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Hydroformylation of Alkenylamines. Concise Approaches toward Piperidines, Quinolizidines, and Related Alkaloids

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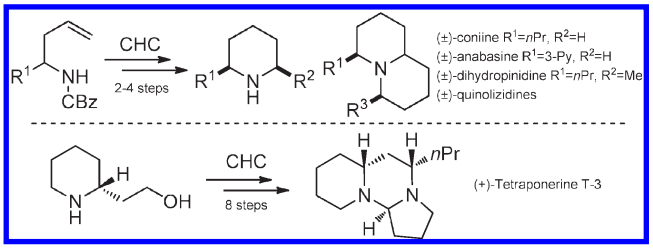

Linear hydroformylation of *N*-protected allyl- or homoallylamines (cyclohydrocarbonylation: CHC), followed by a reductive amination constitute the two key steps toward convenient routes to aza-heterocycles.

The development of new and efficient strategies for the construction of aza-heterocycles remains an active field in organic synthesis.[1,2] Among them the intramolecular reductive amination is a frequently used tactic.[2i−k] For instance, the linear hydroformylation of an amino-alkene provides a terminal aldehyde that may cyclize to an imine (or an iminium ion), which is further converted to an aza-heterocycle.[3−5] Moreover, a protocol for hydroformylation under microwave dielectric heating has been recently described[6] using commercial devices.[6,7]

Herein we describe a general strategy based on the linear hydroformylation of allyl- and homoallylamines for the syntheses of different alkaloids encompassing the piperidine ring system. Indeed a well-balanced use of hydroformylation and hydrogenation allows the controlled assembly of different substituted heterocycles simplifying their syntheses, removing the need for functional group protection and reducing the number of steps.[8] The versatility of our strategy is demonstrated herein by expeditious syntheses of piperidines such as (±)-coniine (**13**), (±)-anabasine (**14**), (±)-dihydropinidine (**17**), and quinolizidines such as **20**, **21**, **25** or (±)-alkaloid 9-epi-195C (**24**) based on the transformation of homoallylamines **6**, **7**, and **8**, and (+)-tetraponerine T-3 obtained from allylamine **32**.

As the terminal double bond of a homoallylamine can be converted to a linear aldehyde by hydroformylation, a convenient method for the preparation of homoallylamine is desirable (Figure 1). From the methods available for the preparation of homoallylamines,[9] we decided to apply a multicomponent reaction based on the aza-Sakurai−Hosomi reaction (aSH).[10]

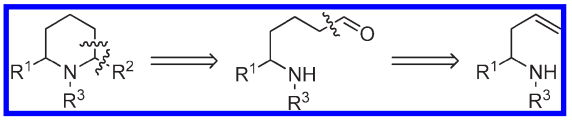

FIGURE 1. General retrosynthetic pathway for piperidines.

In the past, we have reported that the aSH reaction of 1,2- or of 1,3-*O*-protected hydroxy aldehydes provided respectively syn 1,2- or anti 1,3- diastereoselectivity.[11] Recently our group proposed concise syntheses of (±)-allo-sedamine and (±)-allo-lobeline combining the hydroformylation and the aSH reactions.[12]

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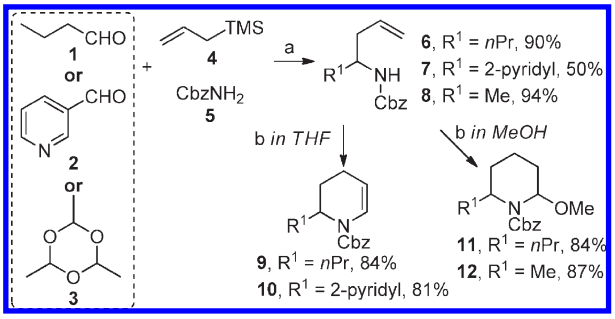
SCHEME 1. Aza-Sakurai−Hosomi Hydroformylation Sequence[a]



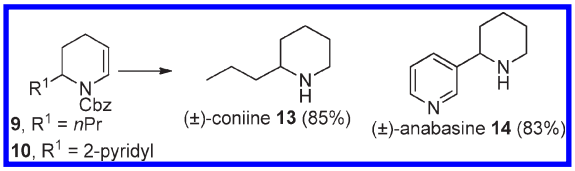
[a]Reagents and conditions: (a) $BF_3 \cdot Et_2O$, 0 °C, CH_2Cl_2, 2 h; (b) $Rh(CO)_2(acac)$ (0.5 mol %), BiPhePhos (1 mol %), H_2/CO (1:1) 5 bar, solvent, 65 °C, 12 h (in THF:PPTS (2.5 mol %)).

Our first effort toward (±)-coniine (**13**) and (±)-anabasine (**14**) was to secure the syntheses of the protected homoallylamines using the aSH reaction from the corresponding aldehydes as electrophiles (Scheme 1).

Allyltrimethylsilane (**4**) and benzylcarbamate (**5**) were selected as the nucleophilic partners and $BF_3 \cdot Et_2O$ as the Lewis acid. With use of butyraldehyde (**1**), the reaction proceeded smoothly to give the desired protected homoallylamine **6**, whereas with pyridine-3-carboxaldehyde (**2**) as the substrate, the reaction was sluggish, and **7** was obtained in moderate yield. Homoallylamines **6** and **7** were submitted to cyclohydrocarbonylation (CHC) reaction in THF with the biphephos[13]/rhodium(I) catalytic system (5 bar, H_2/CO (1:1)) in an autoclave (60 °C, 12 h).[3g] The hydroformylation proceeded in the presence of pyridinium *p*-toluenesulphonate (PPTS) with a very good catalyst-based regiocontrol as shown by the clean formation of enamides **9** and **10** in excellent yields (84% and 81%, respectively).

Enamides **9** and **10** originate from a cyclohydro-carbonylation: homoallylamines **6** or **7** were transformed by hydroformylation to the corresponding linear aldehydes which subsequently produced the six-membered enamides in the presence of PPTS. After optimization, the amount of catalyst and ligand could be reduced to respectively 0.5 and 1 mol %, demonstrating the efficiency of the Rh-based hydroformylation reaction. Enamides **9** and **10** were submitted to a catalytic hydrogenation employing Pearlman's catalyst (Scheme 2). A clean tandem piperidine deprotection/double bond reduction took place to form (±)-coniine (**13**) (64% overall for three steps) and (±)-anabasine (**14**) (34% overall for three steps).[14]

SCHEME 2. Synthesis of (±)-Coniine 13 and (±)-Anabasine 14[a]



[a]Reagents and conditions: H_2 5 bar, $Pd(OH)_2/C$ (10%), MeOH, rt, 24 h.

Next *cis*-2,6-disubstituted alkaloid (±)-dihydropinidine[15] (**17**) was selected as a target. To further functionalize the piperidine ring, we took advantage of the possibility to carry out the CHC reaction in a protic solvent.[3b] Indeed, using methanol (Scheme 1), homoallylamine **6** was tranformed into hemiaminal **11** (84% yield). Thus, the aSH reaction was repeated with paraldehyde **3** and the expected homoallylamine **8** was obtained in very good yield (94%). From **8**, CHC in methanol gave **12** in 87% yield, confirming the versatility of the intramolecular CHC reaction in different solvents.

The reaction of aminals **11** and **12** with allyltrimethylsilane (**4**) in the presence of $BF_3 \cdot Et_2O$ gave rise to a highly diastereoselective transformation, via the corresponding transient *N*-acyliminium ions, yielding the *cis*-2,6-disubstituted piperidines **15** and **16** (only one diastereomer was observed, 400 MHz ^1H NMR) in 56% and 58% yields, respectively (Scheme 3).[16] Unfortunately, screening of different conditions (temperature, nature, or amount of Lewis acid) did not improve the yields. The cis relationship of the two products **15** and **16** was secured observing a positive NOE between hydrogens at *C*-2 and *C*-6.[16b]

To complete the synthesis of (±)-dihydropinidine (**17**), the tandem piperidine deprotection/double bond reduction was performed on disubstituted piperidine **15** to give (±)-dihydropinidine (**17**) (34% overall yield over four steps).

Piperidines **15** and **16** were homologated to the corresponding linear aldehydes **18** (85%) and **19** (79%) by hydroformylation under standard conditions. Then aldehydes **18** and **19** were submitted to the deprotection/reductive amination sequence to give the racemic quinolizidines **20** and **21**, respectively, in 32% overall yield from butyraldehyde and 34% overall yield from paraldehyde. Cross-metathesis of **15** and **16** with methyl vinyl ketone[17] gave α,β-unsaturated

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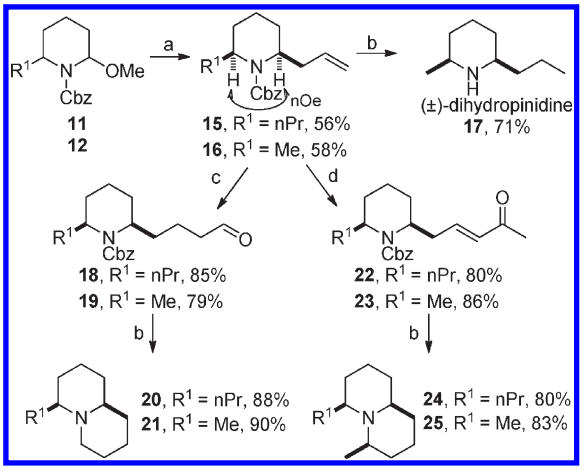
SCHEME 3. Synthesis of (±)-Dihydropinidine and Quinolizidines[a]



[a]Reagents and conditions: (a) **4**, $BF_3 \cdot Et_2O$, 0 °C, CH_2Cl_2; (b) H_2 5 bar, $Pd(OH)_2/C$ (10%), MeOH, rt, 24 h; (c) $Rh(CO)_2(acac)$ (0.8 mol %), BiPhePhos (1.6 mol %), H_2/CO (1:1) 5 bar, solvent, 60 °C, 12 h; (d) Grubbs II (3 mol %), methyl vinyl ketone, CH_2Cl_2, 12 h, reflux.

ketones **22** (R = *n*Pr, 80%) and **23** (R = Me, 86%) as predominantly the *E*-isomers.

Interestingly, the following one-pot piperidine deprotection/double bond reduction/reductive amination yielded, as single diastereomers, the desired disubstituted quinolizidines **24** (80%) and **25** (83%).

Again, the relative stereochemistry was determined by NOE experiments and was also confirmed by comparison with reported data.[18] In this CHC reaction driven sequence, two quinolizidines, alkaloid (±)-9-epi-195C (**24**) and dimethyl quinolizidine **25**, were obtained in five steps in 27% and 34% overall yields starting from butyraldehyde and paraldehyde, respectively.

With an established route to bicyclic piperidines we set out to synthesize (+)-tetraponerine T-3 (**33**) using a related approach.[19] Disconnection of the carbon−nitrogen bonds at *C*-11a reveals aldehyde diamine **A** (Figure 2). The carbon atom *C*-11a can be introduced via hydroformylation of allylamine **B**, with the concomitant formation of a fused ring system by reductive CHC reaction on the two nitrogen atoms *N*-4 and *N*-11. In turn allylamine **B** could be obtained from homopipecolic alcohol **26**, available in enantiomerically pure form.

Thus, (*R*)-piperidine ethanol (**26**) was oxidized to (*R*)-pipecolic acid (**27**), *N*-protected, and transformed into the Weinreb amide **28**, which on treatment with propylmagnesium chloride

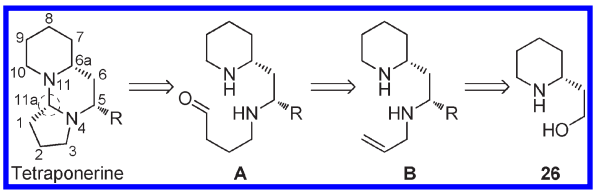
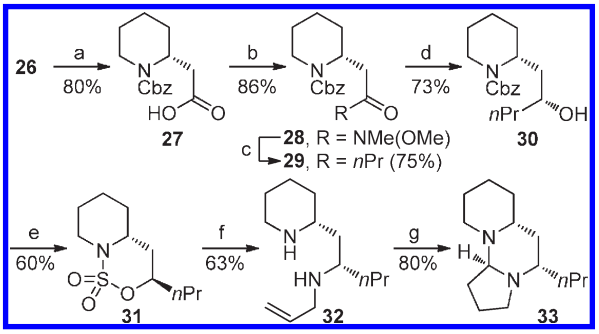


FIGURE 2. Retrosynthesis of tetraponerine.

SCHEME 4. (+)-Tetraponerine T-3 Synthesis[a]



[a]Reagents and conditions: (a) (i) CrO_3/H_2SO_4, H_2O; (ii) BnOCOCl, THF, NaOH (10%), rt; (b) DMTMM, MeNHOMe; (c) *n*PrMgCl, THF, 0 °C; (d) $LiAlH(Ot\text{-}Bu)_3$, THF, 0 °C, 24 h; (e) (i) H_2 1 bar, $Pd(OH)_2/C$, MeOH, rt, 12 h; (ii) $SOCl_2$, Et_3N, imidazole, $RuCl_3$, $NaIO_4$, H_2O, MeCN, 0 °C, 6 h; (f) $AllylNH_2$, μW, 100 °C, 12 h; (g) $RhCl(CO)(PPh_3)_2$ (2 mol %), xanthphos (8 mol %), H_2/CO (1:1) 7 bar, THF, μW, 110 °C, 1 h. DMTMM = 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride.

in THF at 0 °C gave ketone **29** (Scheme 4).[20] Stereocontrolled reduction of the carbonyl was then achieved with $LiAlH(Ot\text{-}Bu)_3$ in THF. As anticipated, this reduction proceeded with high diastereoselctivity (>8:1 as determined in the ^1H NMR spectrum of the crude reaction mixture).[21] Compound **30** was isolated as a single isomer after column chromatography (73% yield).

To minimize unproductive protecting group manipulation the cyclic sulfamidate **31** was obtained by using the following chemistry: **30** was deprotected by hydrogenolysis and reacted with $SOCl_2$ followed by $RuCl_3$-mediated oxidation with $NaIO_4$.[22] Then under microwave irradiations with a large excess of allylamine, the six-membered cyclic sulfamidate **31** was transformed to the allylamine **32**,[23] which was submitted to the hydroformylation reaction. Again, the reductive version of the CHC reaction could be realized with $RhCl(CO)(PPh_3)_2$ catalyst and Xantphos.

The reaction provided a single compound (GC mass analysis) that matched the reported spectroscopic and optical features of (+)-tetraponerine T-3 (**33**), prepared from homopipecolic alcohol (**26**) in eight steps in 14% overall yield.

Rh(I)-catalyzed CHC of alkenylamines proved to be an expeditive method for the preparation of six-membered azaheterocycles. The synthetic sequence encompasses a aSH reaction, followed by CHC, and final hydrogenolysis for a convenient access to (±)-coniine (**13**) (3 steps, 64%), (±)-anabasine (**14**) (3 steps, 34%), and (±)-dihydropinidine (**17**)

(18) by comparison with the compounds *trans*-**2a** and *cis*-**2a** in: Diaz-Gavilan, M.; Galloway, W. R. J. D.; O'Connell, K. M. G.; Hodkingson, J. T.; Spring, D. R. *Chem. Commun.* **2010**, *46*, 776.

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(4 steps, 34%); if the piperidine rings are decorated with an allylic side chain, the sequence was applicable to the synthesis of quinolizidines such as (±)-9-epi-195C (**24**) (5 steps, 27%). Following a related approach the CHC ring closing provided a synthesis of (+)-tetraponerine T-3 (8 steps, 14%). Previous asymmetric synthesis of Tetraponerine T-3 were accomplished in more than 8 steps including chromatographic separations of diastereomers.[19g,j] Our group is currently exploring further applications of the hydroformylation in the synthesis of biologically active heterocycles.

Experimental Section

General Procedure for Aza-Sakurai−Hosomi. In a dry flask under argon was introduced aldehyde (**1**, **2**, or **3**) in CH_2Cl_2 (to reach a concentration of 0.4 M) and the solution was cooled at 0 °C by means of an ice bath. Benzylcarbamate **5** (1 equiv) and allyltrimethylsilane **4** (1 equiv) were added. $BF_3 \cdot Et_2O$ (1 equiv; 2 equiv for **2**) was added dropwise and the solution was stirred for 2 h at 0 °C and allowed to warm to room temperature for 30 min. Na_2CO_3 solution was added and the aqueous layer was extracted with CH_2Cl_2 (3 times). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography to yield the desired homoallylamine.

Benzyl hept-1-en-4-ylcarbamate (6): yield 90%; white solid; R_f 0.33 (90:10 pentane/Et_2O); mp 38−40 °C; IR (film) 3300, 2952, 1686, 1541, 1264, 1234, 1020, 745, 696 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.37−7.30 (m, 5H), 5.78 (ddt, J = 17.8, 9.3, 6.9 Hz, 1H), 5.10−5.05 (m, 4H), 4.55 (br d, J = 6.9 Hz, 1H), 3.75 (m, 1H), 2.32−2.16 (m, 2H), 1.51−1.45 (m, 1H), 1.43−1.34 (m, 3H), 0.92 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.1 (C), 136.8 (C), 134.4 (CH), 128.6 (2×CH), 128.1 (3×CH), 117.9 (CH_2), 66.6 (CH_2), 50.6 (CH), 39.6 (CH_2), 36.9 (CH_2), 19.2 (CH_2), 14.0 (CH_3); LRMS-ESI (m/z) 248.1 (M + 1), 204.1 (M − 44); HRMS-ESI (m/z) calcd for $C_{15}H_{21}NO_2K$ $[M + K]^+$ 286.1204, found 286.1217 (Δ = 3.5 ppm).

Benzyl 1-(pyridin-3-yl)but-3-enylcarbamate (7): yield 50%; pale yellow oil; R_f 0.45 (95:5 CH_2Cl_2/MeOH); IR (film) 3305, 3033, 1695, 1530, 1328, 1254, 1040, 1025, 713, 696 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.57 (br s, 1H), 8.53 (dd, J = 4.7, 1.3 Hz, 1H), 7.6 (br d, J = 8.0 Hz, 1H), 7.38−7.33 (m, 6H), 5.67 (ddt, J = 17.5, 9.8, 6.7 Hz, 1H), 5.17−5.07 (m, 5H), 4.83 (br d, 2H), 2.56 (br t, J = 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.7 (C), 148.7 (CH), 148.2 (CH), 136.4 (C), 134.2 (C), 133.0 (CH), 128.8 (2×CH), 128.7 (CH), 128.4 (CH), 128.2 (2×CH), 123.6 (CH), 119.4 (CH_2), 67.2 (CH_2), 52.7 (CH), 40.8 (CH_2); LRMS-ESI (m/z) 283.1 (M + 1); HRMS-ESI (m/z) calcd for $C_{17}H_{18}N_2O_2K$ $[M + K]^+$ 321.0999, found 321.1014 (Δ = 3.5 ppm).

Typical Procedure for Hydroformylation. Benzyl 2-Methoxy-6-methylpiperidine-1-carboxylate (11). A solution of $Rh(CO)_2$-acac (0.25 mol %, 2.6 mg, 0.010 mmol) and biphephos (0.5 mol %, 15.9 mg, 0.020 mmol) in anhydrous degassed THF (0.5 mL), prepared in a Schlenk glassware under inert atmosphere, was introduced under inert atmosphere into a stainless steel autoclave containing **6** (1000 mg, 4.04 mmol) in anhydrous degassed MeOH to reach a final concentration of 0.2 M. The autoclave was flushed with H_2/CO (1:1) three times. Then, the autoclave was filled with 5 bar of H_2/CO (1:1) and heated to 60 °C with stirring for 12 h. Then, the autoclave was cooled to room temperature and gases were slowly and carefully released. The solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (95:5 pentane/Et_2O) to give **11** as a colorless oil (990 mg, 84%). R_f 0.50 (90:10 pentane/Et_2O); IR (film) 2954, 2871, 1694, 1411, 1306, 1069, 696 cm^{-1}; ^1H NMR ($CDCl_3$ filtered on basic Al_2O_3, 400 MHz) δ 7.37−7.32 (m, 5H), 5.51 (br s, 0.5H), 5.38 (br s, 0.5H), 5.18−5.15 (m, 2H), 4.25 (br s, 0.5 H), 4.17 (br s, 0.5H), 3.31 (br s, 1.5H), 3.23 (br s, 1.5H), 1.93−1.81 (m, 2H), 1.75−1.68 (m, 3H), 1.62−1.52 (m, 2H), 1.43−1.24 (m, 3H), 0.95−0.89 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.9/156.1 (C), 136.8 (C), 128.6 (CH), 128.2 (2×CH), 128.1 (2×CH), 82.4 (CH), 67.4/67.3 (CH_2), 55.7/55.2 (CH), 51.0 (CH_3), 36.0/35.5 (CH_2), 30.8 (CH_2), 27.7/27.3 (CH_2), 20.6 (CH_2), 14.1 (CH_3), 13.8 (CH_2); HRMS-ESI (m/z) calcd for $C_{17}H_{25}NO_3Na$ $[M + Na]^+$ 314.1727, found 314.1729 (Δ = 1.8 ppm).

General Procedure for Hydrogenolysis. In a high-pressure reactor under inert atmosphere, to a solution of substrate in MeOH (10 mL) was added Pearlman's catalyst ($Pd(OH)_2$/C 20%, 10% w/w). The mixture was set under 5 bar of hydrogen and was shacked overnight. The residue was filtrated over a Celite pad and concentrated HCl was added (1−2 mL). The solvent was removed under reduced pressure. Et_2O and NaOH 15% were added and the aqueous layer was extracted with Et_2O (3 times). The organic layer was dried over Na_2SO_4, filtered, and carefully concentrated under reduced pressure to give the desired alkaloid.

(±)-Coniine (13): yield 85%; colorless oil; IR (film) 3270, 2955, 2925, 2855, 1461, 1262, 1120, 743 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.07 (dddd, J = 11.7, 4.0, 2.2, 1.8 Hz, 1H), 2.62 (ddd, J = 11.7, 11.6, 2.6 Hz, 1H), 2.48−2.43 (m, 1H), 1.80−1.74 (m, 1H), 1.68−1.56 (m, 2H), 1.42−1.28 (m, 7H), 1.11−1.01 (m, 1H), 0.91 (dd, J = 7.0, 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 56.8 (CH), 47.3 (CH_2), 39.7 (CH_2), 33.0 (CH_2), 26.7 (CH_2), 25.0 (CH_2), 19.1 (CH_2), 14.4 (CH_3); LRMS-ESI (m/z) 128.2 (M + 1); HRMS-ESI (m/z) calcd for $C_8H_{18}N$ $[M + H]^+$ 128.1434, found 128.1436 (Δ = 2.1 ppm).

(4*R,6*S**,9a*R**)-4-Methyl-6-propyloctahydro-1*H*-quinolizine, (±)-9-epi-195C (24):** yield 80%; slightly yellow oil; IR (film) 2962, 1455, 1375 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.64−2.59 (m, 1H), 2.56−2.51 (m, 1H), 2.46 (t app, J = 10.5 Hz, 1H), 1.83−1.75 (m, 1H), 1.67−1.61 (m, 3H), 1.52−1.44 (m, 5H), 1.40−1.20 (m, 7H), 1.12 (, J = 6.4 Hz, 3H), 0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 58.1 (CH), 57.1 (CH), 55.9 (CH), 39.7 (CH_2), 34.3 (CH_2), 33.4 (CH_2), 30.6 (CH_2), 23.7 (CH_2), 22.7 (CH_2), 22.4 (CH_3), 20.2 (CH_2), 17.7 (CH_2), 14.4 (CH_3); HRMS-ESI (m/z) calcd for $C_{13}H_{26}N$ $[M + H]^+$ 196.2060, found 196.2070 (Δ = 0.1 ppm).

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Supporting Information Available: Full experimental procedures, characterization data, and copies of ^1H and ^{13}C spectra. This material is available free of charge via the Internet at http://pubs.acs.org.