83 (s, 3H, C(CH₃)₂), 1.75 (s, 3H, C(CH₃)₂), 1.30 (t, *J* = 7.0 Hz, 3H, CO₂CH₂CH₃). ¹³C NMR (CDCl₃, 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).



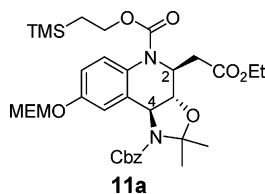
Zinc dust (2.25 g, 33.7 mmol) and glacial acetic acid (1.93 mL, 33.7 mmol) were added to a solution of **9b** (1.98 g, 3.5 mmol) in 30 mL of anhydrous ethanol at room temperature. The reaction mixture was stirred for 1 h and then filtered through celite. After concentration under vacuum to remove ethanol, a saturated solution of NaHCO₃ (30 mL) was added. The aqueous layer was extracted with Et₂O (3 × 50 mL), and the organic layer was dried over MgSO₄. 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). ¹H NMR (CDCl₃, 400 MHz): δ 7.40–7.13 (m, 5H, H_{Ph}), 6.92 (dd, *J* = 15.8 Hz, *J* = 4.5 Hz, 1H, CH=CHCO₂Et), 6.91 (broad s, 1H, CHCOMEM), 6.83 (dd, *J* = 8.5 Hz, *J* = 2.8 Hz, 1H, CHCHCNH₂), 6.55 (broad d, *J* = 8.5 Hz, 1H, CHCNH₂), 6.08 (d, *J* = 15.8 Hz, 1H, CH=CHCO₂Et), 5.08 (broad s, 2H, OCH₂O), 5.02 (broad d, *J* = 12.3 Hz, 1H, PhCH₂OCO), 4.85 (broad d, *J* = 12.3 Hz, 1H, PhCH₂OCO), 4.70 (broad

s, 2H, NH₂), 4.67 (d, *J* = 7.0 Hz, CHNCO), 4.15 (q, *J* = 7.0 Hz, 2H, CO₂CH₂CH₃), 3.77–3.72 (m, 2H, OCH₂CH₂O), 3.51–3.47 (m, 2H, OCH₂CH₂O), 3.49–3.45 (m, 1H, CHOCMe₂), 3.32 (s, 3H, CH₃O), 1.74 (broad s, 3H, C(CH₃)₂), 1.68 (broad s, 3H, C(CH₃)₂), 1.23 (t, *J* = 7.0 Hz, 3H, CO₂CH₂CH₃). ¹³C NMR (CDCl₃, 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 NH₄Cl. The aqueous layer was extracted with ethyl acetate (3 × 30 mL), and the organic layer was dried over MgSO₄. 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). ¹H NMR (CDCl₃, 400 MHz): δ 7.42–7.26 (m, 5H, Ph), 6.86 (broad s, 1H, MEMOC–CH=C), 6.78 (dd, *J* = 8.5 Hz, *J* = 2.3 Hz, 1H, CH–CH=C–N), 6.44 (d, *J* = 8.5 Hz, 1H, CH–CH=C–N), 5.29 (d, *J* = 12.3 Hz, 1H, PhCH₂OCO), 5.20 (d, *J* = 12.3 Hz, 1H, PhCH₂OCO), 5.06 (broad s, 2H, OMEM), 4.47 (d, *J* = 9.8 Hz, 1H, CH–NCO), 4.42 (broad s, 1H, NH), 4.16 (2q, *J* = 7.0 Hz, 2H, CO₂CH₂CH₃), 3.95 (td, *J* = 9.8 Hz, *J* = 2.5 Hz, 1H, CHCH₂CO₂Et), 3.79–3.74 (m, 2H, OMEM), 3.66 (t, *J* = 9.8 Hz, 1H, CHOCMe₂), 3.54–3.49 (m, 2H, OMEM), 3.34 (s, 3H, OMEM), 2.84 (dd, *J* = 16.0 Hz, *J* = 2.5 Hz, 1H, CHCH₂CO₂Et), 2.38 (dd, *J* = 16.0 Hz, *J* = 9.8 Hz, 1H, CHCH₂CO₂Et), 1.66 (broad s, 3H, CMe₂), 1.56 (s, 3H, CMe₂), 1.25 (t, *J* = 7.0 Hz, 3H, CO₂CH₂CH₃). ¹³C NMR (CDCl₃, 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).



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_2Cl_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_2Cl_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_2Cl_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). ^1H NMR (CDCl_3 , 400 MHz): δ 7.44–7.23 (m, 6H, $5H_{\text{Ph}}$ and $\text{CH}-\text{CH}=\text{C}-\text{N}$), 6.96 (dd, $J = 8.8$ Hz, $J = 2.5$ Hz, 1H, $\text{CH}-\text{CH}=\text{C}-\text{N}$), 6.82 (broad s, 1H, MEMOC- $\text{CH}=\text{C}$), 5.30–5.09 (m, 4H, 2H from OMEM and PhCH_2OCO), 4.56 (broad m, 1H, $\text{CHCH}_2\text{CO}_2\text{Et}$), 4.35–4.26 (m, 2H, $\text{TMSCH}_2\text{CH}_2\text{O}$), 4.29–4.19 (m, 1H, $\text{CH}-\text{NCO}$), 4.10–3.96 (m, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.84–3.76 (m, 2H, OMEM), 3.71 (t, $J = 9.5$ Hz, 1H, CHOCMe_2), 3.57–3.51 (m, 2H, OMEM), 3.37 (s, 3H, OMEM), 2.81–2.71 (m, 2H, $\text{CHCH}_2\text{CO}_2\text{Et}$), 1.73 (broad s, 3H, CMe_2), 1.57 (s, 3H, CMe_2), 1.16 (t, $J = 7.0$ Hz, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.06 (broad s, 2H, $\text{TMSCH}_2\text{CH}_2\text{O}$), 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

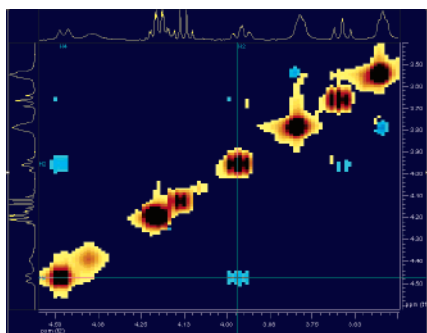
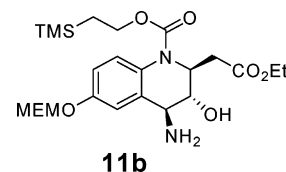
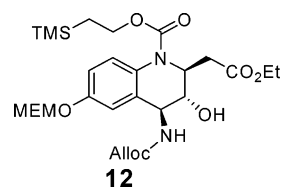


Figure 3. NOE between H_2 and H_4 for compound **11a**.

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

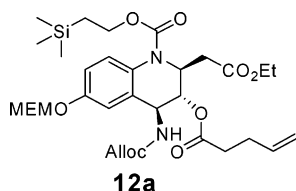


Palladium (10 wt %) on activated carbon (63 mg) was added to a solution of Teoc-protected amine (503 mg, 0.75 mmol) in 15 mL of anhydrous ethanol and stirred for 8.5 h under a hydrogen atmosphere. The reaction mixture was filtered through celite and concentrated under vacuum. The crude product was chromatographed on silica gel (eluent = CH_2Cl_2 /methanol 98/2) to give **11b** (210 mg, 56%). Colorless oil. R_f : 0.16 (98/2 CH_2Cl_2 /methanol). ^1H NMR (CDCl_3 , 400 MHz): δ 7.26 (broad d, $J = 8.5$ Hz, 1H, $\text{CH}-\text{CH}=\text{C}-\text{N}$), 7.05 (d, $J = 2.5$ Hz, 1H, MEMOC- $\text{CH}=\text{C}$), 6.89 (dd, $J = 8.5$ Hz, $J = 2.5$ Hz, 1H, $\text{CH}-\text{CH}=\text{C}-\text{N}$), 5.24–5.19 (m, 2H, OMEM), 4.46–4.44 (m, 1H, $\text{CHCH}_2\text{CO}_2\text{Et}$), 4.28–4.12 (m, 2H, $\text{TMSCH}_2\text{CH}_2\text{O}$), 4.05–3.95 (m, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.80–3.75 (m, 2H, OMEM), 3.65 (t, $J = 9.8$ Hz, 1H, CHOH), 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, CHNH_2), 2.74–2.64 (m, 1H, OH), 2.71 (dd, $J = 15.3$ Hz, $J = 4.5$ Hz, 1H, $\text{CHCH}_2\text{CO}_2\text{Et}$), 2.52 (dd, $J = 15.3$ Hz, $J = 8.5$ Hz, 1H, $\text{CHCH}_2\text{CO}_2\text{Et}$), 2.01 (broad s, 2H, NH_2), 1.14 (t, $J = 7.0$ Hz, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 0.99 (t, $J = 8.5$ Hz, 2H, $\text{TMSCH}_2\text{CH}_2\text{O}$), -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).



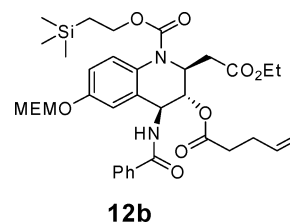
N,N-Diisopropylethylamine (135 μL , 0.77 mmol, one portion) and allylchloroformate (77 μL , 0.71 mmol, dropwise addition) were added to a solution of free amine **11b** (320 mg, 0.64 mmol) in 50 mL of anhydrous CH_2Cl_2 at -70 °C. The reaction mixture was slowly warmed to room temperature in 3 h, stirred for an additional 2.5 h, and quenched via the addition of 40 mL of a saturated solution of NH_4Cl . The aqueous layer was extracted with CH_2Cl_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_2Cl_2 /methanol 98/2) to give **12** (340 mg, 91%). Colorless oil. R_f : 0.19 (1/1 hexane/ethyl acetate). ^1H NMR (CDCl_3 , 400 MHz): δ 7.27 (broad d, $J = 8.8$ Hz, 1H, $\text{CH}-\text{CH}=\text{C}-\text{N}$), 6.94 (dd, $J = 8.8$ Hz, $J = 2.5$ Hz, 1H, $\text{CH}-\text{CH}=\text{C}-\text{N}$), 6.92 (broad s, 1H, MEMOC- $\text{CH}=\text{C}$), 6.00–5.87 (m, 1H, $\text{H}_2\text{C}=\text{CH}-\text{CH}_2\text{O}$), 5.36 (broad d, $J = 7.5$ Hz, 1H, NH), 5.33 (broad d, $J = 17.1$ Hz, 1H, $\text{H}_2\text{C}=\text{CH}-\text{CH}_2\text{O}$), 5.25–5.19 (m, 2H, OMEM), 4.70–4.62

(m, 1H, CH–NH), 4.62 (d, $J = 5.5$ Hz, 2H, H₂C=CH–CH₂O), 4.62–4.56 (m, 1H, CHCH₂CO₂Et), 4.32–4.16 (m, 2H, OCH₂CH₂TMS), 4.10–3.97 (m, 2H, CO₂CH₂CH₃), 3.93 (broad s, 1H, OH), 3.80 (dd, $J = 6.0$ Hz, $J = 4.5$ Hz, 2H, OMEM), 3.61–3.54 (m, 1H, CH–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, CHCH₂CO₂Et), 2.54 (dd, $J = 15.1$ Hz, $J = 8.3$ Hz, 1H, CHCH₂CO₂Et), 1.17 (t, $J = 7.0$ Hz, 3H, CO₂CH₂CH₃), 1.03 (t, $J = 8.5$ Hz, 2H, OCH₂CH₂TMS), 0.01 (s, 9H, TMS). ¹³C NMR (CDCl₃, 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).

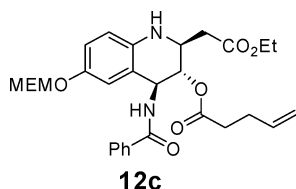


1,3-Diisopropylcarbodiimide (183 μ L, 1.17 mmol), 4-pentenoic acid (92.1 μ L, 0.88 mmol), and 4-(dimethylamino)pyridine (7.2 mg, 0.06 mmol) were added at once to a solution of alcohol **12** (340 mg, 0.58 mmol) in 5 mL of anhydrous CH₂Cl₂ at room temperature. After the mixture was stirred for 3 h 40 min, a saturated solution of Na₂CO₃ (10 mL) was added, and the aqueous layer was extracted with CH₂Cl₂ (3 \times 20 mL); the organic layer was dried over MgSO₄. 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). ¹H NMR (CDCl₃, 400 MHz): δ 7.34 (broad s, 1H, CH–CH=C–N), 7.00 (dd, $J = 8.8$ Hz, $J = 2.3$ Hz, 1H, CH–CH=C–N), 6.95 (s, 1H, MEMOC–CH=C), 5.95 (ddt, $J = 16.1$ Hz, $J = 10.8$ Hz, $J = 5.0$ Hz, 1H, H₂C=CH–CH₂O), 5.82 (ddt, $J = 16.6$ Hz, $J = 10.0$ Hz, $J = 6.0$ Hz, 1H, H₂C=CH–CH₂CH₂CO), 5.34 (broad d, $J = 16.1$ Hz, 1H_{trans}, H₂C=CH–CH₂O), 5.25 (broad d, $J = 10.8$ Hz, 1H_{cis}, H₂C=CH–CH₂O), 5.26 (s, 2H, OMEM), 5.14 (broad d, $J = 8.3$ Hz, 1H, NH), 5.07 (dd, $J = 16.6$ Hz, $J = 1.3$ Hz, 1H_{trans}, H₂C=CH–CH₂CH₂CO), 5.02 (dd, $J = 10.0$ Hz, $J = 1.3$ Hz, 1H_{cis}, H₂C=CH–CH₂CH₂CO), 4.98 (dd, $J = 8.3$ Hz, $J = 5.0$ Hz, 1H, CHOC–OCH₂), 4.90 (dt, $J = 5.0$ Hz, $J = 6.5$ Hz, 1H, CHCH₂CO₂Et), 4.83 (t, $J = 8.3$ Hz, 1H, CH–NH), 4.62 (d, $J = 5.0$ Hz, 2H, H₂C=CH–CH₂O), 4.33–4.17 (m, 2H, OCH₂CH₂TMS), 4.02 (q, $J = 7.3$ Hz, 2H, CO₂CH₂CH₃), 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, CHCH₂CO₂Et), 2.49–2.42 (m, 1H, CHCH₂CO₂Et), 2.46 (dt, $J = 6.0$ Hz, $J = 6.3$ Hz, 2H, H₂C=CH–CH₂CH₂CO), 2.39 (t, $J = 6.3$ Hz, 2H, H₂C=CH–CH₂CH₂CO), 1.18 (t, $J = 7.3$ Hz, 3H, CO₂CH₂CH₃), 1.04 (t, $J = 8.5$ Hz, 2H, OCH₂CH₂TMS), 0.03 (s, 9H, TMS). ¹³C NMR (CDCl₃, 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,

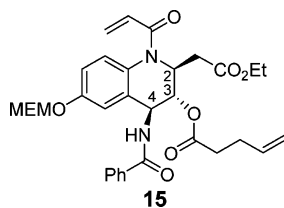
115.7, 115.6, 112.3, 93.6, 76.1, 71.5, 67.6, 66.0, 64.7, 60.8, 59.0, 54.1, 52.1, 37.6, 33.4, 28.5, 17.7, 14.0, –1.6 (3C). LRMS: MS (ES+) $m/z = 665.4$ (M + 1).



Redistilled morpholine (44 μ L, 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 CH₂Cl₂ at room temperature. The alloc removal was followed on TLC and was completed after 20 min of stirring. Then, triethylamine (106 μ L, 0.75 mmol) and benzoyl chloride (59 μ L, 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 Na₂CO₃ (5 mL) was added, and the aqueous layer was extracted with CH₂Cl₂ (3 \times 10 mL); the organic layer was dried over MgSO₄. 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). ¹H NMR (CDCl₃, 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–CH=C–N), 6.99 (dd, $J = 8.8$ Hz, $J = 2.5$ Hz, 1H, CH–CH=C–N), 6.89 (d, $J = 2.0$ Hz, 1H, MEMOC–CH=C), 6.78 (broad d, $J = 8.3$ Hz, 1H, NH), 5.68 (ddt, $J = 16.8$ Hz, $J = 10.3$ Hz, $J = 6.3$ Hz, 1H, CH₂=CH–CH₂CH₂CO), 5.31 (t, $J = 8.5$ Hz, 1H, CH–NH), 5.20–5.15 (m, 2H, OMEM), 5.13 (dd, $J = 8.8$ Hz, $J = 5.0$ Hz, 1H, CHOCO), 4.98–4.91 (m, 1H, CHCH₂CO₂Et), 4.94 (dd, $J = 17.1$ Hz, $J = 1.3$ Hz, 1H_{trans}, H₂C=CH–CH₂CH₂CO), 4.85 (d, $J = 10.3$ Hz, 1H_{cis}, H₂C=CH–CH₂CH₂CO), 4.33–4.18 (m, 2H, OCH₂CH₂TMS), 4.04–3.95 (m, 2H, CO₂CH₂CH₃), 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, CHCH₂CO₂Et), 2.51 (dd, $J = 14.6$ Hz, $J = 6.5$ Hz, 1H, CHCH₂CO₂Et), 2.41 (t, $J = 7.0$ Hz, 2H, H₂C=CH–CH₂CH₂CO), 2.28 (dt, $J = 6.8$ Hz, $J = 7.0$ Hz, 2H, H₂C=CH–CH₂CH₂CO), 1.16 (t, $J = 7.0$ Hz, 3H, CO₂CH₂CH₃), 1.04 (t, $J = 8.8$ Hz, 2H, OCH₂CH₂TMS), 0.02 (s, 9H, TMS). ¹³C NMR (CDCl₃, 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 μ L, 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 Et₂O (3 \times 10 mL), and the organic

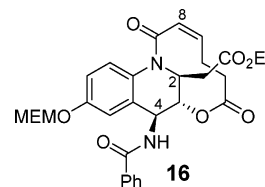


layer was dried over MgSO_4 . After filtration and concentration under vacuum, the crude product was chromatographed using the Biotage chromatograph system (A = hexane, B = ethyl acetate, CV = 12 mL, vol fract = 12 mL, flow = 6 mL/min, EQ[5CV] 10%B, 1CV[1] 105%B, 10CV[2] 10%B to 50%B, 10CV[3] 50%B) to give **12c** (74 mg, 87%). White solid. R_f : 0.29 (1/1 hexane/ethyl acetate). ^1H 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, $\text{CH}=\text{CH}=\text{C}-\text{NH}$ and $\text{MEMOC}-\text{CH}=\text{C}$), 6.53 (broad d, $J = 9.5$ Hz, 1H, NH), 6.44 (dd, $J = 9.5$ Hz, $J = 7.0$ Hz, 1H, $\text{CH}=\text{CH}=\text{C}-\text{NH}$), 5.68 (ddt, $J = 16.8$ Hz, $J = 10.3$ Hz, $J = 6.3$ Hz, 1H, $\text{CH}_2=\text{CH}-\text{CH}_2\text{CH}_2\text{CO}$), 5.64 (t, $J = 9.5$ Hz, 1H, $\text{CH}-\text{NH}$), 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} , $\text{H}_2\text{C}=\text{CH}-\text{CH}_2\text{CH}_2\text{CO}$), 4.86 (dd, $J = 10.3$ Hz, $J = 1.3$ Hz, 1H_{cis} , $\text{H}_2\text{C}=\text{CH}-\text{CH}_2\text{CH}_2\text{CO}$), 4.62 (broad s, 1H, NH), 4.19 (q, $J = 7.0$ Hz, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.90 (td, $J = 9.8$ Hz, $J = 2.5$ Hz, 1H, $\text{CH}-\text{CH}_2\text{CO}_2\text{Et}$), 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, $\text{CHCH}_2\text{CO}_2\text{Et}$), 2.43 (dd, $J = 16.3$ Hz, $J = 9.8$ Hz, 1H, $\text{CHCH}_2\text{CO}_2\text{Et}$), 2.41 (t, $J = 7.0$ Hz, 2H, $\text{H}_2\text{C}=\text{CH}-\text{CH}_2\text{CH}_2\text{CO}$), 2.27 (dt, $J = 6.5$ Hz, $J = 7.0$ Hz, 2H, $\text{H}_2\text{C}=\text{CH}-\text{CH}_2\text{CH}_2\text{CO}$), 1.29 (t, $J = 7.0$ Hz, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$). ^{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).



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_2Cl_2 . After the mixture was stirred for 20 min at room temperature, a saturated solution of Na_2CO_3 (5 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 \times 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). ^1H 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, $\text{CH}=\text{CH}=\text{C}-\text{N}$ and $\text{CH}=\text{CH}=\text{C}-\text{N}$), 6.94 (d, $J = 1.0$ Hz, 1H, $\text{MEMOC}-\text{CH}=\text{C}$), 6.81 (broad d, $J = 8.0$ Hz, 1H, NH), 6.49 (dd, $J = 16.8$ Hz, $J = 3.0$ Hz, 1H_{trans} , $\text{H}_2\text{C}=\text{CHCO}$), 6.44 (d, $J = 10.0$ Hz, 1H_{cis} , $\text{H}_2\text{C}=\text{CHCO}$), 5.73 (dd, $J = 16.6$ Hz, $J = 10.0$ Hz, 1H, $\text{H}_2\text{C}=\text{CHCO}$), 5.69 (ddt, $J = 16.8$ Hz, $J = 10.3$ Hz, $J = 6.3$ Hz, 1H, $\text{CH}_2=\text{CH}-\text{CH}_2\text{CH}_2\text{CO}$), 5.28 (dd, $J = 9.8$ Hz, $J = 8.0$ Hz, 1H, $\text{CH}-\text{NH}$), 5.25–5.19 (m, 2H, OMEM), 5.22–5.17 (m, 1H, $\text{CHCH}_2\text{CO}_2\text{Et}$), 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} , $\text{H}_2\text{C}=\text{CH}-\text{CH}_2\text{CH}_2\text{CO}$), 4.85 (dd, $J = 10.3$ Hz, $J = 1.3$ Hz, 1H_{cis} , $\text{H}_2\text{C}=\text{CH}-\text{CH}_2\text{CH}_2\text{CO}$), 4.01 (2q, $J = 7.0$ Hz, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 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, $\text{CHCH}_2\text{CO}_2\text{Et}$), 2.55 (dd, $J = 14.6$ Hz, $J = 7.3$ Hz, 1H, $\text{CHCH}_2\text{CO}_2\text{Et}$), 2.47 (td, $J = 7.0$ Hz, $J = 1.5$ Hz, 2H, $\text{H}_2\text{C}=\text{CH}-\text{CH}_2\text{CH}_2\text{CO}$), 2.32 (dt, $J = 6.3$ Hz, $J = 7.0$ Hz, 2H, $\text{H}_2\text{C}=\text{CH}-\text{CH}_2\text{CH}_2\text{CO}$), 1.18 (t, $J = 7.0$ Hz, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$). ^{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).



Second-generation Grubbs catalyst (2 mg, 0.002 mmol) was

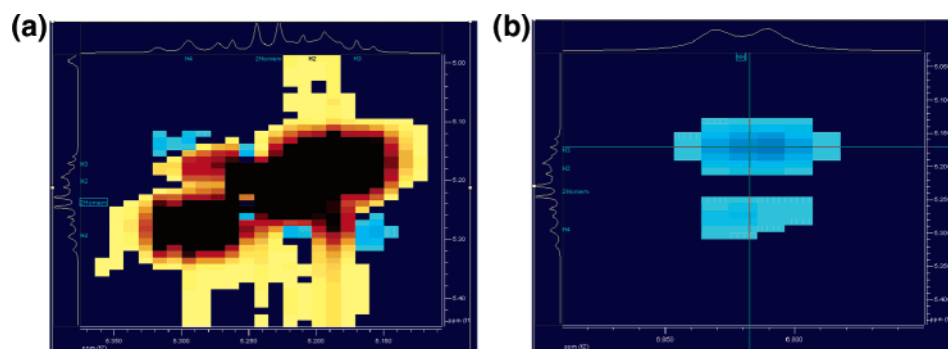


Figure 4. (a) NOEs between H_2 and H_4 and (b) NH and H_3 for compound **15**.

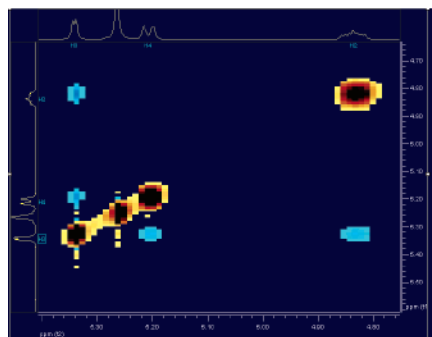


Figure 5. Compound **16** has no NOE between H₂ and H₄.

added to a solution of compound **15** (13 mg, 0.022 mmol) in 13 mL of anhydrous CH₂Cl₂. 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). ¹H NMR (C₆D₆/CDCl₃, 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–CH₂CO₂Et), 3.91–3.76 (m, 2H, CO₂CH₂CH₃), 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, CH₂CH₂CO₂), 2.32 (dd, *J* = 16.1 Hz, *J* = 10.0 Hz, 1H, CHCH₂CO₂Et), 2.10 (broad ddd, *J* = 13.0 Hz, *J* = 12.6 Hz, *J* = 5.5 Hz, 1H, CH₂CH₂CO₂), 1.94 (dd, *J* = 16.1 Hz, *J* = 4.5 Hz, 1H, CHCH₂CO₂Et), 1.88 (td, *J* = 13.0 Hz, *J* = 5.0 Hz, 1H, CH₂CH₂CO₂), 1.74 (tdd, *J* = 12.6 Hz, *J* = 5.5 Hz, *J* = 4.5 Hz, 1H, CH₂CH₂CO₂), 0.91 (t, *J* = 7.0 Hz, 3H, CO₂CH₂CH₃). ¹³C NMR (CDCl₃, 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.

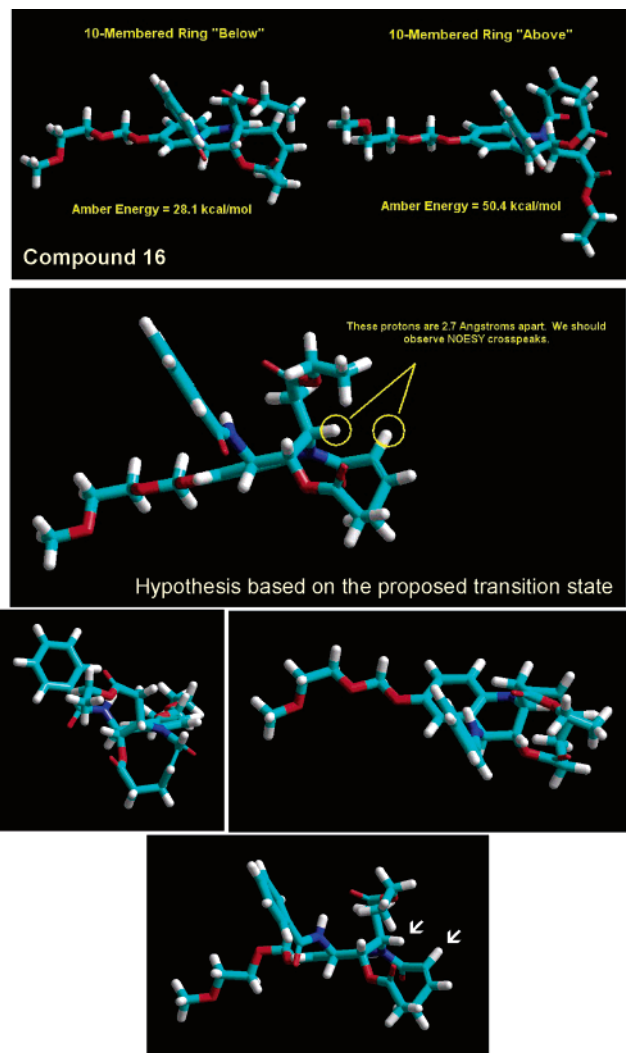
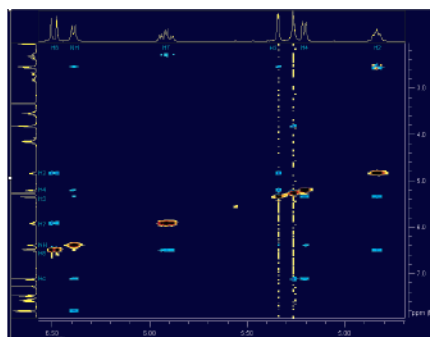


Figure 6. Compound **16**.

There is a strong NOE between H₂ and H₈ which confirmed the orientation of the 10-membered ring (Figure 7). As predicted, there was no NOE observed between H₂ and H₄. Triethylamine (6 μL, 0.044 mmol) and 4-pentenyl 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 CH₂Cl₂. After the mixture was stirred for 11.5 h at room temperature, a saturated solution of Na₂CO₃ (5 mL) was added; the aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL), and the organic layer was dried over MgSO₄. After filtration and concentration under vacuum, the crude product was chromatographed using the Biotage

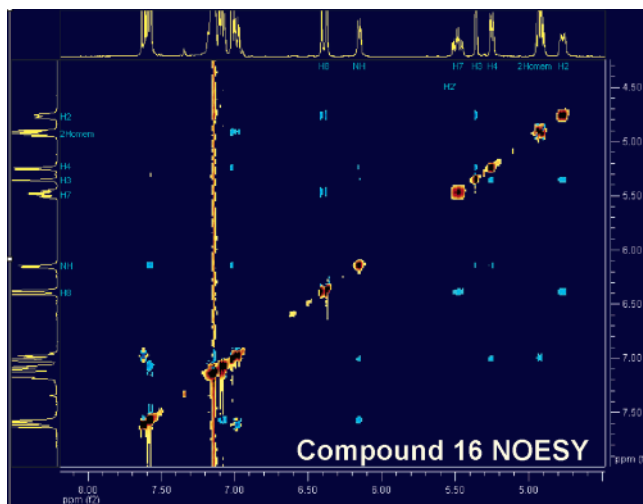
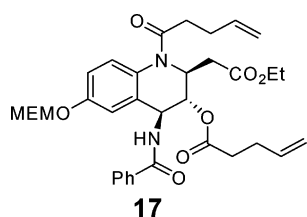
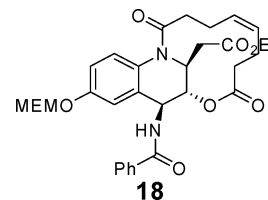


Figure 7. NOESY of compound 16.

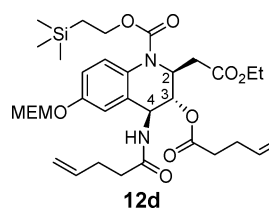


chromatograph system (A = hexane, B = ethyl acetate, CV = 12 mL, vol fract = 6 mL, flow = 7 mL/min, EQ[5CV] 10%B, 1CV[1] 10%B, 10CV[2] 10%B to 50%B, 10CV[3] 50%B) to give **17** (7.0 mg, 76%). Colorless oil. R_f : 0.21 (1/1 hexane/ethyl acetate). ^1H NMR (CDCl_3 , 400 MHz): δ 7.85 (d, $J = 7.5$ Hz, 2H, 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–CH=C–N), 7.04 (dd, $J = 8.5$ Hz, $J = 2.5$ Hz, 1H, CH–CH=C–N), 6.93 (d, $J = 1.5$ Hz, 1H, MEMOC–CH=C), 6.78 (broad d, $J = 8.0$ Hz, 1H, NH), 5.85–5.75 (m, 1H, CHCH₂CO₂Et), 5.85 (ddt, $J = 15.1$ Hz, $J = 10.0$ Hz, $J = 6.5$ Hz, 1H, CH₂=CH–CH₂CH₂CON), 5.70 (ddt, $J = 17.1$ Hz, $J = 10.0$ Hz, $J = 6.0$ Hz, 1H, CH₂=CH–CH₂CH₂COO), 5.30–5.23 (m, 1H, CH–NH), 5.27–5.20 (m, 2H, OMEM), 5.08 (dd, $J = 9.0$ Hz, $J = 5.5$ Hz, 1H, CHOCO), 5.04 (d, $J = 15.1$ Hz, 1H_{trans}, H₂C=CH–CH₂CH₂CON), 5.02 (d, $J = 10.0$ Hz, 1H_{cis}, H₂C=CH–CH₂CH₂CON), 4.97 (dd, $J = 17.1$ Hz, $J = 1.5$ Hz, 1H_{trans}, H₂C=CH–CH₂CH₂COO), 4.85 (broad d, $J = 10.0$ Hz, 1H_{cis}, H₂C=CH–CH₂CH₂COO), 4.02 (q, $J = 7.0$ Hz, 2H, CO₂CH₂CH₃), 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, CHCH₂CO₂Et), 2.62–2.28 (m, 8H, H₂C=CH–CH₂CH₂COO and H₂C=CH–CH₂CH₂CON), 1.19 (t, $J = 7.0$ Hz, 3H, CO₂CH₂CH₃). ^{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 CH₂Cl₂. 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-



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). ^1H NMR (CDCl_3 , 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–CH₂CO₂Et), 3.91–3.76 (m, 2H, CO₂CH₂CH₃), 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, CH₂CH₂CO₂), 2.32 (dd, $J = 16.1$ Hz, $J = 10.0$ Hz, 1H, CHCH₂CO₂Et), 2.10 (broad ddd, $J = 13.0$ Hz, $J = 12.6$ Hz, $J = 5.5$ Hz, 1H, CH₂CH₂CO₂), 1.94 (dd, $J = 16.1$ Hz, $J = 4.5$ Hz, 1H, CHCH₂CO₂Et), 1.88 (td, $J = 13.0$ Hz, $J = 5.0$ Hz, 1H, CH₂CH₂CO₂), 1.74 (tdd, $J = 12.6$ Hz, $J = 5.5$ Hz, $J = 4.5$ Hz, 1H, CH₂CH₂CO₂), 0.91 (t, $J = 7.0$ Hz, 3H, CO₂CH₂CH₃). ^{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).



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 CH₂Cl₂ 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 Na₂CO₃ (5 mL) was added; the aqueous layer was extracted with CH₂Cl₂ (3 \times 10 mL), and the organic layer was dried over MgSO₄. After filtration and concentration under vacuum, the crude product was chromatographed using the Biotage chromatograph system (A = hexane, B = ethyl acetate, CV

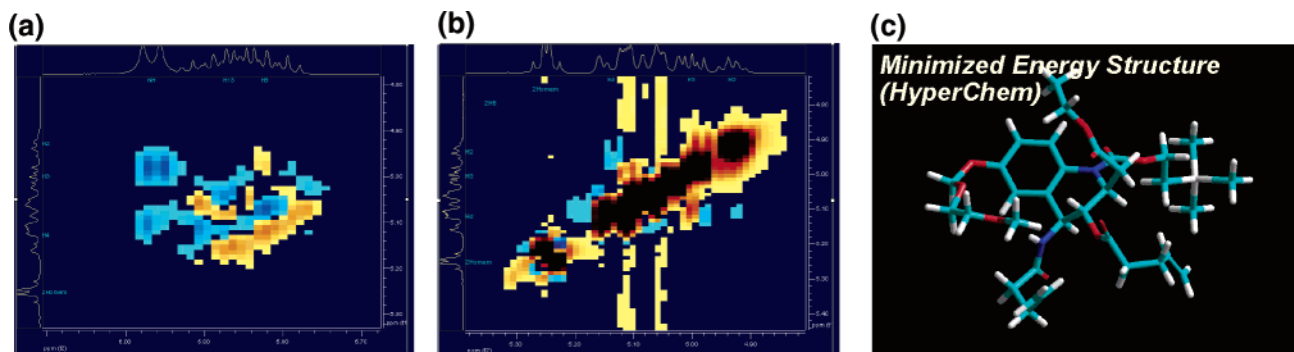
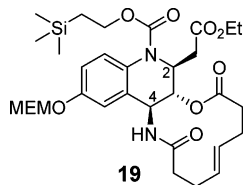


Figure 8. NOEs between (a) NH and H3 and (b) H2 and H4 and (c) the minimized energy structure (HyperChem) of compound **12d**.

= 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). $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 7.33 (broad d, $J = 8.8$ Hz, 1H, $\text{CH}=\text{CH}=\text{C}-\text{N}$), 6.99 (dd, $J = 8.8$ Hz, $J = 2.5$ Hz, 1H, $\text{CH}=\text{CH}=\text{C}-\text{N}$), 6.86 (d, $J = 2.5$ Hz, 1H, MEMOC- $\text{CH}=\text{C}$), 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, $\text{H}_2\text{C}=\text{CHCH}_2\text{CH}_2\text{CONH}$), 5.83 (ddt, $J = 16.6$ Hz, $J = 10.3$ Hz, $J = 6.0$ Hz, 1H, $\text{H}_2\text{C}=\text{CHCH}_2\text{CH}_2\text{COO}$), 5.27–5.21 (m, 2H, OMEM), 5.13 (dd, $J = 17.1$ Hz, $J = 1.5$ Hz, 1H_{trans}, $\text{H}_2\text{C}=\text{CHCH}_2\text{CH}_2\text{CONH}$), 5.07 (dd, $J = 17.1$ Hz, $J = 1.5$ Hz, 1H_{trans}, $\text{H}_2\text{C}=\text{CHCH}_2\text{CH}_2\text{COO}$), 5.06 (dd, $J = 10.3$ Hz, $J = 1.5$ Hz, 1H_{cis}, $\text{H}_2\text{C}=\text{CHCH}_2\text{CH}_2\text{CONH}$), 5.03 (dd, $J = 10.3$ Hz, $J = 1.5$ Hz, 1H_{cis}, $\text{H}_2\text{C}=\text{CHCH}_2\text{CH}_2\text{COO}$), 5.11 (dd, $J = 8.8$ Hz, $J = 8.3$ Hz, 1H, $\text{CH}-\text{NH}$), 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, $\text{CHCH}_2\text{CO}_2\text{Et}$), 4.32–4.17 (m, 2H, $\text{OCH}_2\text{CH}_2\text{TMS}$), 4.03 (2q, $J = 7.3$ Hz, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 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, $\text{CHCH}_2\text{CO}_2\text{Et}$), 2.49 (dd, $J = 14.3$ Hz, $J = 6.0$ Hz, 1H, $\text{CHCH}_2\text{CO}_2\text{Et}$), 2.49–2.42 (m, 4H, $\text{H}_2\text{C}=\text{CHCH}_2\text{CH}_2\text{COO}$ and $\text{H}_2\text{C}=\text{CHCH}_2\text{CH}_2\text{CONH}$), 2.42–2.35 (m, 4H, $\text{H}_2\text{C}=\text{CHCH}_2\text{CH}_2\text{COO}$ and $\text{H}_2\text{C}=\text{CHCH}_2\text{CH}_2\text{CONH}$), 1.19 (t, $J = 7.3$ Hz, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.04 (t, $J = 8.5$ Hz, 2H, $\text{OCH}_2\text{CH}_2\text{TMS}$), 0.03 (s, 9H, TMS). $^{13}\text{C NMR}$ (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+) $m/z = 663.6$ ($M + 1$).



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_2Cl_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

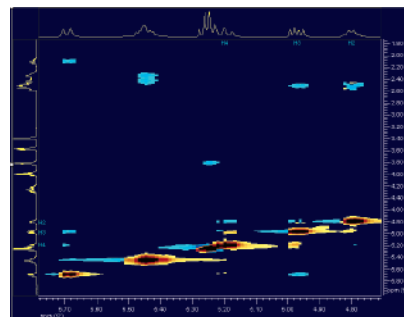
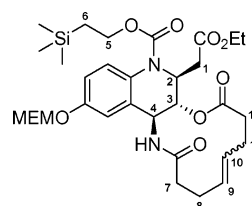


Figure 9. NOE between H2 and H4 for compound **19**.

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). $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 7.29 (broad d, $J = 8.8$ Hz, 1H, $\text{CH}=\text{CH}=\text{C}-\text{N}$), 6.99 (dd, $J = 8.8$ Hz, $J = 2.5$ Hz, 1H, $\text{CH}=\text{CH}=\text{C}-\text{N}$), 6.85 (d, $J = 2.5$ Hz, 1H, MEMOC- $\text{CH}=\text{C}$), 5.68 (broad d, $J = 9.5$ Hz, 1H, NH), 5.51–5.36 (m, $J = 15.3$ Hz can be read, 2H, $\text{CH}_2\text{CH}=\text{CHCH}_2$), 5.27–5.21 (m, 2H, OMEM), 5.19 (dd, $J = 10.8$ Hz, $J = 9.5$ Hz, 1H, $\text{CH}-\text{NH}$), 4.96 (dd, $J = 10.8$ Hz, $J = 5.8$ Hz, 1H, CHOCO), 4.79 (broad q, $J = 6.0$ Hz, 1H, $\text{CHCH}_2\text{CO}_2\text{Et}$), 4.32–4.16 (m, 2H, $\text{OCH}_2\text{CH}_2\text{TMS}$), 3.99 (q, $J = 7.0$ Hz, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 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 $\text{NHCOCH}_2\text{CH}_2\text{CH}=\text{CHCH}_2\text{CH}_2$ and 2H from $\text{CHCH}_2\text{CO}_2\text{Et}$), 2.10 (td, $J = 12.8$ Hz, $J = 3.0$ Hz, 1H, NHCOCH_2), 1.16 (t, $J = 7.0$ Hz, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.04 (t, $J = 8.8$ Hz, 2H, $\text{OCH}_2\text{CH}_2\text{TMS}$), 0.03 (s, 9H, TMS). $^{13}\text{C NMR}$ (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.



It is difficult to make this determination from the NMR because the olefinic protons have almost identical chemical

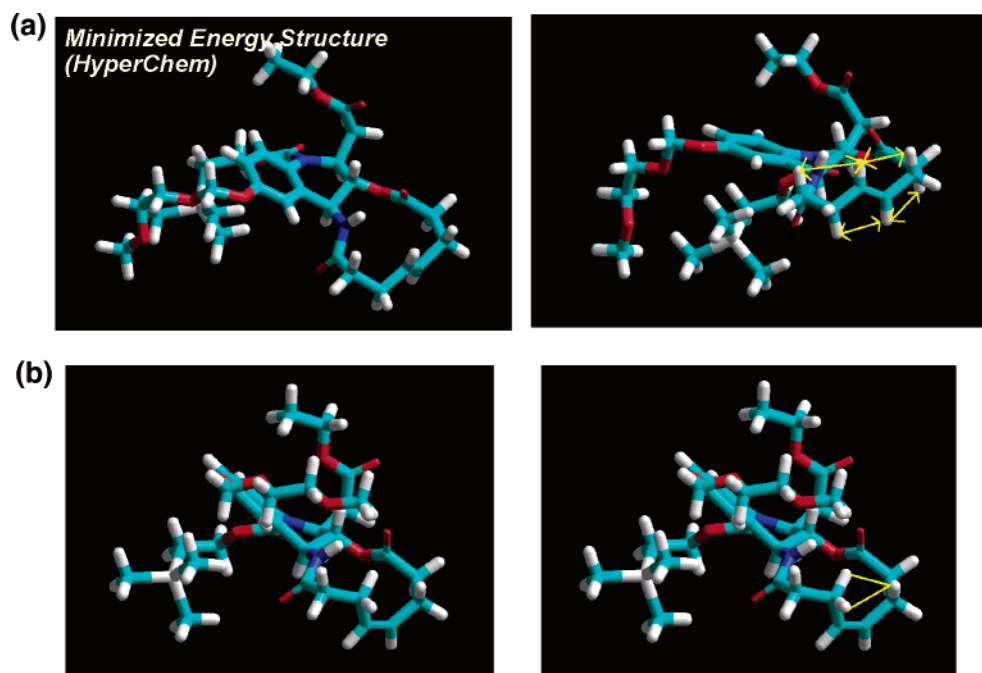
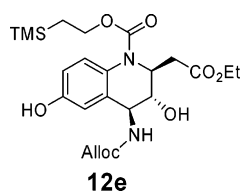


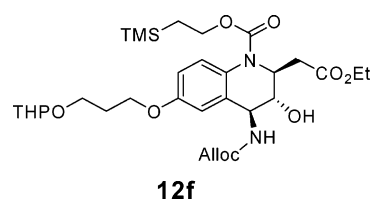
Figure 10. (a) Lowest-energy conformation of 800 minimized structures with a trans olefinic moiety and (b) the lowest-energy conformation of 800 minimized structures with a cis olefinic moiety for compound **19**.

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



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 NH₄Cl (20 mL) was added. The aqueous layer was extracted with Et₂O (3 × 40 mL), and the organic layer was dried over MgSO₄. 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). ¹H NMR (CDCl₃, 400 MHz): δ 7.41–7.29 (broad s, 1H, PhOH), 7.15 (broad d, *J* = 8.0 Hz, 1H, CH–CH=C–N), 6.74–6.56 (broad m, 2H, CH–CH=C–N and MEMOC–CH=C), 5.95–5.73 (m, 2H, H₂C=CH–CH₂O and NH), 5.27 (broad d, *J* = 17.3 Hz, 1H, H₂C=CH–CH₂O), 5.16 (broad d, *J* = 10.0 Hz, 1H, H₂C=CH–CH₂O), 4.65–4.50 (broad m, 2H, CH–NH and CHCH₂CO₂Et), 4.54 (broad d, *J* = 5.3 Hz, 2H, H₂C=CH–CH₂O), 4.29 (broad

s, 1H, OH), 4.30–4.15 (broad m, 2H, OCH₂CH₂TMS), 4.07–3.94 (m, 2H, CO₂CH₂CH₃), 3.60–3.47 (m, 1H, CH–OH), 2.67 (broad dd, *J* = 14.6 Hz, *J* = 5.0 Hz, 1H, CHCH₂–CO₂Et), 2.56 (broad dd, *J* = 14.6 Hz, *J* = 6.5 Hz, 1H, CHCH₂CO₂Et), 1.16 (t, *J* = 7.0 Hz, 3H, CO₂CH₂CH₃), 1.02 (broad t, *J* = 8.0 Hz, 2H, OCH₂CH₂TMS), 0.00 (s, 9H, TMS). ¹³C NMR (CDCl₃, 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).



3-(Tetrahydro-2H-pyran-2-yloxy)propyl 4-methylbenzenesulfonate (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 Et₂O (3 × 30 mL) and CH₂Cl₂ (1 × 30 mL). The organic layer was dried over MgSO₄, 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). ¹H NMR (CDCl₃, 400 MHz): δ 7.26 (broad d, *J* =

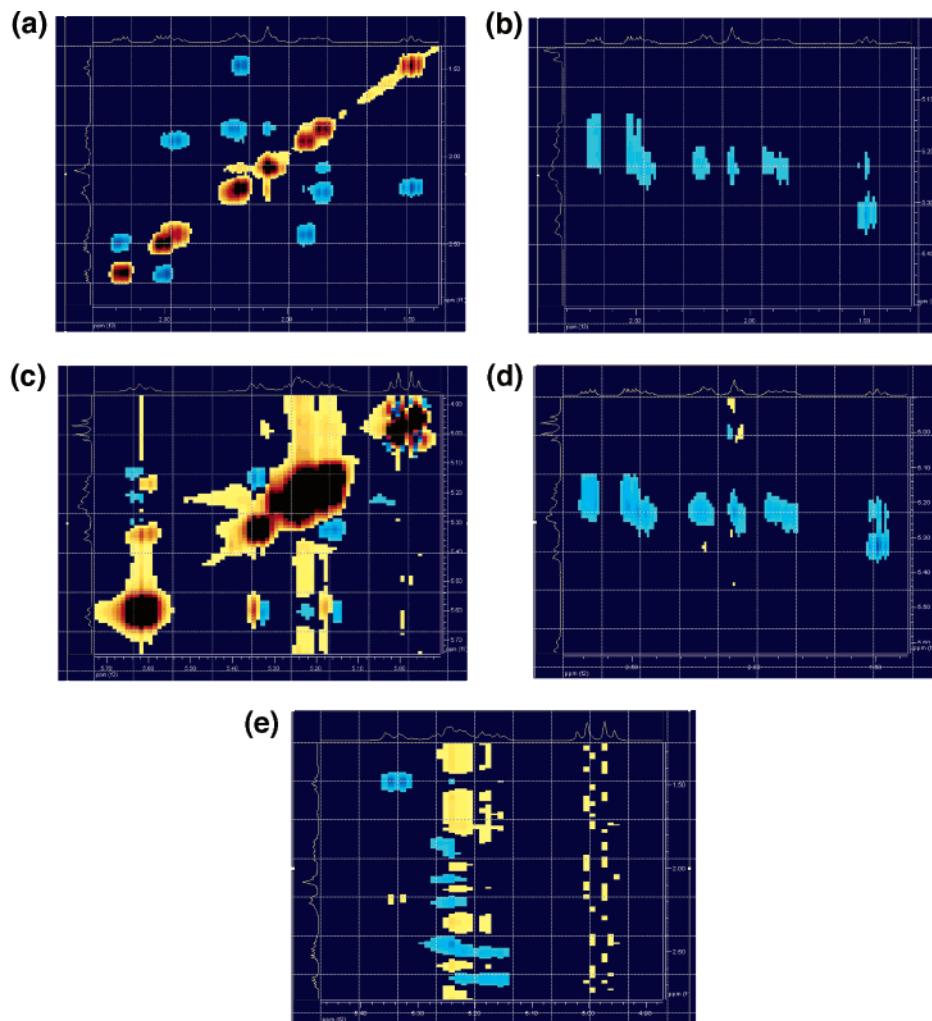
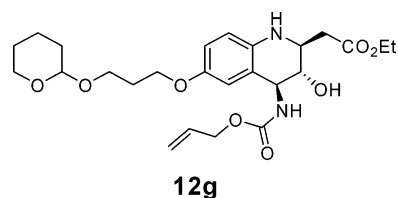


Figure 11. NOEs between (a) H₁ and H₈, (b) H₁ and H₃/H₇ and NH, (c) NH and H₃/H₄ and H₄ and H₂, (d) H₇ and H₉/H₁₀ and H₈ and H₉/H₁₀, and (e) H₉/H₁₀ and H₁₁ for the NOESY of compound **19**.

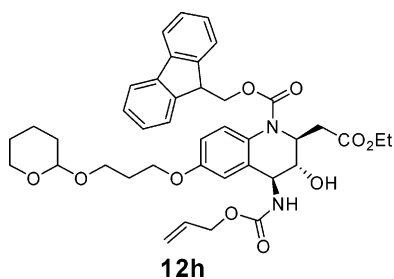
8.8 Hz, 1H, CH=CH=C-N), 6.79 (s, 1H, MEMOC-CH=C), 6.77 (dd, $J = 8.8$ Hz, $J = 2.8$ Hz, 1H, CH=CH=C-N), 6.02–5.85 (m, 1H, H₂C=CH-CH₂O), 5.34 (d, $J = 17.1$ Hz, 1H_{trans}, H₂C=CH-CH₂O), 5.32–5.24 (m, 1H, NH), 5.23 (d, $J = 11.1$ Hz, 1H_{cis}, H₂C=CH-CH₂O), 4.70–4.60 (broad m, 1H, OCHO), 4.63 (broad d, $J = 5.5$ Hz, 2H, H₂C=CH-CH₂O), 4.61–4.56 (broad m, 2H, CH-NH and CHCH₂CO₂-Et), 4.31–4.16 (broad m, 2H, OCH₂CH₂TMS), 4.09–4.00 (m, 4H, CO₂CH₂CH₃ and CH₂Oph), 3.95–3.80 (m, 3H, CH₂-OCHO and OH), 3.60–3.53 (m, 2H, CH₂CH₂CH₂Oph), 3.53–3.46 (m, 1H, CH-OH), 2.75 (dd, $J = 15.3$ Hz, $J = 5.0$ Hz, 1H, CHCH₂CO₂Et), 2.52 (dd, $J = 15.3$ Hz, $J = 8.5$ Hz, 1H, CHCH₂CO₂Et), 2.05 (quint, $J = 6.0$ Hz, 2H, CH₂CH₂CH₂Oph), 1.81 (qd, $J = 8.8$ Hz, $J = 3.5$ Hz, 1H, CH₂CHO), 1.72 (dt, $J = 12.6$ Hz, $J = 3.0$ Hz, 1H, CH₂-CH₂CHO), 1.61–1.47 (m, 4H, 1H from CH₂CHO, 1H from CH₂CH₂CHO and 2H from CH₂CH₂O), 1.18 (t, $J = 7.3$ Hz, 3H, CO₂CH₂CH₃), 1.03 (broad t, $J = 8.8$ Hz, 2H, OCH₂CH₂-TMS), 0.01 (s, 9H, TMS). ¹³C NMR (CDCl₃, 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).



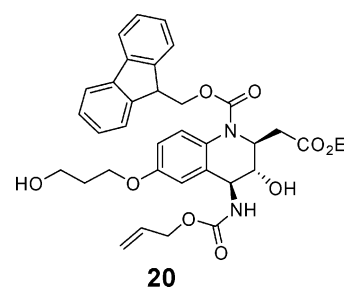
A molar solution of TBAF (405 μ L, 0.40 mmol) at room temperature was added to a solution of Teoc-protected compound **12f** (129 mg, 0.20 mmol) in 10 mL of anhydrous THF. The reaction mixture was stirred for 25 min at room temperature and then concentrated under vacuum. The crude product was chromatographed 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). ¹H NMR (CDCl₃, 400 MHz): δ 6.74 (d, $J = 2.0$ Hz, 1H, MEMOC-

$CH=C$), 6.69 (dd, $J = 8.8$ Hz, $J = 2.8$ Hz, 2H, $CH-CH=C-N$), 6.51 (d, $J = 8.8$ Hz, 1H, $CH-CH=C-N$), 5.95 (ddt, $J = 17.1$ Hz, $J = 10.5$ Hz, $J = 5.8$ Hz, 1H, $H_2C=CH-CH_2O$), 5.35 (dd, $J = 17.1$ Hz, $J = 1.3$ Hz, 1H_{trans}, $H_2C=CH-CH_2O$), 5.25 (d, $J = 10.5$ Hz, 1H_{cis}, $H_2C=CH-CH_2O$), 5.28–5.21 (broad m, 1H, NH), 4.87 (broad t, $J = 7.3$ Hz, 1H, OCHO), 4.64 (d, $J = 5.5$ Hz, 2H, $H_2C=CH-CH_2O$), 4.61–4.56 (broad m, 1H, $CH-NH$), 4.44 (broad s, 1H, NH), 4.17 (2q, $J = 7.0$ Hz, 2H, $CO_2CH_2CH_3$), 3.98 (t, $J = 6.0$ Hz, 2H, CH_2OPh), 3.93–3.80 (m, 3H, CH_2OCHO and OH), 3.59–3.46 (m, 4H, $CH_2CH_2CH_2OPh$ and $CHCH_2CO_2Et$ and $CH-OH$), 3.11 (broad d, $J = 16.3$ Hz, 1H, $CHCH_2CO_2Et$), 2.39 (dm, $J = 16.3$ Hz, 1H, $CHCH_2CO_2Et$), 2.02 (quint, $J = 6.3$ Hz, 2H, $CH_2CH_2CH_2OPh$), 1.81 (qd, $J = 8.3$ Hz, $J = 3.5$ Hz, 1H, CH_2CHO), 1.71 (dt, $J = 12.8$ Hz, $J = 3.0$ Hz, 1H, CH_2CH_2CHO), 1.61–1.46 (m, 4H, 1H from CH_2CHO , 1H from CH_2CH_2CHO and 2H from CH_2CH_2O), 1.29 (t, $J = 7.0$ Hz, 3H, $CO_2CH_2CH_3$). ^{13}C 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 diastereomers), 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 diastereomers), 14.2. LRMS: MS (ES+) $m/z = 493.2$ (M + 1).



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 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 **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, $CH-CH=C-N$), 6.80 (s, 1H, MEMOC- $CH=C$), 6.67 (broad d, $J = 7.3$ Hz, 1H, $CH-CH=C-N$), 6.03–5.89 (m, 1H, $H_2C=CH-CH_2O$), 5.36 (d, $J = 17.3$ Hz, 1H_{trans}, $H_2C=CH-CH_2O$), 5.25 (d, $J = 10.0$ Hz, 1H_{cis}, $H_2C=CH-CH_2O$), 5.13 (dd, $J = 11.3$ Hz, $J = 8.5$ Hz, 1H, OCHO), 4.65 (broad d, $J = 5.5$ Hz, 2H, $H_2C=CH-CH_2O$), 4.65–4.54 (broad m, 4H, $CH-NH$ and

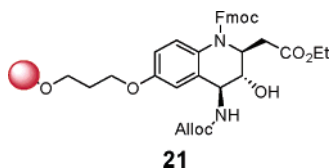
$CHCH_2CO_2Et$ and $NCOOCH_2$), 4.51 (broad s, 1H, NH), 4.22 (broad t, $J = 5.8$ Hz, 1H, $NCOOCH_2CH$), 4.10–4.00 (m, 4H, $CO_2CH_2CH_3$ and CH_2OPh), 3.97–3.83 (m, 2H, CH_2OCHO), 3.75 (broad s, 1H, OH), 3.63–3.56 (m, 1H, $CH-OH$), 3.54–3.48 (m, 2H, $CH_2CH_2CH_2OPh$), 2.63 (broad d, $J = 14.6$ Hz, 1H, $CHCH_2CO_2Et$), 2.40 (broad dd, $J = 14.6$ Hz, $J = 8.5$ Hz, 1H, $CHCH_2CO_2Et$), 2.07 (quint, $J = 6.0$ Hz, 2H, $CH_2CH_2CH_2OPh$), 1.83 (qd, $J = 8.8$ Hz, $J = 3.8$ Hz, 1H, CH_2CHO), 1.74 (dt, $J = 12.5$ Hz, $J = 3.0$ Hz, 1H, CH_2CH_2CHO), 1.64–1.49 (m, 4H, 1H from CH_2CHO , 1H from CH_2CH_2CHO and 2H from CH_2CH_2O), 1.19 (t, $J = 7.3$ Hz, 3H, $CO_2CH_2CH_3$). ^{13}C 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).



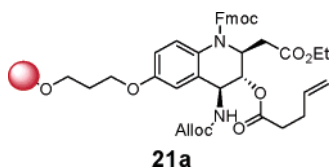
Pyridinium *p*-toluenesulfonate (16 mg, 0.06 mmol) was added to a solution of THP-protected compound **12g** (45 mg, 0.06 mmol) in 8 mL of anhydrous ethanol at room temperature. The reaction mixture was stirred for 2 h at 50 °C. After it was cooled to room temperature, the reaction mixture was concentrated 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, $CH-CH=C-N$), 6.80 (s, 1H, MEMOC- $CH=C$), 6.67 (broad d, $J = 7.5$ Hz, 1H, $CH-CH=C-N$), 6.02–5.88 (m, 1H, $H_2C=CH-CH_2O$), 5.35 (d, $J = 17.1$ Hz, 1H_{trans}, $H_2C=CH-CH_2O$), 5.24 (d, $J = 10.0$ Hz, 1H_{cis}, $H_2C=CH-CH_2O$), 5.25 (broad s, 1H, OH), 4.64 (broad d, $J = 5.5$ Hz, 2H, $H_2C=CH-CH_2O$), 4.65–4.52 (broad m, 4H, $CH-NH$ and $CHCH_2CO_2Et$ and $NCOOCH_2$), 4.50 (broad s, 1H, NH), 4.25–4.18 (broad m, 1H, $NCOOCH_2CH$), 4.09 (broad t, $J = 5.5$ Hz, 2H, $HOCH_2CH_2CH_2O$), 4.09–3.99 (m, 2H, $CO_2CH_2CH_3$), 3.85 (broad t, $J = 5.5$ Hz, 2H, $HOCH_2CH_2CH_2O$), 3.56–3.48 (broad m, 1H, $CH-OH$), 3.54–3.48 (m, 2H, $CH_2CH_2CH_2OPh$), 2.60 (broad d, $J = 14.3$ Hz, 1H, $CHCH_2CO_2Et$), 2.39 (broad dd, $J = 14.3$ Hz, $J = 8.3$ Hz,

1H, CHCH₂CO₂Et), 2.03 (quint, *J* = 5.5 Hz, 2H, HOCH₂CH₂-CH₂O), 1.18 (t, *J* = 7.3 Hz, 3H, CO₂CH₂CH₃). ¹³C NMR (CDCl₃, 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.

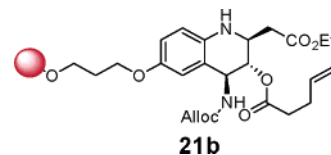


The resin (49.6 mg, 0.064 mmol) and compound **20** (80.8 mg, 0.1281 mmol) were dried on a freeze dryer for 24 h hours. The beads were placed in a vial, and 1 mL of anhydrous CH₂Cl₂ was added at room temperature to allow the bead to swell. The solution containing the beads was gently shaken for 30 min. The CH₂Cl₂ 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 CH₂Cl₂ twice (3 mL). Then 1 mL of anhydrous CH₂Cl₂ 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 CH₂Cl₂) 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%). *R_f*: 0.36 (1/9 hexane/ethyl acetate). LRMS: MS (ES⁺) *m/z* = 631.2 (M + 1). HPLC: 14.005 min.

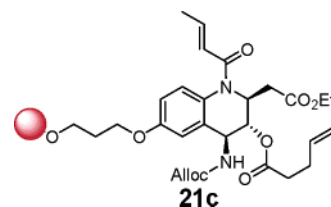


The compound loaded onto resin **21** (43.2 mg, 0.0361 mmol) was swelled in 3 mL of anhydrous CH₂Cl₂ for 30 min. The solvent was removed and replaced with 1 mL of anhydrous CH₂Cl₂. 1,3-Diisopropylcarbodiimide (34 μL, 0.217 mmol), 4-pentenoic acid (15.2 μL, 0.144 mmol), and 4-(dimethylamino)-pyridine (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 CH₂Cl₂ (3 × 5 mL), THF (3 × 5 mL), and CH₂Cl₂ (3 × 5 mL) and dried under vacuum overnight. The compound was obtained after the cleavage

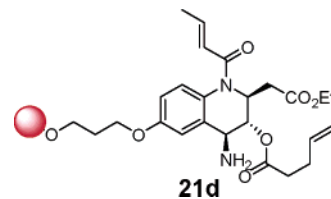
of 3 beads. *R_f*: 0.67 (1/9 hexane/ethyl acetate). LRMS: MS (ES⁺) *m/z* = 713.1 (M + 1). HPLC: 15.771 min. HPLC yield: 99%.



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), 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*: 0.62 (1/9 hexane/ethyl acetate). LRMS: MS (ES⁺) *m/z* = 491.2 (M + 1). HPLC: 11.125 min. HPLC yield: 85%.

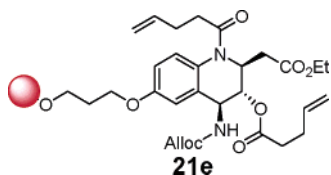


Resin **21b** (38.7 mg, 0.0487 mmol) was swelled in 3 mL of anhydrous CH₂Cl₂ for 30 min. The solvent was removed and replaced with 1 mL of anhydrous CH₂Cl₂. 2,4,6-Collidine (65 μL, 0.487 mmol) and crotonyl chloride (26.2 μL, 0.243 mmol) were added to the beads at 0 °C. The mixture was shaken with a tumble shaker for 19 h. The mixture was filtered; the resin was washed with 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* = 559.3 (M + 1). HPLC: 9.86 min. HPLC yield: 99%.

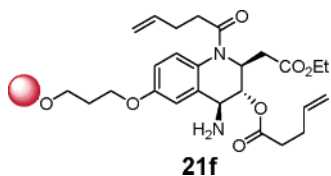


Resin **21c** (40 mg, 0.0487 mmol) was swelled in 3 mL of anhydrous THF for 30 min. The solvent was removed and replaced with 1 mL of a mixture of anhydrous CH₂Cl₂ (5 mL), 4-methyl morpholine (0.32 mL), and acetic acid (0.66 mL). Triphenylphosphine (165 mg, 0.621 mmol) and tetrakis(triphenylphosphine) 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 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*: 0.12 (1/9 hexane/ethyl acetate). LRMS: MS

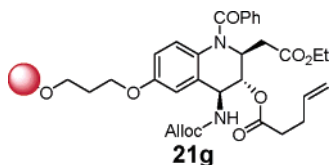
(ES+) $m/z = 475.3$ ($M + 1$). HPLC: 7.79 min. HPLC yield: 98%.



Resin **21b** (38 mg, 0.0425 mmol) was swelled in 3 mL of anhydrous CH_2Cl_2 for 30 min. The solvent was removed and replaced with 1 mL of anhydrous CH_2Cl_2 . 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 CH_2Cl_2 (3 \times 5 mL), THF (3 \times 5 mL), and CH_2Cl_2 (3 \times 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%.

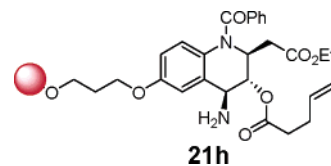


Resin **21e** (40 mg, 0.0425 mmol) was swelled in 3 mL of anhydrous THF for 30 min. The solvent was removed and replaced with 1 mL of a mixture of anhydrous CH_2Cl_2 (5 mL), 4-methyl morpholine (0.32 mL), and acetic acid (0.66 mL). Triphenylphosphine (144 mg, 0.542 mmol) and tetrakis(triphenylphosphine) 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 CH_2Cl_2 (3 \times 5 mL), THF (3 \times 5 mL), and CH_2Cl_2 (3 \times 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%.

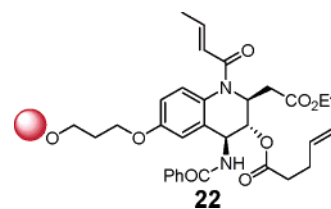


Resin **21b** (18.6 mg, 0.0181 mmol) was swelled in 3 mL of anhydrous CH_2Cl_2 for 30 min. The solvent was removed and replaced with 1 mL of anhydrous CH_2Cl_2 . 2,4,6-Collidine (24.1 μL , 0.181 mmol) and benzoyl chloride (10.6 μL , 0.0903 mmol) were added to the beads at room temperature. The mixture was shaken with a tumble shaker for 16 h. The mixture was filtered; the resin was washed with CH_2Cl_2 (3 \times 5 mL), THF (3 \times 5 mL), and CH_2Cl_2 (3 \times 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).

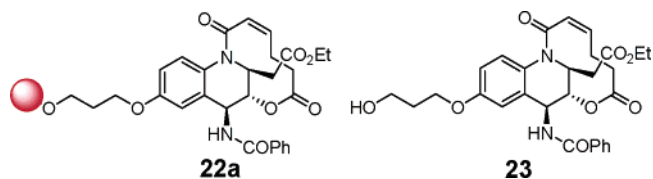
LRMS: MS (ES+) $m/z = 595.2$ ($M + 1$). HPLC: 13.649 min. HPLC yield: 78%.



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 CH_2Cl_2 (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 CH_2Cl_2 (3 \times 5 mL), THF (3 \times 5 mL), and CH_2Cl_2 (3 \times 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%.

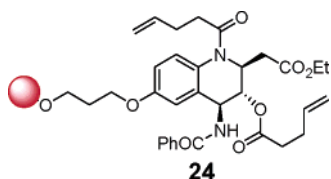


Resin **21d** (36 mg, 0.0487 mmol) was swelled in 3 mL of anhydrous CH_2Cl_2 for 30 min. The solvent was removed and replaced with 1 mL of anhydrous CH_2Cl_2 . 2,4,6-Collidine (65 μL , 0.487 mmol) and benzoyl chloride (28.5 μL , 0.243 mmol) were added to the beads at room temperature. The mixture was shaken with a tumble shaker for 19 h. The mixture was filtered; the resin was washed with CH_2Cl_2 (3 \times 5 mL), THF (3 \times 5 mL), and CH_2Cl_2 (3 \times 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%.

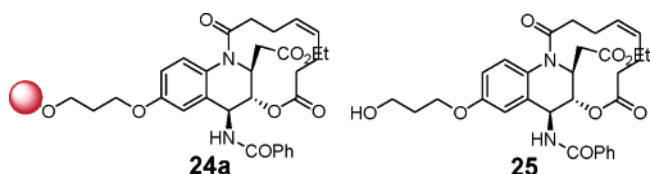


Resin **22** (38 mg, 0.487 mmol) was swelled in 2 mL of anhydrous CH_2Cl_2 for 30 min. Second-generation Grubbs' catalyst (41 mg, 0.0487 mmol) was added to the beads at room temperature. The mixture was heated to reflux for 19 h. After it was cooled, the mixture was filtered, and the resin was washed with THF (3 \times 5 mL), CH_2Cl_2 (3 \times 5 mL), THF (3 \times 5 mL), and CH_2Cl_2 (3 \times 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

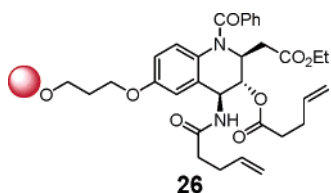
cleavage of all resin **22a**, the crude product was chromatographed on silica gel (eluent = hexane/ethyl acetate, 1/9 to pure ethyl acetate) to give the title compound as a white solid.



Resin **21f** (35 mg, 0.0425 mmol) was swelled in 3 mL of anhydrous CH_2Cl_2 for 30 min. The solvent was removed and replaced with 1 mL of anhydrous CH_2Cl_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_2Cl_2 (3 \times 5 mL), THF (3 \times 5 mL), and CH_2Cl_2 (3 \times 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%.

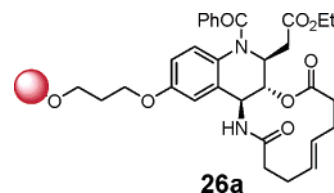


Resin **24** (38 mg, 0.425 mmol) was swelled in 2 mL of anhydrous CH_2Cl_2 for 30 min. Second-generation Grubbs catalyst (36 mg, 0.0425 mmol) was added to the beads at room temperature. The mixture was heated to reflux for 17 h. After it was cooled, the mixture was filtered, and the resin was washed with THF (3 \times 5 mL), CH_2Cl_2 (3 \times 5 mL), THF (3 \times 5 mL), and CH_2Cl_2 (3 \times 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.

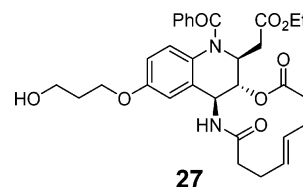


Resin **21h** (16.4 mg, 0.0181 mmol) was swelled in 3 mL of anhydrous CH_2Cl_2 for 30 min. The solvent was removed and replaced with 1 mL of anhydrous CH_2Cl_2 . 2,4,6-Collidine (24.1 μL , 0.181 mmol) and 4-pentenyl chloroide (10.2 μL , 0.0903 mmol) were added to the beads at room temperature. The mixture was shaken with a tumble shaker for 2 days. The mixture was filtered, and the resin was washed with CH_2Cl_2 (3 \times 5 mL), THF (3 \times 5 mL) and CH_2Cl_2 (3 \times 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%.



Resin **26** (17.9 mg, 0.0181 mmol) was swelled in 2 mL of anhydrous CH_2Cl_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 \times 5 mL), CH_2Cl_2 (3 \times 5 mL), THF (3 \times 5 mL), and CH_2Cl_2 (3 \times 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.



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). ^1H 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, $\text{CH}_2\text{CH}=\text{CHCH}_2$), 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, $\text{CH}_2\text{CH}_2\text{O}$ and $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.84 (t, J = 6.0 Hz, 1H, CH_2OH), 2.70–2.31 (m, 9H, 7H from $\text{NHCOCH}_2\text{CH}_2\text{CH}=\text{CHCH}_2\text{CH}_2$ and 2H from $\text{CHCH}_2\text{CO}_2\text{Et}$), 2.16 (td, J = 12.0 Hz, J = 2.5 Hz,

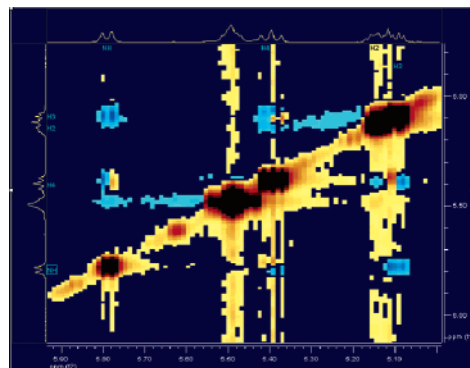


Figure 12. NOESY of compound **27** showing NOEs between H_2 and H_4 and NH and H_4 .

¹H, NHCOCH₂), 2.01 (quint, *J* = 6.0 Hz, 2H, CH₂CH₂O), 1.21 (t, *J* = 7.0 Hz, 3H, CO₂CH₂CH₃). ¹³C NMR (CDCl₃, 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.

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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>.

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