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Cobalt- versus Ruthenium-Catalyzed Alder–Ene Reaction for the Synthesis of Credneramide A and B

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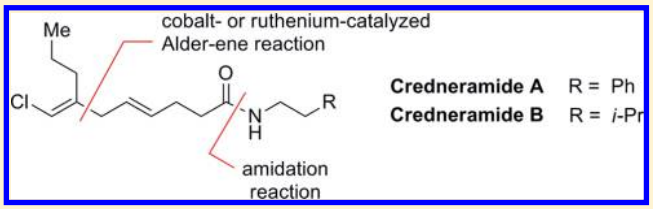
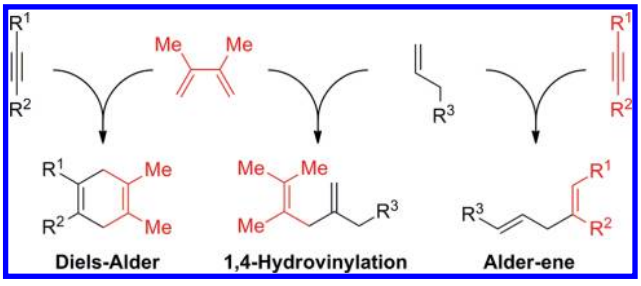
Supporting Information

ABSTRACT: The first synthesis of the natural products credneramide A and B was accomplished by utilizing Alder–ene reactions between a terminal alkene and an internal alkyne to generate the rather uncommon 1,4-diene substructure of these compounds. Moreover, two different short linear sequences toward these targets are evaluated using either a cobalt-catalyzed Alder–ene reaction of 1-chloropent-1-yne or a ruthenium-catalyzed Alder–ene reaction of 1-trimethylsilyl-1-pentyne with 5-hexenoic acid derivatives in the key step transformation. In addition, saponification of the primary Alder–ene product derived from the cobalt-catalyzed Alder–ene reaction led to credneric acid, the biological precursor of both natural products.



The ultimate benchmark for every established synthetic method is application in natural product synthesis, in advanced materials science, and in industrial processes. As shown in the past decade, cobalt-catalyzed transformations[1] are a powerful tool for the atom-economic and stereoselective construction of cyclic[2] and acyclic[3] organic building blocks. The immediate product of cobalt-catalyzed carbon–carbon bond formation reactions between unsaturated starting materials such as alkenes, alkynes, or 1,3-dienes exhibits cyclic as well as acyclic 1,4-diene substructures (Scheme 1).

Scheme 1

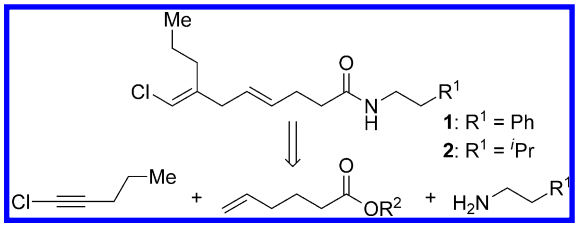


As a consequence, we are particularly interested in natural products and materials bearing the rather infrequent acyclic 1,4-diene motif which by retrosynthetic analysis can be constructed via a cobalt-catalyzed 1,4-hydrovinylation or an Alder–ene reaction. In fact, we have already applied the 1,4-hydrovinylation successfully in the short synthesis of moenocinol, the aglycon of the antibiotic moenomycin A.[4] On the other hand, we realized a short racemic synthesis of hepialone as well as of a lipid isolated from vanilla beans via ozonolysis of branched 1,4-dienes generated by cobalt-catalyzed 1,4-hydrovinylation reactions of allyl pinacolboronic ester.[5]

The recent discovery of credneramide A (**1**) and B (**2**) prompted us to address their synthesis utilizing a cobalt-catalyzed Alder–ene reaction as the key step of the formation of the carbon backbone of these natural products.[6] The compounds were isolated from the organic extract of the cyanobacterium cf. *Trichodesmium* sp. nov. which was collected near the Credner Islands, Papua New Guinea, from which the compounds' names originate. It was found that both compounds are biologically active, especially in the inhibition of calcium oscillation in cerebrocortical mouse neurons at low micromolar concentrations (**1**, IC_{50} 4.0 μM; **2**, IC_{50} 3.8 μM).

From a synthetic point of view, the scaffold of both substances should be concisely accessible by amidation of a suitable 5-hexenoic acid derivative and a transition-metal-catalyzed Alder–ene reaction with a 1-pentyne-derived component as is outlined in Scheme 2.

Scheme 2



At first, we began our investigation concerning the synthesis of the credneramides utilizing the well-established ruthenium-catalyzed Alder–ene reaction described by Trost.[7] However, in a simple test reaction, we immediately recognized that the

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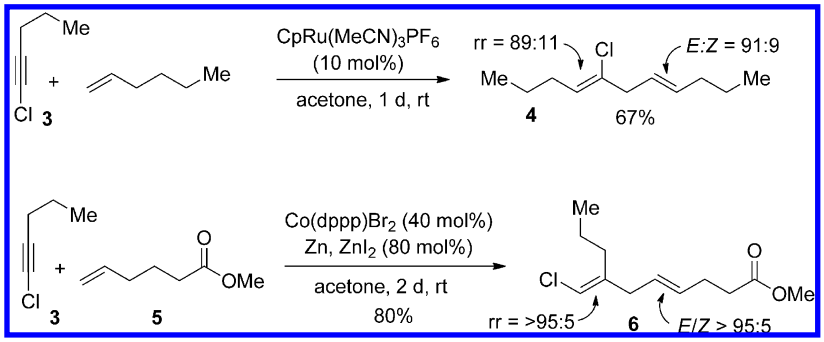
Scheme 3



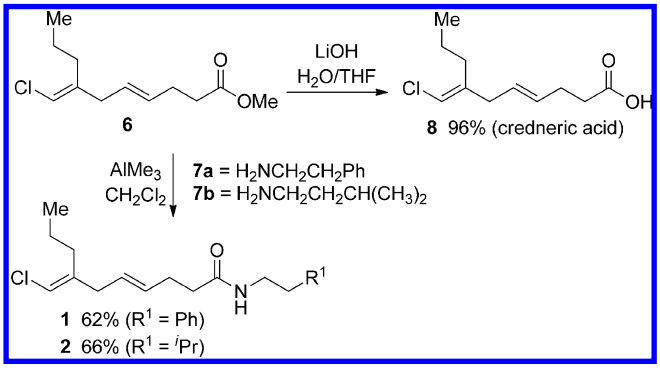
ruthenium-catalyzed Alder–ene reaction of a 1-chloro-1-pentyne (**3**)[8] with 1-hexene provided predominantly the wrong linear regioisomer **4** concerning the carbon–carbon bond formation at the alkyne subunit, while the desired *E*-double bond configuration could be formed via the ruthenium-induced double bond migration in the alkene component (Scheme 3).

Therefore, we investigated the alternative route involving a cobalt-catalyzed Alder–ene reaction[9] by reacting 1-chloro-1-pentyne (**3**) with methyl 5-hexenoate (**5**) for the formation of the desired branched regioisomer found in the natural products.[10] As free carboxylic acids and amides are not tolerated by the cobalt catalyst, 5-hexenoic acid was introduced as its methyl ester. Unfortunately, the reaction proceeded sluggishly in dichloromethane with poor conversion of the alkene component **5** and the major product in these reactions was trichlorotripropylbenzene, which was formed in a cyclotrimerization reaction of the alkyne.[11] We observed that increasing the amount of the chloroalkyne or the catalyst loading did not lead to complete conversion of the alkene component but produced even more cyclotrimerization by-product. These inhibited the Alder–ene reaction by catalyst deactivation. As known from our initial studies,[9] the use of acetone as a solvent led to the best chemoselectivity in the cobalt-catalyzed Alder–ene reaction, associated by diminished reactivity. Nevertheless, the reaction conditions could be optimized by using acetone as solvent of choice and also by portioning the catalyst and alkyne loadings over 2 days. With these modified conditions and applying a higher catalyst loading, we were able to obtain the desired methyl ester of credneric acid (**6**) with high regio- and stereocontrol in a good yield of 80%, accompanied by small amounts of unreacted methyl 5-hexenoate which could not be separated from the desired product completely.

To date, we attribute the different regioselectivities of the ruthenium versus the cobalt catalyst in the Alder–ene reaction to the electronic nature of these metal fragments; assigning a more nucleophilic character to the $CpRu^+$ and a more electrophilic reactivity to the $Co(dppp)^+$ fragment, while steric factors are not believed to be of high relevance for the observed regioselectivities. These electronically based assumptions could explain the formation of different regioisomers of the metallacyclic intermediates, but more detailed investigations for the cobalt-catalyzed Alder–ene reaction are necessary to obtain additional data and to establish the cobalt catalysis as a complementary synthetic method.

With the key intermediate methyl credneroate (**6**) in hand, the completion of the syntheses of credneramides A (**1**) and B (**2**) was accomplished via $AlMe_3$-mediated amidation reactions with the respected amines **7a**/**7b**.[12] Furthermore, credneric acid (**8**), the natural product and the biological precursor of credneramide A and B, could be obtained by simple saponification (Scheme 4).[13]

Scheme 4



Hence, both credneramide A and B as well as credneric acid could be synthesized in two steps starting from methyl 5-hexenoate in excellent overall yields of 50%, 53% and 77%.

In addition, we were also interested in comparing these results obtained with the cobalt-catalyzed Alder–ene reaction with a ruthenium-catalyzed route for the synthesis of credneramide A and B. Therefore, we substituted the chloro-substituted 1-pentyne (**3**) with the trimethylsilyl-substituted alkyne **11** (Scheme 4).[7] This alternative approach led us to three commercially available building blocks: 1-trimethylsilyl-1-pentyne (**11**), 5-hexenoic acid (**9**), and the two primary amines **7a** and **7b**, respectively. As ruthenium-catalyzed Alder–ene reactions between carboxylic acid functionalized alkenes with 1-trimethylsilyl-1-alkynes are not known, purification of carboxylic acids are difficult and because of the rather expensive ruthenium-based catalyst, we decided to perform first the amidation between 5-hexenoic acid (**9**) with the respective amine **7a**/**7b**. Adopting an amidation procedure with very similar substrates,[14] we could obtain the respective 5-hexenoic amides **10a**/**10b** in good yields (Scheme 5).

Although the ruthenium-catalyzed Alder–ene reaction tolerates all kinds of functional groups as acetals, alcohols, ether, ester, carbonates, ketones, sulfonamides, and silyl groups,[7,10a] we were not sure if the catalyst accepted simple amides. Fortunately, the ruthenium-catalyzed Alder–ene reaction between 1-trimethylsilyl-1-pentyne (**11**) and the respective 5-hexenoic amides **10a** and **10b** proceeded smoothly within 3 h at ambient temperature to give the corresponding products **12a** and **12b** in good yields as single regio- and

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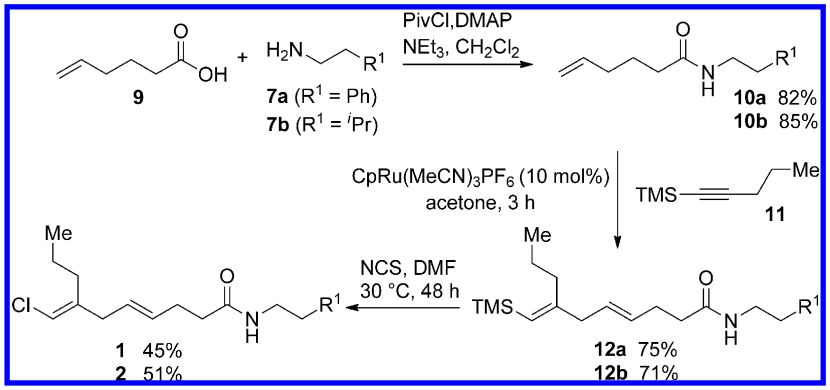
Scheme 5



stereoisomers. Next, the credneramides **1** and **2** were accessible via chlorodesilylation reaction, which is described to proceed with retention of the double-bond configuration. However, the use of the original protocol[15] established by Paige et al. for the synthesis of (*S*)-jamaicamide C carboxylic acid, a building block of related natural products also isolated from a cyanobacterium, led to the generation of various byproducts which were difficult to separate from the products due to their very similar polarity. We found, that the reaction proceeded best by lowering the original reaction temperature from 50 to 30 °C to inhibit side-reactions. Nonetheless, the desired products were always accompanied by their minor *Z*-configurated vinyl chloride isomers, which diminished the yields in the last step. Thus, credneramide A (**1**) and B (**2**) could be obtained after three linear steps starting from 5-hexenoic acid in good overall yields of 28% and 31%, respectively.

In conclusion, we have demonstrated that the natural products credneramides A and B can be accessed by a transition-metal-catalyzed Alder−ene reaction, constructing the rather challenging 1,4-diene subunit in a single step. The ruthenium and the cobalt catalyst proved again to complement each other, as the ruthenium-catalyst tolerated a 1-trimethylsilyl-substituted alkyne and a free amide as substrates in contrast to the cobalt catalyst, which is unable to perform a reaction between such components. On the other hand, the cobalt catalyst produces, unlike its opponent, the desired regioisomer in the Alder−ene reaction of a 1-chlorinated alkyne with the corresponding terminal olefin. In comparison, the ruthenium-route proved to be advantageous concerning the availability of starting materials and the straightforward synthesis, though the sequence suffers from the final chlorodesilylation reaction. In contrast, the cobalt-catalyzed route is disadvantaged by the commercial unavailability of the chloroalkyne but displays its benefits by generating the 1,4-dienyl chloride subunit efficiently and stereoselectively in a single step.

EXPERIMENTAL SECTION

General Experimental Methods. All reactions were carried out under an argon atmosphere in heat gun-dried glassware and were stirred magnetically. Unless otherwise noted, all reactions were performed with anhydrous solvents, and ZnI_2 was dried in vacuo at 150 °C prior to use. Commercially available materials were used without further purification. Flash chromatography was performed on silica gel 60 (230−400 mesh), and analytical thin-layer chromatography (TLC) was carried out on silica gel 60 F-254 precoated aluminum plates. The TLC plates were analyzed by short-wave UV illumination and by dipping in CAM stain (composed of 40 g of ammonium molybdate, 1.6 g of ceric ammonium molybdate, 80 mL of concentrated sulfuric acid, and 720 mL of water) with subsequent heating by using a heat gun. ^{1}H and ^{13}C NMR spectra were obtained using $CDCl_3$ as a solvent and tetramethylsilane as internal standard. Chemical shifts δ are reported in ppm downfield from tetramethylsilane. Coupling constants are indicated in Hz with multiplicities denoted as s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), sext (sextet), and m (multiplet). Broad singlets are reported as bs. IR spectra were measured on an FT-IR spectrometer and are reported in wave numbers (cm^{-1}). High-resolution mass spectra were acquired using electron impact ionization (EI) or atmospheric pressure chemical ionization (APCI).

Preparation of 1-Chloro-pent-1-yne (3). Following a literature procedure,[8a] a solution of triphenylphosphine (4.0 equiv) in dichloromethane (0.625 M) was treated with butyraldehyde (1.0 equiv) and tetrachloromethane (2.0 equiv) and was stirred overnight at room temperature. The solvent was then evaporated (40 °C, 400 mbar), and the residue was treated with pentane (1.0 mL/g residue). The solid was filtered, and the filtrate was distilled to give 1,1-dichloropent-1-ene in 43% yield as a clear and colorless liquid. The compound was mixed with powdered potassium hydroxide (1.0 equiv) and Aliquat 336 (6 mol−%). The reaction mixture was stirred for 2 h at 90 °C. Then the product was distilled off directly and dried by filtration through a short plug of a mixture of silica gel and magnesium sulfate. The product was obtained as a clear and colorless liquid in 62% yield.

1-Chloro-pent-1-yne (3): colorless liquid; 2.70 g (26.36 mmol, 62%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.15 (t, J = 7.0 Hz, 2H), 1.53 (sext, J = 7.3 Hz, 2H), 0.98 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 69.6, 57.1, 21.8, 20.7, 13.4; HRMS (EI, ICP, m/z) calcd for $C_5H_7{}^{35}Cl$ 102.0236, found 102.0236; IR (film, cm^{-1}) 2965, 2936, 2875, 2241, 1618, 1459, 1381, 1336, 1273, 1225, 1087, 1007, 915, 848, 786, 745, 645, 603, 555, 476.

General Procedure A for the Ruthenium-Catalyzed Alder−Ene Reaction. Following a literature procedure by Trost,[7] the alkyne (1.0 equiv), the alkene (1.0 equiv), and tris(acetonitrile)-cyclopentadienylruthenium(II) hexafluorophosphate (10 mol %) were dissolved in acetone (1 M) and stirred for 3 h at room temperature. The reaction mixture was then filtered over a small plug of silica gel. After evaporation of the solvent, the crude product was purified by flash column chromatography (SiO_2, eluent) to give the Alder−ene products **4**/**12a**/**12b** as clear oils.

(4*Z*,7*E*)-5-Chloroundeca-4,7-diene (4): pale yellow oil; 124 mg (0.67 mmol, 67%); eluent pentane; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.58−5.37 (m, 3H), 2.98 (d, J = 6.2 Hz, 2H), 2.15 (q, J = 7.4 Hz, 2H), 2.01 (q, J = 6.8 Hz, 2H), 1.47−1.34 (m, 4H), 0.94−0.87 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.6, 125.7, 125.5, 42.7, 34.5, 30.6, 22.4, 21.9, 13.7, 13.6; MS (EI) m/z (%) 186 (M^+, 73), 159 (2), 151 (22), 144 (10), 129 (20), 121 (14), 109 (36), 101 (56), 93 (57), 79 (100), 65 (42), 55 (24); HRMS (EI, ICP, m/z) calcd for $C_{11}H_{19}{}^{35}Cl$ 186.1175, found 186.1183; IR (film, cm^{-1}) 2959, 2927, 2870, 1659, 1458, 1379, 1339, 1258, 1136, 1091, 1035, 967, 871, 796, 739, 675,

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635, 542. The chloro-functionalized carbon atom could not be detected in ^{13}C NMR.

(4*E*,7*E*)-*N*-Phenethyl-7-((trimethylsilyl)methylene)dec-4-enamide (12a): colorless oil; 268 mg (0.75 mmol, 75%); eluent pentane/diethyl ether = 1:2; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.29 (m, 2H), 7.25−7.22 (m, 1H), 7.20−7.18 (m, 2H), 5.48−5.33 (m, 3H), 5.16 (s, 1H), 3.52 (q, J = 6.0 Hz, 2H), 2.81 (t, J = 6.9 Hz, 2H), 2.72 (d, J = 4.5 Hz, 2H), 2.36−2.30 (m, 2H), 2.22−2.17 (m, 2H), 2.09−2.04 (m, 2H), 1.47−1.34 (m, 2H), 0.90 (t, J = 7.4 Hz, 3H), 0.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 158.2, 138.9, 130.1, 129.5, 128.7, 128.6, 126.5, 124.2, 42.1, 40.5, 38.1, 36.6, 35.7, 28.5, 22.1, 14.1, 0.4; MS (EI) m/z 357 (M^+, 4), 342 (40), 328 (5), 314 (4), 288 (1), 274 (4), 261 (1), 248 (7), 235 (98), 220 (3), 178 (2), 163 (5), 144 (11), 120 (3), 104 (100), 91 (18), 73 (48), 59 (9); HRMS (EI, ICP, m/z) calcd for $C_{22}H_{35}NOSi$ 357.2488, found 357.2493; IR (film, cm^{-1}) 3287, 3077, 3027, 2954, 1642, 1548, 1447, 1361, 1247, 1199, 1152, 1084, 1031, 969, 920, 836, 744, 694, 621, 496.

(4*E*,7*E*)-*N*-Isopentyl-7-((trimethylsilyl)methylene)dec-4-enamide (12b): colorless oil; 229 mg (0.71 mmol, 71%); eluent pentane/diethyl ether = 1:2; ^1H NMR (300 MHz, $CDCl_3$) δ 5.52−5.36 (m, 3H), 5.17 (s, 1H), 3.26 (td, J = 7.3, 5.6 Hz, 2H), 2.73 (d, J = 5.3 Hz, 2H), 2.39−2.33 (m, 2H), 2.25−2.20 (m, 2H), 2.09−2.04 (m, 2H), 1.67−1.54 (m, 1H), 1.47−1.34 (m, 4H), 0.92−0.87 (m, 9H), 0.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 158.2, 130.2, 129.5, 124.2, 42.1, 38.6, 38.1, 37.8, 36.7, 28.6, 25.9, 22.4, 22.1, 14.1, 0.4; MS (EI) m/z (%) 323 (M^+, 3), 308 (53), 294 (6), 280 (7), 266 (3), 254 (2), 240 (6), 214 (7), 201 (22), 186 (19), 172 (2), 158 (100), 145 (51), 129 (8), 114 (3), 99 (2), 86 (2), 73 (53), 59 (9); HRMS (APCI, FT-ICR, m/z) calcd for $C_{19}H_{37}NOSiH$ 324.2717, found 324.2716; IR (film, cm^{-1}) 3288, 3086, 2954, 2871, 1641, 1550, 1457, 1367, 1247, 1159, 1069, 1015, 969, 920, 837, 747, 688, 621.

Preparation of Methyl Credneroate (6) via Cobalt-Catalyzed Alder−Ene Reaction. Zinc iodide (40 mol %), zinc powder (40 mol %), and $CoBr_2$(dppp) (20 mol %) were suspended in acetone (1 M) under argon atmosphere. Then methyl hex-5-enoate (**5**) (1.0 equiv) and 1-chloropent-1-yne (**3**) (1.0 equiv) were added, and the mixture was stirred at room temperature for 16 h. The reaction mixture was treated with additional zinc iodide (40 mol %), zinc powder (40 mol %), $CoBr_2$(dppp) (20 mol %), and 1-chloropent-1-yne (1.0 equiv) and was stirred at room temperature for further 16 h. Afterward, the suspension was filtered over a short pad of silica gel, and the solvent was removed under vacuum. The residue was purified by flash column chromatography (SiO_2, eluent). The product was accompanied by small amounts of inseparable methyl hex-5-enoate (purity ~90 w%).

Methyl credneroate (6): yellow liquid; 103 mg (0.40 mmol, 80%); eluent pentane/diethyl ether = 15:1; ^1H NMR (300 MHz, $CDCl_3$) δ 5.78 (s, 1H), 5.52−5.34 (m, 2H), 3.66 (s, 3H), 2.72 (d, J = 5.5 Hz, 2H), 2.41−2.29 (m, 4H), 2.18−2.12 (m, 2H), 1.43 (sext, J = 7.5 Hz, 2H), 0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 141.5, 130.9, 127.8, 113.1, 51.5, 37.9, 33.8, 32.2, 27.7, 20.2, 13.9; MS (EI) m/z (%) 230 (M^+, 5), 194 (10), 179 (1), 164 (5), 156 (72), 147 (7), 135 (26), 121 (77), 113 (13), 105 (40), 91 (81), 79 (100), 67 (27), 59 (22), 51 (10); HRMS (APCI, FT-ICR, m/z) calcd for $C_{12}H_{19}{}^{35}ClO_2H$ 231.1146, found 231.1146; IR (film, cm^{-1}) 2957, 2871, 1737, 1632, 1436, 1358, 1244, 1158, 1086, 1025, 971, 921, 848, 795, 737, 628, 520, 441.

General Procedure B for the Amidation of Methyl Credneroate (6). Following a literature procedure,[12] a solution of the corresponding amine (7.0 equiv) in dichloromethane (0.77 M) was treated with trimethylaluminium (5.0 equiv, 1.0 M solution in heptane) at 0 °C dropwise. The solution was stirred for 30 min at this temperature. Then a solution of methyl credneroate (1.0 equiv) in dichloromethane (0.55 M) was injected dropwise at room temperature. The solution was stirred overnight and was then quenched carefully with aqueous 0.5 M HCl. The mixture was then transferred into aqueous 0.5 M HCl/dichloromethane (1:1), and the aqueous phase was extracted three times with dichloromethane. The combined organic extracts were dried over $MgSO_4$ and filtered, and the solvent was evaporated in vacuo. The residue was purified by flash column chromatography (SiO_2, eluent) and bulb-to-bulb distillation to afford **1** and **2** as clear, orange oils.

Credneramide A (1): orange oil; 65 mg (0.20 mmol, 62%); eluent: pentane diethyl ether = 1:4; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (t, J = 7.4 Hz, 2H), 7.23 (t, J = 7.4 Hz, 1H), 7.19 (d, J = 7.0 Hz, 2H), 5.77 (s, 1H), 5.49 (bs, 1H), 5.45 (dt, J = 15.3, 6.4 Hz, 1H), 5.37 (dt, J = 15.1, 6.7 Hz, 1H), 3.52 (dt, J = 7.0, 6.0 Hz, 2H), 2.81 (t, J = 6.9 Hz, 2H), 2.70 (d, J = 6.6 Hz, 2H), 2.32 (dt, J = 7.3, 6.7 Hz, 2H), 2.18 (t, J = 7.8 Hz, 2H), 2.15 (t, J = 7.8 Hz, 2H), 1.43 (sext, J = 7.8 Hz, 2H), 0.91 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 141.5, 138.9, 131.2, 128.7, 128.6, 127.7, 126.5, 113.1, 40.5, 37.8, 36.3, 35.7, 32.2, 28.3, 20.2, 13.9; MS (EI) m/z (%) 319 (M^+, 18), 284 (45), 268 (4), 254 (2), 242 (1), 228 (3), 216 (1), 202 (9), 192 (8), 176 (3), 163 (70), 148 (3), 135 (8), 122 (9), 104 (100), 91 (45), 79 (26), 65 (11), 53 (4); HRMS (APCI, FT-ICR, m/z) calcd for $C_{19}H_{26}{}^{35}ClNOH$ 320.1776, found 320.1775; IR (film, cm^{-1}) 3287, 3070, 3028, 2958, 2928, 2869, 1714, 1640, 1547, 1449, 1359, 1261, 1196, 1163, 1082, 1032, 969, 922, 849, 792, 744, 697, 570, 497.

The data are in good accordance to the literature.[6]

Credneramide B (2): orange oil; 62 mg (0.22 mmol, 66%); eluent pentane/diethyl ether = 1:4; ^1H NMR (500 MHz, $CDCl_3$) δ 5.78 (s, 1H), 5.48 (dt, J = 15.4, 6.4 Hz, 1H), 5.41 (dt, J = 16.0, 6.1 Hz, 1H), 5.38 (bs, 1H), 3.26 (dt, J = 7.8, 6.6 Hz, 2H), 2.72 (d, J = 6.4 Hz, 2H), 2.35 (dt, J = 7.2, 7.1 Hz, 2H), 2.21 (t, J = 7.3 Hz, 2H), 2.16 (t, J = 7.3 Hz, 2H), 1.64−1.56 (m, 1H), 1.44 (sext, J = 7.8 Hz, 2H), 1.37 (dt, J = 7.8, 7.1 Hz, 2H), 0.93−0.90 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 141.5, 131.3, 127.7, 113.1, 38.6, 37.9, 37.8, 36.4, 32.2, 28.4, 25.9, 22.4, 20.2, 13.9; MS (EI) m/z 285 (M^+, 18), 270 (3), 250 (56), 234 (6), 220 (4), 206 (3), 192 (5), 182 (2), 168 (27), 156 (1), 142 (8), 129 (100), 114 (28), 105 (7), 91 (19), 81 (6), 73 (78), 65 (6), 55 (14); HRMS (APCI, FT-ICR, m/z) calcd for $C_{16}H_{28}{}^{35}ClNOH$ 286.1932, found 286.1931; IR (film, cm^{-1}) 3291, 3082, 2957, 2871, 1640, 1551, 1458, 1367, 1264, 1230, 1162, 969, 793, 717, 594, 507.

The data are in good agreement with the literature.[6]

Saponification of Methyl Credneroate to Credneric Acid (8). Following a literature procedure,[13] a solution of methyl credneroate (**6**) (1.0 equiv) in tetrahydrofuran (0.05 M) was treated with a mixture of lithium hydroxide (20 equiv) in water (1 M). The solution was stirred overnight and was then quenched carefully with 5 mL of aqueous 2 M HCl. The mixture was then transferred into aqueous 0.5 M HCl/ethyl acetate (1:1), and the aqueous phase was extracted three times with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and filtered, and the solvent was evaporated in vacuo. The residue was purified by flash column chromatography (SiO_2, eluent) and subsequent drying under high vacuum at 50 °C to afford credneric acid (**8**) as a yellow oil.

Credneric acid (8): yellow oil; 104 mg (0.48 mmol, 96%); eluent: diethyl ether; ^1H NMR (400 MHz, $CDCl_3$) δ 5.79 (s, 1H), 5.46 (dt, J = 14.9, 5.9 Hz, 2H), 2.73 (d, J = 6.1 Hz, 2H), 2.43 (t, J = 6.1 Hz, 2H), 2.36 (dt, J = 13.0, 6.1 Hz, 2H), 2.16 (t, J = 7.3 Hz, 2H), 1.44 (sext, J = 7.4 Hz, 2H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.3, 141.4, 130.5, 128.1, 113.1, 37.9, 33.8, 32.2, 27.4, 20.2, 13.9; MS (EI) m/z 216 (M^+, 24), 180 (7), 163 (26), 156 (33), 145 (6), 135 (16), 127 (18), 121 (100), 113 (13), 107 (41), 101 (11), 91 (89), 85 (1), 79 (91), 73 (4), 67 (25), 60 (6), 53 (18); HRMS (APCI, FT-ICR, m/z) calcd for $C_{11}H_{17}{}^{35}ClO_2H$ 217.0990, found 217.0989; IR (film, cm^{-1}) 2960, 2928, 2871, 1706, 1419, 1282, 1212, 1161, 1083, 968, 927, 794, 739, 604, 482.

General Procedure C for the Amidation of 5-Hexenoic Acid. Following a literature procedure,[14] 4-*N*,*N*-dimethylaminopyridine (30 mol %), triethylamine (2.2 equiv), 5-hexenoic acid (**9**) (1.0 equiv), and pivaloyl chloride (1.0 equiv) were dissolved in dichloromethane (0.1 M) and stirred for 1 h at room temperature. Then the respected amine **7a**/**7b** (1.1 equiv) was added, and the reaction mixture was stirred overnight. After quenching with aqueous 1 M HCl and phase separation, the organic phase was washed with aqueous $NaHCO_3$ solution and dried over $MgSO_4$ followed by evaporation of the solvent. The crude product was then purified by flash column chromatography (silica gel, eluent) to obtain the respective amides **10a**/**10b** as clear and colorless oils.

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***N*-Phenethylhex-5-enamide (10a):** white solid; 535 mg (2.46 mmol, 82%); eluent pentane/diethyl ether = 1:2; mp = 48−50 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.23 (m, 5H), 5.81 (td, J = 16.8, 6.8 Hz, 1H), 5.53 (bs, 1H), 5.05 (d, J = 10.4 Hz, 1H), 5.01 (s, 1H), 3.58 (q, J = 6.4 Hz, 2H), 2.87 (t, J = 6.8 Hz, 2H), 2.20−2.08 (m, 4H), 1.76 (qd, J = 7.3, 7.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 138.9, 137.9, 128.7, 128.6, 126.5, 115.2, 40.5, 35.9, 35.7, 33.1, 24.7; MS (EI) m/z 217 (M^+, 45), 174 (2), 163 (36), 126 (16), 120 (3), 104 (100), 97 (23), 91 (28), 77 (10), 69 (21), 63 (2), 55 (8); HRMS (EI, ICP, m/z) calcd for $C_{14}H_{19}NO$ 217.1467, found 217.1464; IR (film, cm^{-1}) 3304, 3067, 3030, 2934, 2870, 1639, 1535, 1451, 1365, 1255, 1208, 1117, 1032, 996, 908, 743, 695, 644, 588, 491.

***N*-Isopentylhex-5-enamide (10b):** colorless oil; 776 mg (4.23 mmol, 85%); eluent pentane/diethyl ether =1: 2; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77 (ddt, J = 17.0, 10.3, 6.7 Hz, 1H), 5.46 (bs, 1H), 5.04−4.95 (m, 2H), 3.25 (td, J = 7.4, 6.0 Hz, 2H), 2.17−2.04 (m, 4H), 1.78−1.68 (m, 2H), 1.67−1.53 (m, 1H), 1.41−1.33 (m, 2H), 0.90 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 137.9, 115.2, 38.6, 37.8, 36.0, 33.1, 25.9, 24.8, 22.4; MS (EI) m/z 183 (M^+, 18), 168 (32), 154 (3), 142 (13), 129 (100), 114 (47), 97 (36), 85 (6), 73 (98), 55 (37); HRMS (EI, ICP, m/z) calcd for $C_{11}H_{21}NO$ 183.1623, found 183.1621; IR (film, cm^{-1}) 3288, 3079, 2952, 2870, 1639, 1548, 1448, 1366, 1256, 1164, 993, 910, 683, 454.

General Procedure D for the Chlorodesilylation Reaction. Following a modified procedure,[15] the respective vinylsilane **10** (1.0 equiv) and *N*-chlorosuccinimide (2.0 equiv) were dissolved in dimethylformamide (0.038 M) and stirred for 48 h at 30 °C in a sealed tube. The reaction mixture was then transferred to a 1:1 mixture of saturated aqueous LiCl solution and diethyl ether. The organic phase was washed once with brine and then dried over $MgSO_4$. After filtration and evaporation of the solvent, the crude product was purified by flash column chromatography (eluent pentane/diethyl ether = 1: 4) to give the credneramides **1** and **2** as clear orange oils.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for selected compounds. 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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