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Oxazolone Cycloadducts as Heterocyclic Scaffolds for Alkaloid Construction: Synthesis of (±)-2-*epi*-Pumiliotoxin C

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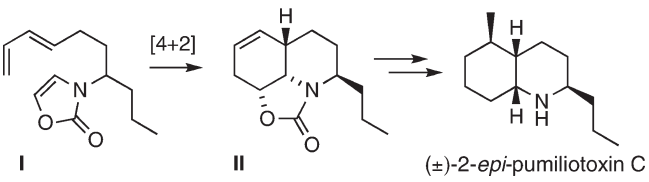

Intramolecular Diels−Alder cycloaddition of *N*-substituted oxazolone triene **I** allows direct entry to the functionalized octahydroquinoline **II**. Further manipulation of this framework by stereo- and regioselective introduction of the 5-methyl substituent, followed by excision of the carbamate, yields (±)-2-*epi*-pumiliotoxin C.

The skin secretions of neotropical frogs have long proven a rich and varied source of alkaloid natural products, many of which possess powerful yet specific bioactivity allied to their complex structure. A case in point is provided by the decahydroquinolines, with over 50 examples reported to date.[1] Several of these mild toxins display intriguing neurological activity as reversible antagonists of the nicotinic acetylcholine receptor channel.[2] As many of the proposed structures are based solely on MS and IR studies, confirmation by synthesis provides further compelling reason for development of a general approach to targets of this type. The parent member of this class, *cis*-195A[3] (the alkaloid formerly known as pumiliotoxin C, **1**), is typical of their general 2,5-disubstituted *cis*-fused decahydroquinoline pattern, Figure 1. Altogether rarer is the 2-*epi*-*cis* motif, represented by 2β,5β-diallyl congener *cis*-219A, **2**, and the related 5β-*Z*-eneyne variant *cis*-243A, **3**.[4] This framework is also found embedded within the tricyclic core of gephyrotoxin 287C, **4**, another related neuroactive alkaloid.[5] Whereas *cis*-195A has been synthesized on numerous occasions,[6] we were intrigued by the potential offered by the 2-*epi*-series and sought to develop a general route to compounds of this ilk. In this paper we describe one such route, culminating in a preliminary synthesis of 2-*epi*-pumiliotoxin C, **5**.

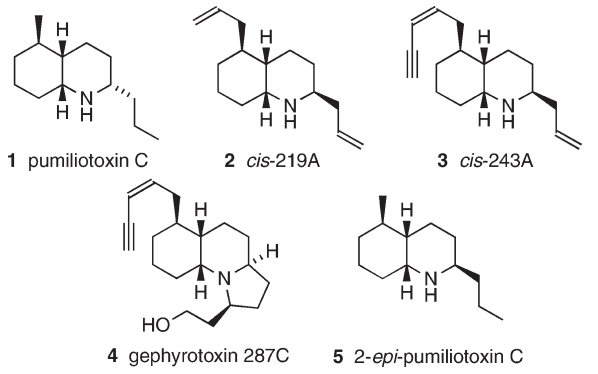

FIGURE 1. Representative decahydroquinoline targets.

As part of an ongoing program of research at the interface of heterocyclic and natural products chemistry, we recently reported the first intramolecular Diels−Alder reaction of *N*-alkylated oxazolones.[7] This thermally activated cycloaddition allows rapid entry into a number of important heterocyclic frameworks, chiefly, densely functionalized hexahydroindoles and octahydroquinolines. As we continued our studies of oxazolone chemistry,[8] it was clear that the latter appeared ideally suited to construction of decahydroquinoline alkaloids via direct incorporation of the initial cycloadduct framework. We therefore selected 2-*epi*-pumiliotoxin C, **5**, by way of example. Although previously synthesized on a number of occasions,[9] most often as a minor byproduct en route to pumiliotoxin C itself, this compound has remained an important benchmark for the testing of new synthetic methodologies and is thus a fitting initial target.

In keeping with the overall theme of our methodology, our proposed synthesis is based on a key intramolecular

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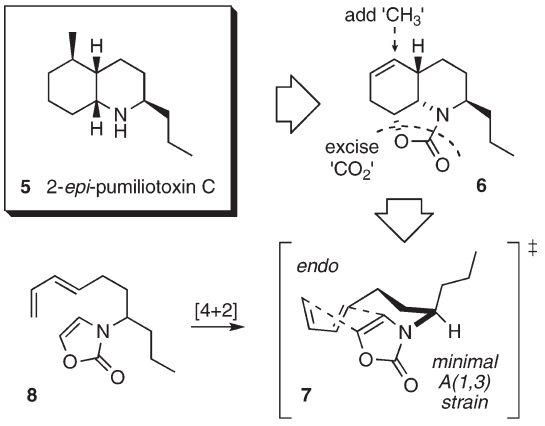
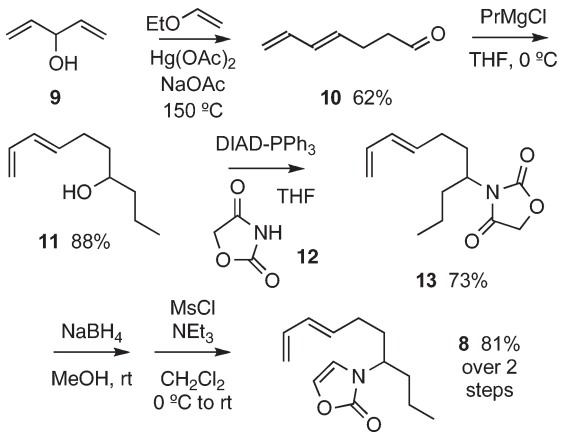
SCHEME 1. Oxazolone IMDA Approach to 2-*epi*-Pumiliotoxin C



SCHEME 2. Synthesis of Triene Precursor



Diels–Alder cycloaddition, the reaction of an oxazolone dienophile with a substituted diene fragment, tethered via nitrogen. This first-generation approach involves trienic system **8**, as shown in our initial retrosynthetic analysis (Scheme 1). Our earlier studies with the heptadienyl parent system had shown the *cis*-cycloadduct to predominate [3.8:1, *cis* to *trans*] via an *endo* mode of cycloaddition.[7] Assuming a similar transition state, the precise aspect of the propyl substituent would now be the critical issue. From early examination of models, we surmised that a pseudoaxial arrangement would minimize unfavorable allylic-type strain[10] with the oxazolone carbonyl. Cycloaddition in this fashion would thus establish three of the four required stereocenters in a single step. It would only remain to introduce the 5-methyl group in regio- and stereoselective fashion and then excise the carbamate functionality, most probably by a hydrolysis–deoxygenation protocol.

Construction of the required triene system proceeded from commercially available divinyl carbinol **9** (Scheme 2). Saucy-type rearrangement[11] afforded heptadienal **10**, which underwent simple Grignard reaction to yield alcohol **11**. A three-step protocol as developed by Shibuya[12] was utilized to introduce the secondary oxazolone moiety: Mitsunobu reaction with oxazolidine-2,4-dione **12** followed by reduction and elimination to generate the dienophilic olefin.

SCHEME 3. Initial Cycloaddition Studies

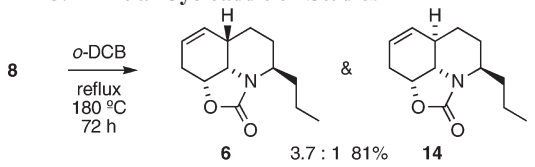


TABLE 1. Reaction Conditions vs Selectivity

conditions (in *o*-dichlorobenzene)	yield (%)	**6**:**14**
sealed tube, 210 °C, 72 h	78	3.1:1
microwave, 225 °C, 5 h	59	2.5:1
1.3 equiv of $EtAlCl_2$, reflux, 72 h	57	1:0

Investigation of the key cycloaddition ensued (Scheme 3). Simple thermal activation proceeded smoothly to furnish two main cycloadducts, **6** and **14**, in 3.7:1 ratio and 81% overall yield. Ring junction stereochemistry was readily assigned as *cis* and *trans* for each, in accordance with our previous findings. However, the signal at C2 was initially occluded, and extensive decoupling studies were required.[13] These indeed confirmed the C2-propyl substituent as axial in both cycloadducts, with added proof for **6** from X-ray crystallography. Considerable effort was spent on optimization of conditions; a brief survey is presented in Table 1 for comparison. In all cases, C2-*epi*-*cis*-cycloadduct **6** predominated, even to the extent that under thermal Lewis acid-promoted conditions[14] it was the sole product isolated.

With the structure of the major cycloadduct confirmed as **6**, we proceeded with the next phase of our approach. This centered on successful installation of the 5-methyl substituent in regio- and stereocontrolled fashion. In order to address both these concerns simultaneously, we chose to pursue a two-step protocol – cyclopropanation followed by reductive cleavage. Given the inherent topology of the cycloadduct, we reasoned that simple cyclopropanation would favor the convex β-face. Subsequent hydrogenolysis of the most sterically accessible edge would locate the 5-methyl as required. If successful, this would offer a fairly novel solution for stereocontrolled installation of an isolated methyl substituent, though precedent does arise from a seminal study on bicyclo[4.1.0]heptane.[15]

In the event, cyclopropanation under modified Denmark conditions[16] proceeded with a high degree of β-facial control to yield the expected tetracycle **15**[13] (Scheme 4). Subsequent rupture at the 6-position was best achieved by simple hydrogenation over Adams' catalyst,[17] with reasonable selectivity in favor of the desired isomer **16** (5.5:1, 5-Me to 6-Me). However, for reasons yet unclear to us this transformation required superstoichiometric quantities of PtO_2 to effect

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(13) See the Supporting Information for details of structural assignment.

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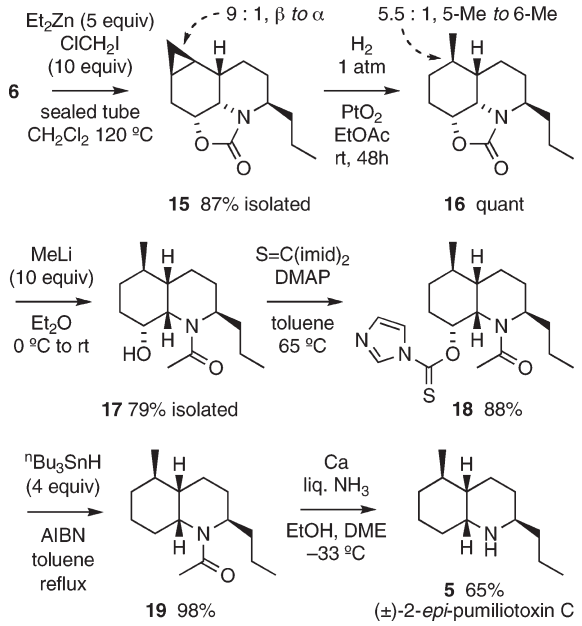
SCHEME 4. Synthesis of (±)-2-*epi*-Pumiliotoxin C



completion. The intermediacy of a discrete platinocyclic species has not been discounted.[18]

As this initial 5.5:1 mix proved inseparable, it was employed directly in studies of oxazolidinone cleavage. We found methyl lithium[19] to be doubly effective in this regard, as not only did this afford the amine conveniently protected as acetamide, but also enabled separation of the required regioisomer **17**, in 79% overall yield from **15**. Once again X-ray crystallography provided unequivocal confirmation of our ongoing structural assignments. Deoxygenation at C8 proceeded smoothly via a modified Barton−McCombie protocol[20] to afford the *N*-acetylated target, **19**.

In these latter stages of the synthesis (**17**−**19**), both ^{1}H and ^{13}C spectra were complicated by the presence of broadened and/or doubled signals. This observation was also noted by Meyers,[9e] and studied in detail by Polniaszek[9f] and Daly,[21] all of whom concluded this arose from rapid equilibration of the *cis*-fused bicyclic systems, in itself a well-established property of *cis*-decahydroquinolines.[22,23] A final deprotection of the *N*-acetamide group under Pearson's dissolving metal conditions[24] yielded (±)-2-*epi*-pumiliotoxin C, **5**, identical in all respects to that previously reported.[9a,c,e]

In summary, this study has demonstrated the utility of oxazolone IMDA cycloadducts as valuable scaffolds for alkaloid construction, culminating in the synthesis of (±)-2-*epi*-pumiliotoxin C by a direct incorporation approach.

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Experimental Section

Diels−Alder Cycloaddition of Triene 8. To a stirred solution of triene **8** (698 mg; 3.16 mmol; 1.0 equiv) in *o*-dichlorobenzene (63.1 mL; ~0.05 M) was added a trace of hydroquinone (14 mg; 2% by wt). The colorless solution was freeze−thaw degassed (3×), placed under an atmosphere of argon, and brought rapidly to reflux. After 72 h, heat was removed and the brown solution partially reduced in vacuo (hi-vac; 85 °C) to yield 878 mg of the crude cycloadducts as a dark brown solid. Further purification by flash chromatography (silica ratio 100:1; hexane/EtOAc, 4:1 to 3:1 to 2:1 to 1:1) yielded each cycloadduct as a colorless solid.

First, the minor *trans*-cycloadduct, (±)-(3^1*S*,4*R*,6a*R*,9a*R*)-4-propyl-4,5,6,6a,9,9a-hexahydrooxazolo[5,4,3-*ij*]quinolin-2(3^1*H*)-one, 14: 120 mg; 0.54 mmol; 17%; R_f 0.36 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz; $CDCl_3$) δ 5.77 (m, 2H), 4.58 (td, J = 2 × 8.1, 5.9 Hz, 1H), 3.96 (dt, J = 10.1, 2 × 5.1 Hz, 1H), 2.99 (dd, J = 10.0, 8.0 Hz, 1H), 2.89 (m, 1H), 2.20 (ddm, J = 14.2, 5.8 Hz, 1H), 1.94 (dq, J = 12.9, 3 × 3.3 Hz, 1H), 1.81 (m, 1H), 1.75 (ddd, J = 13.4, 5.8, 4.2 Hz, 1H), 1.61−1.71 (m, 2H), 1.58 (qd, J = 3 × 12.8, 3.2 Hz, 1H), 1.29−1.43 (m, 3H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DEPT) (100.6 MHz; $CDCl_3$) δ 157.6 (C), 132.0 (CH), 125.4 (CH), 71.6 (CH), 57.2 (CH), 49.8 (CH), 37.0 (CH), 33.2 (CH_2), 28.7 (CH_2), 28.4 (CH_2), 23.4 (CH_2), 19.5 (CH_2), 13.7 (CH_3); IR (thin film) ν_{max} 2958, 2932, 1744, 1020 cm^{-1}; HRMS m/z [M + H]$^+$ calcd for $C_{13}H_{20}NO_2$ 222.1494, found 222.1489.

Next, the major *cis*-cycloadduct, (±)-(3^1*S*,4*R*,6a*S*,9a*R*)-4-propyl-4,5,6,6a,9,9a-hexahydrooxazolo[5,4,3-*ij*]quinolin-2(3^1*H*)-one, 6: 444.4 mg; 2.01 mmol; 64%; R_f 0.22 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz; $CDCl_3$) δ 5.91 (ddt, J = 9.5, 6.4, 2 × 3.1 Hz, 1H), 5.67 (dm, J = 9.5 Hz, 1H), 4.88 (dddd, J = 9.3, 4.0, 1.9, 1.2 Hz, 1H), 4.04 (ddd, J = 9.3, 4.6, 1.4 Hz, 1H), 3.88 (dt, J = 9.6, 2 × 4.8 Hz, 1H), 2.59 (ddd, J = 16.3, 7.0, 2.0 Hz, 1H), 2.13 (m, 1H), 2.02 (ddq, J = 16.4, 3.9 Hz, 3 × 2.9 Hz, 1H), 1.90 (tt, J = 2 × 13.9, 2 × 3.8 Hz, 1H), 1.64−1.80 (m, 3H), 1.43 (dm, J = 13.9 Hz, 1H), 1.26−1.39 (m, 3H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DEPT) (100.6 MHz; $CDCl_3$) δ 157.2 (C), 131.4 (CH), 126.7 (CH), 72.4 (CH), 51.9 (CH), 48.5 (CH), 31.8 (CH_2), 30.9 (CH), 27.6 (CH_2), 23.3 (CH_2), 22.6 (CH_2), 19.4 (CH_2), 13.8 (CH_3); IR: (thin film) ν_{max} 3024, 2943, 2867, 1731, 1047 cm^{-1}; HRMS m/z [M + H]$^+$ calcd for $C_{13}H_{20}NO_2$ 222.1494, found 222.1487. Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.51; H, 8.64; N, 6.24.

Direct Cyclopropanation of Major Cycloadduct: (±)-(3*R*,4^1*S*,6a*R*,7a*R*,8a*R*,8b*S*)-3-Propyloctahydro-1*H*-cyclopropa[*f*]oxazolo-[5,4,3-*ij*]quinolin-5(4^1*H*)-one, 15. A 75-mL heavy-walled sealed tube, fitted with septum and stir-bar, was flame-dried under vacuum, flushed with Ar, and allowed to cool to rt. CH_2Cl_2 (2 mL) was added, followed by diethylzinc (Aldrich, 1.0 M in heptane; 2.65 mL; 2.65 mmol; 5.0 equiv) and the solution cooled to 0 °C. Neat chloroiodomethane (0.39 mL; 5.36 mmol; 10.1 equiv) was added dropwise with caution over a period of 2 min in order to prevent exotherm. During addition, a heavy colorless gum was precipitated; this was broken up by addition of further CH_2Cl_2 (5 mL), followed by vigorous stirring, to yield a milky suspension. The mixture was allowed to warm to rt. After 10 min, a solution of *cis*-cycloadduct **6** (117 mg; 0.53 mmol; 1.0 equiv) in CH_2Cl_2 (2 mL + 2 mL rinse) was added dropwise. The tube was sealed and heated immediately to 120 °C with vigorous stirring. After 5 h, heat was removed and the reaction allowed to cool to rt. The tube was opened, the contents poured onto 1 M HCl (25 mL), and the residue broken up with further 1 M HCl (25 mL) and CH_2Cl_2 (25 mL). The resulting mixture was partitioned, and the aqueous phase extracted with further CH_2Cl_2 (2 × 25 mL). The combined organic phases were dried ($MgSO_4$), filtered, and reduced in vacuo to yield 161 mg of crude cyclopropanes as a yellow oil. Further purification by flash chromatography (silica ratio 300:1; hexane/EtOAc 4:1 to 3:1)

yielded the title β-cyclopropane **15** as a colorless oil: 107 mg; 0.46 mmol; 86%; R_f 0.25 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz; $CDCl_3$) δ 4.72 (dt, J = 9.2, 2 × 2.6 Hz, 1H), 3.98 (dt, J = 10.3, 2 × 5.2 Hz, 1H), 3.72 (dd, J = 9.4, 3.8 Hz, 1H), 2.51 (ddd, J = 15.3, 6.7, 2.9 Hz, 1H), 1.95 (m, 1H), 1.86 (m, 2H), 1.71 (m, 1H), 1.43 (dm, J = 12.8 Hz, 1H), 1.29−1.40 (m, 3H), 1.09 (app sextet, J = 3.6 Hz, 1H), 0.94 (t, J = 7.0 Hz, 3H), 0.91−0.97 (occluded m, 1H), 0.87 (td, J = 2 × 8.2, 4.4 Hz, 1H), 0.82 (ddd, J = 15.5, 8.4, 2.3 Hz, 1H), 0.73 (qd, J = 3 × 8.2, 4.3 Hz, 1H), −0.03 (q, 4.3 Hz, 1H); ^{13}C NMR (DEPT) (100.6 MHz; $CDCl_3$) δ 156.6 (C), 73.1 (CH), 51.5 (CH), 48.4 (CH), 32.4 (CH), 32.2 (CH_2), 27.5 (CH_2), 22.6 (CH_2), 22.1 (CH_2), 19.5 (CH_2), 15.4 (CH_2), 13.8 (CH_3), 6.7 (CH), 4.4 (CH); IR (thin film) ν_{max} 2933, 2868, 1739, 1051 cm^{-1}; HRMS m/z [M + H]$^+$ calcd for $C_{14}H_{22}NO_2$ 236.1651, found 236.1641.

Regioselective Hydrogenolysis of Cyclopropane Ring: (±)-(3^1*S*,4*R*,6a*S*,7*R*,9a*R*)-7-Methyl-4-propyloctahydrooxazolo-[5,4,3-*ij*]quinolin-2(3^1*H*)-one, 16. To a stirred solution of β-cyclopropane **15** (123 mg; 0.52 mmol; 1.0 equiv) in EtOAc (15 mL), cooled to 0 °C, was added platinum oxide (95 mg; 0.42 mmol; 0.8 equiv) and the dark brown suspension evacuated−-flushed with H_2 (3×). Cooling was removed and stirring maintained under an atmosphere of H_2 (1 atm) at rt. After 8 h, additional PtO_2 (48 mg; 0.21 mmol; 0.4 equiv) was added and stirring maintained under H_2. Further PtO_2 (2 × 0.4 equiv) was added at 24 h, and again at 33 h, for a total of 2.0 equiv. At each addition, the suspension would darken from brown to black and then precipitate a fine metallic solid, which could be resuspended upon vigorous stirring. After 48 h total, the suspension was filtered through Celite (1 cm × 3 cm plug), flushing with EtOAc (3 × 10 mL). The combined organic phases were reduced in vacuo to yield an inseparable mixture of the desired 5-methyl isomer **16**, along with the minor 6-isomer (5.5 to 1 by NMR): 120 mg. This was used directly in the ensuing step without further purification: R_f 0.37 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz; $CDCl_3$) (major isomer) δ 4.52 (dt, J = 7.6, 2 × 7.2 Hz, 1H), 3.84 (qm, J = 7.2 Hz, 1H), 3.80 (dd, J = 7.2, 4.4 Hz, 1H), 1.98 (m, 1H), 1.78 (dq, J = 13.6, 3 × 2.9 Hz, 1H), 1.25−1.72 (m, 12H total), 0.92 (t, J = 7.4 Hz, 3H), 0.91 (d, J = 6.4 Hz, 3H).

Final Deprotection to (±)-2-*epi*-Pumiliotoxin C: (2*R*,4a*S*,5*R*,8a*R*)-5-Methyl-2-propyldecahydroquinoline, 5. A two-necked 25 mL flask, equipped with septum, stir bar, dry ice coldfinger condenser, and bubbler, was flushed with liquid NH_3 (~9 mL) and allowed to reflux (−33 °C). To this was added, dropwise, a cosolution of acetamide **19** (26.7 mg; 0.112 mmol; 1.0 equiv) and anhydrous EtOH (18.5 mL; 0.317 mmol; 2.82 equiv) in DME (1.03 mL), followed by calcium (32.5 mg; 0.812 mmol; 7.22 equiv), resulting in a dark blue solution. After 3.5 h under reflux, excess calcium was quenched by addition of EtOH (2 mL) and the ammonia allowed to evaporate. The resulting white slurry was taken up in $CHCl_3$ (10 mL) and water (10 mL), and the pH of the aqueous layer adjusted from pH 14 to 1 using 6 M HCl. Sat. aq. K_2CO_3 (10 mL) was added, resulting in a flocculent colorless precipitate. The biphasic mixture was filtered, rinsing with additional $CHCl_3$ (5 mL), partitioned, and the aqueous phase extracted with further $CHCl_3$ (2 × 10 mL). The combined organic phases were dried (K_2CO_3), filtered, and reduced in vacuo to yield 2-*epi*-pumiliotoxin C **5** as a colorless oil: 14.3 mg; 0.073 mmol; 65%; R_f 0.05 (hexane/EtOAc 1:2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.06 (dt, J = 10.5, 2 × 4.3 Hz, 1H), 2.75 (dm, J = 6.0 Hz, 1H), 1.61−1.84 (m, 4H total), 1.21−1.56 (m, 11H total), 0.99−1.13 (m, 2H total), 0.95 (d, J = 7.2 Hz, 3H), 0.86 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ 50.0, 49.7, 42.2, 38.4 (br), 32.5 (br), 31.4 (br), 28.8 (v. br − 2 signals), 25.3 (br), 20.6, 19.4, 19.3, 14.1; IR (thin film) ν_{max} 2926, 2868, 1461, 1376 cm^{-1}; HRMS m/z [M + H]$^+$ calcd for $C_{13}H_{26}N$ 196.2065, found 196.2058.

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Supporting Information Available: Full experimental procedures and data for all remaining new compounds; ^{1}H and ^{13}C NMR spectra for compounds **8**, **6**, **14**, **15**−**19**, and **5**; solved X-ray structures for **6** and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.