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Three-Step Synthesis of (±)-Preussin from Decanal

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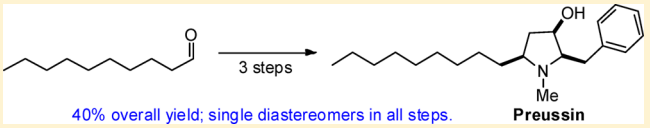
Supporting Information

ABSTRACT: A straightforward and stereoselective synthesis of the alkaloid preussin is described starting from decanal and diethyl 3-diazo-2-oxopropylphosphonate. The key steps are an aza-Michael reaction from an α,β-unsaturated diazoketone followed by a highly stereoselective Cu-catalyzed ylide formation and then a [1,2]-Stevens rearrangement. This strategy is feasible for extension to preussin analogues, demonstrating its utility for the rapid construction of *all-cis*-substituted pyrrolidines.



2,5-*Cis*-disubstituted pyrrolidine alkaloids[1] are vastly found in nature from animal, vegetable, and fungal sources. Possessing a diverse array of interesting biological properties, these natural products and their synthetic analogues are constantly targeted. Figure 1 illustrate some examples of 2,5-*cis*-disubstituted

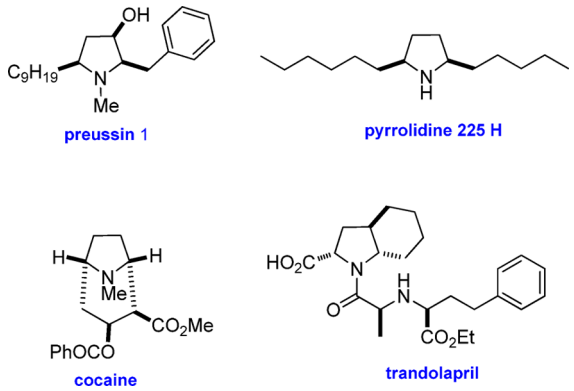


Figure 1. Natural and synthetic 2,5-*cis*-substituted pyrrolidines.

pyrrolidines as well as preussin (**1**), which was isolated in 1988 from the fungi *Aspergillus ochraceus* and *Preussia* sp.[2] Preussin exhibits significant antifungal, antiviral, and antibacterial activities and induces apoptosis in several human cancer cell lines.[2,3] Interestingly, all eight stereoisomers of preussin also display some biological activity,[4] and it is possible that their analogues have the same behavior. Because of this, several research groups have been involved with the synthesis of preussin and its analogues, and thus far, more than 20 syntheses have been described.[5] The majority have either long synthetic sequences or low diastereoselectivities. For example, the shortest synthesis of preussin to date (three steps), described in the ingenious work of Britton,[5e] suffers from low diastereoselectivity in two key steps.

While there are many methods of preparing 2,5-disubstituted pyrrolidines in the *trans* relationship, there are just a few for synthesizing the *cis* isomers. The reason is related to their abundance in nature. That is, the *trans* isomers are much more common.[1] In view of this and as a part of our studies employing α,β-unsaturated diazoketones[6,7] for constructing piperidine, indolizidine, and quinolizidine alkaloids, we envisioned that *all-cis*-trisubstituted pyrrolidines could also be prepared in a stereoselective fashion and in two to three steps from these building blocks. To illustrate, a retrosynthetic analysis is depicted in Scheme 1 for the synthesis of preussin (**1**). Diazoketone (**2**) could bring the long alkyl chain and could easily be prepared from decanal and the olefination reagent diethyl 3-diazo-2-oxopropylphosphonate.[6] To incorporate preussin's methyl and benzyl groups, an aza-Michael addition[8] in the presence of methylbenzylamine could be carried out. Finally, to construct the pyrrolidine ring and adjust the position of these groups, ylide formation followed by a [1,2]-Stevens rearrangement[9] could translocate the benzyl group (best migratory aptitude), leading to the thermodynamically more stable[10] 2,5-*cis*-pyrrolidinone (**4**). Hydride attack at the less hindered α face would complete the synthesis.

The synthesis of cyclic amines employing ammonium salts has been described, and important contributions can be found in the works of West[11] and Clark.[12] West described, for the first time, the synthesis of 2-substituted piperidinones using the [1,2]-Stevens rearrangement. Clark studied the same cyclization by means of a [2,3]-sigmatropic rearrangement and obtained disubstituted pyrrolidines and piperidines, but with no stereocontrol (or the *trans* isomer preferentially formed). In spite of these seminal contributions, to the best of our knowledge, neither preparation of 2,5-disubstituted pyrrolidines by the [1,2]-Stevens rearrangement nor study of the stereochemical outcome of these reactions in a nitrogen containing 5-membered ring was carried out. Herein, we describe how we accomplished both of these by preparing 2,5-*cis*-disubstituted pyrrolidines as single isomers and further synthesizing only *cis* alkaloid preussin from decanal in three steps.

First, unsaturated diazoketone (**2**) was prepared in 92% yield[13] from decanal, using our recently described method.[6] Next, Michael addition of benzylmethylamine furnished the

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Scheme 1. Synthetic Strategy for the Synthesis of Preussin from Decanal

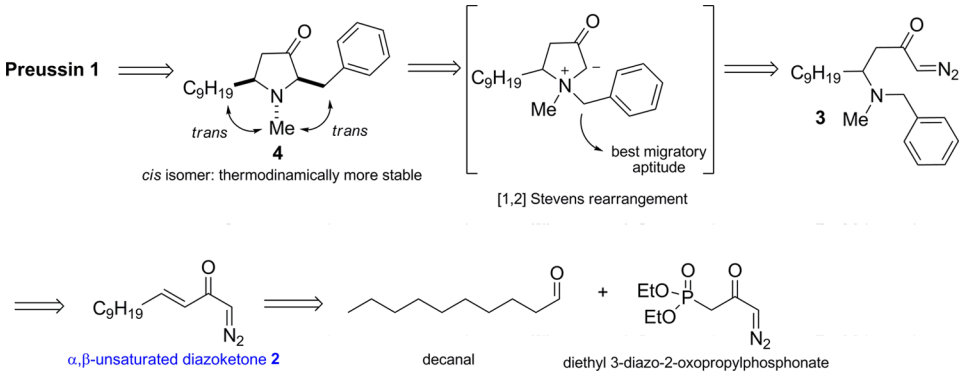
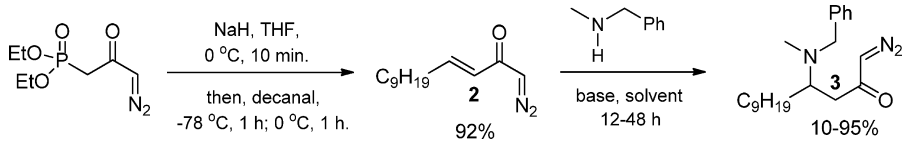


Table 1. Optimization Study for the Aza-Michael Reaction from Unsaturated Diazoketone (2)



entry[a]	amine (equiv)	base (equiv)	solvent	time (h)	yield[b] (%)	RSM[c] (%)
1	2	none	Et_2O	48	10	
2	2	none	THF	48	22	40
3	2	TEA (0.5)	THF	36	45	22
4	5	TEA (0.5)	THF	12	60	
5	2	DBU (0.5)	THF	36	50	15
6	**5**	**DBU (0.5)**	**THF**	**12**	**95**	
7	10	DBU (0.5)	THF	12	95	

[a]Unless otherwise noted, all the reactions were carried out using ~0.1 mmol of diazoketone. [b]Yields after column chromatography purification. [c]RSM = recovered starting material.

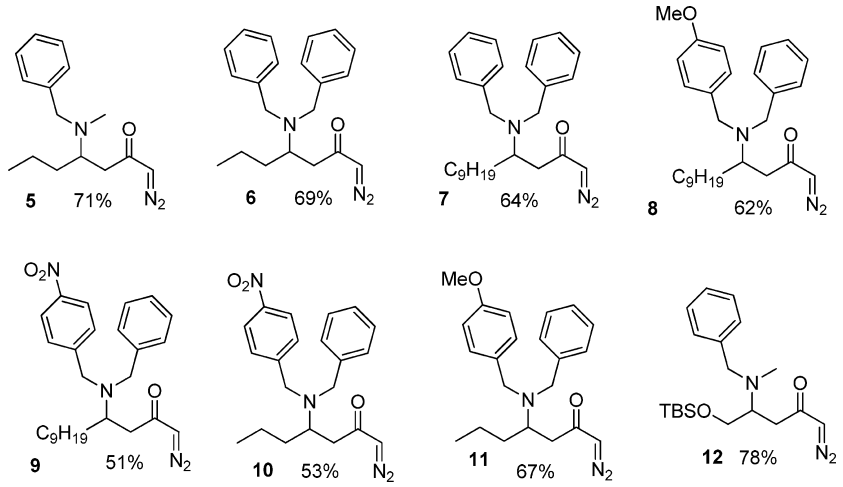


Figure 2. Aza-Michael adducts from reactions employing different amines and diazoketones.

aza-Michael adduct (**3**) in 95% yield[13] after a careful optimization study (Table 1). Using the best conditions (entry 6 in Table 1), adducts **5**–**12** were prepared in good yields from different diazoketones[6] and/or secondary amines (Figure 2) and can also be applied in the synthesis of preussin analogues.

After synthesis of *β*-amino diazoketone (**3**), cyclization to the ammonium ylide was performed followed by a [1,2] Stevens rearrangement. We initially used the conditions described by West in the synthesis of 2-substituted piperidinones[11] (entry 1, Table 2). Though all the starting material was consumed in 5 min, a complex and inseparable mixture of products was formed (probably by competing reactions such as C–H insertions, Wolff rearrangement, ylide decomposition, and nonselective [1,2]-Stevens rearrangements).[14] Changing the rhodium catalysts to copper ones was not sufficiently effective because, at best, a 35% yield was observed. This occurred when **3** was heated to 80 °C (entries 3–9 in Table 2). Finally, the use of a higher reaction temperature (110 °C) and $Cu(acac)_2$ as the catalyst proved to be the best choice, furnishing (**4**) in 57% yield as a single isomer.[15]

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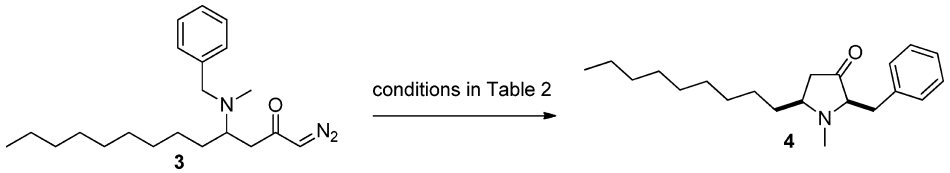
Table 2. Optimization Studies for the Ammonium Ylide formation and [1,2]-Stevens Rearrangement



entry	catalyst (equiv)	solvent	temp (°C)	time (min)	yield (%)
1	$Rh_2(OAc)_4$ (5%)	CH_2Cl_2	25	5	complex mixture
2	$Rh_2(TFA)_4$ (5%)	CH_2Cl_2	25	1	complex mixture
3	$Cu(acac)_2$ (10%)	CH_2Cl_2	25	120	no reaction
4	$Cu(tfacac)_2$ (10%)	CH_2Cl_2	25	60	complex mixture
5	$Cu(hfacac)_2$ (10%)	CH_2Cl_2	25	1	32
6	$Cu(AcO)_2.H_2O$ (10%)	CH_2Cl_2	25	120	no reaction
7	$Cu(acac)_2$ (10%)	benzene	reflux	1	35
8	$Cu(tfacac)_2$ (10%)	benzene	reflux	1	complex mixture
9	$Cu(hfacac)_2$ (10%)	benzene	reflux	1	complex mixture
10	**$Cu(acac)_2$ (10%)**	**toluene**	**reflux**	**1**	**57**

Michael adducts **5**–**11** were also subjected to the conditions described in entry 10, Table 2. Similar results were observed with respect to the reaction in the presence of **3**, and pyrrolidinones **13**–**15** could be obtained in moderate (44–51%) yields as *cis* isomers (Figure 3). In the case of the insertion reactions starting from compounds **8**–**11**, containing 4-methoxy- or 4-nitrobenzyl groups, a complex mixture of products was observed. Several studies strongly suggest that the mechanism of the [1,2]-Stevens rearrangement takes place by a diradical mechanism[16] (Scheme 2). Considering this mechanistic proposal, the result described above is probably caused by similar migratory aptitudes in these groups, as might be predicted by the relative stabilities of benzyl, 4-methoxybenzyl, and 4-nitrobenzyl radicals.[17]

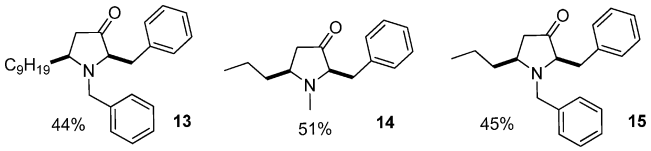
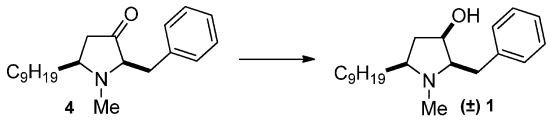


Figure 3. Extension of the method to new 2,5-*cis*-disubstituted pyrrolidines.

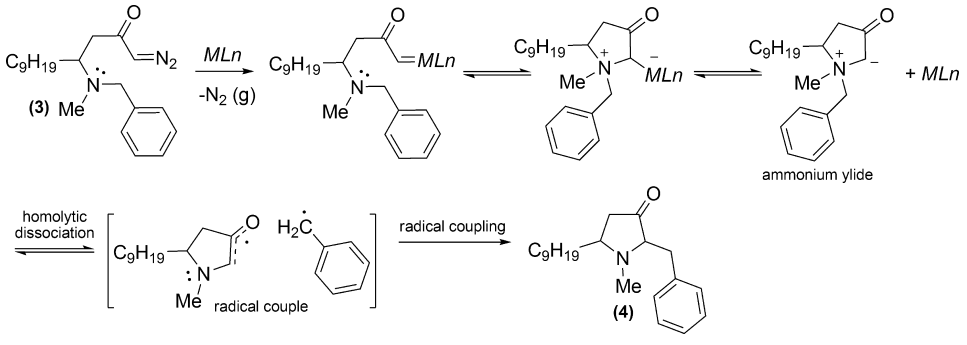
Completion of the synthesis was straightforward after hydride reduction. Although the reduction with sodium borohydride led to preussin in 98% yield, a 7:1 diastereoisomeric ratio was observed. This was easily circumvented by the use of L-Selectride, furnishing preussin in 80% yield as a single isomer (Scheme 3). All the data for preussin agree with those in the literature.[2] With the intent to perform the last two steps in a single reaction vessel, after addition of $Cu(acac)_2$ to the Michael adduct (**3**) in toluene under reflux, the solution was cooled to −10 °C (for $NaBH_4$) or −78 °C (for L-Selectride) before the hydride was added (neat or as a THF solution, respectively). Overall yields of 55% and 46% were observed for each reductant, respectively (Scheme 4). Presumably there was no change in the diastereoselectivity observed when two different reductants in the one-pot process were used versus carrying out the reduction in the purified ketone **4**.

Scheme 3. Hydride Reduction and Synthesis of Preussin



In conclusion, we have developed a highly stereoselective three-step synthesis of (±)-preussin from decanal with an overall yield of 40%. This work employed *α*,*β*-unsaturated diazoketones as the main building blocks, providing another example of how these platforms are useful for the short

Scheme 2. Proposed Mechanism for the Conversion of 3 to 4: Metal-Catalyzed Ylide Formation Followed by [1,2]-Stevens Rearrangement



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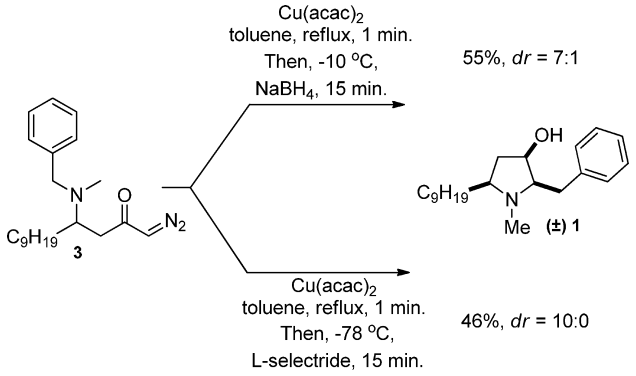
Scheme 4. One-Pot Synthesis of Preussin from Aza-Michael Adduct 3



synthesis of heterocycles. The strategy can be extended not only to preussin analogues but also to other *all-cis*-substituted pyrrolidines. Moreover, this sequence can be adjusted to be applied in an asymmetric synthesis of preussin, employing chiral amines in the aza-Michael reaction.[18]

EXPERIMENTAL SECTION

(*E*)-1-Diazotridec-3-en-2-one (2). In a flame-dried, round-bottom flask (10 mL) under argon atmosphere were added NaH (60% in mineral oil) (5.5 mg, 0.227 mmol, 2.0 equiv) and 1.2 mL of dry THF. The suspension was cooled to 0 °C, and a solution of diethyl (3-diazo-2-oxopropyl)phosphonate (50.0 mg, 0.227 mmol, 2.0 equiv) in dry THF (0.2 M) was added. After 10 min, the solution was cooled to −78 °C, and a solution of decanal (21.5 μL, 0.114 mmol, 1.0 equiv) in dry THF (0.1 M) was added. After 1 h, the temperature was immediately allowed to rise to 0 °C and stirred for an additional 1 h, when a saturated aqueous NH_4Cl solution (5 mL) was added to the reaction vessel. Next, the aqueous layer was extracted with ethyl acetate (3 × 20 mL), the combined organic layers were washed with water (15 mL) and brine (15 mL), dried over Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, diethyl ether/*n*-hexanes = 8:2) to give (*E*)-1-diazotridec-3-en-2-one (23.3 mg; 92% yield) as a yellow solid (80% in a 2 mmol scale; 70% in a 5 mmol scale): mp = 65−67 °C; R_f = 0.43 (*n*-hexanes/acetone 95:05); IR ν_{max} = 3072, 2955, 2918, 2870, 2847, 2118, 1661, 1603, 1470, 1460, 1389, 1340, 1151, 1109, 976, 943, 681, 584, 525 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.81 (dt, J = 15.4, 7.0 Hz, 1H), 5.98 (d, J = 15.4 Hz, 1H), 5.32 (s, 1H), 2.19 (2q, J = 7.0 Hz, 2H), 1.53−1.38 (m, 2H), 1.37−1.20 (m, 12H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.8, 145.4, 127.1, 54.9, 32.2, 31.8, 29.4, 29.3, 29.2, 29.1, 28.1, 22.6, 14.0 ppm/ HRMS (ESI-TOF) calcd for $C_{13}H_{23}N_2O$ [M + H^+] 223.18049, found 223.17950.

General Procedure for the Michael Addition. *4-(Benzylmethylamino)-1-diazotridecan-2-one (3).* In a flame-dried, round-bottom flask (10 mL), under argon atmosphere, were added (*E*)-1-diazotridec-3-en-2-one (**2**) (1 equiv, 0.091 mmol, 20 mg) and dry THF (1.3 mL, 0.07 M). To this solution were added methylbenzylamine (5 equiv, 0.45 mmol, 60 μL) and a catalytic amount of DBU (0.5 equiv, 0.045 mmol, 7 μL). The reaction was stirred for 12 h, and the solvent was then removed. The crude product was purified by flash column chromatography (silica gel, *n*-hexanes/ethyl acetate/TEA = 78:20:02) to give 4-(benzylmethylamino)-1-diazotridecan-2-one (**3**) (29.7 mg; 95% yield) as a yellow oil. When necessary, a second purification by column chromatography or preparative TLC was performed: R_f = 0.25 (*n*-hexanes/acetone 95:05); IR ν_{max} = 2953, 2926, 2853, 2102, 1651, 1637, 1362 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30−7.20 (m, 5H), 5.24 (s, 1H), 3.59 (d, J = 13.4 Hz, 1H), 3.51 (d, J = 13.4 Hz, 1H), 3.21−3.02 (m, 1H), 2.59 (m, 1H), 2.23 (m, 1H), 2.14 (s, 3H), 1.64−1.54 (m, 1H), 1.47−1.39 (m, 1H), 1.35−1.22 (m, 14H), 0.88 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.6, 139.9, 128.6 (2C), 128.1 (2C), 126.8, 60.6, 58.0, 54.9, 41.5, 36.4, 31.9, 31.0, 29.6 (2C), 29.6, 29.3, 26.8, 22.7, 14.1 ppm; HRMS (ESI-TOF) calcd for $C_{21}H_{34}N_3O$ [M + H^+] 344.26964, found 344.26721.

4-(Benzylmethylamino)-1-diazoheptan-2-one (5): yellow oil, 26.7 mg (71%); R_f = 0.20 (*n*-hexanes/AcOEt 7:3); IR ν_{max} = 3083, 3060, 3026, 2955, 2929, 2870, 2789, 2100, 1634, 1454, 1361, 1205, 1151, 734, 699, 617 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30−7.23 (m, 5H), 5.25 (s, 1H), 3.60 (d, J = 13.5 Hz, 1H), 3.52 (d, J = 13.5 Hz, 1H), 3.13 (quin, J = 6.5, 1H), 2.62−2.58 (m, 1H), 2.26−2.21 (m, 1H), 2.15 (s, 3H), 1.64−1.31 (m, 4H), 0.93 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.7, 139.9, 128.6 (2C), 128.2 (2C), 126.9, 60.4, 58.0, 53.4, 36.4, 33.4, 29.7, 20.0, 14.1 ppm; HRMS (ESI-TOF) calcd for $C_{15}H_{22}N_3O$ [M + H^+] 260.17574, found 260.17508.

4-(Dibenzylamino)-1-diazoheptan-2-one (6): yellow oil, 33.5 mg (69%); R_f = 0.43 (*n*-hexanes/AcOEt 8:2); IR ν_{max} = 3060, 3026, 2953, 2927, 2100, 1650, 1495, 1454, 1362, 1205, 1140, 698, 621, 600 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.20 (m, 10H), 4.97 (s, 1H), 3.64 (d, J = 13.6 Hz, 2H), 3.47 (d, J = 13.6 Hz, 2H), 3.05−3.01 (m, 1H), 2.67 (dd, J = 13.6, 6.0 Hz, 1H), 2.24−2.22 (m, 1H), 1.68−1.64 (m, 1H), 1.48−1.45 (m, 1H), 1.34−1.24 (m, 2H), 0.82 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.3, 139.8 (2C), 129.0 (4C), 128.2 (4C), 126.9 (2C), 55.5, 53.5 (2C), 41.9, 33.1, 29.7, 20.0, 14.0 ppm; HRMS (ESI-TOF) calcd for $C_{21}H_{26}N_3O$ [M + H^+] 336.20704, found 336.20584.

4-(Dibenzylamino)-1-diazotridecan-2-one (7): yellow oil, 24.2 mg (64%); R_f = 0.55 (*n*-hexanes/AcOEt 8:2); IR ν_{max} = 3084, 3061, 3026, 2926, 2852, 2102, 1647, 1454, 1360, 1246, 1205, 1150, 746, 698, 667, 613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.21 (m, 10H), 4.97 (s, 1H), 3.63 (d, J = 13.6 Hz, 2H), 3.47 (d, J = 13.6 Hz, 2H), 3.03−2.98 (m, 1H), 2.66 (dd, J = 13.7, 6.1 Hz, 1H), 2.24−2.21 (m, 1H), 1.71−1.64 (m, 1H), 1.47−1.39 (m, 1H), 1.36−1.22 (m, 14H), 0.89 (t, J = 7 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.3, 139.8 (2C), 129.0 (4C), 128.2 (4C), 126.9 (2C), 55.7, 53.5 (2C), 53.2, 42.0, 31.9, 30.7, 29.6, 29.6, 29.5, 29.3, 26.8, 22.7, 14.1 ppm; HRMS (ESI-TOF) calcd for $C_{27}H_{38}N_3O$ [M + H^+] 420.30094, found 420.29984.

4-(Benzyl(4-methoxybenzyl)amino)-1-diazotridecan-2-one (8): yellow oil, 25.0 mg (62%); R_f = 0.46 (*n*-hexanes/AcOEt 8:2); IR ν_{max} = 3065, 2953, 2924, 2853, 2102, 1651, 1510, 1458, 1362, 1300, 1248, 1175, 1039, 667, 615 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31−7.23 (m, 7H), 6.85 (d, J = 8.5 Hz, 2H), 4.97 (s, 1H), 3.79 (s, 3H), 3.62 (d, J = 13.6 Hz, 1H), 3.56 (d, J = 13.4 Hz, 1H), 3.45 (d, J = 13.6 Hz, 1H), 3.41 (d, J = 13.4 Hz, 1H), 3.05−2.97 (m, 1H), 2.69−2.62 (m, 1H), 2.26−2.26 (m, 1H), 1.69−1.59 (m, 1H), 1.35−1.28 (m, 1H), 1.27−1.20 (m, 14H), 0.90−0.86 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.4, 158.6, 140.0, 131.8, 130.1 (2C), 129.0 (2C), 128.1 (2C), 126.9, 113.6 (2C), 55.6 (2C), 55.2, 53.3, 52.8, 31.9, 30.7, 29.7, 29.6, 29.6, 29.5, 29.4, 26.8, 22.7, 14.1 ppm; HRMS (ESI-TOF) calcd for $C_{28}H_{40}N_3O_2$ [M + H^+] 450.31150, found 450.31039.

4-(Benzyl(4-nitrobenzyl)amino)-1-diazotridecan-2-one (9). yellow oil, 21.3 mg (51%); R_f = 0,33 (*n*-hexanes/AcOEt 8:2); IR ν_{max} = 3059, 3026, 2924, 2853, 2102, 1643, 1603, 1520, 1493, 1454, 1344, 1203, 1153, 1109, 851, 745, 700, 617 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.8 Hz, 2H), 7.36−7.29 (m, 5H), 5.03 (s, 1H), 3.92−3.44 (m, 4H), 3.06−2.96 (m, 1H), 2.65−2.61 (m, 1H), 2.31−2.24 (m, 1H), 1.73−1.64 (m, 1H), 1.44−1.36 (m, 1H), 1.35−1.15 (m, 14H), 0.89 (t, J = 7.0 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.7, 148.0, 147.1, 139.1, 129.5 (2C), 129.0 (2C), 128.3 (2C), 127.3, 123.4 (2C), 56.4, 53.8, 54.4, 53.3, 31.9, 30.9, 29.7, 29.6, 29.6, 29.5, 29.3, 26.9, 22.7, 14.1 ppm/ HRMS (ESI-TOF) calcd for $C_{27}H_{37}N_4O_3$ [M + H^+] 465.28602, found 465.28500.

4-(Benzyl(4-nitrobenzyl)amino)-1-diazoheptan-2-one (10): yellow oil, 29.2 mg (53%); R_f = 0,17 (*n*-hexanes/AcOEt 8:2); IR ν_{max} = 3063, 3026, 2955, 2928, 2870, 2854, 2359, 2102, 1636, 1518, 1456, 1342, 1136, 1107, 744, 698, 667, 615 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.8 Hz, 2H), 7.31−7.20 (m, 5H), 5.04 (s, 1H), 3.81−3.40 (m, 4H), 3.11−2.99 (m, 1H), 2.69−2.62 (m, 1H), 2.32−2.24 (m, 1H), 1.69−1.61 (m, 1H), 1.47−1.39 (m, 1H), 1.36−1.25 (m, 2H), 0.84 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7, 147.9, 147.1, 139.1, 129.5 (2C), 129.0

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(2C), 128.3 (2C), 127.3, 123.4 (2C), 56.2, 53.78, 53.3, 41.9, 33.3, 29.7, 20.1, 14.0 ppm; HRMS (ESI-TOF) calcd for $C_{21}H_{25}N_4O_3$ [M + H$^+$] 381.19212, found 381.19138.

*4-(Benzyl(4-methoxybenzyl)amino)-1-diazoheptan-2-one (**11**):* yellow oil, 35.4 mg (67%); R_f = 0,3 (*n*-hexanes/AcOEt 8:2); IR ν_{max} = 3026, 2955, 2928, 2869, 2853, 2100, 1653, 1612, 1510, 1460, 1454, 1362, 1300, 1247, 1171, 1038, 976, 824, 802, 743, 698, 619, 606 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.29 (m, 4H), 7.29−7.21 (m, 3H), 6.89−6.84 (m, 2H), 5.00 (s, 1H), 3.80 (s, 3H), 3.64 (d, J = 13.6 Hz, 1H), 3.58 (d, J = 13.4 Hz, 1H), 3.46 (d, J = 13.6 Hz, 1H), 3.42 (d, J = 13.4 Hz, 1H), 3.06−3.04 (m, 1H), 2.69−2.63 (m, 1H), 2.26−2.23 (m, 1H), 1.73−1.63 (m, 1H), 1.52−1.44 (m, 1H), 1.34−1.22 (m, 2H), 0.83 (t, J = 7.1 Hz, 3H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.4, 158.6, 139.9, 131.7, 130.1 (2C), 128.9 (2C), 128.12 (2C), 126.9, 113.5 (2C), 55.4, 55.2, 53.2, 52.7 (2C), 33.0, 29.7, 20.0, 14.0 ppm; HRMS (ESI-TOF) calcd for $C_{22}H_{28}N_3O_2$ [M + H$^+$] 366.21760, found 366.21667.

*4-(Benzyl(methyl)amino)-5-((tert-butyldimethylsilyl)oxy)-1-diazopentan-2-one (**12**):* yellow oil, 23.5 mg (78%); R_f = 0.38 (*n*-hexanes/AcOEt 8:2); IR ν_{max} = 3086, 2952, 2930, 2889, 2856, 2104, 1655, 1541, 1466, 1360, 1256, 1132, 1111, 1007, 945, 839, 779, 735, 698, 669, 613, 519 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30−7.20 (m, 5H), 5.33 (s, 1H), 4.36 (m, 2H), 3.80−3.68 (m, 3H), 3.35−3.28 (m, 1H), 2.57−2.51 (m, 1H), 2.26 (s, 3H), 1.06−0.83 (m, 9H), 0.09 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.2, 139.9, 128.5 (2C), 128.1 (2C), 126.8, 62.9, 62.2, 61.5, 58.9, 37.7, 29.7, 25.8 (3C), 18.2, −5.4 (2C) ppm; HRMS (ESI-TOF) calcd for $C_{19}H_{32}N_3O_2Si$ [M + H$^+$] 362.22583, found 362.22565.

General Procedure to the Ylide Formation/Stevens Rearrangement. *2-Benzyl-1-methyl-5-nonylpyrrolidin-3-one (**4**).* In a flame-dried round-bottom flask (10 mL), under argon atmosphere, was added 4-(benzylmethylamino)-1-diazotridecan-2-one (20 mg, 0.0583 mmol, 1 equiv) dissolved in dry toluene (1.2 mL, 0.05 M). The system was heated to reflux temperature, and then Cu(acac)$_2$ (1.6 mg, 5.83 μmol, 0.1 equiv) was added at once. The reaction proceeded instantly with N_2 release. Next, the reaction was cooled to room temperature, and the solvent was removed. The crude material was purified by flash column chromatography (silica gel, *n*-hexanes/acetone/TEA = 94:04:02) to give 2-benzyl-1-methyl-5-nonylpyrrolidin-3-one (**4**) (10.5 mg; 57% yield). When necessary, a second purification by column chromatography or preparative TLC was performed: colorless oil; R_f = 0.55 (*n*-hexanes/acetone 95:05); IR ν_{max} = 2953, 2924, 2853, 1705, 1637, 1628, 1601, 1562, 1522, 1510, 1497, 1456, 1439, 1410, 1377, 1286, 1265, 700, 611 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30−7.11 (m, 5H), 3.05 (dd, J = 14.3, 4.7 Hz, 1H), 2.85 (dd, J = 14.4, 5.2 Hz, 1H), 2.75 (t, J = 4.9 Hz, 1H), 2.51−2.43 (m, 1H), 2.38 (dd, J = 17.9, 6.1 Hz, 1H), 2.31 (s, 3H), 1.77 (dd, J = 17.8, 10.9 Hz, 1H), 1.25 (m, 16H), 0.88 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.8, 138.5, 129.7 (2C), 128.0 (2C), 126.1, 74.4, 62.5 42.8, 39.3, 35.9, 32.9, 31.9, 29.8, 29.6, 29.5, 29.3, 25.6, 22.7, 14.1 ppm/ HRMS (ESI-TOF) calcd for $C_{21}H_{34}NO$ [M + H$^+$] 316.26349, found 316.26187.

*1,2-Dibenzyl-5-nonylpyrrolidin-3-one (**13**):* colorless oil, 8.2 mg (44%); R_f = 0.45 (*n*-hexanes/acetone 95:05); IR ν_{max} = 3078, 3026, 2955, 2926, 2853, 1717, 1653, 1558, 1456, 1373, 1205, 1153, 1080, 1030, 752, 698, 667, 611, 547 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42−7.15 (m, 10H), 4.23 (2d, J = 4.5 Hz, 1H), 3.63 (m, 2H), 3.10 (m, 1H), 2.75 (dd, J = 14.4, 8.9 Hz, 1H), 2.68−2.61 (m, 1H), 2.33 (dd, J = 14.0, 4.6, Hz, 1H), 2.06−2.00 (m, 1H), 1.75−1.70 (m, 1H), 1.30−1.21 (m, 15H), 0.88 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.7, 142.0, 139.6, 128.7 (2C), 128.5 (2C), 128.4 (2C), 127.6 (2C), 127.5, 127.0, 60.0, 55.4, 50.8, 44.7, 43.9, 31.9, 29.7, 29.7, 29.6, 29.5, 29.4, 29.3, 22.7, 14.1 ppm; HRMS (ESI-TOF) calcd for $C_{27}H_{38}NO$ [M + H$^+$] 392.29479, found 392.29367.

*2-Benzyl-1-methyl-5-propylpyrrolidin-3-one (**14**):* colorless oil, 9.1 mg (51%); R_f = 0.40 (*n*-hexanes/acetone 95:05); IR ν_{max} = 3085, 3062, 3027, 2955, 2930, 2870, 2789, 2100, 1634, 1454, 1361, 1151, 734, 699, cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26−7.12 (m, 5H), 3.06 (dd, J = 14.4, 4.9 Hz, 1H), 2.85 (dd, J = 14.3, 4.9 Hz, 1H), 2.75 (t, J = 4.9 Hz, 1H), 2.31 (s, 3H), 1.82−1.72 (m, 2H), 1.58−1.46 (m, 1H), 1.36−1.19 (m, 4H), 0.91 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.7, 138.5, 129.8 (2C), 128.0 (2C), 126.1, 74.4, 62.4, 42.8, 39.3, 29.7, 21.3, 19.0, 14.3 ppm; HRMS (ESI-TOF) calcd for $C_{15}H_{22}NO$ [M + H$^+$] 232.16959, found 232.16907.

*1,2-Dibenzyl-5-propylpyrrolidin-3-one (**15**):* colorless oil, 8.3 mg (45%); R_f = 0.38 (*n*-hexanes/acetone 95:05); IR ν_{max} = 3059, 3028, 2957, 2924, 2870, 2853, 1699, 1651, 1493, 1454, 1207, 698, 667, 621, 596 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.10 (m, 10H), 3.94 (d, J = 14.5 Hz, 1H), 3.84 (d, J = 14.5 Hz, 1H), 3.17 (t, J = 4.7 Hz, 1H), 2.88−2.81 (m, 3H), 2.36 (dd, J = 17.5, 6.0 Hz, 1H), 1.71 (dd, J = 17.5, 10.5 Hz, 1H), 1.28−1.25 (m, 4H), 0.87 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.3, 138.1, 137.4, 130.0 (2C), 129.4 (2C), 128.3 (2C), 127.9 (2C), 127.2, 126.1, 70.9, 59.1, 55.5, 43.0, 36.5, 29.7, 18.8, 14.3 ppm; HRMS (ESI-TOF) calcd for $C_{21}H_{26}NO$ [M + H$^+$] 308.20089, found 308.19992.

(±)-2-Benzyl-1-methyl-5-nonylpyrrolidin-3-ol, Preussin (1). *Reduction with NaBH$_4$.* In a flame-dried, round-bottom flask (10 mL), under argon atmosphere, was added 2-benzyl-1-methyl-5-nonylpyrrolidin-3-one (**4**) (8.4 mg, 0.026 mmol, 1 equiv) in dry MeOH (530 μL). This solution was cooled to −10 °C and $NaBH_4$ (2.1 mg, 0.052 mmol, 2 equiv) added. The reaction was stirred at this temperature for 15 min. The solvent was removed under low pressure, and the material was purified by flash column chromatography (silica gel, *n*-hexanes/acetone = 50:50) to give preussin (**1**) (8.08 mg; 98% yield, dr = 7:1)[19] as a colorless oil: R_f = 0.20 (*n*-hexanes/acetone 95:05); IR ν_{max} = 3369, 2855, 2924, 2853, 1456, 743, 700, 611 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.25 (m, 4H), 7.22−7.17 (m, 1H), 3.83 (s, 1H), 2.97−2.81 (m, 2H), 2.36 (s, 3H), 2.33−2.29 (m, 1H), 2.20 (m, 3H), 1.72 (t, J = 10.5 Hz, 2H), 1.45 (dd, J = 13.7, 6.2 Hz, 1H), 1.45−1.20 (m, 14H), 0.88 (t, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.3, 129.3 (2C), 128.4 (2C), 126.1, 73.7, 70.4, 66.0, 39.3, 38.5, 33.5, 31.9, 29.9, 29.7, 29.6, 29.6, 29.3, 26.3, 22.7, 14.1 ppm; HRMS (ESI-TOF) calcd for $C_{21}H_{36}NO$ [M + H$^+$] 318.27914, found 318.27744.

Reduction with L-Selectride. In a flame-dried, round-bottom flask (10 mL), under argon atmosphere, was added 2-benzyl-1-methyl-5-nonylpyrrolidin-3-one **4** (20 mg, 0.063 mmol, 1 equiv) in dry THF (2.6 mL). This solution was cooled to −78 °C, and a 1 M solution of L-Selectride in THF (220 μL, 0.222 mmol, 3.5 equiv) was added. The reaction was stirred at this temperature for 15 min. Next, the reaction was quenched with 100 μL of MeOH, 100 μL of H_2O, 100 μL of a 40% solution of H_2O_2, and 100 μL of a solution of NaOH 2 M. After that, 10.0 mL of H_2O was added. The mixture was extracted with AcOEt (3 × 50 mL) and dried with Na_2SO_4 ,and the solvent was removed. The material was purified by flash column chromatography (silica gel, *n*-hexanes/acetone = 50:50) to give 2-benzyl-1-methyl-5-nonylpyrrolidin-3-ol (16.0 mg; 80% yield, dr = 100:0) as colorless oil.

One-Pot Ylide Formation/Stevens Rearrangement/Carbonyl Reduction. In a flame-dried, round-bottom flask (10 mL), under argon atmosphere, was added 4-(benzylmethylamino)-1-diazotridecan-2-one (30 mg, 0.0874 mmol, 1 equiv) dissolved in dry toluene (1.2 mL, 0.05 M). The system was heated to reflux, and then Cu(acac)$_2$ (2.4 mg, 8.74 μmol, 0.1 equiv) was added. Next, the reaction was cooled to −10 °C ($NaBH_4$ reduction) or −78 °C (L-Selectride reduction). Next, an ethanolic solution of $NaBH_4$ (2 equiv) or a 1 M THF solution of L-Selectride (3.5 equiv) was added. After 15 min, the reaction was quenched and the product isolated as described above for each type of reduction. The crude material was then purified by flash column chromatography (silica gel, *n*-hexanes/acetone = 50:50) to give (±)-2-benzyl-1-methyl-5-nonylpyrrolidin-3-ol, preussin (**1**) in 55% yield (15.2 mg; dr = 7:1; $NaBH_4$) or 46% yield (12.7 mg; dr = 10:0; L-Selectride).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra of all new compounds and preussin. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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