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Total Synthesis of Quinolizidine (−)-217A

Mouloud Fellah, Marco Santarem, Gérard Lhommet,* and Virginie Mouriès-Mansuy*

UPMC Univ Paris 06, Institut Parisien de Chimie Moléculaire (UMR CNRS 7201), C. 43, Equipe Hétérocycle, 4 place Jussieu, 75005 Paris, France

gerard.lhommet@upmc.fr; virginie.mansuy@upmc.fr

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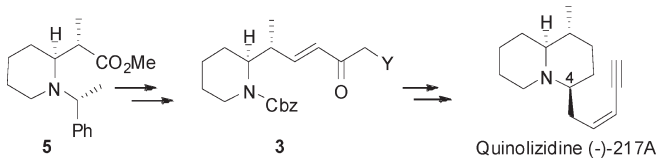

We report here the construction of quinolizidine ring systems by intramolecular cyclization of suitable functionalized piperidines via a reductive amination sequence. This reaction proceeds with a total stereocontrol at C4. The preparation of the piperidine precursors is based on a chain elongation of a piperidine aldehyde either by aldolization or by Wittig reaction. We applied this second route to the total synthesis of quinolizidine (−)-217A from (*S*)-methyl 2-((*S*)-1-((*R*)-1-phenylethyl)piperidin-2-yl)propanoate **5**.

Introduction

Alkaloids containing saturated six-membered nitrogen heterocycles such as piperidines,[1] indolizidines, and quinolizidines[2] are abundant in nature. Many of these alkaloids exhibit interesting and potent biological activities and are important targets in organic synthesis. Alkaloid 217A, a 1,4-disubstituted quinolizidine, was isolated as a major component from the Madagascan frog *Mantella baroni* by Daly in 1993.[3] Because of the scarcity of this natural product, its biological activities remain largely unexplored. To date, only three syntheses of this alkaloid have been reported in the literature. The racemic synthesis of quinolizidine 217A described by Pearson's group[4] in 1998 has confirmed the relative stereochemistry of this natural product. This synthesis is based on a double cyclization of a chloro azidoalkene to generate the quinolizidine system. More recently Panek[5] and co-workers resolved the absolute configuration by an asymmetric synthesis of quinolizidine (−)-217A. The key step is a highly stereoselective synthesis of a trisubstituted tetrahydropyridine obtained by intramolecular imine crotylation.[5] The synthesis of alkaloid (−)-217A was accomplished in 11 steps and 19% overall yield from (2*R*,3*S*,*E*)-methyl 2-amino-3-(dimethyl(phenyl)silyl)hex-4-enoate prepared in six steps from racemic butyn-2-ol.[6] Finally Danheiser's[7] group performed the synthesis of quinolizidine (−)-217A through an intramolecular iminoacetonitrile [4 + 2] cycloaddition function to generate the quinolizidine skeleton. This synthesis supports the preparation of significant quantities of the target alkaloid but requires a resolution step. Amphibian alkaloid 217A was obtained in 12 steps and 7% overall yield from 5-hexenol.

Our goal was to develop a simple and efficient procedure providing an easy access to natural quinolizidine 217A in sufficient amounts from readily accessible compounds and without a resolution step. As part of a program aimed at the synthesis of alkaloids using cyclic aminoesters as versatile synthons, we report herein a highly stereoselective synthesis of quinolizidine (−)-217A from a chiral piperidine ester. Our approach to the synthesis of the target alkaloid **1** is outlined in Scheme 1. It is based on the use of the chiral methyl

(1) Schneider, M. J. *Alkaloids: Chemical and Biological Perspectives*, 1st ed.; Pelletier, S. W., Ed.; Pergamon: New York, 1996; Vol. 10, Chapter 2, pp 155−299.

(2) Daly, J. W.; Garraffo, H. M.; Spande, T. F. *Alkaloids: Chemical and Biological Perspectives*, 1st ed.; Pelletier, S. W., Ed.; Pergamon: Oxford, U. K., 1999; Vol. 13, Chapter 1, pp 1−161.

(3) (a) Garraffo, H. M.; Caceres, J.; Daly, J. W.; Spande, T. F.; Andriamaharavo, N. R.; Andriantsiferana, M. *J. Nat. Prod* **1993**, *56*, 1016–1038. (b) Jain, P.; Garraffo, H. M.; Yeh, H. J. C.; Spande, T. F.; Daly, J. W.; Andriamaharavo, N. R.; Andriantsiferana, M. *J. Nat. Prod.* **1996**, *59*, 1174–1178.

(4) Pearson, W. H.; Suga, H. *J. Org. Chem.* **1998**, *63*, 9910–9918.

(5) Huang, H.; Spande, T., F.; Panek, J., S. *J. Am. Chem. Soc.* **2003**, *125*, 626–627.

(6) This amino silyl hexenoate was prepared by mild acid hydrolysis of a triphenylphosphine imine intermediate obtained from the corresponding azido silyl hexenoate. The latter was synthetized in five steps and 21% overall yield from racemic butyn-2-ol. See: (a) Beresis, R. T.; Solomon, J. S.; Yang, M. G.; Jain, N. F.; Panek, J. S. *Org. Synth.* **1998**, *75*, 78–86. (b) Panek, J. S.; Beresis, R.; Xu, F.; Yang, M. *J. Org. Chem.* **1991**, *56*, 7341–7344. (c) Panek, J. S.; Zhang, J. *J. Org. Chem.* **1993**, *58*, 294–296.

(7) Maloney, K. M.; Danheiser, R., L. *Org. Lett.* **2005**, *7*, 3115–3118.

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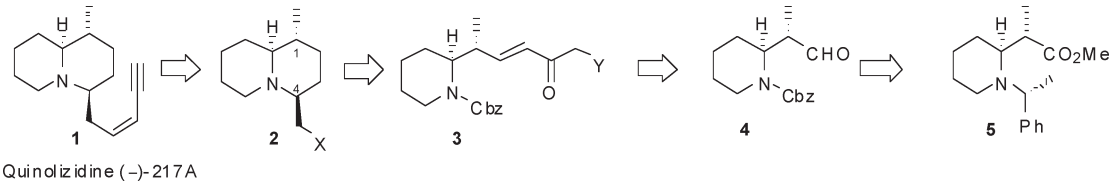
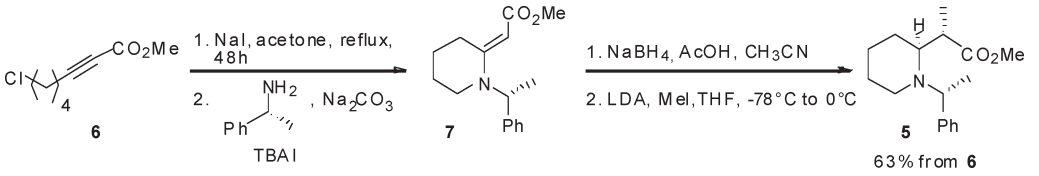
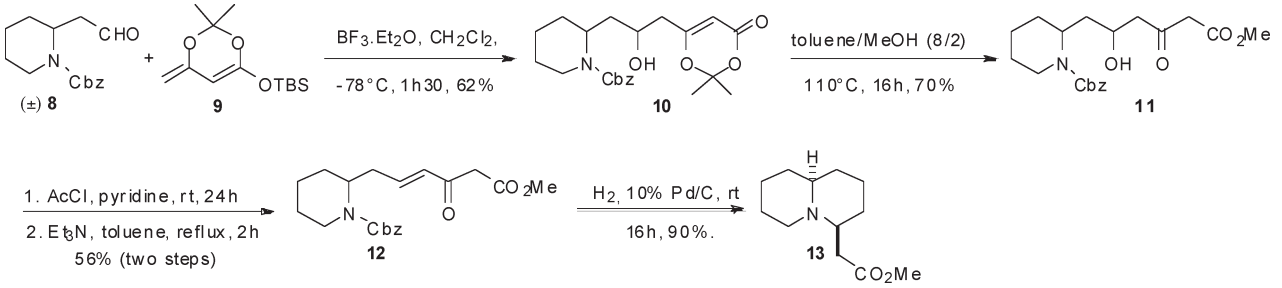
SCHEME 1. Retrosynthetic Analysis for Quinolizidine (−)-217A



SCHEME 2. Synthesis of (2*S*,2′*S*)-Methyl-2-piperidin-2-ylpropanoate 5



SCHEME 3. Synthesis of Quinolizidine 13



piperidin-2-ylpropanoate **5** that was obtained by a diastereodivergent synthesis from piperidine enaminoester **7**.[8]

We envisioned that quinolizidine (−)-217A could stem from quinolizidine **2**, the stereocontrol at C4 being expected to be obtained in the intramolecular cyclization of piperidine **3**.[9] Elaboration of the appropriate side chain of piperidine **3** could arise from aldehyde **4**. The latter would be obtained from (*S*)-methyl 2-((*S*)-1-((*R*)-1-phenylethyl)piperidin-2-yl)propanoate **5**.

Indeed, compound **5** was easily prepared as outlined in Scheme 2. Methyl 7-chlorohept-2-ynoate **6** (obtained from the commercially available chlorohexyne) underwent halogen exchange with sodium iodide to afford methyl 7-iodohept-2-ynoate. The latter was condensed with (*R*)-1-phenylethylamine to provide (*R*,*E*)-methyl 2-(1-(1-phenylethyl)piperidin-2-ylidene)acetate **7**.[10] A two-step reduction/alkylation procedure afforded chiral piperidine **5** by a method previously described for its enantiomer.[8]

It is noteworthy that this strategy could allow the diastereoselective introduction of various alkyl groups giving access to chiral piperidine **5** analogues.

Results and Discussion

We initially focused our attention on the construction of a piperidine substituted by an appropriate functionalized side chain and its subsequent intramolecular cyclization into a quinolizidine. An elongation study based on aldolization or Wittig reaction was conducted on a racemic model, the commercially avalaible Cbz-*N* protected aldehyde **8**. As a first attempt, we performed an aldolization reaction between aldehyde **8** and the dianion of methyl acetoacetate. This reaction failed and only led to degradation products. We then turned our attention toward the vinylogous Mukaiyama aldol reaction between aldehyde **8** and the dioxanone-derived dienol ether **9** (Scheme 3).[11] This condensation carried out in the presence of boron trifluoride−diethyl ether provided the expected piperidine **10** as a 1:1 mixture of diastereomers in a 62% isolated yield. Thermolysis of the latter in a refluxing toluene/methanol mixture afforded the desired piperidine **11** as a 1:1 mixture of diastereomers in 70% isolated yield. Dehydration reaction attempted in acidic medium (PTSA in refluxing toluene) provided the undesired corresponding decarboxylation product. This result is probably due to the formation of water during the process. It is noteworthy that the reaction in the presence of PTSA in toluene at room temperature or in the presence of molecular sieves in refluxing toluene left compound **11** unchanged. To solve this problem a two-step procedure was envisaged. The expected ethylenic β-ketoester moiety was obtained via the corresponding acetate prepared by treatment of piperidine **11** with acetyl chloride in pyridine followed by subsequent elimination of the acetate group in the presence of triethylamine in refluxing toluene.[12] Piperidine **12** was then obtained in a 56% isolated yield as a single *E* isomer. Finally compound **12** was submitted to both benzyl carbamate removal

(8) Pereira, J.; Calvet-Vitale, S.; Fargeau-Bellassoued, M.-C.; Mouriès-Mansuy, V.; Vanucci-Bacqué, C.; Lhommet, G. *Heterocycles* **2007**, *71*, 437–444.

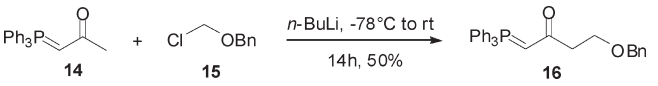
(9) For an example of aza annulation involving the formation of a tetrahydropyridine followed by subsequent reduction of the imine function see: Evans, D. A.; Adams, D. J. *J. Am. Chem. Soc.* **2007**, *129*, 1048–1049.

(10) David, O.; Fargeau-Bellassoued, M.-C.; Lhommet, G. *Tetrahedron Lett.* **2002**, *43*, 3471–3474.

(11) (a) Denmark, S. E.; Beutner, G. L. *J. Am. Chem. Soc.* **2003**, *125*, 7800–7801. (b) Munakata, R.; Katakai, H.; Ueki, T.; Kurosaka, J.; Takao, K.; Tadano, K. *J. Am. Chem. Soc.* **2003**, *125*, 14722–14723.

(12) White, J. D.; Skeean, R. W.; Trammell, G. L. *J. Org. Chem.* **1985**, *50*, 1939–1948.

SCHEME 4. Synthesis of Phosphorane 16



and reductive amination in a one-pot procedure to afford quinolizidine **13** as a single diastereoisomer in 90% isolated yield.

The second route to build the side chain was then investigated. The Wittig reaction was first performed from racemic aldehyde **8** and methyl-4-(triphenylphosphoranylidene) acetoacetate. Unfortunately this condensation in basic conditions (NaH,[13] NaHMDS[14]) failed and yielded intractable mixtures.

We then turned our attention to the use of 4-benzyloxy-1-(triphenyl-λ^5-phosphanylidene)-butan-2-one **16** in which the acetate group is replaced by a benzyl ether moiety. This compound is prepared as outlined in Scheme 4.

Reaction of the anion of (2-oxopropyl)triphenylphosphorane **14** with benzyl chloromethyl ether afforded **16** in 50% isolated yield. Condensation of aldehyde **8** with this new more reactive phosphorane **16** performed in toluene (80 °C) provided the expected piperidine **17** as a single *E* alkene isomer in 74% isolated yield (Scheme 5).

Catalytic hydrogenation of precursor **17** was then tested in the presence of Pd/C (10%) in order to obtain the corresponding *O*-deprotected quinolizidine. This reaction performed either in methanol under 1 or 10 bar of H_2 (Table 1, entries 1 and 2) or in acetic acid (entry 3) exclusively afforded quinolizidine **18a** in which the alcohol function remained protected. However, when the reaction was conducted in a $HClO_4$/MeOH[15] mixture (entry 4) the expected debenzylated quinolizidine **18b** was obtained as a single isomer in 90% isolated yield.

TABLE 1. Catalytic Hydrogenation of 17

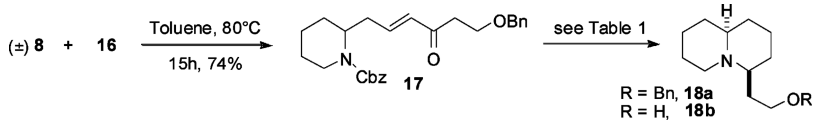
entry	conditions[a]	pressure (bar)	product (% yield)
1	MeOH	1	**18a** (87)
2	MeOH	10	**18a** (90)
3	AcOH	1	**18a** (85)
4	MeOH, $HClO_4$[b]	1	**18b** (90)

[a] H_2, 10% Pd/C. [b] 3 equiv of 60% aqueous acid.

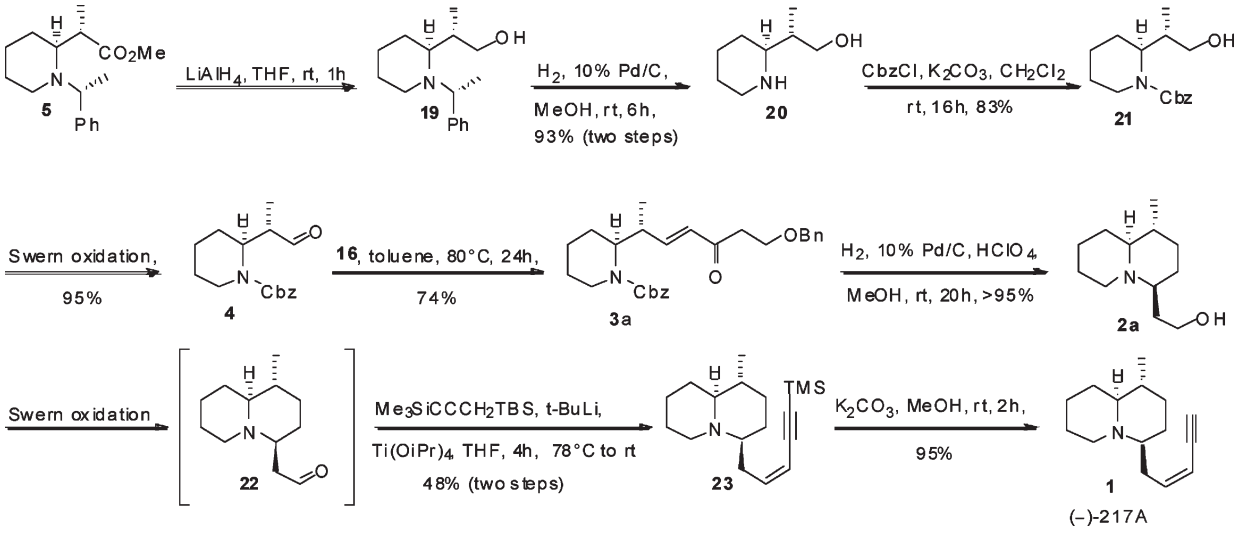
Our study clearly showed that this second route is very effective to generate the quinolizidine ring system. Thus, quinolizidine **13** was prepared via the aldolization route in a 19% overall yield from aldehyde **8** whereas quinolizidine **18b** was obtained via the Wittig reaction in a 67% overall yield. Therefore we decided to prepare quinolizidine (−)-217A through this second methodology. The requisite aldehyde **4** was prepared in four steps from (2*S*,2′*S*)-methyl-2-piperidin-2-ylpropanoate **5** (Scheme 6).

Reduction of the ester moiety of piperidine **5** with lithium aluminum hydride afforded the corresponding piperidine alcohol **19** in quantitative yield. The latter was submitted to a debenzylation/carbamatation sequence to give *N*-Cbz-protected piperidine **21** in a 77% isolated yield from **19**. Swern oxidation of piperidine **21** led to the enantiopure aldehyde **4**, which was subjected to a Wittig reaction with ylide **16** (as in Scheme 5) to afford unsaturated ketone **3a** as a single *E* alkene isomer in 70% isolated yield in two steps. Piperidine **3a** was then submitted to catalytic hydrogenation (Table 1, entry 4) to give the quinolizidine alcohol **2a** as a single isomer in quantitative yield. This compound was converted into aldehyde **22** (Swern oxidation), which was submitted without purification to the Yamamoto's olefination to provide enyne **23**.[16] Finally desilylation of the terminal alkyne[5] with potassium carbonate provided quinolizidine (−)-217A **1** in a 95% isolated yield. The spectral characteristics and the optical rotation of **1**

SCHEME 5. Synthesis of Quinolizidine 18



SCHEME 6. Total Synthesis of Quinolizidine (−)-217A



($[\alpha]^{20}_D$ −14.0 (*c* 0.8, $CHCl_3$)) were in complete agreement with those reported in the literature for the natural product.[3,5,7]

Conclusion

In summary, we have achieved a simple and efficient synthesis of quinolizidine (−)-217A via enantiopure methyl piperidine propanoate **5** in 13 steps and 15% overall yield. Our synthesis was based on two strategic steps: a chain elongation by the Wittig reaction between two readily available precursors, the enantiopure aldehyde **4** and the novel ylide **16**, and a totally strereocontrolled aza-annulation into quinolizidine **2**. Considering that the starting material is the 7-chlorohept-2-ynoate **6**, our approach represents the most efficient synthesis of quinolizidine (−)-217A to date. Further applications of this strategy toward more complex biologically active alkaloids are currently under investigation.

Experimental Section

The preparation and characterization of the starting materials **5** and **7** are described in the Supporting Information.

Benzyl 2-(3-(2,2-Dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-2-hydroxypropyl)piperidine-1-carboxylate (10). To a solution of aminoaldehyde **8** (1.36 g, 5.2 mmol) in CH_2Cl_2 (25 mL), cooled at −78 °C, were successively added dropwise $BF_3 \cdot Et_2O$ (0.504 mL, 5.47 mmol) and silyl derivative[11a] **9** (1.43 g, 5.57 mmol). The reaction mixture was stirred for 2 h at −78 °C. The reaction was then warmed to room temperature and quenched with a saturated $NaHCO_3$ solution (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by silica gel chromatography with 50% EtOAc/cyclohexane afforded **10** as a 1:1 mixture of diastereomers (1.29 g, 62%) as a colorless oil. **10a**: IR (neat) 3420, 1750, 1690 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.20−1.85 (m, 14H), 2.00 (dt, J = 1.7, 13 Hz, 1H), 2.22−2.43 (m, 2H), 2.72 (t, J = 12.5 Hz, 1H), 3.57 (m, 1H), 4.06 (d, J = 15.0 Hz, 1H), 4.46 (br d, J = 12.2 Hz, 1H), 5.04−5.20 (m, 2H), 5.29 (s, 1H), 7.28−7.35 (m, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 19.2, 24.6, 25.3, 25.4, 29.3, 37.6, 39.4, 40.8, 47.2, 64.5, 67.5, 94.9, 106.4, 127.8, 128.6, 136.4, 157.0, 161.2, 169.3. **10b**: IR (neat) 3420, 1750, 1690 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.27−1.75 (m, 13H), 1.86 (m, 1H), 2.20−2.50 (m, 2H), 2.86 (t, J = 12.5 Hz, 1H), 3.59−4.15 (m, 3H), 4.42 (m, 1H), 5.09 (s, 2H), 5.27 (s, 1H), 7.21−7.42 (m, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 18.7, 24.4, 25.2, 28.7, 37.5, 39.4, 41.3, 48.2, 66.5, 67.0, 94.8, 106.3, 127.6, 127.9, 128.3, 129.4, 136.4, 155.6, 161.2, 169.4; HRMS (ESI) m/z calcd for $C_{22}H_{29}NO_6Na$ (MNa^+) 426.4580, found 426.4575.

Benzyl 2-(2-Hydroxy-6-methoxy-4,6-dioxohexyl)piperidine-1-carboxylate (11). A degassed solution of **10** (0.252 g, 0.63 mmol) in toluene/MeOH (8:2, 10 mL) was stirred in a sealed tube for 16 h at 110 °C.[9b] After the mixture was cooled to room temperature, the solvents were removed under reduced pressure. Purification by silica gel chromatography with 20% EtOAc/cyclohexane afforded **11** (0.162 g, 70%) as a colorless oil: IR (neat) 1690, 1430 cm^{-1}. **11a**: ^1H NMR (250 MHz, $CDCl_3$) δ 1.17−1.86 (m, 7H), 1.97−2.15 (m, 1H), 2.56 (dd, J = 5.2, 16.0 Hz, 1H), 2.70−2.91 (m, 2H), 3.51 (s, 2H), 3.73 (s, 3H), 3.81 (br s, 1H), 4.05 (br d, J = 14.7 Hz, 1H), 4.28 (br s, 1H), 4.50 (m, 1H), 5.14 (s, 2H), 7.31−7.40 (m, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 19.2, 25.5, 29.4, 37.4, 39.5, 47.3, 49.6, 50.1, 52.4, 64.4, 67.7, 128.0, 128.3, 128.7, 136.6, 157.1, 167.8, 202.4. **11b**: ^1H NMR (250 MHz, $CDCl_3$) δ 1.20−1.70 (m, 7H), 1.86−2.10 (m, 1H), 2.62 (dd, J = 7.5, 17.5 Hz, 1H), 2.71−2.98 (m, 2H), 3.24−3.56 (m, 3H), 3.71 (s, 3H), 3.92−4.12 (m, 2H), 4.32−4.49 (m, 1H), 5.09 (s, 2H), 7.24−7.40 (m, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 18.9, 25.4, 29.0, 36.9, 39.4, 48.1, 49.4, 49.5, 52.4, 65.7, 67.1, 127.8, 128.0, 128.5, 136.8, 155.7, 167.4, 203.3; HRMS (ESI) m/z calcd for $C_{20}H_{27}NO_6Na$ (MNa^+) 400.1730, found 400.1724.

Benzyl 2-(6-Methoxy-4,6-dioxohex-2-enyl)piperidine-1-carboxylate (12). To a solution of **11** (0.187 g, 0.50 mmol) in CH_2Cl_2 (6 mL), cooled at 0 °C, were successively added dropwise pyridine (0.046 mL, 0.57 mmol) and AcCl (0.037 mL, 0.52 mmol). The reaction was warmed to room temperature and stirred for 24 h. The mixture was diluted with Et_2O (15 mL), then washed with water (2 × 10 mL). The organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give crude acetate (0,173 g) as a yellow oil that was used in the next step without purification.

The crude **11** acetate was dissolved in toluene (6 mL) and Et_3N (0.065 mL, 0.50 mmol) was added. The mixture was stirred for 2 h at 110 °C then cooled to 0 °C, diluted with Et_2O (15 mL), and washed with water (2 × 10 mL). The organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by silica gel chromatography with 20% EtOAc/cyclohexane afforded **12** (0.099 g, 56% over 2 steps) as a colorless oil: IR (neat) 1690, 1430 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.20−1.74 (m, 6H), 2.26−2.88 (m, 3H), 3.47 (m, 1.4H), 3.70 (s, 2.1H), 3.72 (s, 0.9H), 3.99−4.14 (m, 1H), 4.48 (br s, 1H), 4.96 (s, 0.3H), 5.09 (s, 2H), 5.80 (d, J = 15.0 Hz, 0.3H), 6.12 (d, J = 15.0 Hz, 0.7H), 6.57 (dt, J = 7.5, 15.0 Hz, 0.3H), 6.75 (dt, J = 7.5, 15.0 Hz, 0.7H), 7.26−7.39 (m, 5H), 11.76 (d, J = 2.5 Hz, 0.3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 18.8, 25.3, 28.2, 33.3, 33.4, 39.3, 46.3, 49.9, 50.3, 51.3, 52.4, 67.2, 90.3, 126.4, 127.9−128.1, 128.5, 128.6, 131.5, 136.7, 136.8, 137.2, 146.3, 155.4, 155.5, 167.8, 169.0, 173.3, 192.0; HRMS (ESI) m/z calcd for $C_{20}H_{25}NO_5Na$ (MNa^+) 382.1630, found 382.1615.

Methyl 2-(Octahydro-1*H*-quinolizin-4-yl)acetate (13). To a solution of **12** (0.091 g, 0.25 mmol) in MeOH (6 mL) was added 10% Pd/C (0.091 g). The reaction flask was purged with H_2 and the reaction was stirred for 14 h at room temperature under H_2 balloon (1 atm). The reaction mixture was filtered through a pad of Celite. The cake was washed with MeOH (3 × 10 mL) and the combined filtrates were evaporated under reduced pressure. Purification by silica gel chromatography with 90% EtOAc/MeOH afforded **13** (0.048 g, 90%) as a colorless oil: IR (neat) 1713 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.10−1.93 (m, 14H), 2.20 (dd, J = 6.5, 15.2 Hz, 1H), 2.36−2.49 (m, 1H), 2.72 (dd, J = 5.2, 15.5 Hz, 1H), 3.03 (m, 1H), 3.64 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 24.2, 24.5, 26.3, 33.3, 33.6, 33.9, 40.1, 51.7, 51.9, 60.4, 63.2, 173.4; HRMS (ESI) m/z calcd for $C_{12}H_{22}NO_2$ (MH^+) 212.1645, found 212.1645.

4-Benzyloxy-1-(triphenyl-λ^5-phosphanylidene)butan-2-one (16). To a solution of (2-oxopropyl)triphenylphosphorane **14** (3.65 g, 11.5 mmol) in THF (100 mL) was added dropwise *n*-BuLi (5.04 mL of a 2.5 M solution in hexane, 12.6 mmol) at −78 °C. The reaction was stirred for 2 h at the same temperature and benzyl chloromethyl ether **15** (1.97 g, 12.6 mmol) was then added dropwise. The reaction mixture was warmed to 0 °C and stirred for 16 h. The reaction was quenched with a mixture of Et_2O/H_2O (1/2, 100 mL) and stirred over 30 min. The organic solvents were removed under reduced pressure and the aqueous layer was extracted with ethyl acetate (5 × 50 mL). The organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by silica gel chromatography (EtOAc) afforded **16** (2.52 g, 50%) as a yellow solid: mp 106−107 °C; IR (neat) 1530,

(13) Pietrusiewicz, K. M.; Monkiewicz, J. *Tetrahedron Lett.* **1986**, *27*, 739–742.
(14) Ceccarelli, S. M.; Piarulli, U.; Gennari, C. *Tetrahedron* **2001**, *57*, 8531–8542.
(15) Fujimoto, R.; Kishi, Y.; Blount, J. F. *J. Am. Chem. Soc.* **1980**, *102*, 7154–7156.
(16) Yamakado, Y.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1981**, *103*, 5568–5570.

1480, 1440 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.68 (t, J = 7.5 Hz, 2H), 3.87 (t, J = 7.5 Hz, 2H), 4.56 (s, 2H), 7.15−7.72 (m, 21H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 41.7 (d, J = 18.7 Hz), 52.3 (d, J = 106.2 Hz), 68.4, 72.9, 126.2, 127.2, 127.5, 127.7, 128.2, 128.6, 128.8, 138.9, 190.5; HRMS (ESI) m/z calcd for $C_{29}H_{27}O_2P$ (MH^+) 439.1821, found 439.1813.

General Procedure for the Wittig Reaction. A solution of aminoaldehyde (1.0 equiv) and ylide **16** (1.4 equiv) in toluene (10 mL) was stirred for 19 h at 80 °C. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography with 20% EtOAc/cyclohexane.

(*E*)-Benzyl 2-(6-(Benzyloxy)-4-oxohex-2-enyl)piperidine-1-carboxylate (17). This compound was prepared from the aminoaldehyde **8** (0.258 g, 0.99 mmol) and ylide **16** (0.609 g, 1.38 mmol) to yield **17** (0.308 g, 74%) as a colorless oil: IR (neat) 1690, 1430 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.31−1.76 (m, 6H), 2.28−2.92 (m, 6H), 3.74 (t, J = 7.5 Hz, 2H), 3.98−4.16 (m, 1H), 4.49 (s, 2H), 5.09 (s, 2H), 6.10 (d, J = 15.0 Hz, 1H), 6.74 (dt, J = 7.5, 15.0 Hz, 1H), 7.23−7.43 (m, 10H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 18.7, 25.2, 28.0, 33.2, 39.3, 44.4, 49.9, 65.4, 67.0, 73.1, 127.6−128.5 (10C), 132.5, 136.7, 138.2, 144.1, 155.4, 198.2; HRMS (ESI) m/z calcd for $C_{26}H_{31}NO_4Na$ (MNa^+) 444.2145, found 444.2138.

4-(2-(Benzyloxy)ethyl)octahydro-1*H*-quinolizine (18a). To a solution of **17** (0.292 g, 0.69 mmol) in MeOH (10 mL) was added 10% Pd/C (0.146 g). The reaction flask was purged with H_2 and the reaction was stirred for 12 h at room temperature under H_2 balloon (1 atm). The reaction mixture was filtered through a pad of Celite. The cake was washed with MeOH (3 × 10 mL) and the solvent was removed under reduced pressure. Purification by silica gel chromatography with 90% EtOAc/MeOH afforded **18a** (0.164 g, 87%) as a colorless oil: IR (neat) 2984, 1461 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.13−1.90 (m, 16H), 1.91−2.16 (m, 2H), 3.26 (br d, J = 10.0 Hz, 1H), 3.52 (br t, J = 7.5 Hz, 1H), 4.48 (s, 2H), 7.18−7.44 (m, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 24.2, 24.3, 26.0, 31.9, 33.3, 33.4, 33.6, 51.4, 61.2, 63.3, 67.7, 72.8, 127.4, 127.5, 128.2, 138.4; HRMS (ESI) m/z calcd for $C_{18}H_{28}NO$ (MH^+) 274.4205, found 274.4201.

General Procedure for the Synthesis of *O*-Deprotected Quinolizidine. To a solution of piperidine olefin (1.0 equiv) in MeOH (10 mL) was added 10% Pd/C (0.5 equiv w/w). The reaction flask was purged with H_2 and the reaction was stirred for 3 h at room temperature under H_2 balloon (1 atm). A 60% $HClO_4$ aqueous solution (3 equiv) was then added. The reaction mixture was stirred for 16 h at room temperature and then filtered through a pad of Celite. The cake was washed with MeOH (3 × 10 mL) and the solvent was removed under reduced pressure. Saturated $NaHCO_3$ solution (20 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (7 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography with 90% EtOAc/cyclohexane.

2-(Octahydro-1*H*-quinolizin-4-yl)ethanol (18b). This compound was prepared from the piperidine olefin **17** (0.150 g, 0.36 mmol), 10% Pd/C (0.075 g), and 60% $HClO_4$ aqueous solution (0.055 mL, 1.70 mmol) to yield **18b** (0.059 g, 90%) as a colorless oil: IR (neat) 3427, 1461 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.08−1.95 (m, 16H), 2.18−2.41 (m, 2H), 3.42−3.76 (m, 2H), 4.03 (dt, J = 5.0 Hz, 12.5 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 24.1, 24.6, 26.1, 30.1, 31.9, 33.7, 34.1, 52.4, 60.3, 61.7, 63.8; HRMS (ESI) m/z calcd for $C_{11}H_{22}NO$ (MH^+) 184.1696, found 184.1692.

(*S*)-2-((*S*)-1-((*R*)-1-Phenylethyl)piperidin-2-yl)propan-1-ol (19). To a suspension of $LiAlH_4$ (1.17 g, 30.8 mmol) in dry THF (30 mL) cooled at 0 °C was added dropwise a solution of aminoester **5**[8] (3.85 g, 14.0 mmol) in THF (10 mL). The reaction mixture was then warmed to room temperature and stirred for 1 h and 30 min. The reaction was cooled at 0 °C and quenched by addition of saturated aqueous Na_2SO_4 solution. The mixture was filtered through a pad of Celite and the cake was washed with ethyl acetate (3 × 15 mL). The combined filtrates were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by silica gel chromatography with 20% EtOAc/cyclohexane afforded **19** (3.22 g, 93%) as a colorless oil: $[\alpha]^{20}_D$ +64.3 (c 1.60, $CHCl_3$); IR (neat) 3380, 2928, 2858 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.52 (d, J = 7.5 Hz, 3H), 1.22−1.34 (m, 2H), 1.37 (d, J = 7.5 Hz, 3H), 1.50−1.86 (m, 4H), 2.31−2.47 (m, 2H), 3.06−3.25 (m, 3H), 3.49 (dd, J = 2.5, 10.0 Hz, 1H), 4.17 (q, J = 7.5 Hz, 1H), 6.88 (br s, 1H), 7.22−7.42 (m, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.6, 19.5, 20.0, 22.0, 31.5, 42.2, 57.8, 61.6, 71.0, 127.3, 127.4, 128.8, 145.3; HRMS (ESI) m/z calcd for $C_{16}H_{26}NO$ (MH^+) 248.2009, found 248.2003.

(*S*)-2-((*S*)-Piperidin-2-yl)propan-1-ol (20). To a solution of **19** (3.40 g, 13.7 mmol) in MeOH (30 mL) was added 10% Pd/C (0.68 g). The reaction flask was purged with H_2 and the reaction was stirred for 6 h at room temperature under H_2 balloon (1 atm). The reaction mixture was filtered through a pad of Celite. The cake was washed with MeOH (3 × 20 mL) and the combined filtrates were evaporated under reduced pressure. Purification by silica gel chromatography with 90% EtOAc/MeOH afforded **20** (1.96 g, 100%) as a white solid: mp 61−62 °C; $[\alpha]^{20}_D$ +4.9 (c 1.00, $CHCl_3$); IR (neat) 3455 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.81 (d, J = 7.5 Hz, 3H), 1.00−1.62 (m, 5H), 1.66−1.91 (m, 2H), 2.39−2.63 (m, 2H), 2.96−3.08 (m, 1H), 3.48 (dd, J = 10.0, 12.5 Hz, 1H), 3.71 (dd, J = 5.0, 10.0 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.1, 24.7, 27.3, 31.5, 39.3, 46.6, 63.5, 69.6; HRMS (ESI) m/z calcd for $C_8H_{18}NO$ (MH^+) 144.1383, found 144.1379.

(*S*)-Benzyl 2-((*S*)-1-Hydroxypropan-2-yl)piperidine-1-carboxylate (21). To a solution of **20** (1.85 g, 14.3 mmol) in CH_2Cl_2 (60 mL) cooled at 0 °C were successively added K_2CO_3 (2.97 g, 21.5 mmol) and benzyl chloroformate (2.23 mL, 15.8 mmol). The reaction mixture was stirred for 16 h at 0 °C. The mixture was filtered and concentrated under reduced pressure. Purification by silica gel chromatography with 20% EtOAc/cyclohexane afforded **21** (3.26 g, 83%) as a colorless oil: $[\alpha]^{20}_D$ −23.9 (c 1.00, $CHCl_3$) IR (neat) 3455, 1670, 1430 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.03 (d, J = 7.5 Hz, 3H), 1.37−1.70 (m, 5H), 1.75−2.11 (m, 2H), 2.76 (br t, J = 12.5 Hz, 1H), 3.12−3.58 (m, 3H), 3.94−4.23 (m, 2H), 5.03−5.24 (m, 2H), 7.27−7.41 (m, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.9, 18.9, 25.5, 25.9, 32.7, 40.0, 52.2, 64.2, 67.6, 128.0, 128.2, 128.7, 136.7, 156.9; HRMS (ESI) m/z calcd for $C_{16}H_{23}NO_3Na$ (MNa^+) 300.1570, found 300.1578.

General Procedure for the Swern Oxidation. To a cooled −60 °C solution of oxalyl chloride (2.1 equiv of a 2 M solution in CH_2Cl_2) in CH_2Cl_2 (80 mL) was added dropwise DMSO (4.2 equiv). The mixture was stirred at this temperature for 15 min, then a solution of alcohol (1 equiv) in dry CH_2Cl_2 (10 mL) was added dropwise. The resulting solution was stirred at −60 °C for 1 h. Finally, triethylamine (6 equiv) was added dropwise. The reaction mixture was allowed to warm to room temperature over 3 h. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution (60 mL). The aqueous layer was extracted with AcOEt (4 × 40 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography with 20% EtOAc/cyclohexane.

(*S*)-Benzyl 2-((*S*)-1-Oxopropan-2-yl)piperidine-1-carboxylate (4). This compound was prepared from oxalyl chloride (12.1 mL of a 2 M solution in CH_2Cl_2, 24.2 mmol,), DMSO (3.44 mL, 48.5 mmol), alcohol **21** (3.20 g, 11.5 mmol) and triethylamine (10.0 mL, 1.5 mmol) to yield **4** (3.00 g, 95%) as a white solid: mp 54−55 °C; $[\alpha]^{20}_D$ −38.4 (c 1.00, $CHCl_3$); IR (neat) 1750, 1690 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.09 (d, J = 7.5 Hz, 3H), 1.31−1.89 (m, 6H), 2.74−3.14 (m, 2H), 4.06 (m, 1H), 4.45 (m, 1H),

5.10 (s, 2H), 7.27−7.50 (m, 5H), 9.47 (d, J = 2.5 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 12.1, 18.9, 25.2, 25.4, 39.9, 45.2, 52.2, 67.4, 128.0, 128.1, 128.6, 136.7, 155.5, 203.7; HRMS (ESI) m/z calcd for $C_{16}H_{21}NO_3Na$ (MNa^+) 298.1414, found 298.1407.

(*S*)-Benzyl 2-((*R*,*E*)-7-(Benzyloxy)-5-oxohept-3-en-2-yl)-piperidine-1-carboxylate (3a). This compound was prepared according to the Wittig reaction general procedure from aminoaldehyde **4** (0.667 g, 2.42 mmol) and ylide **16** (3.11 g, 3.39 mmol) to yield **3a** (0.781 g, 74%) as a colorless oil: $[\alpha]^{20}_D$ −28.8 (c 0.95, $CHCl_3$); IR (neat) 1690, 1430 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.01 (d, J = 5.0 Hz, 3H), 1.32−1.67 (m, 6H), 1.70−1.87 (m, 1H), 2.50−2.91 (m, 4H), 3.59−3.79 (m, 2H), 3.92−4.28 (m, 2H), 4.45 (s, 2H), 5.05 (s, 1H), 6.02 (d, J = 15.0 Hz, 1H), 6.55−6.76 (m, 1H), 7.12−7.44 (m, 10H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 17.2, 18.5, 25.0, 25.2, 26.6, 36.1, 38.7, 39.4, 54.7, 65.1, 66.7, 72.7, 127.2, 127.3, 127.5, 127.6, 128.0, 128.2, 128.0, 130.1, 136.6, 138.0, 150.2, 155.2, 198.2; HRMS (ESI) m/z calcd for $C_{27}H_{33}NO_4Na$ (MNa^+) 458.2302, found 458.2289.

2-((1*R*,4*S*,9a*S*)-1-Methyloctahydro-1*H*-quinolizin-4-yl)ethanol (2a). This compound was prepared according to the general procedure for the synthesis of *O*-deprotected quinolizidine from the piperidine olefin **3a** (0.494 g, 1.13 mmol), 10% Pd/C (0.148 g), and 60% $HClO_4$ aqueous solution (0.171 mL, 1.70 mmol) to yield **2a** (0.223 g, 100%) as a white solid: mp 49−50 °C; $[\alpha]^{20}_D$ −32.8 (c 1.0, $CHCl_3$); IR (neat) 3427, 1461 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.78 (d, J = 5.0 Hz, 3H), 0.88−2.01 (m, 14H), 2.04−2.42 (m, 2H), 3.33−3.70 (m, 2H), 3.83−4.06 (m, 1H), 4.74 (br s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 19.2, 24.5, 25.9, 29.7, 30.2, 32.5, 33.3, 35.6, 51.9, 60.3, 61.5, 69.8; HRMS (ESI) m/z calcd for $C_{12}H_{24}NO$ (MH^+) 198.1852, found 198.1848.

(1*R*,4*S*,9a*S*)-1-Methyl-4-((*Z*)-5-(trimethylsilyl)pent-2-en-4-ynyl)octahydro-1*H*-quinolizine (23). The aldehyde **22** was first prepared according to the general Swern oxidation procedure from oxalyl chloride (2.66 mL, 5.32 mmol, 2 M in CH_2Cl_2 solution), DMSO (0.751 mL, 8.05 mmol), alcohol **2a** (0.50 g, 2.53 mmol), and triethylamine (2.20 mL, 15.7 mmol) to afford the crude aldehyde **22** (0.498 g) as a pale yellow oil that was used immediately in the next step without purification.

To a solution of 3-(*tert*-butyldimethylsilyl)-1-(trimethylsilyl)-1-propyne[14] (0.573 g, 2.53 mmol) in THF (5 mL) cooled at −78 °C was added dropwise *t*-BuLi (2.06 mL of a 1.6 M solution in hexane, 3.29 mmol). After 1 h Ti(O*i*-Pr)$_4$ (0.97 mL, 3.29 mmol) was added at −78 °C. The reaction mixture was stirred for 10 min and a solution of the crude aldehyde **22** previously prepared in THF (2 mL) was added dropwise. The resulting mixture was stirred at −78 °C for 1 h, −20 °C for 1 h, and at room temperature for 1 h. The reaction was quenched by addition of a saturated aqueous NH_4Cl solution (30 mL) and the mixture was extracted with AcOEt (4 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by silica gel chromatography with 50% EtOAc/cyclohexane afforded **23** (0.352 g, 48% over 2 steps) as a colorless oil: $[\alpha]^{25}_D$ −17.0 (c 0.31, $CHCl_3$); IR (neat) 2850 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.14 (s, 9H), 0.81 (d, J = 5.0 Hz, 3H), 0.85−1.78 (m, 12H), 1.81−2.07 (m, 2H), 2.33−2.66 (m, 2H), 3.26 (br d, J = 10.0 Hz, 1H), 5.50 (d, J = 10.0 Hz, 1H), 6.00 (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 0.1, 19.3, 24.7, 26.3, 26.4, 30.2, 32.0, 33.9, 35.0, 36.4, 51.9, 63.5, 69.7, 98.9, 102.3, 110.4, 142.8; HRMS (ESI) m/z calcd for $C_{18}H_{32}NSi$ (MH^+) 290.2299, found 290.2298.

(1*R*,4*S*,9a*S*)-1-Methyl-4-((*Z*)-pent-2-en-4-ynyl)octahydro-1*H*-quinolizine (−)-217A (1). To a solution of **23** (0.274 g, 0.95 mmol) in MeOH (16 mL) was added K_2CO_3 (0.144 g, 1.04 mmol). The reaction mixture was stirred for 2 h at room temperature. The reaction was quenched with water (30 mL) and the mixture was extracted with Et_2O (4 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by silica gel chromatography with 50% EtOAc/cyclohexane afforded **1** (0.195 g, 95%) as a colorless oil: $[\alpha]^{25}_D$ −14.0 (c 0.8, $CHCl_3$); IR (neat) 3312, 2972, 1452 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.82 (d, J = 5.0 Hz, 3H), 0.86−1.80 (m, 12H), 1.81−1.93 (m, 1H), 1.96−2.08 (m, 1H), 2.40−2.67 (m, 2H), 3.05 (m, 1H), 3.18−3.29 (m, 1H), 5.48 (m, 1H), 6.07 (dt, J = 7.5, 10.0 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 19.3, 24.7, 26.2, 30.2, 31.8, 33.9, 35.0, 36.3, 51.8, 63.1, 69.6, 80.7, 81.7, 109.4, 143.4; HRMS (ESI) m/z calcd for $C_{15}H_{24}N$ (MH^+) 218.1903, found 218.1897.

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Supporting Information Available: Characterization data and ^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.