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A Formal Synthesis of Porantheridine and an Epimer

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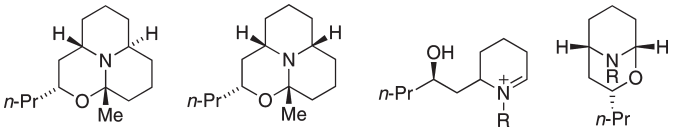
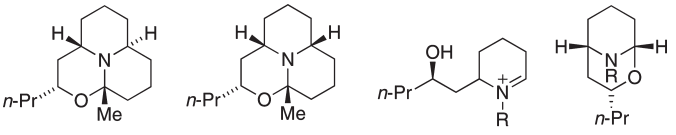


A formal synthesis of porantheridine and a synthesis of its C6-epimer have been completed, employing silver-catalyzed allene cyclization to form a common *cis*-isoxazolidine intermediate and related *N*-acyl iminium ion intermediates for side-chain introduction. The stereochemistry of this step can be controlled by choice of the *N*-protection method.

Introduction

Porantheridine **1** is a tricyclic piperidine alkaloid isolated from *Corymbosa porantherida*, a shrub native to New South Wales. The structure was determined by X-ray crystallography of the hydrobromide salt.[1] Four syntheses of this natural product have, to our knowledge, been reported.[2] With the continuing interest in the stereoselective synthesis of piperidines,[3] porantheridine makes an interesting target.



Given the presence of a cyclic *N*,*O*-acetal, a reasonable disconnection would lead to a 2,6-*trans*-piperidine, which might be obtained by addition of an appropriate nucleophile to a cyclic iminium ion **3**, or a derivative, in an axial fashion. A bicyclic *N*,*O*-acetal **4** would be a suitable precursor for the iminium ion **3**. Given our recent work with *N*,*O*-acetals,[4] we felt that an acetal such as **4** would be an appropriate iminium ion precursor, leading to either porantheridine **1** or its epimer **2** according to the preferred conformation of the iminium ion.[5] Such a precursor is essentially a *syn*-1,3-amino alcohol which could be prepared using the allenic hydroxylamine methodology, an extension of the Claesson cyclization, that we have recently reported.[6] This disconnection also reveals the structural relationship between porantheridine and the sedum alkaloids.[7] We have previously employed the allene methodology in the synthesis of sedamine.[6a] In this paper, we report the realization of this scheme and a formal synthesis of porantheridine **1** and a synthesis of its C6-epimer **2** (numbering from ref 1).

Results and Discussion

(*S*)-Epichlorohydrin underwent ring-opening with ethylmagnesium bromide in the presence of a copper(I) catalyst (Scheme 1). Reclosing of the epoxide under basic conditions

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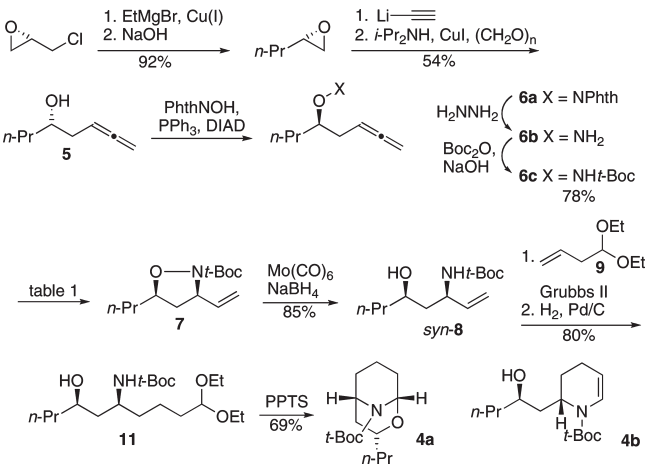
SCHEME 1. Bicyclic *N*,*O*-Acetal Synthesis



yielded (*S*)-pentene oxide.[8] Ring-opening again with lithium acetylide and Searles−Crabbé homologation[9] gave the desired allenic alcohol **5**. Following our previous procedure, the hydroxylamine moiety was installed with inversion by a Mitsunobu reaction with *N*-hydroxyphthalimide,[10] cleavage of the phthaloyl group with hydrazine hydrate, and *N*-reprotection. Cyclization to isoxazolidine **7** was studied using a range of silver and gold[11] catalysts (Table 1). Cyclization using gold(III) chloride in a dichloromethane−acetonitrile mixture in the presence of calcium carbonate (entry 1), which we have used in carbamate cyclization,[12] and a gold(I) triflate complex[13] (entry 2) resulted in modest diastereoselectivity. Cyclization using gold(I) was notably less selective than gold(III), probably due to the lesser steric demand of the linear gold(I). Cyclization using silver(I) triflate in anhydrous dichloromethane also proceeded with modest diastereoselectivity (entries 3 and 4). A combination of silver nitrate and tetramethylguanidine (TMG) in wet acetone, conditions that we previously used in a synthesis of sedamine,[6a] resulted in a slightly improved diastereoselectivity which showed a modest dependence on the loading of silver (entries 5−9). In contrast, a substantially improved diastereoselectivity was observed using silver(I) tetrafluoroborate in anhydrous dichloromethane. With this catalyst, a dependence on silver loading was also observed. Happily, in this case, selectivity was improved with a lower silver loading (entries 10−12).[14] Thus, the optimum conditions proved to be the use of silver(I) tetrafluoroborate at a loading of 10 mol %. A lower loading of this catalyst resulted in an incomplete

TABLE 1. Cyclization of Allenic Hydroxylamine 6c

entry	catalyst/ solvent	metal loading (mol %)	yield (%)	ratio
1	$AuCl_3$, $CaCO_3$, CH_2Cl_2, CH_3CN[a]	5	76	4.0:1
2	Ph_3PAuCl, AgOTf	10, 10	86	2.6:1
3	AgOTf, CH_2Cl_2	10	99	4.6:1
4	AgOTf, CH_2Cl_2	20	95	4.0:1
5	$AgNO_3$, TMG, acetone, H_2O[b]	5	30	ND
6	$AgNO_3$, TMG, acetone, H_2O[b]	10	93	4.8:1
7	$AgNO_3$, TMG, acetone, H_2O[b]	20	97	5.1:1
8	$AgNO_3$, TMG, acetone, H_2O[b]	40	99	5.0:1
9	$AgNO_3$, TMG, acetone, H_2O[b]	60	99	5.4:1
10	$AgBF_4$, CH_2Cl_2	40	99	4.0:1
11	$AgBF_4$, CH_2Cl_2	20	99	9.0:1
12	$AgBF_4$, CH_2Cl_2	10	94	11.5:1

[a]Concentration of acetonitrile: 0.165 M. [b]The loading of TMG is half that of Ag; the ratio of acetone to water is 5:1 v/v.

reaction. The *cis* isomer was presumed, on the basis of our previous results,[6a] to be the major isomer in all cases.

The N−O bond was cleaved using a combination of molybdenum hexacarbonyl and sodium borohydride in wet acetonitrile.[15] At this point, the two diastereoisomers could be separated and pure *syn*-**8** obtained. The remaining carbon atoms required for the construction of the piperidine ring were installed by cross-metathesis[16] with acetal **9**.[17] The alkene **10**, obtained as an inconsequential 8:1 *trans*/*cis* mixture of isomers, was hydrogenated over palladium on carbon. Under mildly acidic conditions, PPTS in dichloromethane at room temperature in the presence of molecular sieves, the two ethoxy groups of acetal **11** exchanged with the alcohol and carbamate groups to give bicyclic *N*,*O*-acetal **4a**. A small amount of the tetrahydropyridine **4b** was also formed, and a small amount of starting acetal **11** could be recovered. Use of stronger acids (such as amberlyst 15) led to lower yields due to competing removal of the *t*-Boc group; use of higher temperatures (dichloromethane at reflux, toluene at reflux) resulted in increased proportions of **4b**.

Ring-opening of bicyclic *N*,*O*-acetal **4a** under our previously reported conditions[4a] using titanium tetrachloride and allyltrimethylsilane yielded the allylation product **12** as a mixture of stereoisomers in 64% yield. As is often the case, the ^{1}H NMR spectrum of the Boc-protected piperidine showed broadening due to restricted rotation. As the two isomers were also inseparable by column chromatography, they could not be thoroughly characterized at his stage. After cyclization by treatment with potassium *tert*-butoxide, sufficient partial (but not complete) separation of the two isomers could be achieved and sharp ^{1}H NMR spectra could be obtained. The ratio of isomers was found to be 9:1. The isomers could be identified by NOESY. The major isomer was found to be the undesired *cis* isomer **13a** from NOE interactions between the methine proton α to oxygen and the nearest proton α to nitrogen; an interaction was also observed between the two protons α to nitrogen. The minor

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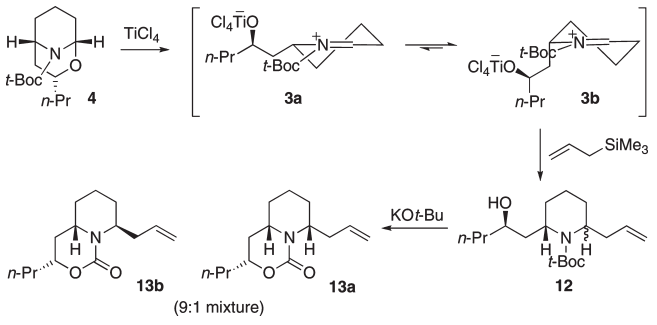
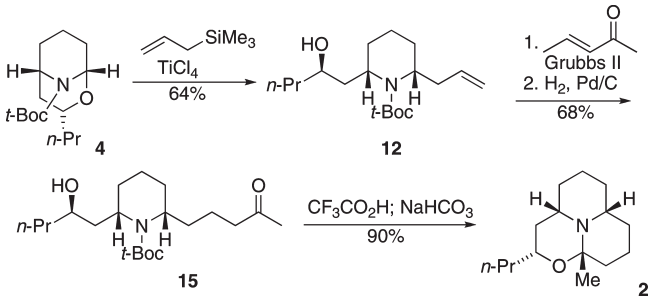
SCHEME 2. Bicyclic *N,O*-Acetal Ring-Opening



SCHEME 3. Synthesis of *epi*-Porantheridine



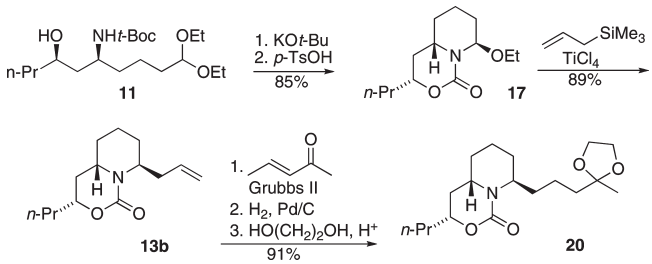
isomer proved to be the desired *trans*-isomer **13b**, characterized by the absence of an NOE interaction between the two protons α to nitrogen and identical to material prepared later by our modified method (see below). This selectivity may be attributed to the iminium ion adopting conformation **3b** with the existing side chain axial in order to avoid A-strain due to the *t*-Boc group present in conformation **3a** (Scheme 2). Axial delivery of the allyl group then results in the undesired *cis* isomer of **12** being the major product.

Nevertheless, the piperidine **12**, as a 9:1 mixture, was taken through to *epi*-porantheridine **2** (Scheme 3) by a simple sequence of cross-metathesis[18] to give a *trans*-unsaturated ketone **14** and hydrogenation of the double bond to give saturated ketone **15**. At this point, the two diastereoisomers could be separated by column chromatography. Upon deprotection of the amino group with trifluoroacetic acid, and subsequent neutralization, the material spontaneously cyclized to *epi*-porantheridine **2**.

In order to achieve the synthesis of the natural product **1**, it was necessary to ensure that the iminium ion intermediate adopted a conformation with the side chain equatorial. Based on the work of Lhommet,[2c] we anticipated that this would become the favored conformation if the side chain and the *N*-protecting group were linked, for instance, by the formation of a cyclic carbamate. Thus, treatment of amino alcohol derivative **11** with potassium *tert*-butoxide gave a cyclic carbamate **16** which, upon acidic treatment, gave bicyclic *N,O*-acetal **17**. Subjecting this material to our previous allylation conditions yielded a single isomer, subsequently shown to be the desired stereoisomer **13b** generated by axial attack, and identical to the minor product of the previous sequence.

(18) Pent-3-en-2-one (Chiu, P.; Wong, S. T. *Synth. Commun.* **1998**, *28*, 4513) was used due to shipping restrictions on MVK.

SCHEME 4. Porantheridine Synthesis



Carbamate **13b** was converted to acetal **20** by a sequence of cross-metathesis, hydrogenation, and protection (Scheme 4). Acetal **20** is a late intermediate in the syntheses of porantheridine **1** reported by Comins[2b] and by Takahata.[2d,e] The spectroscopic and optical rotation data for our material were in good agreement with the data reported by Comins. A formal synthesis of porantheridine **1** has therefore been completed. Comins' intermediate is obtained in 17 steps and 18% overall yield from (*S*)-epichlorohydrin. In addition, we have shown that the sense of stereoselectivity of the addition to such *N*-acyl iminium ions can be controlled by choosing either an acylic or an internal protecting group. The synthesis also illustrates the ease with which a functionalized *syn*-1,3-amino alcohol can be constructed using allene cyclization chemistry.

Experimental Section

(3*R*,5*R*)-*tert*-Butyl 5-Propyl-3-vinylisoxazolidine-2-carboxylate 7. $AgBF_4$ (16.3 mg, 0.083 mmol) was added to a solution of the *N*-protected hydroxylamine **6** (0.2 g, 0.83 mmol) in dried CH_2Cl_2 (6 mL) at room temperature. The reaction mixture was stirred at room temperature in the absence of light for 8 h and filtered through Celite. The filtrate was washed with satd $NaHCO_3$ solution and brine and dried over anhydrous Na_2SO_4. After filtration, the filtrate was then evaporated in vacuo to give the residue which was purified by flash chromatography (EtOAc/hexane = 1: 9) to afford a inseparable mixture of *trans*-**7** and *cis*-**7** (*trans*-**7**/*cis*-**7** = 1:11.5, 0.188 g, 94%). *cis*-**7**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (1H, ddd, J = 17.0, 10.0, 6.8 Hz), 5.21 (1H, d, J = 17.0 Hz), 5.06 (1H, d, J = 10.0 Hz), 4.56 (1H, td, J = 7.2, 7.2 Hz), 3.86−3.83 (1H, m), 2.52 (1H, ddd, J = 13.1, 7.2, 5.8 Hz), 1.68−1.60 (2H, m), 1.54−1.33 (2H, m), 1.45 (9H, s), 0.91 (3H, t, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.5, 137.8, 114.1, 81.6, 81.0, 62.1, 41.2, 34.4, 28.1 (3C), 19.2, 13.8; IR (neat) 2976, 2965, 1732 cm^{-1}; MS (m/z) 242 $[M + H]^+$; HRMS m/z calcd for $C_{13}H_{23}O_3NNa$ $[M + Na]^+$ 264.1576, found 264.1573.

***tert*-Butyl (3*R*,5*R*)-5-Hydroxyoct-1-en-3-ylcarbamate 8.** $Mo(CO)_6$ (0.24 g, 0.89 mmol) was added to a solution of isoxazolidines **7** (0.20 g, 0.56 mmol) in CH_3CN-H_2O (14 mL−2 mL). The mixture was stirred at room temperature for 15 min, and $NaBH_4$ (25 mg, 0.67 mmol) was added in one portion. The reaction mixture was heated at 90 °C overnight and cooled to room temperature. The suspension was filtered through Celite, washing with Et_2O (3 × 8 mL). The filtrate was then concentrated in vacuo to afford the crude product which was purified by flash chromatography (EtOAc/hexane = 1:9) to give *syn*-**8** (0.16 g, 78%) and *anti*-**8** (14 mg, 7%). *syn*-**8**: colorless oil; $[\alpha]^{24.8}_D$ −16.0 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (1H, ddd, J = 17.0, 10.4, 6.1 Hz), 5.19 (1H, d, J = 17.0 Hz), 5.10 (1H, d, J = 10.4 Hz), 4.71 (1H, br), 4.24 (1H, br), 3.71 (1H, br), 1.64−1.59 (2H, m), 1.48−1.33 (4H, m), 1.45 (9H, s), 0.91 (3H, t, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 138.9,

114.7, 79.5, 69.4, 51.3, 42.6, 40.0, 28.3 (3C), 18.7, 14.0; IR (neat) 3442, 3345, 2974, 2930, 2872, 1694 cm^{-1}; MS (*m*/*z*) 266 [M + Na]$^+$; HRMS *m*/*z* calcd for $C_{13}H_{25}O_3NNa$ [M + Na]$^+$ 266.1732, found 266.1729.

Anti-8. colorless solid; mp 46−47 °C; $[\alpha]^{24.8}_D$ +6.1 (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.83 (1H, ddd, *J* = 17.0, 10.5, 5.4 Hz), 5.18 (1H, d, *J* = 17.0 Hz), 5.10 (1H, d, *J* = 10.5 Hz), 4.75 (1H, d, *J* = 8.8 Hz), 4.42 (1H, brs), 3.59 (1H, brs), 1.64−1.51 (2H, m), 1.48−1.33 (13H, m), 0.90 (3H, t, *J* = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 138.5, 114.4, 79.5, 67.2, 49.3, 43.4, 39.1, 28.3 (3C), 19.0, 14.0.

***tert*-Butyl (*E*,5*R*,7*R*)-1,1-Diethoxy-7-hydroxydec-3-en-5-ylcarbamate 10.** A solution of Grubbs II catalyst (87 mg, 5 mol %) in CH_2Cl_2 (5 mL) was added to a refluxing solution of compound **8** (0.5 g, 2.06 mmol) and 1,1-diethoxybut-3-ene **9**[17] (1.10 mL, 6.17 mmol) in CH_2Cl_2 (5 mL) in four portions via syringe over 1 h. The mixture was heated at reflux overnight and then concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexane = 2:8) to provide *trans*-**10** (0.55 g, 75%) and *cis*-**10** (70 mg, 9%) as colorless oils. *trans*-**10**: $[\alpha]^{24.8}_D$ +3.6 (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.59 (1H, dt, *J* = 15.6, 6.8 Hz), 5.48 (1H, dd, *J* = 15.6, 6.4 Hz), 4.72 (1H, br), 4.46 (1H, t, *J* = 5.7 Hz), 4.21 (1H, br), 3.66−3.58 (3H, m), 3.49−3.44 (2H, m), 2.33 (2H, dd, *J* = 6.8, 6.8 Hz), 1.60 (2H, dd, *J* = 6.3, 6.3 Hz), 1.48−1.33 (4H, m), 1.40 (9H, s), 1.17 (6H, t, *J* = 7.1 Hz), 0.88 (3H, t, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 133.4, 125.7, 102.2, 79.3, 76.6, 61.2 (2C), 50.5, 42.9, 39.9, 36.8, 28.3 (3C), 18.7, 15.2 (2C), 13.9; IR (neat) 3443, 3350, 2974, 2930, 2874, 1694 cm^{-1}; MS (*m*/*z*) 382 [M + Na]$^+$; HRMS *m*/*z* calcd for $C_{19}H_{37}O_5NNa$ [M + Na]$^+$ 382.2569, found 382.2566.

***cis*-10.** colorless oil; $[\alpha]^{21.9}_D$ −54.9 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.51 (1H, dt, *J* = 10.0, 5.6 Hz), 5.25 (1H, dd, *J* = 10.0, 10.0 Hz), 4.61 (1H, br), 4.54 (1H, dd, *J* = 4.0, 4.0 Hz), 4.51 (1H, brs), 3.71−3.45 (5H, m, 3.00 (1H, brs), 2.72 (1H, dt, *J* = 14.0, 8.3 Hz), 2.42 (1H, brs), 1.69 (1H, ddd, *J* = 14.0, 10.0, 4.0 Hz), 1.48−1.28 (4H, m), 1.40 (9H, s), 1.18 (6H, td, *J* = 7.0, 3.0 Hz), 0.87 (3H, t, *J* = 6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 132.3, 126.3, 102.2, 79.1, 68.0, 62.5, 60.6, 46.0, 43.0, 39.9, 32.5, 28.3 (3C), 18.9, 15.1, 15.0, 14.0; IR (neat) 1689 cm^{-1}; MS (*m*/*z*) 382 [M + Na]$^+$; HRMS *m*/*z* calcd for $C_{19}H_{37}O_5NNa$ [M + Na]$^+$ 382.2569, found 382.2568.

***tert*-Butyl (5*S*,7*R*)-1,1-Diethoxy-7-hydroxydecan-5-ylcarbamate 11.** A suspension of alkenes **10** (0.24 g, 0.67 mmol), palladium on carbon (10%) (35.5 mg, 0.033 mmol), and a trace of calcium carbonate in MeOH (10 mL) was stirred at room temperature for 3 h under H_2 (1 atm). The reaction mixture was filtered through Celite, washing with MeOH (5 × 5 mL). The filtrate was concentrated to give the product **11** (0.23 g, 95%) as a colorless oil. $[\alpha]^{24}_D$ −6.5 (*c* 2.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.61 (1H, brs), 4.46 (1H, t, *J* = 5.6 Hz), 3.59−3.51 (4H, m), 3.49−3.44 (2H, m), 2.45 (1H, m), 1.79−1.36 (21H, m), 1.19 (6H, t, *J* = 7.1 Hz), 0.91 (3H, t, *J* = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 102.7, 79.4, 70.0, 61.1, 60.9, 49.3, 43.6, 39.8, 35.9, 33.4, 28.4 (3C), 21.0, 18.8, 15.3 (2C), 14.0; IR (neat) 3443, 3343, 2974, 2932, 2872, 1694 cm^{-1}; MS (*m*/*z*) 384 [M + Na]$^+$; HRMS *m*/*z* calcd for $C_{19}H_{39}O_5NNa$ [M + Na]$^+$ 384.2711, found 384.2726.

(1*S*,3*R*,5*S*)-*tert*-Butyl 3-Propyl-2-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate 4a. PPTS (0.36 g, 1.44 mmol) was added to a solution of compound **11** (0.52 g, 1.44 mmol) in CH_2Cl_2 (10 mL) at room temperature. The mixture was stirred at room temperature for 14 h. After water was added, the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered through Celite, and concentrated in vacuo to afford the crude product which was purified by flash chromatography (EtOAc/hexane = 2: 8) to provide the cyclic *N*,*O*-acetal **4a** (0.27 mg, 69%) and tetrahydropyridine **4b** (33 mg, 8%) as colorless oils. Compound **4a**: $[\alpha]^{23.1}_D$ −6.7 (*c* 1.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (mixture of rotamers) 5.78 (brs,) and 5.66 (brs) (1H), 4.45(brd, *J* = 11.6 Hz) and 4.32 (brd, *J* = 11.6 Hz) (1H), 3.37−3.31 (1H, m), 2.18−2.20 (2H, m), 1.79−1.60 (3H, m), 1.47 (9H, s), 1.43−1.34 (7H, m), 0.90 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (mixture of rotamers) 154.7, 80.1 and 79.8, 79.0 and 77.8, 67.3 and 67.2, 44.9 and 43.3, 37.1 and 37.0, 35.2 and 34.6, 30.7 and 30.6, 30.5 and 30.3, 28.3 (3C), 18.6 and 18.5, 14.1 and 14.0, 13.6; IR (neat) 2957, 2936, 2870, 1697 cm^{-1}; MS (*m*/*z*) 269 [M]$^+$; HRMS *m*/*z* calcd for $C_{15}H_{27}O_3N$ [M]$^+$ 269.1985, found 269.1969.

Compound 4b. ^1H NMR (300 MHz, $CDCl_3$) δ 6.63 (1H, d, *J* = 8.5 Hz), 4.85−4.82 (1H, m), 4.51 (1H, brd, *J* = 11.6 Hz), 4.30 (1H, d, *J* = 3.2 Hz), 3.39−3.33 (1H, m), 2.08−1.99 (2H, m), 1.90−1.78 (1H, m), 1.75−1.65 (2H, m), 1.53−1.15 (5H, m), 1.49 (9H, s), 0.89 (3H, t, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 124.4, 105.3, 81.1, 69.7, 47.9, 39.9, 39.8, 28.3 (3C), 25.7, 19.0, 17.5, 14.0; IR (neat) 1700, 1650 cm^{-1}; MS (*m*/*z*) 292 [M + Na]$^+$; HRMS *m*/*z* calcd for $C_{15}H_{27}O_3NNa$ [M]$^+$ 292.1889, found 292.1886.

(2*R*,6*S*)-*tert*-Butyl 2-Allyl-6-((*R*)-2-hydroxypentyl)piperidine-1-carboxylate 12. $TiCl_4$ (1 M in toluene, 0.67 mL, 0.67 mmol) via syringe was added to a cooled (−78 °C) solution of cyclic *N*,*O*-acetal **4a** (0.15 g, 0.56 mmol) and allyltrimethylsilane (0.11 mL, 0.67 mmol) in CH_2Cl_2 (8 mL). After being stirred at −78 °C for 1 h, the reaction mixture was quenched with saturated $NaHCO_3$ solution at this temperature and then allowed to warm to room temperature. The mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered through Celite, and concentrated in vacuo to afford the crude product. The crude product was purified by flash chromatography (EtOAc/hexane = 1: 9) to provide an inseparable mixture of *trans*-**12** and *cis*-**12** (0.10 g, 64%) as a colorless oil. *cis*-**12**: ^1H NMR (300 MHz, $CDCl_3$) δ 5.78−5.66 (1H, m), 5.07−5.00 (2H, m), 4.17−4.09 (2H, brs), 3.50−3.46 (1H, m), 2.27−2.22 (2H, m,), 1.83−1.33 (21H, m), 0.91 (3H, t, *J* = 6.9 Hz). *cis*-Isomer: ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 136.2, 116.8, 79.9, 70.0, 50.3, 47.7, 44.2, 40.1, 39.0, 28.7, 28.5 (3C), 26.6, 18.9, 14.1, 13.7; IR (neat) 3431, 2954, 2934, 2870, 1660 cm^{-1}; MS (*m*/*z*) 312 [M + H]$^+$; HRMS *m*/*z* calcd for $C_{18}H_{33}O_3NNa$ [M + Na]$^+$ 334.2358, found 334.2344.

8-Allyl-3-propylhexahydropyrido[1,2-*c*][1,3]oxazin-1(3*H*)-one 13a and 13b. ^{t}BuOK (7.1 mg, 0.063 mmol) was added to a solution of compounds **12** (13 mg, 0.042 mmol) in THF (7 mL) at 0 °C. The mixture was allowed to warm to room temperature and it was stirred for 4 h. The mixture was quenched with saturated NH_4Cl solution and extracted with $CHCl_3$ (3 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered through Celite, and concentrated in vacuo to afford the crude product. The crude product was purified by flash chromatography (EtOAc/hexane = 2: 8) to provide compound **13a** (9 mg, 90%) and compound **13b** (1.1 mg, 10%) as colorless oils.

Compound 13a: ^1H NMR (300 MHz, $CDCl_3$) δ 5.83−5.73 (1H, m), 5.09 (1H, brd, *J* = 17.2 Hz), 5.04 (1H, brd, *J* = 9.6 Hz), 4.21−4.25 (1H, m), 3.79−3.74 (1H, m), 3.55 (1H, tt, *J* = 12.0, 4.0 Hz), 2.80 (1H, dt, *J* = 13.4, 4.8 Hz), 2.18 (1H, *J* = 13.4, 9.6 Hz), 1.94 (1H, ddd, *J* = 13.4, 4.6, 2.2 Hz), 1.84−1.36 (11H, m), 0.92 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 135.7, 116.7, 75.4, 54.1, 51.3, 38.1, 37.2, 35.7, 29.5, 22.9, 17.9, 16.4, 13.8; IR (neat) 2956, 2935, 2873, 1666 cm^{-1}; MS (*m*/*z*) 238 [M + H]$^+$.

Compound 13b. See below.

(2*S*,6*R*)-*tert*-Butyl 2-((*R*)-2-Hydroxypentyl)-6-((*E*)-4-oxopent-2-enyl)piperidine-1-carboxylate 14. A solution of Grubbs II catalyst (8 mg, 5 mol %) in CH_2Cl_2 (2 mL) was added to a

refluxing solution of piperidines **12** (56 mg, 0.18 mmol) and 3-buten-2-one (53 μL, 0.54 mmol) in CH_2Cl_2 (2 mL) in four portions via syringe over 1 h. The mixture was heated at reflux overnight and then concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexane = 2: 8) to provide **14** (51 mg, 80%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (1H, dt, J = 15.8, 7.7 Hz), 6.07 (1H, d, J = 15.8 Hz), 4.25 (2H, brs), 3.54−3.51 (1H, m), 2.44−2.38 (2H, m), 2.22 (3H, s), 1.76−1.33 (21H, m), 0.91 (3H, t, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 155.4, 144.9, 132.9, 80.2, 69.6, 49.5, 47.5, 44.0, 40.0, 37.8, 28.4 (3C), 27.4, 27.0, 26.1, 18.8, 14.0, 13.7; IR (neat) 3447, 2957, 2932, 2860, 1655, 1643 cm^{-1}; MS (m/z) 376 [M + Na]$^+$; HRMS m/z calcd for $C_{20}H_{35}O_4NNa$ [M + Na]$^+$ 376.2464, found 376.2452.

(2*S*,6*R*)-*tert*-Butyl 2-((*R*)-2-Hydroxypentyl)-6-(4-oxopentyl)-piperidine-1-carboxylate 15. A suspension of alkenes **14** (51 mg, 0.14 mmol) and palladium on carbon (10%) (8 mg, 5 mol %) in MeOH (5 mL) was stirred at room temperature for 2 h under H_2 (1 atm). The reaction mixture was filtered through Celite, washing with MeOH (5 × 3 mL). The filtrate was concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/hexane = 2:8) to afford *cis*-**15** (35 mg, 77%) and *trans*-**15** (4 mg, 8%) as colorless oils. *cis*-**15**: $[\alpha]^{24}_D$ −27.1 (*c* 1.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (1H, brs), 4.04 (1H, brs), 3.51 (1H, brs), 2.46−2.43 (2H, m), 2.12 (3H, s), 1.55−1.35 (25H, m), 0.91 (3H, t, J = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.6, 155.9, 79.9, 69.9, 50.4, 47.8, 44.3, 43.4, 40.0, 34.0, 29.9, 29.3, 28.4 (3C), 27.4, 21.3, 18.9, 14.1, 13.9; IR (neat) 3447, 2957, 2932, 2860, 1655, 1643 cm^{-1}; MS (m/z) 378 [M + Na]$^+$; HRMS m/z calcd for $C_{20}H_{37}O_4NNa$ [M + Na]$^+$ 378.2620, found 378.2615.

***trans*-15.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.92−3.89 (1H, brs), 3.72−3.68 (1H, brs), 3.59−3.56 (1H, brs), 2.48−2.44 (2H, m), 2.14 (3H, s), 1.81−1.76 (2H, m), 1.73−1.70 (2H, m), 1.65−1.33 (12H, m), 1.46 (9H, s), 0.91 (3H, t, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.8, 155.9, 79.9, 70.0, 51.8, 49.5, 44.1, 43.4, 40.1, 33.6, 29.9, 28.5 (3C), 25.2, 23.6, 21.2, 18.9, 14.1, 13.5.

(2*R*,3a*S*,6a*R*,9a*S*)-Decahydro-9a-methyl-2-propyl-2*H*-[1,3]oxazino[2,3,4-*de*]quinolizine 2. Trifluoroacetic acid (0.46 mL) was added to a solution of compound **15** (23 mg, 0.062 mmol) in CH_2Cl_2 (4 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. The volatiles were evaporated, and the residue was partitioned between aqueous $NaHCO_3$ and CH_2Cl_2. The aqueous lawyer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered through Celite, and concentrated in vacuo to afford the crude product which was purified by flash chromatography (MeOH/CH_2Cl_2 = 1: 9) to give product **2** (13 mg, 90%) as a colorless oil: $[\alpha]^{24}_D$ +6.0 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79−3.76 (1H, m), 2.51−2.47 (1H, m), 2.15−2.10 (1H, m), 1.55−1.35 (21H, m), 0.88 (3H, t, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 86.5, 67.8, 55.2, 51.9, 39.6, 39.2, 38.6, 34.4, 34.2, 33.8, 23.5, 20.8, 18.4, 14.1, 11.6; IR (neat) 2930, 2868, 2799 cm^{-1}; MS (m/z) 238 [M + H]$^+$; HRMS m/z calcd for $C_{15}H_{28}ON$ [M + H]$^+$ 238.2171, found 238.2164.

(4*S*,6*R*)-4-(4,4-Diethoxybutyl)-6-propyl-1,3-oxazinan-2-one 16. ^{t}BuOK (83.0 mg, 7.38 mmol) was added to a solution of compound **11** (178 mg, 4.92 mmol) in THF (7 mL) at 0 °C. The mixture was allowed to warm to room temperature, and it was stirred at room temperature for 4 h. The mixture was quenched with saturated NH_4Cl solution and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered through Celite, and concentrated in vacuo to afford the crude product. The crude product was purified by flash chromatography (EtOAc/hexane = 3: 7) to provide cyclic carbamate **16** (133 mg, 93%) as a colorless oil: $[\alpha]^{24}_D$ +5.7 (*c* 1.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.49 (1H, brs), 4.46 (1H, t, J = 5.5 Hz), 4.22 (1H, tdd, J = 9.8, 5.0, 2.8 Hz), 3.63 (2H, qd, J = 7.1, 9.3 Hz), 3.51−3.40 (3H, m), 1.96 (1H, ddt, J = 13.5, 4.5, 1.5 Hz), 1.70−1.34 (11H, m), 1.20 (6H, t, J = 7.1 Hz), 0.93 (3H, t, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 102.5, 76.8, 61.2, 61.1, 50.8, 37.2, 36.0, 33.3, 33.1, 20.0, 17.9, 15.3(2C), 13.8; IR (neat) 2961, 2932, 2874, 2243, 1697 cm^{-1}; MS (m/z) 310 [M + Na]$^+$; HRMS m/z calcd for $C_{15}H_{29}O_4NNa$ [M + Na]$^+$ 310.1994, found 310.1989.

(3*R*,4a*S*,8*R*)-8-Ethoxyhexahydro-3-propylpyrido[1,2-*c*][1,3]oxazin-1(3*H*)-one 17. *p*-TsOH (0.48 g, 2.39 mmol) was added to a solution of compound **16** (133 mg, 0.48 mmol) in EtOH (5 mL) at room temperature. The mixture was stirred at room temperature for 4 h. Saturated aqueous $NaHCO_3$ (5 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered through Celite, and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/hexane = 1:9) to provide *trans*-**17** (0.11 g, 91%) as a single isomer and as a colorless solid: mp 57−59 °C; $[\alpha]^{23.6}_D$ +30.0 (*c* 1.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71 (1H, br), 4.14−4.07 (1H, m), 3.56−3.39 (3H, m), 2.07−1.42 (12H, m), 1.18 (3H, t, J = 7.0 Hz), 0.93 (3H, t, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1, 80.3, 75.0, 62.4, 49.1, 37.0, 35.3, 33.1, 29.9, 17.9, 17.6, 15.1, 13.9; IR (neat) 2957, 2936, 2874, 1694, 1422 cm^{-1}; MS (m/z) 264 [M + Na]$^+$; HRMS m/z calcd for $C_{13}H_{23}O_3NNa$ [M + Na]$^+$ 264.1576, found 264.1567.

(3*R*,4a*S*,8*S*)-8-Allylhexahydro-3-propylpyrido[1,2-*c*][1,3]oxazin-1(3*H*)-one 13b. To a solution of *N*,*O*-acetal **17** (48 mg, 0.21 mmol) and allyltrimethylsilane (0.10 mL, 0.63 mmol) in CH_2Cl_2 (5 mL) was added $TiCl_4$ (0.63 mmol, 0.63 mL of 1 M solution in toluene) via syringe at −78 °C. After being stirred at −78 °C for 0.5 h, the reaction mixture was quenched at this temperature with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered through Celite, and concentrated in vacuo to afford the crude product. The crude product was purified by flash chromatography (EtOAc/hexane = 2: 8) to provide *trans*-**13b** (44 mg, 89%) as a single isomer and as a colorless oil: $[\alpha]^{24.4}_D$ +6.9 (*c* 2.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80−5.73 (1H, m), 5.04 (1H, d, J = 17.0 Hz), 5.03 (1H, brd, J = 9.5 Hz), 4.70−4.66 (1H, m), 4.03 (1H, tt, J = 5.2, 5.2 Hz), 3.37 (1H, tdd, J = 11.4, 5.2, 2.9 Hz), 2.44 (1H, dt, J = 13.8, 8.3 Hz), 2.24 (1H, dt, J = 13.8, 6.8 Hz), 1.99 (1H, ddd, J = 13.8, 5.2, 1.5 Hz), 1.79−1.76 (1H, m), 1.66−1.12 (10H, m), 0.92 (3H, t, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.0, 135.3, 117.0, 74.2, 49.7, 49.3, 36.8, 35.7, 34.8, 33.3, 27.0, 18.1, 17.8, 13.8; IR (neat) 2957, 2934, 2872, 1687, 1427 cm^{-1}; MS (m/z) 237 [M]$^+$; HRMS m/z calcd for $C_{14}H_{23}O_2NNa$ [M + Na]$^+$ 260.1623, found 260.1618.

(3*R*,4a*S*,8*S*)-Hexahydro-8-((*E*)-4-oxopent-2-enyl)-3-propylpyrido[1,2-*c*][1,3]oxazin-1(3*H*)-one 18. A solution of Grubbs II catalyst (11 mg, 5 mol %) in CH_2Cl_2 (2 mL) was added to a refluxing solution of compound **13b** (60 mg, 0.25 mmol) and 3-buten-2-one (74 μL, 0.76 mmol) in CH_2Cl_2 (2 mL) in four portions via syringe over 1 h. The mixture was heated at reflux overnight and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexane = 3:7) to provide *trans*-**18** (68 mg, 96%) as a single isomer and as a colorless oil: $[\alpha]^{24}_D$ −2.6 (*c* 1.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.74 (1H, ddd, J = 15.7, 8.7, 6.5 Hz), 6.02 (1H, d, J = 15.7 Hz), 4.84−4.78 (1H, m), 4.01−3.94 (1H, m), 3.34 (1H, tdd, J = 11.3, 5.0, 2.9 Hz), 2.63 (1H, dt, J = 13.9, 8.7 Hz), 2.24 (1H, dt, J = 13.9, 6.5 Hz), 2.24 (3H, s), 1.99 (1H, ddd, J = 11.2, 5.2, 1.5 Hz), 1.82−1.12 (11H, m), 0.89 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.8, 153.9, 144.7, 133.7, 74.6, 49.6, 49.4, 36.8, 35.5, 33.9, 33.1, 27.5, 26.2, 18.1, 17.8, 13.7; IR (neat) 2957, 2936, 2874, 1674, 1429 cm^{-1}; MS (m/z) 302 [M + Na]$^+$;

HRMS m/z calcd for $C_{16}H_{25}O_3NNa$ $[M + Na]^+$ 302.1732, found 302.1737.

(3*R*,4a*S*,8*S*)-Hexahydro-8-(4-oxopentyl)-3-propylpyrido[1,2-*c*]-[1,3]oxazin-1(3*H*)-one 19. A suspension of alkene **18** (68 mg, 0.24 mmol) and palladium on carbon (10%) (13 mg, 5 mol %) in MeOH (5 mL) was stirred at room temperature for 2 h under H_2 (1 atm). The reaction mixture was filtered through Celite, washing with MeOH (5 × 2 mL). The filtrate was concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/hexane = 3: 7) to afford product **19** (68 mg, 99%) as colorless oil: $[\alpha]^{24}_D$ +16.8 (*c* 1.0, $CHCl_3$) [lit.[2d] $[\alpha]_D^{26}$ +9.67 (*c* 0.76, $CHCl_3$)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.59−4.54 (1H, m), 4.10−4.05 (1H, m), 3.40 (1H, tdd, J = 11.3, 5.4, 2.8 Hz), 2.56−3.39 (2H, m), 2.11 (3H, s), 2.02 (1H, ddd, J = 13.6, 5.4, 1.6 Hz), 1.62−1.45 (15H, m), 0.91 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.9, 154.2, 74.5, 50.0, 49.0, 42.8, 36.9, 35.8, 33.6, 30.0, 29.2, 27.7, 20.0, 18.2, 17.8, 13.9; IR (neat) 2934, 2872, 1713, 1674,1429 cm^{-1}; MS (m/z) 282 $[M+H]^+$; HRMS m/z calcd for $C_{16}H_{28}O_3N$ $[M + H]^+$ 282.2069, found 282.2061.

(3*R*,4a*S*,8*S*)-Hexahydro-8-(3-(2-methyl-1,3-dioxolan-2-yl)-propyl)-3-propylpyrido[1,2-*c*][1,3]oxazin-1(3*H*)-one 20. A mixture of compound **19** (68 mg, 0.24 mmol), ethylene glycol (66 μL, 1.21 mmol), and *p*-toluenesulfonic acid monohydrate (9.6 mg, 0.048 mmol) in benzene (5 mL) was heated at reflux overnight using a Dean−Stark apparatus. Saturated $NaHCO_3$ was added to the mixture. The mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered through Celite, and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc: Hexane = 3: 7) to yield **20** (75 mg, 96%) as a colorless oil: [α]1 +10.4 (*c* 1.1, $CHCl_3$) [lit.[2d] $[\alpha]^{26}_D$ +10.0 (*c* 0.25, $CHCl_3$), lit.[2b] $[\alpha]_D$ +10.3 (*c* 1.96, $CHCl_3$)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.58−4.56 (1H, m), 4.08−4.03 (1H, m), 3.90 (4H, s), 3.38 (1H, tdd, J = 11.3, 5.5, 2.9 Hz), 2.01 (1H, ddd, J = 13.6, 5.5, 2.9 Hz), 1.80−1.11 (17H, m), 1.31 (3H, s), 0.91 (3H, t, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 110.0, 74.4, 64.6(2C), 50.5, 49.2, 38.8, 36.9, 35.8, 33.7, 29.8, 27.2, 23.8, 20.7, 18.2, 17.9, 13.8; IR (neat) 2936, 2872, 1672, 1427 cm^{-1}; MS (m/z) 326 $[M + H]^+$; HRMS m/z calcd for $C_{18}H_{32}O_4N$ $[M + H]^+$ 326.2331, found 326.2333.

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Supporting Information Available: Experimental details and spectroscopic data for (*S*)-1-chloropentan-2-ol, (*S*)-1,2-epoxypentane, (*S*)-hept-1-yn-4-ol, and compounds **5**−**7**. ^{1}H and ^{13}C NMR spectra for compounds **5**−**20**. HPLC traces for **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.