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Diastereoselective synthesis of a highly substituted *cis*-decahydroquinoline via a Knoevenagel condensation

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ABSTRACT

A diastereoselective approach to 3,7,8-trisubstituted *cis*-decahydroquinolines is described. This ring system forms the core of rings B and E of the norditerpenoid alkaloid methyllycaconitine. This approach starts with a known disubstituted cyclohexene. The remaining carbons are attached via a Knoevenagel condensation followed by an intramolecular lactam formation. The stereochemistry of the substituents is controlled by the cis-substitution of the starting cyclohexene ring.

1. Introduction

Methyllycaconitine (MLA), a norditerpenoid alkaloid isolated from plants of the genera *Aconitum* and *Delphinium*,[1,2] is the most potent nonpeptide antagonist at the α7 nicotinic acetylcholine receptors (nAChRs).[3,4] The interesting structure and biological activities of methyllycaconitine have stimulated numerous synthetic efforts in the past decades.[5–25] In our efforts to identify structure–activity relationships of methyllycaconitine, we have synthesized numerous simple analogues of methyllycaconitine, which contain only the E ring and the succinimidoylanthranilate ester.[26–29] All of the simple E-ring analogues have been shown to be noncompetitive antagonists to the α3β4* nAChR, with no affinity to the agonist binding sites of either α7, α4β2, or α3β4* nAChRs.[30] We hoped that introducing a more rigid conformation to our previous E-ring analogues might provide a selective and competitive ligand to the α7 nAChR. A simple removal of the A, C, D, and F rings of MLA provides a BE-ring analogue. This analogue should thus be available from the *cis*-decahydroquinoline core structure (Fig. 1).

In addition, the *cis*-decahydroquinoline ring system is an essential component of many interesting and pharmacologically useful compounds. These include amphibian alkaloids such as *cis*-195A, isolated from the skin extract of the Panamanian frog *Dendrobates pumilio* in 1969.[31] Since that time, over 50 *cis*-decahydroquinoline alkaloids have been isolated from amphibian sources.[32] Moreover, this cis-fused heterocyclic ring system frequently occurs as a subunit of many polycyclic natural alkaloids, such as huperzine B[33] and cylindricines A–K.[34,35]

Much of the methodology for the synthesis of the *cis*-decahydroquinoline ring system has focused on the synthesis of the 2,5-disubstituted ring system (e.g., *cis*-195A, Lepadins).[36–38] These methods are not well suited for the synthesis of the desired 3,7,8-trisubstituted ring system **1**. Many of these methods are focused on carbon substitution at the 2- and 5-position as seen in natural products such as *cis*-195A and Lepadin A. For the synthesis of our required bicyclic amine **1**, we need a carbon substituent at position 3 and the ability to introduce hydroxyl groups at positions 7 and 8.

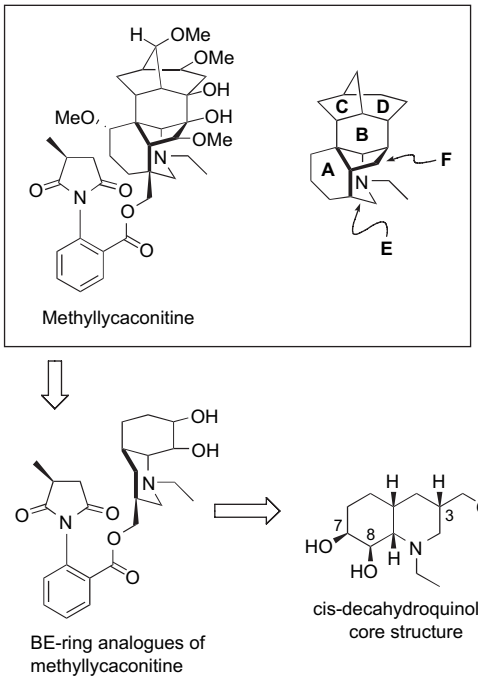

Figure 1. Methyllycaconitine and necessary decahydroquinoline core structure.

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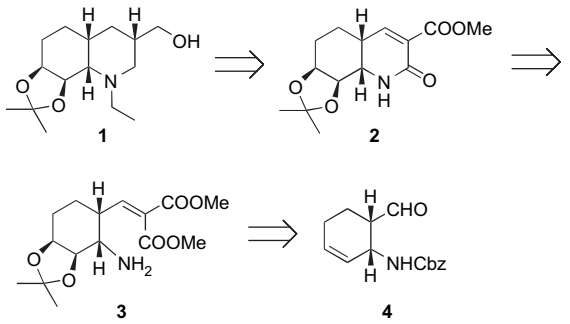


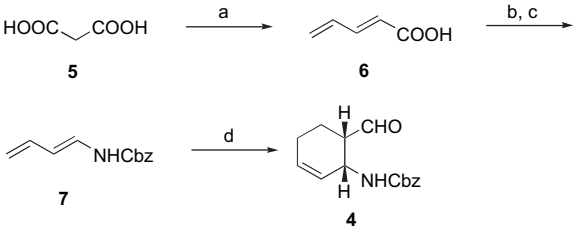
Scheme 1. Retrosynthesis of the *cis*-decahydroquinoline core structure **1**.

Equally important is the ability to control the relative stereochemistry at position 3. While some of the known methods for the synthesis of the *cis*-decahydroquinoline ring system might be adapted by omitting a carbon chain or two, they lack a method to control the newly instituted stereocenter at position 3. Herein, we wish to describe a diastereoselective route to this *cis*-decahydroquinoline ring core, which includes five stereocenters. The *cis*-decahydroquinoline system **1** can be obtained via the reduction of the lactam-ester **2** (Scheme 1). This bicycle can be formed from an intramolecular cyclization reaction of diester-amine **3**. The diester compound **3** can be obtained from aldehyde **4** via a Knoevenagel condensation. The starting aldehyde **4** is known[39] and can be readily prepared via a Diels–Alder cycloaddition.[40–44]

2. Results and discussion

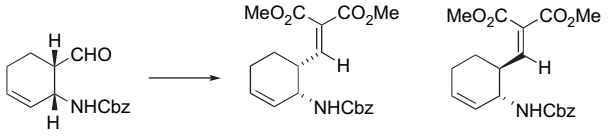
As outlined in Scheme 2, our synthesis of aldehyde **4** follows the previously published method of Overman and co-workers. We have made slight changes in the procedure that have improved the yield of diene **7**.[44–46] Reaction of acid **6** with diphenyl phosphoryl azide[47] provides the intermediate acylazide. In the original procedure,[45,46] the acylazide was prepared in situ by using ethyl chloroformate and sodium azide. Our modification avoids any formation of ethanol, a good nucleophile that can react with the acylazide in the work-up process and lower the overall yield. The acylazide was sufficiently stable at rt that was quickly chromatographed to remove the very polar by-product formed in the reaction. Curtius rearrangement of the acylazide in the presence of benzyl alcohol provides diene **7** in 70% yield from acid **6**. The Diels–Alder reaction of **7** with acrolein was carried out in a sealed tube and provided an 80% yield of predominantly cis-compound **4** (cis/trans=10:1). cis-Compound **4** can be further purified via recrystallization from a 20% EtOAc/hexane solution.

The synthetic approach was designed to use the Knoevenagel condensation for the installation of the remaining carbons of the decahydroquinoline ring system. The Knoevenagel condensation is a well known method for the synthesis of alkylidine malonates.[48,49] As shown in Table 1, the use of standard reaction conditions



Scheme 2. (a) Acrolein, pyridine, rt, 3 h, 50%; (b) Et_3N, $(PhO)_2P(O)N_3$, CH_2Cl_2, rt, 1 h; (c) $PhCH_2OH$, toluene, 0.5 h, 110 °C, 70% over two steps; (d) acrolein, toluene, 110 °C, 90 min, 80%.

Table 1
Comparison of Knoevenagel reaction conditions



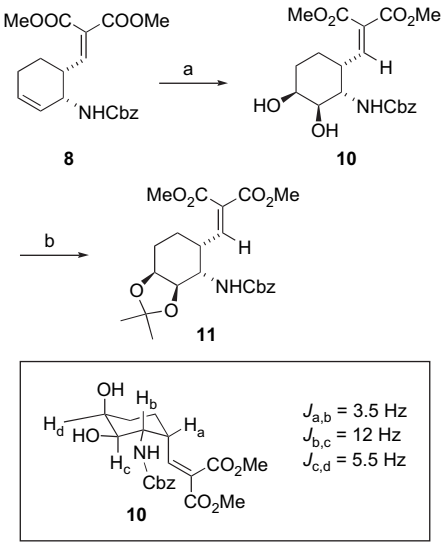
Entry	Conditions	Product ratio (**8**/**9**)[a] (yield, %)[b]
1	10 mol % piperidine, 10 mol % HOAc, rt, 8 h	1:1 (95)
2	10 mol % piperidine, 10 mol % HOAc, 4 Å MS, 0 °C, 4 h	4:1 (90)
3	Pyridine (solvent), 100 mol % HOAc, rt, 20 h	1:0 (80)
4	200 mol % Et_3N, 200 mol %, HOAc, rt, 8 h	1:0 (70)
5	20 mol % Et_3N, 20 mol % HOAc, 4 Å MS, rt, 4 h	1:0 (80)

[a] Determined by ^1H NMR.
[b] Isolated yield of an inseparable mixture of **8** and **9**.

provides the expected product and its diastereomer in a 1:1 ratio. While the yield of the product was excellent, the large amount of epimerization was unacceptable for the preparation of our target compounds. Adding 4 Å molecular sieves to the reaction and decreasing the reaction temperature to 0 °C reduce the amount of trans-product **9**, giving a cis/trans ratio of 4:1. While considering the reaction mechanism, we hypothesized that the piperidine first reacted with aldehyde **4** to form an iminium salt.[49] This iminium salt can subsequently tautomerize to form an enamine[50] and then tautomerization again provides the more stable trans-isomer. To avoid this epimerization, we changed the secondary amine catalyst to tertiary amine such as Et_3N or pyridine to preclude iminium ion formation (and the subsequent epimerization). We believe that the change in base from piperidine to Et_3N may shift the mechanism from the Knoevenagel mechanism (iminium formation) to the Hann–Lapworth mechanism (β-hydroxy ester formation).[49] This shift in mechanistic pathway should eliminate the possibility for enamine formation and consequently epimerization. We were pleased to see that reaction using either pyridine or Et_3N provided solely the cis-diastereomer. Decreasing the amount of Et_3N and adding molecular sieves decrease the reaction time while retaining the good yields and excellent diastereoselectivity. Decreasing the amount of Et_3N to 10 mol % did provide similar levels of diastereoselectivity, however, the reaction took over 24 h to provide an 80% yield. Compared with the only 2 h required with 20 mol % of Et_3N, this seemed to be as low as was practical for this transformation.

The next step was to carry out a selective dihydroxylation of the cyclohexene double bond. The use of catalytic OsO_4/NMO provided an excellent yield of diol **10**.[51] Our expectation was that diol **10** would be the preferred product with osmylation occurring from the least hindered face of the molecule. An examination of the coupling constants between H_b and H_c showed the expected large diaxial coupling constant (Scheme 3 inset). The corresponding all cis product would not have any diaxial couplings. The relatively polar diol was converted to the acetonide in 85% yield by treatment with 2,2-dimethoxypropane. The relative stereochemistry of **10** was further confirmed by single crystal X-ray of acetonide **11** as shown in Figure 2.[52]

Our plan for the conversion of **11** to **2** required the selective removal of the carbobenzyloxy group followed by an intramolecular cyclization to lactam **2**. Reduction of the double bond at this stage would generate a 1,3-dicarbonyl compound (**12**), which would likely readily epimerize. As shown in Table 2, the use of standard deprotection conditions provided over-reduced compound **12** as the sole product in excellent yield. The use of different hydrogen sources (Table 1, entries 2 and 3) such as cyclohexadiene or ammonium formate also provided only the over-reduced



Scheme 3. (a) OsO_4 (5 mol %), NMO, acetone/H_2O (3:1), 8 h, rt, 85%; (b) $(CH_3)_2C(OCH_3)_2$, 2 mol % *p*-TSA, 6 h, rt, 95%.

product **12**. Interestingly, decreasing the amount of catalyst and reducing the reaction time (entry 4) provided **13** as the major product. Sakaitani and Ohfune described the conversion of a Cbz group into a triethylsilyl carbamate ($NH–CO_2SiEt_3$), which is converted to the corresponding carbamic acid in situ and decarboxylated to give the free amine.[53] Applying these conditions to our substrate provided no product at all (entry 5). Using the Coleman modification of a stoichiometric amount of Pd salt to significantly increase the reaction rate[54,55] (entry 6) provided some of the desired product. We thus increased the loading of $Pd(OAc)_2$ to 300 mol % and found that the deprotection and cyclization reaction occurred in only 30 min (entry 7). In addition to the changes in catalyst loading, we also changed the solvent to the more polar EtOAc/EtOH mixture.[56] We were then able to decrease the $Pd(OAc)_2$ to only 30 mol %, which provided the desired product in acceptable yield without using a large excess of the palladium salt (entry 8).

With lactam **2** in hand, we need to reduce either the lactam or the ester without reducing the double bond. Upon reduction of one of these carbonyl moieties, the double bond can be stereoselectively reduced and the final stereocenter introduced into the molecule. The reaction of **2** with a slight excess of DIBAL cleanly provided the alcohol with no concomitant 1,4-reduction of the double bond. The double bond was then stereoselectively reduced with 10% Pd/C and H_2 to provide **14** as a single diastereomer.

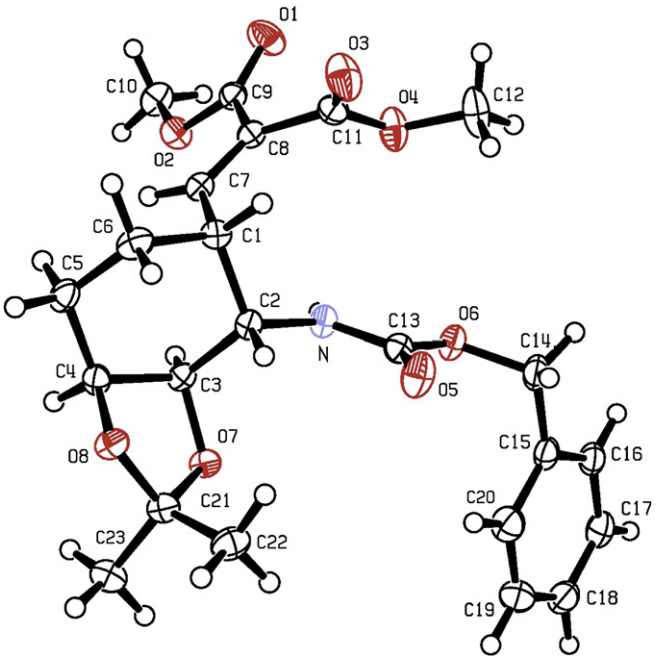
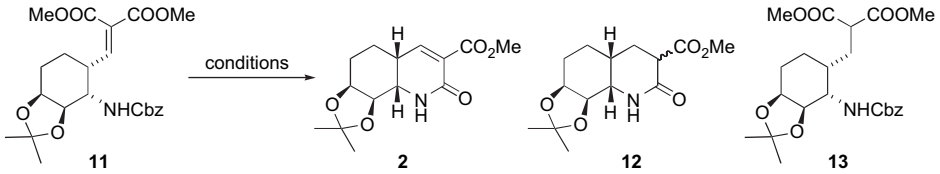


Figure 2. Perspective view of the molecular structure of **11** with the atom labeling scheme. The thermal ellipsoids are scaled to enclose 30% probability.

Compound **14** was unfortunately too polar to readily purify and we thus converted it directly to the target compound **1**. The lactam of **14** was reduced with $LiAlH_4$ to the amine and then alkylated with ethyl iodide to provide **1** in 45% overall yield from **2**. With compound **1** in hand, we were now able to confirm the relative stereochemistry that was set in the hydrogenation of **2**. A NOESY experiment with compound **1** clearly showed NOE crosspeaks between H-3 and H-9 as well as between H-9 and H-10 (Scheme 4, inset). This confirms the hydrogenation occurring from the less hindered face of the bicycle **2** as one would predict.

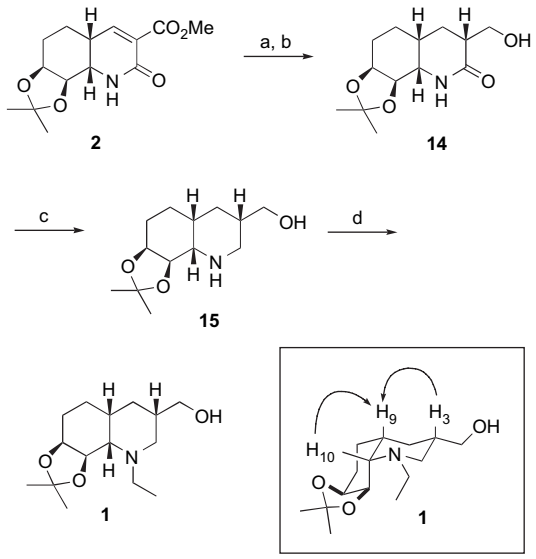
In summary, we have developed an efficient and highly diastereoselective approach to the cis-fused 3,7,8-trisubstituted decahydroquinoline **1**. The epimerization in the Knoevenagel condensation was prevented by using a tertiary amine catalyst. The removal of the Cbz group and subsequent intramolecular cyclization was accomplished using catalytic $Pd(OAc)_2$ and triethylsilane. This methodology provides synthetic flexibility and opens the door for the controlled construction of more complex alkaloids with *cis*-decahydroquinoline subunits. The conversion of **1** to MLA

Table 2
Conditions for selective removal of a Cbz group from **11**



Entry	Conditions	Product	Yield (%)
1	10 mol % of 10% Pd/C, H_2, MeOH, 8 h	**12**	90
2	10 mol % of 10% Pd/C, 1,4-cyclohexadiene, solvent, 8 h	**12**	80
3	10 mol % of 10% Pd/C, HCO_2NH_4, solvent, 8 h	**12**	70
4	3 mol % of 10% Pd/C, H_2, MeOH, solvent, 2 h	**13**	50 (+20% of **11**)[a]
5	400 mol % Et_3SiH, 10 mol % $Pd(OAc)_2$, 100 mol % Et_3N, CH_2Cl_2, rt, 16 h		NR
6	120 mol % Et_3SiH, 100 mol % $Pd(OAc)_2$, 120 mol % Et_3N, EtOAc, rt, 6 h	**2**	10
7	120 mol % Et_3SiH, 300 mol % $Pd(OAc)_2$, 120 mol % Et_3N, EtOAc/EtOH (1:1), rt, 0.5 h	**2**	50
8	120 mol % Et_3SiH, 30 mol % $Pd(OAc)_2$, 120 mol % Et_3N, EtOAc/EtOH (1:1), rt, 4 h	**2**	50 (+10% of **11**)

[a] Isolated yield of an inseparable mixture of **13** and **11**, ratio of **13** to **11** determined by ^1H NMR.



Scheme 4. (a) DIBAL-H, THF, 0 °C, 4 h; (b) 10 mol % of 10% Pd/C, H_2 (1 atm), MeOH, rt, 4 h; (c) $LiAlH_4$, THF, rt, 24 h; (d) iodoethane, K_2CO_3, acetone, rt, 16 h, 45% over four steps. Inset: observed NOE crosspeaks from NOESY spectra of **1**.

analogues and subsequent pharmacological assays are underway and will be reported in due course.

3. Experimental

3.1. General

All reagents used were purchased from commercial sources or prepared according to standard literature methods using references given in the text and purified as necessary prior to use by standard literature procedures. THF and CH_2Cl_2 were dried using a Solv-Tek solvent purification system. Dry DMF was distilled from calcium hydride and degassed for 10 min prior to use. Dry toluene was distilled from calcium hydride prior to use. Column chromatography was performed using ICN silica gel 60A. Proton (^{1}H) and carbon (^{13}C) magnetic resonance spectra (NMR) were recorded on a Bruker 300 MHz spectrometer, and chemical shift values are expressed in parts per million (δ) relative to tetramethylsilane (TMS, 0 ppm) as an internal reference. All high-resolution mass spectra (HRMS) were acquired using positive electrospray ionization (ESI) at the Mass Spectrometry Center of the University of Tennessee. The relative stereochemistry of all compounds is noted using the *R** or *S** notation.[57]

3.2. Benzyl *trans*-1,3-butadiene-L-carbamate (7)

To a solution of *trans*-2,4-pentadienoic acid **6** (2.45 g, 25 mmol) in Et_2O (50 mL) at 0 °C was added Et_3N (3.8 mL, 27.5 mmol) followed by diphenyl phosphoryl azide (6.0 mL, 27.5 mmol). The reaction mixture was warmed to rt and stirred for 30 min. The mixture was cooled to 0 °C, and saturated aqueous $NaHCO_3$ and Et_2O were added. The aqueous layer was separated and extracted with Et_2O, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Chromatography (15% EtOAc in hexane) of the residue with a short column to remove the polar impurity provided 3.0 g of the acylazide as a brown oil. The acylazide was diluted with dry toluene (10 mL), and was then added over 30 min to a vigorously stirred solution of benzyl alcohol (2.4 mL, 23 mmol) and 2,6-di-*tert*-butyl-4-methylphenol (20 mg) in dry toluene (30 mL) while a rapid reflux was maintained. Reflux was continued for an additional 30 min, and then the reaction mixture was cooled to rt and concentrated to afford a brown semisolid residue, which was purified immediately by chromatography (10% EtOAc in hexanes) to give 4 g (79%) of **7** as a white solid, mp 70–73 °C. R_f 0.7 (20% EtOAc in hexanes), which matched the reported analytical data.[45]

3.3. Carbamic acid, [(1*R**,6*S**)-6-formyl-2-cyclohexen-1-yl]-, phenylmethyl ester (4)

A solution of **7** (3 g, 14.8 mmol), acrolein (1.1 mL, 14.8 mmol), and 2,6-di-*tert*-butyl-4-methylphenol (10 mg) in toluene (10 mL) was placed in an Ace glassware resealable sealed tube (Cat. # 8648–86). The tube was degassed with three freeze/thaw cycles and then filled with Ar. The tube was heated to 110 °C for 90 min, then cooled, concentrated, and chromatographed (15% EtOAc in hexanes) to give 2.9 g (80% considering recovered **7**) of **4** as a white solid, mp 80–82 °C. R_f 0.4 (20% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.80 (s, 1H), 7.35 (m, 5H), 5.90 (m, 1H), 5.72 (d, *J*=9.8 Hz, 1H), 5.12 (m, 3H), 4.75 (br s, 1H), 2.80 (br s, 1H), 1.92–2.15 (m, 3H), 1.58–1.80 (m, 1H); ^{13}C NMR ($CDCl_3$, 70 MHz) δ 202.7, 136.2, 135.8, 130.7, 128.6, 128.2, 128.1, 126.3, 67.0, 51.0, 45.6, 23.4, 18.6; HRMS calcd for $C_{15}H_{17}NO_3Na^+$ 282.1101, found 282.1105 (1.4 ppm).

3.4. Benzyl (1*R**,6*R**)-6-(2,2-di(methoxycarbonyl)vinyl)-cyclohex-2-enylcarbamate (8)

Et_3N (0.43 mL, 3.1 mmol) and HOAc (0.18 mL, 3.1 mmol) were simultaneously added by syringe to a vigorously stirred EtOH (50 mL) solution of methyl malonate (1.94 mL, 17.0 mmol), aldehyde **4** (4.0 g, 15.4 mmol), and 4 Å molecular sieves (5.0 g). After stirring for 6 h at rt, the solvent was removed by rotary evaporator at rt. The resulting slurry was diluted with Et_2O and filtered. The filtrate was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, concentrated, and chromatographed (20% EtOAc in hexanes) to provide 4.6 g (80%) of **8** as a white solid, mp 92–94 °C. R_f 0.3 (20% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36 (m, 5H), 7.04 (d, *J*=10.8 Hz, 1H), 5.89 (m, 1H), 5.62 (d, *J*=9.6 Hz, 1H), 5.12 (m, 2H), 4.75 (d, *J*=8.9 Hz, 1H), 4.46 (br s, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.05 (br s, 1H), 2.12 (br s, 2H), 1.60–1.92 (m, 2H); ^{13}C NMR ($CDCl_3$, 70 MHz) δ 165.7, 164.1, 155.8, 148.5, 136.4, 130.2, 129.6, 128.5, 128.1, 127.9, 126.4, 66.9, 52.4, 48.7, 38.1, 24.8, 22.6; HRMS calcd for $C_{20}H_{23}NO_3Na^+$ 396.1418, found 396.1408 (2.3 ppm).

3.5. Benzyl (1*S**,2*R**,3*S**,4*R**)-4-(2,2-di(methoxycarbonyl)vinyl)cyclohexyl-1,2-diol-3-enylcarbamate (10)

To a 0 °C solution of **8** (5.7 g, 15.2 mmol) and NMO (3.6 g, 30.7 mmol) in acetone/water (3:1, 100 mL) was added OsO_4 (7.0 mL of a 2.5% solution in H_2O, 0.7 mmol). The reaction mixture was warmed to rt and stirred for 8 h. A solution of $Na_2S_2O_4$ (1 g) in H_2O (10 mL) was added to the reaction mixture and stirred for 20 min. The reaction mixture was extracted with EtOAc (3×50 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, concentrated, and chromatographed (50% EtOAc in hexanes) to provide 5.3 g (85%) of **10** as a colorless oil. R_f 0.3 (50% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35 (m, 5H), 7.05 (d, *J*=11.5 Hz, 1H), 5.30 (d, *J*=9.6 Hz, 1H), 5.11 (m, 2H), 4.10 (ddd, *J*=12.2, 9.5, 3.5 Hz, 1H), 4.04 (br s, 1H), 3.79 (s, 6H), 3.72 (dd, *J*=12.2, 4.5 Hz, 1H), 3.10 (m, 1H), 2.05 (br s, 1H), 1.84 (br s, 1H), 1.75 (t, *J*=12.5 Hz, 1H), 1.46 (dd, *J*=14.0, 4.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 70 MHz) δ 165.7, 163.8, 157.7, 145.9, 136.1, 130.8, 128.6, 128.3, 71.7, 68.8, 67.3, 53.5, 52.7, 38.5, 25.8, 23.5; HRMS calcd for $C_{20}H_{23}NO_8Na^+$ 430.1472, found 430.1476 (1.0 ppm).

3.6. Benzyl (1*S**,2*R**,3*S**,4*R**)-4-(2,2-di(methoxycarbonyl)-vinyl)cyclohexyl-1,2-diol-1,2-*O*-isopropylidine-3-enylcarbamate (11)

The diol **10** (5.0 g, 12.3 mmol) was dissolved in a 2,2-dimethoxypropane/acetone (2:1) solution (60 mL), then $TsOH \cdot H_2O$ (25 mg, 0.13 mmol) and $MgSO_4$ (5.0 g) were added. The reaction mixture was stirred for 6 h at rt, filtered, concentrated, and chromatographed (30% EtOAc in hexane) to provide 5.2 g of **11** (95%) as a white solid, mp 143–146 °C. R_f 0.7 (50% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (m, 5H), 6.94 (d, J=11.5 Hz, 1H), 5.15 (m, 2H), 4.98 (d, J=7.9 Hz, 1H), 4.33 (br s, 1H), 3.95 (m, 2H), 3.78 (s, 3H), 3.71 (s, 3H), 3.15 (dd, J=11.1, 3.4 Hz, 1H), 2.05 (m, 3H), 1.54 (m, 4H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 70 MHz) δ 166.0, 164.5, 156.7, 145.8, 136.9, 131.8, 129.1, 128.9, 128.8, 109.5, 76.2, 73.9, 67.6, 54.4, 53.4, 53.3, 39.0, 28.8, 26.8, 23.1, 21.7; HRMS calcd for $C_{23}H_{29}NO_8Na^+$ 470.1785, found 470.1788 (1.0 ppm).

3.7. (4a*R**,7*S**,8*R**,8a*R**)-Methyl 1,2,4a,5,6,7,8,8a-octahydro-2-oxoquinoline-7,8-diol-7,8-*O*-isopropylidine-3-carboxylate (2)

$Pd(OAc)_2$ (68 mg, 0.3 mmol) was added to a solution of **11** (450 mg, 1.0 mmol) in dry EtOAc (6 mL). Dry EtOH (6 mL) was then added and the reaction mixture stirred for 5 min, and then freshly distilled triethylsilane (0.19 mL, 1.2 mmol) was added, immediately followed by the addition of dry Et_3N (0.17 mL, 1.2 mmol). The reaction mixture was stirred for an additional 30 min (until TLC indicated the starting material was consumed) and the reaction mixture was diluted with CH_2Cl_2, filtered through a Celite pad, washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, concentrated, and chromatographed (5% MeOH in CH_2Cl_2) to provide 140 mg (50%) of **2** as a brown oil. R_f 0.2 (50% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.90 (d, J=11.5 Hz, 1H), 6.45 (d, J=10.5 Hz, 1H), 4.09 (m, 1H), 3.85 (s, 3H), 3.78 (m, 2H), 3.50 (m, 1H), 1.98 (m, 3H), 1.36 (m, 4H), 1.20 (m, 3H); ^{13}C NMR ($CDCl_3$, 70 MHz) δ 166.7, 160.5, 143.8, 131.0, 109.5, 75.5, 73.6, 54.4, 52.5, 38.4, 28.2, 26.2, 22.4, 21.1; HRMS (ESI) $C_{14}H_{19}NO_5$ m/z calculated $M+H^+$ 282.1341, measured $M+H^+$ 282.1346 (1.8 ppm).

3.8. ((3*S**,4a*R**,7*S**,8*R**,8a*R**)-1-Ethyl-decahydroquinolin-7,8-diol-7,8-*O*-isopropylidine-3-yl)methanol (1)

Compound **2** (310 mg, 1.1 mmol) was dissolved in THF (20 mL) and cooled to 0 °C. DIBAL-H (1.3 mL of a 1.0 M solution in hexane, 1.3 mmol) was added and the reaction mixture stirred for 4 h. The reaction was quenched with MeOH until no additional gas (H_2) release was observed and then NaF (50 mg, 1.19 mmol) was added. The mixture was stirred for 2 h at rt, filtered, and concentrated to provide the crude allylic alcohol. The crude alcohol was dissolved in MeOH (20 mL) and then 10% Pd/C (106 mg) was added. The reaction mixture was then stirred under an H_2 atmosphere (balloon) for 4 h. The reaction mixture was filtered through a Celite pad and concentrated to give 216 mg (77%) of crude **14**, which was used directly in next step. Crude compound **14** (216 mg, 0.85 mmol) was dissolved in THF (10 mL) and cooled to 0 °C, followed by the addition of $LiAlH_4$ (100 mg, 2.6 mmol). The reaction mixture was warmed to rt and stirred for 24 h. The reaction mixture was then diluted with Et_2O. To this mixture was sequentially added H_2O (0.11 mL), 15% aqueous NaOH (0.11 mL), and H_2O (2.6 mL). The reaction mixture was stirred for an additional 30 min at rt, filtered, and concentrated to give 144 mg (0.6 mmol, 70% yield) crude **15** as a colorless oil. Amine **15** was dissolved in acetone (8 mL), then iodoethane (0.06 mL, 0.72 mmol) and K_2CO_3 (332 mg, 2.4 mmol) were added, and the reaction mixture was stirred for 16 h at rt. The reaction mixture was then filtered, concentrated, and chromatographed (5% MeOH in CH_2Cl_2) to provide 133 mg (81%, 45% from compound **2**) of **1** as a yellow oil. R_f 0.35 (10% MeOH in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.21 (m, 2H), 3.38 (m, 2H), 2.82 (m, 3H), 2.53 (m, 1H), 2.17 (m, 1H), 1.80 (m, 6H), 1.44 (m, 4H), 1.25 (m, 5H), 1.02 (t, J=14.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 70 MHz) δ 107.4, 74.2, 71.7, 68.0, 60.1, 49.2, 48.8, 38.1, 33.6, 28.3, 28.2, 28.1, 24.9, 13.4; HRMS (ESI) $C_{15}H_{27}NO_3$ m/z calculated $M+H^+$ 270.2069, measured $M+H^+$ 270.2067 (0.7 ppm).

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