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J. Comb. Chem., **2004**, 6 (5), 724-734• DOI: 10.1021/cc049941o • Publication Date (Web): 23 July 2004

A Solution- and Solid-Phase Approach to Tetrahydroquinoline-Derived Polycyclics Having a 10-Membered Ring

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Received March 6, 2004

With the goal of library generation using a polycyclic derivative **5** having an enamide functional group, a simple and practical, enantioselective synthesis of tetrahydroquinoline derivative **2** was achieved. The phenolic hydroxyl group in compound **2** was utilized as an anchoring site for solid-phase synthesis. The ring closing metathesis approach yielded the desired polycyclic product **5** on solid phase in five steps (overall 40% yield). Compound **5** is a novel scaffold for the library generation of natural product-like polycyclics having a functionalized medium ring for obtaining a new class of small molecules to be utilized as chemical probes.

Introduction

Over the years, it has been shown that natural products which are capable of acting as modulators (i.e., activators or inhibitors) of protein−protein interactions are highly complex and possess three-dimensional architectures with several chiral centers and a diverse range of protein-binding elements.[1] These features appear to be required when it comes to dissecting protein functions with the help of small molecules.[2] Therefore, it is not surprising that an interest in developing natural product-like small molecules which could aid in understanding protein−protein interactions-based cellular signaling pathways is growing.[3] The success of the chemical genomics program that is aimed toward understanding complex protein networking and its roles in cellular signaling pathways depends on the availability of a diverse range of such chemical probes.[4]

Synthesis Plan

We have initiated a program that is targeted at developing solid-phase, high-throughput synthesis of natural product-like tetrahydroquinoline-based polycyclics having different ring skeletons. The choice of the tetrahydroquinoline scaffold was made on the basis of the fact that this is one of the commonly found building blocks in a wide variety of bioactive natural products.[5] In particular, we were interested in developing a practical enantioselective synthesis of tetrahydroquinoline-based β-hydroxycarboxylic ester, **1**, and of the dihydroxyl derivative, **2** (Scheme 1). These two building blocks offer unique features. The presence of three orthogonally protected functional groups (i.e., amine, hydroxyl, and the carboxyl ester) in compound **1** could further be utilized in building complexity and to explore the three-dimensional chemical space. The phenolic hydroxyl in compound **3** provides a useful anchoring site for developing a solid-phase synthesis. Having a practical method to obtain compound **1** in hand, our next plan was to utilize the aminohydroxyl groups to obtain a functionalized medium-macrocyclic ring on this scaffold. As shown in compound **4**, this could be achieved by a ring-closing metathesis approach from the *N*-acryloyl group and an unsaturated carboxyl ester, giving a polycyclic **5** that has a 10-membered ring with an enamide functional group. Compound **5** could further be utilized in exploring the diversity-oriented reactions. For example, an enamide group in a 10-membered ring could be utilized as a Michael acceptor site to explore the scope of the ring conformation controlled reaction. There are very few examples in combinatorial literature that are focused on the functionalized polycyclics having medium to large ring derivatives.[6,7] To our knowledge, the application of the ring-closing metathesis approach for the synthesis (solution- and solid-phase) of a functionalized ring having an enamide group has not been utilized before.[8]

Results and Discussion

Our model solution synthesis to obtain enantiopure tetrahydroquinoline derivative **12** is shown in Scheme 2. Safrole (**6**), a commercially available starting material was converted into compound **7** having the desired unsaturated carboxyl ester and the nitro functional group at the ortho position.[9]

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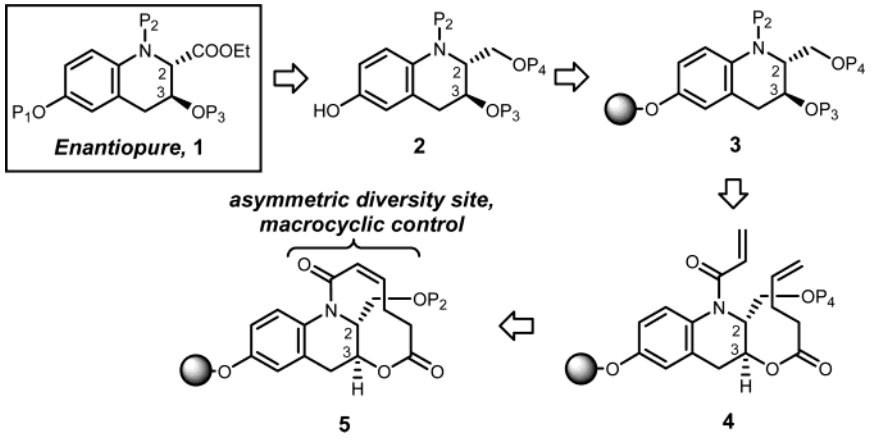
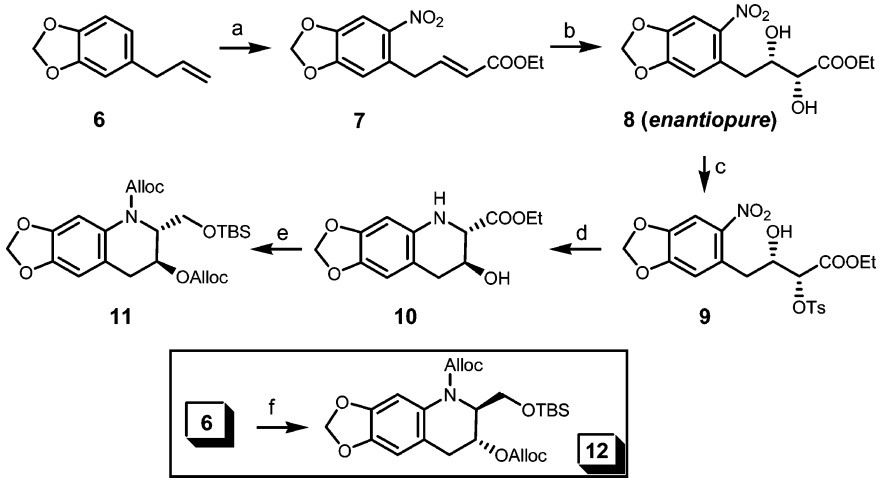
10.1021/cc049941o CCC: $27.50
Published on Web 07/23/2004

Scheme 1. Natural Product-Like, Tetrahydroquinoline-Based Polycyclics Having a Functionalized 10-Membered Ring



Scheme 2

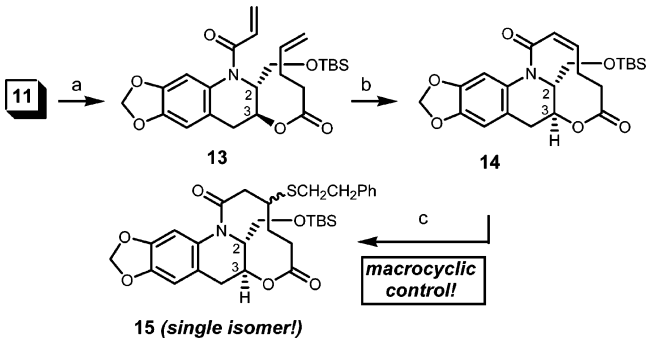


(a) (i) Glacial AcOH, HNO_3, H_2SO_4 (70%); (ii) O_3, MeOH. 95%; $Ph_3P{=}CHCOOEt$, CH_2Cl_2, 82%. (b) Sharpless dihydroxylation reaction-AD mix-α, 68%. (c) *p*-TsCl, Et_3N, 88%. (d) H_2, 10% Pd/C, K_2CO_3, room temp, 82%. (e) (i) $LiBH_4$, room temp; (ii) allylchloroformate, pyridine, 54% for two steps; (iii) TBDMSCl, imidazole, 81%; (iv) allylchloroformate, pyridine, 92%; (f) repeat steps a−e, except in the synthesis of other enantiomer by Sharpless enantioselective dihydroxylation reaction with AD mix-*β*.

This was achieved in a few steps as follows. The nitration of Safrole followed by the ozonolysis gave the *o*-nitrophenyl acetaldehyde derivative. This was then subjected to two-carbon homologation by the Wittig reaction, giving compound **7**. The enantiopure diol **8** was obtained from the Sharpless dihydroxylation reaction, which went very smoothly. The enantiomeric excess of the product was 90% as determined by chiral HPLC. The regioselective derivatization of an α-hydroxyl group provided the corresponding *O*-tosyl (**9**), which gave the tetrahydoquinoline derivative **10** upon reductive conditions in the presence of a mild base. All the products were well-characterized by NMR and MS studies. We were pleased to have a simple, practical method in hand that allowed us to obtain an enantio-rich tetrahydroquinoline scaffold in large quantities. Further, functional groups manipulations included the reduction of the carboxyl ester with lithium borohydride, a selective *N*-alloc protection, silylation of the primary hydroxyl, and finally, the protection of the secondary hydroxyl group. Using a similar sequence, the synthesis of an enantiomer of compound **11** was also achieved (**12**).

Our model solution synthesis to obtain the 10-membered ring on a tetrahydroquinoline scaffold is shown in Scheme 3. Compound **11** was subjected to mild base hydrolysis for the removal of the *O*-Alloc group. The free hydroxyl group was then acylated with pentenoic acid under standard acylation conditions. Following the *N*-Alloc removal, the free amine was converted into *N*-acryloyl derivative, giving compound **13**, a precursor to explore the key ring-closing metathesis reaction. To our pleasant surprise, the ring closing

Scheme 3



(a) (i) NaOMe, MeOH; (ii) 4-pentenoic acid, DIC, DMAP, 81%; (iii) $Pd(PPh_3)_4$, morpholine, room temp; (ii) acryloyl chloride, pyridine, 0 °C, 53% for two steps. (b) 20 mol % second-generation Grubbs' catalyst, dichloromethane, reflux, 1 h, 65%. (c) $PhCH_2CH_2SH$, BuLi, 76%.

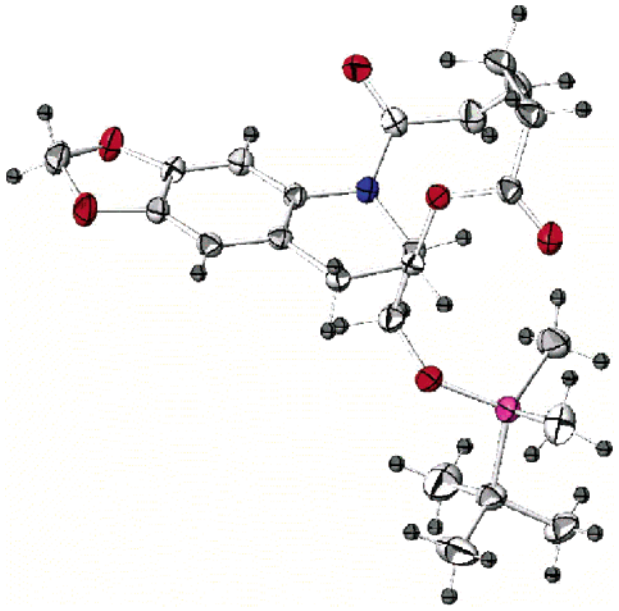
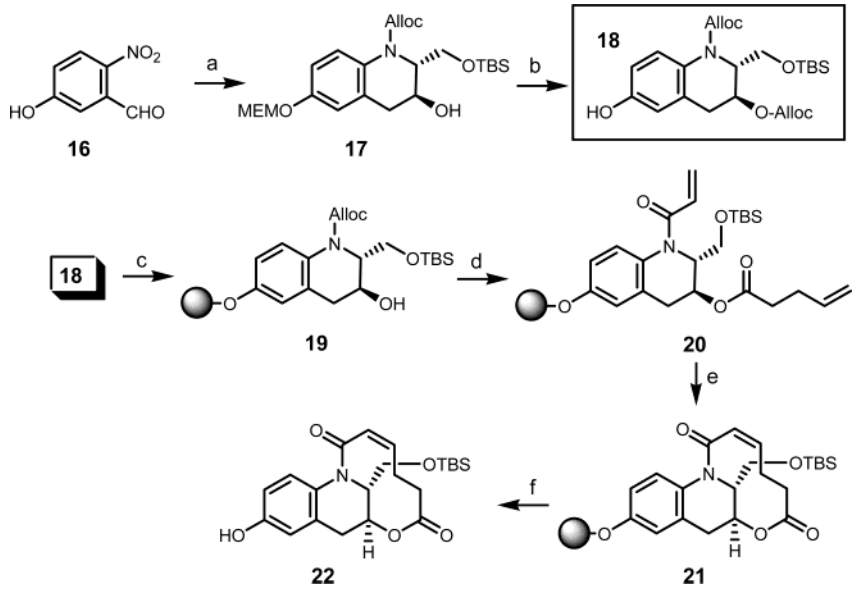


Figure 1. X-ray structure of compound **14**.

metathesis went smoothly, giving only the cis olefin-based 10-membered ring (**14**), having an enamide functional group in high yields. There was no sign of the formation of the 10-membered ring with the trans olefin moiety. These findings are novel, and the ease of the ring closing metathesis reaction prompted us to explore this strategy on solid phase. The cis geometry across the double bond was established by extensive NMR studies and finally confirmed by X-ray analysis (Figure 1).[10] A careful examination of the X-ray revealed several interesting features of this polycyclic derivative. It appears that the 10-membered ring is projected out of the tetrahydroquinoline plane and that the double bond is not aligned with the amide functional group. To explore the scope of a macrocyclic ring-confirmation controlled reaction, compound **14** was then subjected to hetero Michael reaction. As expected, the approach of the thiol nucleophile occurred only from one side, giving the hetero Michael product as a single isomer. At this stage, several attempts were made to assign the stereochemistry of the new stereogenic center on the 10-membered ring. So far, we have not been successful in the stereochemical assignment of the conjugate addition product. Further, work is in progress to assign this stereochemistry of the new steroegenic center on the macrocycle. Following the successful development of a ring-closing metathesis approach to obtain a polycyclic derivative having a 10-membered ring, we then focused our attention to developing a solid-phase method. These attempts are shown in Scheme 4.

For developing a solid-phase synthesis project, we needed compound **18**, in which the phenolic hydroxyl moiety could be utilized as an anchoring site for the solid phase. Thus, an enantioselective synthesis of compound **18** was developed that utilized an approach similar to that discussed earlier. The synthesis of compound **17** was achieved in a number of steps from 5-hydroxy-2-nitrobenzaldehyde (**16**). Subjection to the secondary hydroxyl protection, followed by the −OMEM removal from the phenolic hydroxyl moiety, provided the required the starting material **18**. This compound was then immobilized onto the solid support. The solid-phase synthesis was carried out on the bromo-Wang resin (1.70 mmol/g), and the loading of the phenolic derivative, **18**, was accomplished nicely (85% loading after cleavage of the product from the solid support). Following the immobilization, it was then subjected to *O*-Alloc removal under basic conditions (NaOMe), giving the free secondary hydroxyl group (**19**). This derivative was then acylated with pentenoic acid (DIC, DMAP). To obtain the precursor of the RCM, the *N*-Alloc group was deprotected, and the free amine was

Scheme 4



(a) (i) (Methoxymethyl)triphenylphosphonium chloride, K-*t*-OBu, 95%; (ii) 1.5 N HCl (98%); (iii) $Ph_3P{=}CHCOOEt$, CH_2Cl_2, 80%; (iv) Sharpless dihydroxylation reaction-AD mix-α, 70%; (v) *p*-TsCl, Et_3N, 88%; (vi) H_2, 10% Pd/C, K_2CO_3, room temp, 84%; (vii) $LiBH_4$, room temp; (viii) allylchloroformate, pyridine, 78% for two steps; (ix) TBDMSCl, imidazole, 83%. (b) (i)Allylchloroformate, pyridine, 85%; (ii) $ZnBr_2$, 60%. (c) (i) BromoWang resin, NaI, Cs_2CO_3; (ii) NaOMe, MeOH. (d) (i) 4-Pentenoic acid, DIC, DMAP; (ii) tetrakis(triphenylphosphine)palladium (0), *N*-methylmorpholine, Ac_2O; (iii) acryloyl chloride, pyridine. (e) Second-generation Grubbs catalyst, dicholoromethane, reflux. (f) 5% TFA.

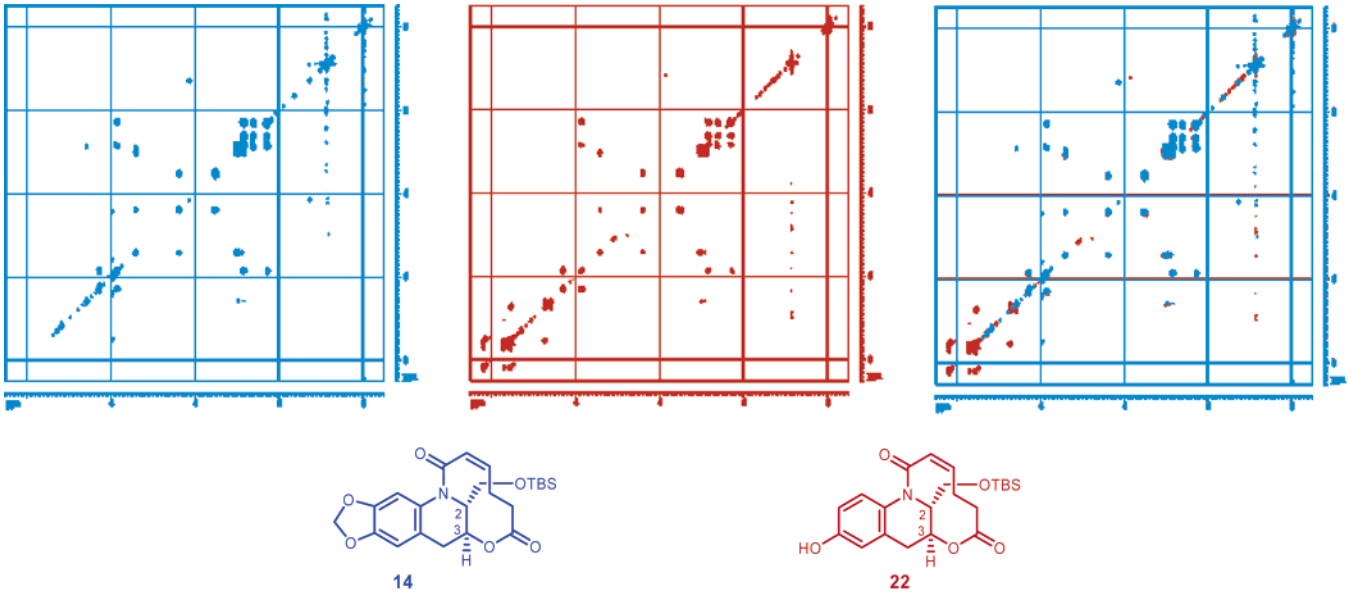


Figure 2. COSY for model compound is blue (left) and for compound synthesized on solid phase is red (middle). Superimposed COSYs (right) for model compound (blue) set over the solid-phase synthesized compound (red). Notice that as expected, the only differences between the two spectra are in the aromatic region.

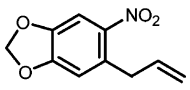
acylated with acryolyl chloride, giving compound **20**. We were pleased to note that when subjected to RCM reaction, compound **20** nicely gave the cyclic product with an additional functionalized 10-membered ring (**21**). Product **22** was well-characterized by NMR and MS upon cleavage from the support, followed by purification by column chromatography (see Figure 2 for a comparison of NMR data of compounds prepared in solution and on solid phase). The overall yield for five steps was 40%. Thus, it is possible to obtain a natural product-like tetrahydroquinoline-derived polycyclic having a functionalized 10-memebred ring on solid phase. This polycyclic-based scaffold is novel and could further be utilized in library generation.

To summarize, we developed a practical, enantioselective synthesis of a tetrahydroquinoline-based scaffold. This was then utilized in developing a solid-phase synthesis of the tricyclic derivative having a functionalized 10-membered ring with an enamide functional group. A ring-closing metathesis was the key reaction in our plan to obtain a functionalized 10-membered derivative that could further be utilized in diversity generation. Using this approach, further work is in progress for the library generation and will be reported as it becomes available.

Experimental Section

General Methods. The materials were obtained from commercial suppliers and used without purification. THF and CH_2Cl_2 were distilled under N_2 over sodium/benzophenone and CaH_2, respectively. All NMR experiments were recorded on a Bruker DRX-400. Unless otherwise noted, proton and carbon chemical shifts are reported in parts per million using residual $CHCl_3$ as an internal standard at 7.26 and 77.0 ppm, respectively. Analysis by mass spectrometry was performed on a VG Quattro I (Micromass) mass spectrometer equipped with pneumatically assisted electrospray ionization source, operating in positive mode. The enantiomeric excess was determined by chiral HPLC using a Hewlett-Packard (Agilent) 1090 LC equipped with a diode array detector and Chiracel-OD column. The HPLC spectra were recorded on a Gilson Combinatorial Chromatography System with 215 liquid handler/injector and equipped with a Vydac C-18 monomeric column and a diode array detector.

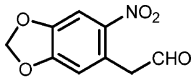
Solution Phase Synthesis. To a solution of Safrole (10 g, 61.73 mmol) in glacial acetic acid (40 mL) at 0 °C, a solution (10:1 ratio) of nitric acid and sulfuric acid (10 mL) was added dropwise. After 2 h at 0 °C, ethyl acetate (350 mL) was added, and the layers were separated. The combined organic layer was washed with water (4 × 250 mL) and saturated sodium bicarbonate solution (2 × 250 mL), dried over magnesium sulfate, and then concentrated after filtration. Purification by column chromatography (20% ethyl acetate in hexanes) afforded 8.93 g (70%) of 6-nitrosafrole (**6a**) as a yellow solid. R_f: 0.53 (4:1, hexane/ethyl acetate). LRMS: MS (ES+) m/z = 208.1 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 6.78 (s, 1H), 6.11 (s, 2H), 5.97 (ddt, J = 13.5, 6.5, 6.4 Hz, 1H), 5.14 (dd, J = 6.5, 1.4 Hz, 1H), 5.10 (dd, J = 13.5, 1.4 Hz, 1H), 3.67 (d, J = 6.4 Hz, 2H) ppm.



6a

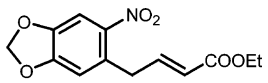
A solution of 8.93 g (43.14 mmol) of **6a** in methanol (100 mL) was treated at 0 °C with a stream of ozone via a sintered diffuser until the TLC showed disappearance of the starting material (~4 h). Excess ozone was then removed under a positive flow of nitrogen. This was then followed by the addition of dimethyl sulfide (9.0 mL, 118.0 mmol), and the mixture was kept at room temperature for 1 h. After being

stored in freezer for overnight, the pale yellow crystals appeared. The solid was then filtered and washed with cold methanol. Recrystalization from methanol afforded pure product, **6b** (8.56 g, 95%). R_f: 0.21 (4:1, hexane.ethyl acetate). LRMS: MS (ES+) m/z = 280.1 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.68 (s, 1H), 6.72 (s, 1H), 6.16 (s, 2H), 4.06 (s, 2H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ 197.3, 152.7, 148.1, 143.2, 125.9, 112.3, 106.5, 103.6, 49.2 ppm.



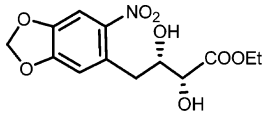
6b

To a solution of **6b** (8.56 g, 40.98 mmol) in dichloromethane (100 mL) was added (carboxymethylene)triphenylphosphorane (18.56 g, 53.27 mmol) at room temperature. The reaction mixture was stirred until the starting material disappeared (4 h). The reaction was quenched with saturated ammonium chloride solution and washed with water and brine. The organic phase was dried over magnesium sulfate. After solvent evaporation, the crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes), giving compound **7** as a yellow solid (82% trans, 16% cis, 9.38 g trans product). R_f: 0.81 (1:1, hexane/ethyl acetate). LRMS: MS (ES+) m/z = 279.1 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 6.72 (s, 1H), 6.13 (d, J = 2.1 Hz, 2H), 7.09 (dt, J = 6.5,15.6 Hz, 1H), 5.80 (d, J = 15.6 Hz, 1H), 4.20 (q, J = 7 Hz, 2H), 3.82 (dd, J = 1.5, 5.5 Hz, 2H), 1.30 (t, J = 7 Hz, 3H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ 166.5, 152.3, 145.4, 130.3, 129.5, 123.5, 111.1, 106.3, 105.5, 103.4, 60.8, 36.6, 14.6 ppm.



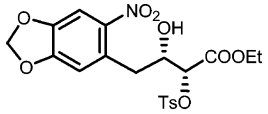
7

To a 1-L round-bottomed flask equipped with a magnetic stirrer were added *t*-BuOH (170 mL), water (170 mL), and AD mix-α (47.27 g). To this mixture, methanesulfonamide (3.19 g, 33.62 mmol) was then added. The mixture was stirred at room temperature until both phases were clear and cooled to 0 °C. Compound **7** (9.39 g, 33.62 mmol) was then added, and the mixture was further stirred vigorously at room temperature until TLC revealed the absence of the starting olefin (time, ~40 h). The reaction was quenched at 0 °C by the addition of sodium sulfite (50.0 g), warmed to room temperature, and further stirred for 1 h. The reaction mixture was then extracted several times with ethyl acetate. The combined organic layer was washed with 2 N KOH, dried over magnesium sulfate, and then concentrated. Purification by flash chromatography (silica gel, 50% ethyl acetate in hexanes) gave pure diol as a yellow oil (8, 7.15 g, 68%). R_f: 0.19 (1:1, hexane/ethyl acetate). LRMS: MS (ES+) m/z = 313.1 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 6.88 (s, 1H), 6.12 (s, 2H), 4.32 (q, J = 7 Hz, 2H), 4.18 (dd, J = 2.5 Hz, 1H), 3.51 (s, 1H), 3.23 (d, J = 1 Hz, 1H), 3.20 (dd, J = 5.5 and 9 Hz, 2H), 2.35 (d, J = 9.1 Hz, 1H), 1.33 (t, J = 7 Hz, 3H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ 173.5, 152.2, 147.4, 143.7, 130.9, 112.2, 108.8, 106.1, 103.6, 73.1, 62.8, 38.4, 14.6 ppm.



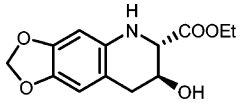
8

To a stirred solution of diol **8** (7.15 g, 22.84 mmol) in dichloromethane (200 mL) at 0 °C under nitrogen was added triethylamine (4.17 mL, 29.69 mmol) followed by *p*-toluenesulfonyl chloride (4.35 g, 22.84 mmol). The solution was then stirred for 90 h at 0 °C, and the reaction mixture was diluted with dichloromethane and water, dried over magnesium sulfate, filtered ,and concentrated. Column chromatography on silica gel (20% ethyl acetate in hexanes) afforded the *O*-tosyl derivative **9** (9.38 g, 88%) as an oil. R_f: 0.67 (1:1, hexane/ethyl acetate). LRMS: MS (ES+) m/z = 467.1 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.88 (d, J = 9.3 Hz, 2H), 7.51 (s, 1H), 7.37 (d, J = 5 Hz, 2H), 6.82 (s, 1H), 6.11 (d, J = 3.8 Hz, 2H), 4.99 (d, J = 3.3 Hz, 1H), 4.15 (q, J = 7 Hz, 2H), 4.16 (m, 1H), 3.06 (dd, J = 3 and 14 Hz, 2H), 2.60 (s, 1H), 2.46 (s, 3H), 1.21 (t, J = 7 Hz, 3H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ 167.3, 152.3, 147.6, 145.9, 143.5, 133.3, 130.1, 128.7, 128.2, 112.3, 106.3, 103.4, 79.9, 72.3, 62.7, 37.7, 22.1, 14.4 ppm.



9

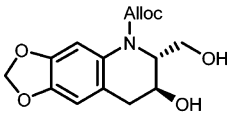
A solution of **9** (9.38 g, 20.08 mmol) in dry THF (250 mL) was added oven-dried potassium carbonate (5.54 g, 40.16 mmol) and Pd−C (1.87 g, 20%, w/w, added under nitrogen). The mixture was then hydrogenated for 40 h (monitored by TLC). After completion of the reaction, the mixture was filtered, washed several times with ethyl acetate, and then concentrated. Column chromatography on silica gel (20−50% ethyl acetate in hexanes) afforded the tetrahydroquinoline derivative **10** as a yellow oil (4.35 g, 82%). R_f: 0.53 (1:1, hexane/ethyl acetate). LRMS: MS (ES+) m/z = 265.1 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.49 (s, 1H), 6.24 (s,1H), 5.85 (s, 2H), 4.35 (q, J = 4.8 Hz, 1H), 4.27 (q, J = 7 Hz, 2H), 3.89 (d, J = 6 Hz, 1H), 3.51 (s, 1H), 2.83 (dd, J = 4.8 and 15.3 Hz, 2H), 1.49 (m,1H), 1.32 (t, J = 7 Hz, 3H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ 109.8, 100.9, 97.1, 65.2, 62.1, 28.7, 59.8, 14.6 ppm.



10

To a stirred solution of **10** (1.0 g, 3.77 mmol) in anhydrous THF (40 mL) at 0 °C under nitrogen was added lithium borohydride (2 M in THF, 3.77 mL, 7.54 mmol). After stirring for 1.5 h at room temperature under nitrogen, the reaction was quenched slowly with saturated aqueous am-

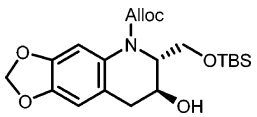
monium chloride. Following evaporation of the solvent, the mixture was extracted with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate, filtered, and concentrated in vacuo. After evaporation of the solvent, the residue was used directly for the next step without further purification.



10a

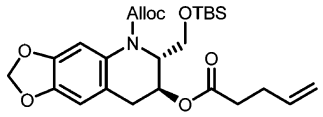
To a stirred solution of the amino alcohol obtained from the above reaction in anhydrous dichloromethane (40 mL) at 0 °C was added pyridine (0.25 mL, 3.14 mmol) and allyl chloroformate (0.34 mL, 3.14 mmol). After stirring for 45 min at 0 °C, the reaction was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted twice with dichloromethane, and the combined organic layer was dried with anhydrous magnesium sulfate, filtered, and then concentrated in vacuo. The residue was purified by column chromatography over silica gel with hexanes and ethyl acetate, giving product **10a** (630 mg, 54% over two steps) as a yellow oil. R_f: 0.09 (1:1, hexane/ethyl acetate). LRMS: MS (ES+) m/z = 307.1 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.48 (s, 1H), 6.16 (s, 1H), 5.95 (m, 1H), 5.83 (s, 2H), 5.39 (d, J = 17.7 Hz, 1H), 5.31 (d, J = 10.2 Hz, 1H), 4.65 (dt, J = 5.7, 1.3 Hz, 2H), 4.32 (m, 1H), 4.20 (m, 1H), 3.97 (q, J = 6.5 Hz, 1H), 3.46 (s, 1H), 2.89 (m, 1H), 2.74 (m, 1H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ 155.5, 147.2, 140.8, 136.9, 131.7, 119.8, 110.2, 109.7, 100.9, 97.1, 69.2, 68.7, 64.9, 56.6, 34.6 ppm.

To a stirred solution of **10a** (630 mg, 2.05 mmol) in dichloromethane (10 mL) at 0 °C was added imidazole (280.0 mg, 4.1 mmol), followed by TBDMSCl (370 mg, 2.46 mmol). The mixture was stirred at 0 °C for an additional 75 min. The reaction was quenched with saturated ammonium chloride, and the aqueous layer was extracted three times with dichloromethane. The combined organic layer was dried over magnesium sulfate, filtered and then concentrated in vacuo. The residue was purified by column chromatography over silica gel with 10−20% ethyl acetate in hexanes, affording 700 mg (81%) of **10b** as a yellow oil. R_f: 0.57 (1:1, hexane/ethyl acetate). LRMS: MS (ES+) m/z = 421.2 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.48 (s, 1H), 6.16 (s, 1H), 5.95 (m, 1H), 5.83 (s, 2H), 5.39 (d, J = 17.7 Hz, 1H), 5.31 (d, J = 10.2 Hz, 1H), 4.65 (dt, J = 5.7 and 1.3 Hz, 2H), 4.32 (m, 1H), 4.20 (m, 1 H), 3.97 (q, J = 6.5 Hz, 1 H), 3.46 (s, 1 H), 2.89 (m, 1H), 2.74 (m, 1H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ 155.5, 147.2, 140.8, 136.9, 131.7, 119.8, 110.2, 109.7, 100.9, 97.1, 69.2, 68.7, 64.9, 56.6, 34.6 ppm.



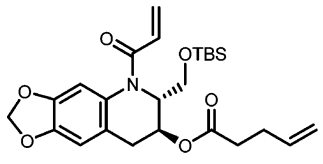
10b

To a stirred solution of **10b** (700 mg, 1.66 mmol) in dichloromethane (50 mL) were added DIC (0.53 mL, 3.32 mmol), DMAP (20 mg, 0.166 mmol), and 4-pentenoic acid (0.26 mL, 2.5 mmol) at room temperature. The reaction mixture was stirred at room temperature for 24 h. After quenching the reaction with saturated ammonium chloride, the aqueous layer was extracted twice with dichloromethane. The combined organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo. Purification by flash chromatography using 10% ethyl acetate in hexanes afforded compound **11b** (680 mg, 81%). R_f: 0.76 (2:1, hexane/ethyl acetate). LRMS: MS (ES+) m/z = 503.2 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.06 (s, 1H), 6.57 (s, 1H), 5.98 (m, 1H), 5.93 (d, J = 7 Hz, 2H), 5.81 (m, 1H), 5.34 (d, J = 17 Hz, 1H), 5.25 (d, J = 10.6 Hz, 1H), 5.16 (q, J = 5.5 Hz, 1H), 5.05 (d, J = 17 Hz, 1H), 5.00 (d, J = 10.6 Hz, 1H), 4.64−4.73 (m, 3H), 5.58 (d, J = 6.5 Hz, 2H), 2.96 (dd, J = 5.6, 15.6 Hz, 1H), 2.69 (dd, J = 6 and 16 Hz, 1H), 2.34−2.43 (m, 4H), 0.82 (s, 9H), 0.01 (d, J = 10.6 Hz, 6H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ 172.6, 155.2, 146.5, 145.1, 136.9, 132.8, 130.7, 118.4, 115.9, 107.9, 106.9, 101.5, 70.0, 67.1, 62.3, 58.6, 34.0, 31.4, 29.2, 26.1, 18.4, −5.2 ppm.



11b

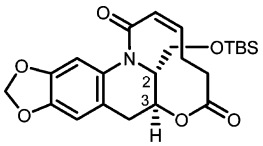
To a solution of **11b** (680 mg, 1.35 mmol) in dichloromethane (25 mL) at 0 °C under nitrogen were added tetrakis-(triphenylphosphine)palladium (0) (88 mg, 0.08 mmol) and morpholine (0.235 mL, 2.7 mmol). After stirring for 40 min at room temperature, the dichloromethane was evaporated. The crude residue obtained was utilized in next reaction without purification.



13

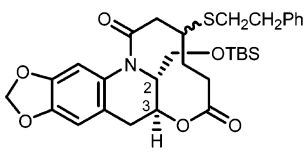
To a solution of the above amine residue in dry dichloromethane (10 mL) at 0 °C under nitrogen were added pyridine (0.22 mL, 2.7 mmol) and acryloyl chloride (0.137 mL, 1.62 mmol). After stirring at room temperature for 70 min, the reaction was quenched with aqueous saturated ammonium chloride. The aqueous layer was extracted two times with dichloromethane. The combined organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo. Purification by flash chromatography over silica gel with 10% ethyl acetate in hexanes afforded compound **13** as an oil (53% for two steps). R_f: 0.28 (4:1, hexane/ethyl acetate). LRMS: MS (ES+) m/z = 474.2 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.67 (s, 1H), 6.53 (m, 2H), 6.47 (s, 1H), 5.99 (s, 1H), 5.94 (s, 1H), 5.82 (m, 1H), 5.71 (d, J = 12.1 Hz, 1H), 5.03−5.12 (m, 3H), 4.80 (s, 1H), 3.67 (d, J = 4 Hz, 2H), 2.97 (dd, J = 5.5, 14.1 Hz, 1H), 2.58 (t, J = 11.3 Hz, 1H), 2.36−2.46 (m, 4H), 0.76 (s, 9H), −0.03 (d, J = 4.5 Hz, 6H) ppm.

To a solution of **13** (340 mg, 0.72 mmol) of in dry dichloromethane (340 mL) at room temperature under nitrogen was added second-generation Grubbs catalyst (122 mg, 0.144 mmol, 0.2 equiv). After refluxing at 45 °C for 1 h under nitrogen, the reaction mixture was cooled to room temperature, and the solvent was evaporated. Purification of the residue by flash chromatography over silica gel using 20% ethyl acetate in hexanes afforded the 10-membered macrocycle derivative **14** (210 mg, 65%) as a light green crystalline solid. R_f: 0.35 (2:1, hexane/ethyl acetate). LRMS: MS (ES+) m/z = 446.4 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.18 (s, 1H), 6.57 (s, 1H), 6.28 (d, J = 11.5 Hz, 1H), 5.96 (d, J = 11.5 Hz, 2H), 5.85 (td, J = 11.6 and 4.5 Hz, 1H), 5.41 (m, 1H), 4.38 (td, J = 8.2 and 2.6 Hz, 1H), 3.49−3.55 (m, 2H), 3.00 (m, 1H), 2.82−2.87 (m, 2H), 2.61 (m, 1H), 2.17−2.23 (m, 2H), 0.87 (s, 9H), −0.03 (d, J = 4 Hz, 6H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$); DEPT 135: δ 101.6, 60.6, 33.4, 29.0, 25.9 ppm (methylenes) and 172.4, 169.7, 146.1, 133.6, 128.9, 119.5, 66.6, 60.8, 32.0, 26.2, 26.1, 26.0, 25.7, 18.5, 5.2 ppm.



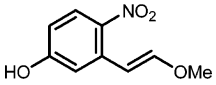
14

To a solution of benzene ethanethiol (0.336 mL, 2.5 mmol) in freshly distilled THF (9.0 mL) was added *n*-butyllithium (1.0 mL, 2.5 mmol) slowly at −78 °C. The mixture was stirred overnight (16 h) at ambient temperature. To a stirred solution of **14** (20.0 mg, 0.045 mmol) in dry THF (10 mL) at −20 °C under nitrogen was added the lithium salt solution (0.36 mL, 0.09 mmol, 2.0 equiv) of the freshly prepared solution. After stirring at this temperature for 2 h, a solution of saturated ammonium chloride was added, and the aqueous layer was extracted by dichloromethane. The combined organic layer was dried by magnesium sulfate, filtered, and concentrated in vacuo. Flash column chromatography over silica gel using 10% ethyl acetate in hexanes afforded the hetero Michael product **15** (20 mg, 76%) as a yellow oil. R_f: 0.60 (2:1, hexane/ethyl acetate). LRMS: MS (ES+) m/z = 584.2 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.29−7.33 (m, 2H), 7.21−7.25 (m, 3H), 6.65 (s, 1H), 6.35 (s, 1H), 5.97 (s, 2H), 5.26−5.30 (m, 1H), 3.71 (m, 1H), 3.50−3.55 (m, 2H), 3.39 (m, 1H), 2.99−3.05 (m, 1H), 2.90−2.93 (m, 2H), 2.84−2.86 (m, 1H), 2.80−2.83 (m, 2H), 2.60−2.69 (m, 2H), 2.56 (m, 1H), 2.38−2.43 (m, 1H), 1.85−1.94 (m, 2H), 0.89 (s, 9H), 0.03 (d, J 11.3 Hz, 6H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ 177.0, 170.6, 146.6, 140.6, 130.7, 128.9, 126.8, 120.1, 109.7, 109.2, 107.6, 107.1, 101.7, 68.0, 61.0, 58.1, 44.3, 42.6, 36.3, 33.5, 32.2, 29.2, 26.1, 18.5, 14.5, −5.1 ppm.



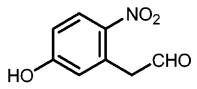
15 (single isomer)

To a suspension of (methoxymethyl)triphenylphosphonium chloride (25.5 g, 72 mmol) in THF (175 mL) at 0 °C was added dropwise potassium *tert*-butoxide (1.0 M in THF, 150 mL, 150 mmol). The resulting mixture was stirred at 0 °C for 1 h. A solution of 5-hydroxy-2-nitrobenzaldehyde (10.0 g, 60 mmol) in THF (100 mL) was added dropwise at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred overnight. The reaction was quenched by adding water (200 mL) at 0 °C. After removal of the THF, the aqueous layer was acidified to pH 6 by adding a 2 N HCl solution at 0 °C and was then extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and concentrated. Purification by column chromatography (25% ethyl acetate in hexanes) afforded **16a** (11.2 g, 95%) as a yellow oil. R_f: 0.68 (1:1, hexane/ethyl acetate). LRMS: MS (ES+) m/z = 196.1 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.02 (d, J = 9.0 Hz, 1H), 7.05 (d, J = 12.8 Hz, 1H), 6.86 (s, 1H), 6.72 (d, J = 9.0 Hz, 1H), 6.56 (d, J = 12.8 Hz, 1H), 5.47 (broad s, 1H, OH), 3.77 (s, 3H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ (trans) 159.9, 152.9, 141.2, 135.9, 128.6, 113.8, 113.4, 101.7, 57.1 ppm.



16a

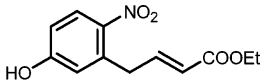
To a solution of **16a** (11.2 g, 57.5 mmol) in THF (150 mL) was added 1.5 N HCl solution (300 mL). The mixture was then heated to 60 °C and stirred overnight. The reaction mixture was cooled to 0 °C and neutralized with saturated sodium carbonate solution. After the THF removal, the aqueous layer was extracted with ethyl acetate (3 × 200 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated to afford 10.15 g (98%) of the crude aldehyde **16b** as a solid (mp 101.8−103.0 °C). R_f: 0.53 (1:1, hexane/ethyl acetate). LRMS: MS (ES+) m/z = 180.1 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 9.79 (s, 1H), 8.13 (d, J = 9.0 Hz, 1H), 6.98 (dd, J = 9.0 and 2.7 Hz, 1H), 6.91 (d, J = 2.6 Hz, 1H), 4.16−4.13 (m, 2H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ 198.0, 163.5, 142.1, 128.9, 120.9, 115.8, 49.5 ppm.



16b

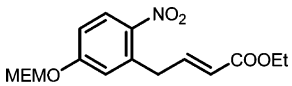
To a solution of **16b** (10.15 g, 56.0 mmol) in dry dichloromethane (200 mL) was added (carboxymethylene)-triphenylphosphorane (23.4 g, 67.0 mmol) at room temperature. The reaction mixture was refluxed at 45 °C until the starting material disappeared (TLC ∼ 1 h). The reaction was quenched with saturated ammonium chloride solution at room temperature and washed with water and brine. The organic phase was dried over magnesium sulfate. After solvent evaporation, the crude product was purified by flash column chromatography on silica gel (10−30% ethyl acetate in hexanes). The product **16c** was obtained as a yellow solid

(80% trans, 10% cis; 11.25 g trans product). R_f: 0.68 (1:1, hexane/ethyl acetate). LRMS: MS (ES+) m/z = 252.1 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.06 (d, J = 9 Hz, 1H), 7.20 (m, 1H), 7.06 (m, 1H), 6.29 (m, 1H), 5.80 (d, J = 16 Hz, 1H), 5.36 (s, 2H), 4.20 (q, J = 7 Hz, 2H), 3.88 (d, J = 6.5 Hz, 1H), 3.82.3.86 (m, 2H), 3.55.3.59 (m, 2H), 3.39 (s, 3H), 3.32 (d, J = 7 Hz, 1H), 1.31(t, J = 7.5 Hz, 3H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ 171.4, 161.3, 145.3, 136.3, 127.9, 123.7, 119.7, 116.3, 115.3, 93.7, 71.8, 68.6, 61.1, 59.5, 37.6, 14.6 ppm.



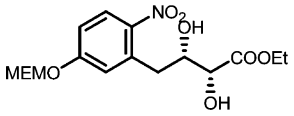
16c

To a solution of **16c** (11.25 g, 44.8 mmol) in dry dichloromethane (150 mL) at 0 °C under nitrogen were added DIPEA (11.7 mL, 67 mmol) and MEMCl (10.4 mL, 67 mmol). After stirring for 2 h at ambient temperature, the reaction mixture was quenched by a solution of saturated ammonium chloride. The aqueous layer was extracted by dichloromethane, and the combined organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo. Flash column chromatography with silica gel using 30% ethyl acetate in hexanes afforded 13.65 g (90%) of compound **16d** as an oil. R_f: 0.69 (1:1, hexane/ethyl acetate). LRMS: MS (ES+) m/z = 340.2 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.06 (d, J = 9 Hz, 1H), 7.20 (m, 1H), 7.06 (m, 1H), 6.29 (m, 1H), 5.80 (d, J = 16 Hz, 1H), 5.36 (s, 2H), 4.20 (q, J = 7 Hz, 2H), 3.88 (d, J = 6.5 Hz, 1H), 3.82−3.86 (m, 2H), 3.55−3.59 (m, 2H), 3.39 (s, 3H), 3.32 (d, J = 7 Hz, 1H), 1.31(t, J = 7.5 Hz, 3H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ 171.4, 161.3, 145.3, 136.3, 127.9, 123.7, 119.7, 116.3, 115.3, 93.7, 71.8, 68.6, 61.1, 59.5, 37.6, 14.6 ppm.



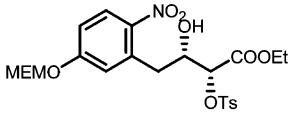
16d

To a 1-L round-bottomed flask equipped with a magnetic stirrer were added *t*-BuOH (200 mL), water (200 mL), and AD mix-α (56.4 g). To this mixture, methanesulfonamide (3.83 g, 40.27 mmol) was then added. The mixture was stirred at room temperature until both phases were clear and then cooled to 0 °C. Compound **16d** (13.65 g, 40.27 mmol) was then added, and the mixture was further stirred vigorously at room temperature until TLC revealed the absence of the starting olefin (time, ∼40 h). The reaction was quenched at 0 °C by the addition of sodium sulfite (60.0 g), warmed to room temperature, and further stirred for 1 h. The reaction mixture was then extracted several times with ethyl acetate. The combined organic layer was washed with 2 N KOH, dried over magnesium sulfate, and then concentrated. Purification by flash chromatography (silica gel, 25−8% ethyl acetate in hexanes) gave pure diol as a yellow oil (**16e**, 10.5 g, 70%; 90% ee determined by chiral HPLC OD column). R_f: 0.29 (1:1, hexane/ethyl acetate). LRMS: MS (ES+) m/z = 374.2 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.23 (d, J = 9.6 Hz, 1H), 7.42 (d, J = 2.5 Hz, 1H), 7.20 (dd, J = 2.5 and 9.1 Hz, 1H), 6.17 (d, J = 4 Hz, 1H), 5.41 (m, 1H), 5.37 (m, 2H), 5.15 (bs, 1H), 3.86 (m, 1H), 3.83 (t, J = 4.6 Hz, 2H), 3.55−3.59 (m, 2H), 3.36−3.40 (m, 1H), 3.36 (s, 3H), 3.03 (dd, J = 6.1, 17.5 Hz, 1H), 2.74 (dd, J = 1.5 and 18 Hz, 1H), 1.94 (bs, 1H), 1.32 (m, 3H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ 174.9, 162.1, 133.4, 128.3, 117.5, 116.1, 93.9, 93.7, 82.6, 71.8, 69.8, 68.6, 59.4, 38.7, 14.5 ppm.



16e

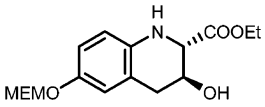
To a stirred solution of diol **16e** (10.5 g, 28.15 mmol) in dichloromethane (100 mL) at 0 °C under nitrogen was added triethylamine (5.9 mL, 42.2 mmol), followed by *p*-toluenesulfonyl chloride (5.37 g, 28.14 mmol). The solution was then stirred for 90 h at 0 °C. The reaction mixture was diluted with dichloromethane and water, dried over magnesium sulfate, filtered, and then concentrated. Column chromatography on silica gel (20% ethyl acetate in hexanes) afforded the *O*-tosyl derivative **16f** (13.0 g, 88%) as an oil. R_f: 0.37 (1:1, hexane/ethyl acetate). LRMS: MS (ES+) m/z = 528.3.1 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.05 (d, J = 9.1 Hz, 1H), 7.89 (d, J = 8 Hz, 2H), 7.37(d, J = 8 Hz, 2H), 7.01−7.06 (m, 2H), 5.33 (q, J = 7.1 Hz, 2H), 5.02 (d, J = 3 Hz, 1H), 4.37 (bs, 1H), 4.12−4.18 (m, 2H), 3.81 (t, J = 4.5 Hz, 2H), 3.54 (t, J = 4.5 Hz, 2H), 3.34 (s, 3H), 3.21 (m, 1H), 3.05 (m, 1H), 2.73 (d, J = 8.1 Hz, 1H), 2.46 (s, 3H), 1.20 (t, J = 7 Hz, 3H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ 167.3, 161.1, 145.8, 143.4, 136.0, 133.6, 130.1, 128.5, 128.1, 120.6, 118.4, 116.9, 115.5, 93.6, 80.1, 72.0, 68.6, 62.6, 60.8, 59.4, 38.2, 21.7, 14.3 ppm.



16f

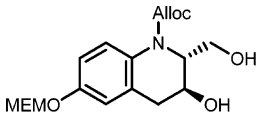
To a solution of **16f** (13.0 g, 24.77 mmol) in dry THF (250 mL) were added oven-dried potassium carbonate (6.84 g, 49.5 mmol) and 10% Pd−C (1.87 g, 20% w/w, added under nitrogen). The mixture was then hydrogenated for 30 h (monitored by TLC). After completion of the reaction, the mixture was filtered, washed several times with ethyl acetate, and then concentrated. Column chromatography on silica gel (20−70% ethyl acetate in hexanes) afforded the tetrahydroquinoline derivative **16g** as an oil (6.8 g, 84%). R_f: 0.56 (1:3, hexane/ethyl acetate). LRMS: MS (ES+) m/z = 326.3 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.58 (d, J = 9 Hz, 1H), 7.00 (dd, J = 2.7, 8.8 Hz, 1H), 6.94 (s, 1H), 5.31 (d, J = 2.5 Hz, 2H), 5.17 (m, 1H), 4.83 (t, J = 6.5 Hz, 1H), 4.45−4.50 (m, 2H), 3.85 (t, J = 4.8 Hz, 2H), 3.58 (t, J = 4.8 Hz, 2H), 3.40 (s, 3H), 3.05−3.09 (m, 2H), 1.63 (bs, 1H), 1.46 (t, J = 7 Hz, 3H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$)

δ 165.8, 158.9, 155.9, 136.9, 131.5, 128.5, 116.5, 115.6, 93.7, 71.9, 68.3, 62.8, 62.2, 59.5, 32.9, 14.7 ppm.



16g

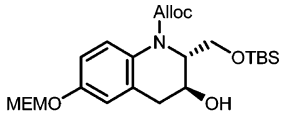
To a stirred solution of **16g** (1.0 g, 3.08 mmol) of in anhydrous THF (30 mL) at 0 °C under nitrogen was added lithium borohydride (2 M in THF, 3.08 mL, 6.16 mmol). After stirring for 1.0 h at room temperature under nitrogen, the reaction was quenched slowly with saturated aqueous ammonium chloride. Following evaporation of the THF, the mixture was extracted with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate, filtered,and concentrated in vacuo. After evaporation of the solvent, the residue was used directly for the next step without further purification.



16h

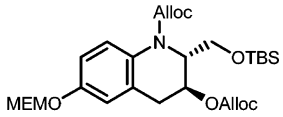
To a stirred solution of the amino alcohol obtained from the above reaction in anhydrous dichloromethane (20 mL) at 0 °C was added pyridine (0.25 mL, 3.14 mmol) and allyl chloroformate (0.34 mL, 3.14 mmol). After stirring for 40 min at 0 °C, the reaction was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted twice with dichloromethane, and the combined organic layer was dried with anhydrous magnesium sulfate, filtered, and then concentrated in vacuo. The residue was purified by column chromatography over silica gel with hexanes and ethyl acetate, giving product **16h** (880 mg, 78% over two steps) as a yellow oil. R_f: 0.48 (1:4, hexane/ethyl acetate). LRMS: MS (ES+) m/z = 368.1 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.34−7.50 (m, 1H), 6.90 (d, J = 9.5 Hz, 1H), 6.84 (s, 1H), 5.84−6.01 (m, 1H), 5.33 (d, J = 17.6 Hz, 1H), 5.27 (d, J = 9.6 Hz, 1H), 5.24 (s, 2H), 4.71 (td, J = 5.1 and 13.6 Hz, 1H), 4.62−4.67 (m, 1H), 4.59 (d, J = 5.5 Hz, 1H), 4.24−4.32 (m, 1H), 4.11−4.19 (m, 1H), 3.94−4.02 (m, 1H), 3.83 (t, J = 5.1 Hz, 2H), 3.58 (t, J = 4.3 Hz, 2H), 3.39 (s, 3H), 2.85−2.93 (m, 1H), 2.72−2.80 (m, 1H) ppm.

To a stirred solution of **16h** (880.0 mg, 2.4 mmol) in dichloromethane (20 mL) at 0 °C was added imidazole (326.0 mg, 4.8 mmol) and TBDMSCl (370 mg, 2.46 mmol). The mixture was stirred at 0 °C for an additional 25 min. The reaction was quenched with saturated ammonium chloride, and the aqueous layer was extracted three times with dichloromethane. The combined organic layer was dried over magnesium sulfate, filtered, and then concentrated in vacuo. The residue was purified by column chromatography over silica gel with 20% ethyl acetate in hexanes and afforded 960 mg (83%) of **17** as a yellow oil. R_f: 0.84 (1:4, hexane/ethyl acetate). LRMS: MS (ES+) m/z = 482.3 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.38 (d, J = 8 Hz, 1H), 6.90 (dd, J = 2.8 and 9 Hz, 1H), 6.87 (s, 1H), 5.96 (m, 1H), 5.33 (d, J = 17.5 Hz, 1H), 5.25 (s, 2H), 5.23 (m, 1H), 4.69 (qd, J = 5.5 Hz, 2H), 4.29 (m, 1H), 4.01 (m, 1H), 3.94 (m, 1H), 3.84 (t, J = 4.5 Hz, 2H), 3.58 (t, J = 4.5 Hz, 2H), 3.46 (t, J = 9.3 Hz, 1H), 3.40 (s, 3H), 2.88 (m, 1H), 2.78 (bs, 1H), 2.71 (m, 1H), 0.87 (s, 9H), 0.06 (d, J = 11.3 Hz, 6H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ 155.1, 154.7, 132.8, 131.0, 130.7, 126.4, 118.3, 115.9, 115.1, 94.1, 72.0, 71.7, 68.0, 67.0, 64.8, 61.9, 59.4, 34.9, 26.2, 18.5, −5.1 ppm.



17

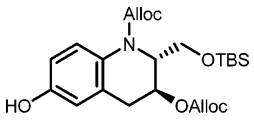
To a stirred solution of **17** (960 mg, 2.0 mmol) in anhydrous dichloromethane (30 mL) at room temperature were added pyridine (0.323 mL, 4.0 mmol) and allylchloroformate (0.437 mL, 4.0 mmol). After stirring for 48 h at room temperature, the reaction was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted twice with dichloromethane, and the combined organic layer was dried with anhydrous magnesium sulfate, filtered, and then concentrated in vacuo. The residue was purified by flash column chromatography over silica gel with hexanes and ethyl acetate and afforded 960 mg (85%) of the product **17a** as a yellow oil. R_f: 0.74 (2:1, hexane/ethyl acetate). LRMS: MS (ES+) m/z = 566.3 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.47(s, 1H), 6.91(dd, J = 2.5, 9 Hz, 1H), 6.84 (d, J = 2.5 Hz, 1H), 5.93−5.98 (m, 2H), 5.35 (m, 1H), 5.30 (m, 1H), 5.24 (s, 2H), 5.20−5.25 (m, 2H), 5.08 (m, 1H), 4.79 (q, J = 5 Hz, 1H), 4.68 (qd, J = 5.5 Hz, 2H), 4.63 (d, J = 5.5 Hz, 2H), 3.83 (t, J = 4.5 Hz, 2H), 3.65 (m, 1H), 3.60 (m, 1H), 3.58 (t, J = 4.5 Hz, 2H), 3.40 (s, 3H), 3.08 (m, 1H), 2.88 (m, 1H), 0.81 (s, 9H), −0.01 (d, J = 8.5 Hz, 6H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ 155.1, 154.5, 132.9, 131.9, 131.3, 126.4, 119.3, 118.2, 116.0, 115.4, 94.1, 73.7, 72.0, 70.1, 68.9, 68.0, 67.0, 62.4, 59.4, 58.2, 31.4, 26.1, 18.4, 10.6, −5.2 ppm.



17a

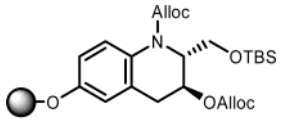
A stirred solution of **17a** (960 mg, 1.7 mmol) and zinc bromide (1.9 g, 8.5 mmol) in dichloromethane (50 mL) under nitrogen was stirred at room temperature for 24 h. After filtration and evaporation of the solvent, the purification was carried out by column chromatography over silica gel using 20−50% ethyl acetate in hexanes giving the free phenol **18** (480 mg, 60%). R_f: 0.24 (2:1, hexane/ethyl acetate). LRMS: MS (ES+) m/z = 478.4 (M + 1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.41 (s, 1H), 6.68 (dd, J = 2.8 and 8.8 Hz, 1H), 6.58 (d, J = 2.5 Hz, 1H), 5.91−6.02 (m, 2H), 5.33−5.41 (m, 2H), 5.32 (m, 1H), 5.29 (d, J = 10.5 Hz, 1H), 5.24 (d, J = 10.5 Hz, 1H), 5.05 (q, J = 5.5 Hz, 1H), 4.78 (q, J = 4.0 Hz, 1H), 4.69 (qd, J = 5.5, 13.5 Hz, 2H), 4.64 (d, J = 5.5 Hz, 2H), 3.59−3.64 (m, 2H), 3.04 (m, 1H), 2.84 (m, 1H), 0.82 (s, 9H), −0.01 (d, J = 7 Hz, 6H) ppm. ^{13}C NMR:

(100 MHz, $CDCl_3$) δ 155.3, 154.7, 153.2, 132.8, 131.8, 129.9, 126.6, 119.4, 118.2, 115.0, 114.4, 73.9, 68.9, 67.1, 62.4, 58.3, 31.3, 26.1, 18.4, −5.2 ppm.



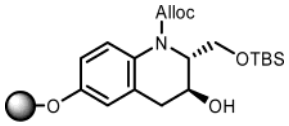
18

Solid-Phase Synthesis. BromoWang resin (1.70 mmol/g; 62 mg, 0.105 mmol) was washed several times with dichloromethane and DMF and then suspended in DMF for 30 min in DMF. To this mixture was added a solution of compound **18** (0.21 mmol) in anhydrous DMF (1.0 mL), sodium iodide (32.0 mg, 0.21 mmol, oven dry), and cesium carbonate (69.0 mg, 0.21 mmol, oven-dried). The mixture was bubbled vigorously with nitrogen for 48 h. The resin was successively washed with methanol (×2), DMF (×2), water (×2), methanol (×2), and dichloromethane (×3) and then dried under vacuum for a few hours. The mother liquor containing the starting material in DMF was evaporated, and the residue was redissolved in DCM. The organic layer was washed with water and brine, dried over magnesium sulfate, filtered, and then evaporated to dryness. The residue was purified by flash chromatography on silica gel (25% ethyl acetate in hexanes), giving the recovered starting material **18** (0.12 mmol). The loading of the compound was determined to be 85% after cleavage from the support.



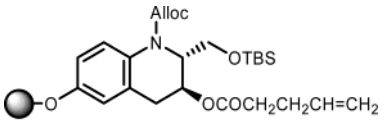
18a

To a suspension of resin (61.0 mg) in methanol (2.5 mL) was added NaOMe (0.4 mL, 0.2 mmol, 0.5 M in methanol) at room temperature. The mixture was stirred gently for 8 h. Following this, the resin was filtered and then washed with methanol (×3), DMF (×3), water (×3), methanol (×3), and dichloromethane (×3) and dried under vacuum.



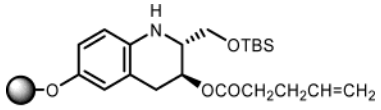
19

To a suspension of resin (61.0 mg) in dry dichloromethane (3.0 mL) were added DIC (0.6 mL, 0.095 mmol), 4-pentenoic acid (0.5 mL, 0.43 mmol), and DMAP (30 mg, 0.25 mmol). The mixture was stirred for 18 h at room temperature and then filtered. The resin was washed with methanol, DMF, water, methanol, and dichloromethane (3 times each) and then dried under vacuum.



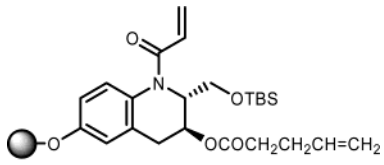
19a

To a suspension of resin obtained from the previous reaction in DCM (3.0 mL) was added tetrakis(triphenylphosphine)palladium (0) (33.0 mg, 0.03 mmol) dissolved in dry dichloromethane (3.0 mL). To this mixture were added a mixture of *N*-methylmorpholine (0.12 mL) and acetic anhydride (0.12 mL). The reaction mixture was bubbled under nitrogen for 18 h. The resin was washed consecutively with DMF, water, methanol, and dichloromethane (two times each) and then dried on a vacuum pump overnight.



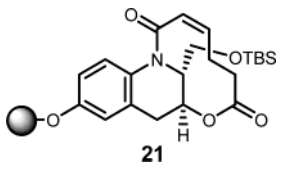
19b

The resin obtained from the previous reaction was suspended in dichloromethane (3.0 mL), and to this were added triethylamine (0.38 mL, 2.7 mmol) and acryloyl chloride (0.17 mL, 2.0 mmol). The mixture was bubbled with nitrogen flow for 24 h. The resin was washed with DMF (×2), methanol (×2), and dichloromethane (×3) and then dried over a high vacuum pump.



20

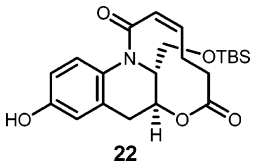
In a round-bottomed flask, the above resin was suspended in dichloromethane (5.0 mL) under nitrogen. To this mixture was added a second-generation Grubbs catalyst (51 mg, 0.06 mmol) dissolved in dichloromethane (4.0 mL). The reaction mixture was warmed to 40 °C and stirred for 6 h. The mixture was brought to room temperature, and then the resin was washed with dichloromethane, methanol, and dichloromethane (3 times each) and finally was dried over a high vacuum pump.



21

The resin was treated with 5% TFA in anhydrous dichloromethane (10.0 mL) at room temperature for 1 h. Following this, it was washed twice with dichloromethane and filtered, and the solvent was evaporated. The residue was then purified by flash column chromatography over silica gel using 10% ethyl acetate and hexanes to give the final product **21** in overall 40% yield for 5 steps. R_f: 0.28 (2:1, hexane/ethyl acetate). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.56 (m, 1H), 6.73 (dd, J = 2.8 and 8.8 Hz, 1H), 6.59 (d, J = 3 Hz, 1H), 6.30 (d, J = 11.6 Hz, 1H), 5.85 (td, J = 4 and 11.8 Hz, 1H), 5.41 (m, 1H), 4.40 (m, 1H), 3.46−3.56 (m, 2H), 3.04 (m, 1H), 2.92 (m, 1H), 2.84 (m, 1H), 2.61 (m, 1H), 2.32 (m, 1H), 2.29 (m, 1H), 0.87 (s, 9H), −0.05 (d, J = 4 Hz, 6H) ppm. ^{13}C NMR: (100 MHz, $CDCl_3$) δ 172.5, 169.8,

162.8, 153.8, 134.9, 133.7, 130.6, 129.4, 128.9, 127.5, 115.2, 114.3, 66.7, 60.8, 33.4, 28.9, 26.1, 18.5, −5.2 ppm.



22

Acknowledgment. We thank the NRC Genomics Program, Special VP-Research NRC Funds for Chemical Biology and the National Cancer Institute of Canada for financial support. S.K. is a graduate student at the Department of Chemistry, University of Ottawa.

Supporting Information Available. Analysis of 1D and 2D NMR spectra of compounds **14**, **15**, and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The diffraction data was collected with $Mo_{K\alpha}$ radiation, ω scan mode, and a graphite monochromator on a Bruker Smart diffractometer equipped with a CCD detector. The structure was solved by direct method using the SHELXTL suite of programs (a). Multiscan absorption correction was made with program sadabs (b). All hydrogen atoms were put in calculated positions. Crystal structure is monoclinic, P2(1); (crystal size 0.3 × 0.25 × 0.2 mm), $a = 7.1242(4)$, $b = 10.3236(5)$, $c = 15.8881(8)$; $\beta = 99.426(1)$; $V = 1152.75(10)$ Å^3; $Z = 2$; $\rho_{calc} = 1.284$ mg/m^3; $2\theta_{max} = 59.16°$; GoF on $F^2 = 0.933$; residual electron density max. 0.34, min. −0.18 e Å^{-3}. Final R indices ($I > 2\sigma(I)$): $R_1 = 0.034$, $wR_2 = 0.090$ (14 543 reflections total, 6357 unique, 5930 > 2σ). (a) Sheldrick, G. M. SHELXTL, version 6.10; Brucker AXS Inc.: Madison, WI, 2000. (b) Sheldrick, G. M. SADABS, version 2.03; University of Gottingen, Germany, 2002.

CC049941O