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Synthesis of γ,δ-Unsaturated and δ,ϵ-Unsaturated α-Amino Acids from Fragmentation of γ- and δ-Lactones

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A noncoded amino acid of cyclomarin A (**1**) was synthesized in a racemic fashion. The method employs a six-membered ring template to control the relative stereochemistry and introduction of the functional groups. Ultimately, Pd-catalyzed fragmentation of the lactone provided γ,δ-unsaturated and δ,ϵ-unsaturated α-amino acids. A Pd-catalyzed ring opening of a γ-lactone is also reported.

Introduction

Unusual amino acids as constituents of natural products provide a classic example of nature's ingenuity in structural modification. These unique structures also present a prolific source of challenges to existing and evolving synthetic methods. Although amino acid synthesis has received much attention from the synthetic organic community, it remains an important problem. The development of efficient methods by either extending the scope of existing methods or developing new strategies for synthesizing these compounds is an ongoing effort in our laboratories. Although there are methods in the literature for the synthesis of γ,δ-unsaturated α-amino acids, there is no general method for synthesizing δ,ϵ-unsaturated α-amino acids. Our interest in these substrates originated from (2*S*,3*R*)-2-amino-3,5-dimethylhex-4-enoic (**2**), a nonproteinogenic amino acid contained in the potent anti-inflammatory agent cyclomarin A (**1**) (Figure 1).[1] Prior to the initiation of this project, this noncoded amino acid had not been previously synthesized. Recently, a synthesis of **2** from Boc-L-Asp(OBzl)-OH was reported.[2] However, there still remained a need for more general methods of synthesizing amino acid compounds with high functional group density and potential for improvement in the efficiency of the previous synthesis.

Results and Discussion

An obvious disconnection for 2-amino-3,5-dimethylhex-4-enoic acid (**2**) is the retro-Claisen rearrangement (Figure 2). Kazmaier and co-workers reported on the ease of this reaction in the synthesis of γ,δ-unsaturated α-amino acids,[3−5] and Bartlett has published extensively on the synthesis of γ,δ-unsaturated lactic acid derivatives[6,7] using similar methods. However, none of the literature examples possessed a degree of steric hindrance equivalent to that of our target. Thus, the challenge in applying this strategy was the development of a convenient synthesis of the requisite ester. Recent methods investigated for the esterification of tertiary alcohols have included the use of phase-transfer reagents[8] or zinc-mediated activation of acid chlorides;[9] $ScOTf_3$/DMAP treatment of *N*-hydroxysuccinimide esters;[10] reaction with $MgBr_2$, tertiary amines, and the appropriate anhydrides;[11] and the use of $Ce(OTf)_4$ with carboxylic acids.[12] Unfortunately, none of these methods proved to satisfactorily effect acylation of the requisite tertiary allylic alcohol.

As an alternative to the [3,3] sigmatropic rearrangement, a fragmentation strategy was undertaken to install the olefin functionality. In this strategy (Figure 2), the six-membered ring template would be employed to control the relative stereochemistry of the 2-amino and 3-methyl groups, as well as to mask the carboxylic acid functionality as the lactone. This approach would allow for significant flexibility in the introduction of the amino group, as a number of methods are available for the functionalization of esters at the α-position. To explore the

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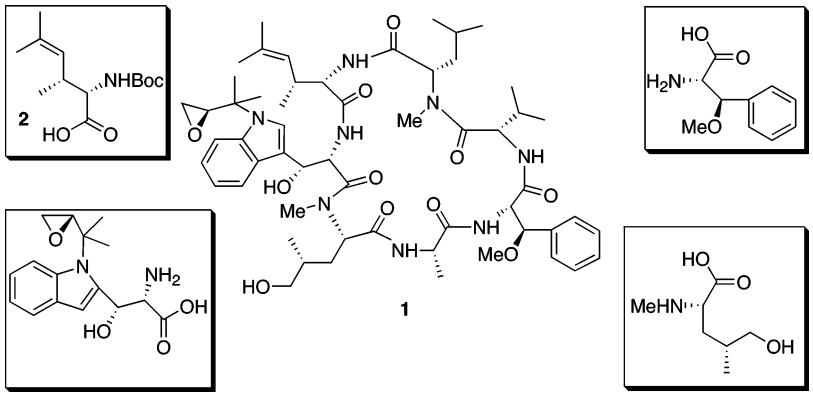

FIGURE 1. Cyclomarin A (**1**) and its noncoded amino acids.

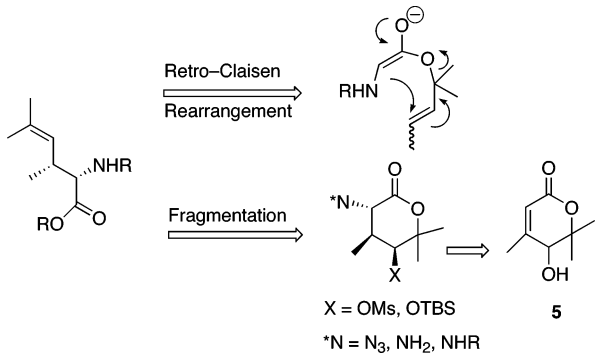

FIGURE 2. Retro-Claisen rearrangement and fragmentation strategies.

feasibility of this method, we chose to examine the racemic synthesis of this amino acid.

The 5-hydroxy-4,6,6-trimethyl-5,6-dihydropyran-2-one (**5**) could be readily synthesized from commercially available mesityl oxide in three steps.[13] A modification of this procedure was employed to generate this ene-lactol. Mesityl oxide was treated with basic peroxide[14] to afford the α,β-epoxyketone **3** (Scheme 1), a system that is known to be a powerful synthetic building block.[15]

The desired *Z*-olefin was prepared with the Horner–Emmons reagent in 1,4-dioxane, as previously described,[13] affording a 1:4 mixture of *E*- and *Z*-olefins, respectively, in 91% yield. Separation of the two isomers proved unnecessary, for when the mixture was treated with either 60% $HClO_4$ in EtOH[16] or triflic acid in dichloromethane, cyclization to the desired δ-lactone **5** was effected in 67% and 96% yields, respectively. The presumed diol side product was easily removed by column chromatography. Thus, the synthesis of lactone **5** was achieved in 76% yield over three steps.

We believed that the most energetically favorable lactone conformation would position the hydroxyl group in a pseudoaxial orientation in order to minimize $A^{1,3}$ strain with the vinylic methyl group, as this group would be required to facilitate the orbital alignment necessary for the elimination (Figure 3).

To remove the possibility of hydroxyl group interference in further manipulations, alcohol **5** was converted to its TBS ether. This reaction led to the production of two compounds that were inseparable by flash chromatography; the desired TBS ether **6** and the TBS ether **7** (in which the olefin had isomerized out of conjugation) were isolated as a 3:1 mixture in 65% yield. The driving force for this isomerization may be the relief of strain energy generated in the product. Examination of a crude model supported this hypothesis, as the *exo*-methylene compound **7** was found to be 1.05 kcal/mol more stable than **6** by MM2 minimized energy calculations (Figure 4). This proclivity for isomerization indicated that an alternative method for functionalization of the α-center would be necessary.

The alternative strategy was designed to utilize the same epoxyketone precursor but to employ a Knoevenagel condensation to avoid the issue of *E*/*Z* selectivity. It was believed that lactonization should proceed in a similar fashion with concomitant hydrolysis and decarboxylation of the nonparticipating ester. It is worth noting that the most effective and general method reported in the literature for achieving the condensation reaction of malonic esters with ketone substrates requires use of $TiCl_4$ and pyridine, as described by Lehnert.[17] Other examples of this methodology have been primarily restricted to cyclohexanones.[18,19] This dehydration reaction has also been effected on acetophenones using a combination of acetic acid and various acetate salts with malonates.[20,21] Other successful conditions have been reported employing dibromomalonates with reductive tributyl antimony with a variety of cyclohexanones,[22] but again the scope of this methodology was limited to cyclohexanones.[22,23] Unfortunately, all attempts to effect the Knoevenagel condensation on the epoxy ketone or mesityl oxide using any of the above methods were unsuccessful.

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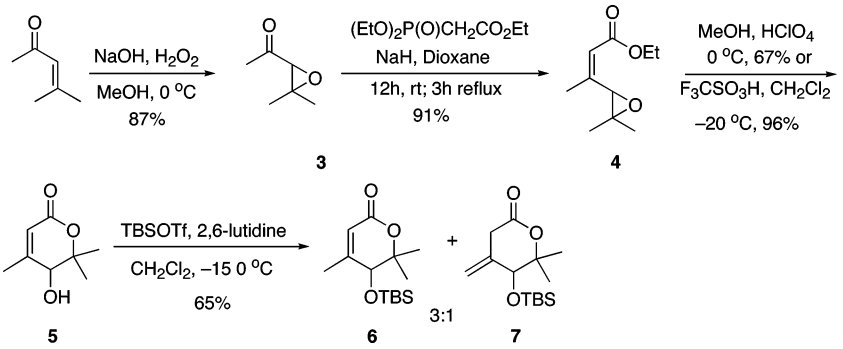
SCHEME 1



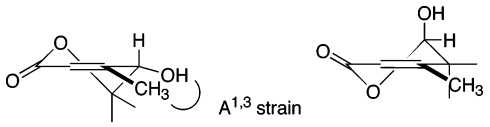


FIGURE 3. Effect of $A^{1,3}$ strain in the lactone.

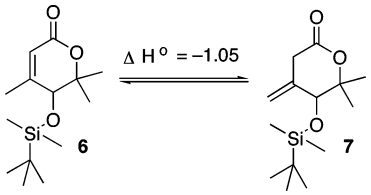
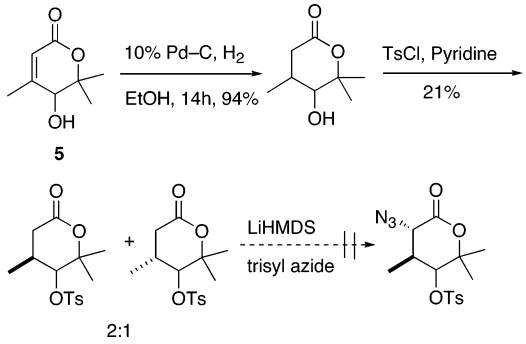


FIGURE 4. Energy barrier to isomerization.

SCHEME 2



After considering the limitations of the Knoevenagel condensation strategy, we revisited the original approach, focusing our efforts on circumvention of the strain inherent in the cyclohexenone system (Scheme 2).

To this end, ene-lactol **5** was reduced by hydrogenation with palladium on carbon to give the saturated lactol as a racemic mixture of *cis*- and *trans*-isomers. The alcohols were protected as both TBS ethers and tosylates. The tosylates proved separable, and their stereochemistry was determined by X-ray crystal diffraction. These protected alcohols were then treated with a variety of azide transfer conditions, including LiHMDS and 2,4,6-triisopropylbenzenesulfonyl azide (trisyl azide), followed by an acetic acid quench.[24] However, all conditions investigated led to complex mixtures.

Further examination of the olefin reduction revealed that hydrogenation of the 3:1 mixture of allylic TBS ethers **6** and **7** led to predominantly the *cis*-substituted saturated TBS ether **8**, along with a trace amount of the *trans*-product (Scheme 3) as determined by comparison of coupling constants for the tosylate series. Treatment of this lactone with Evans' modified azide transfer conditions for esters,[25] which include inverse addition of the potassium enolate to trisyl azide followed by an acetic acid quench with extended stirring at room temperature for 15 h, yielded the desired azido-lactone **9** in 63% yield. The azide was reduced using hydrogen and catalytic palladium on carbon, and the subsequent amine was trapped as its *tert*-butyl carbamate. The hydroxyl group was liberated by cleavage of the silyl ether with tetrabutylammonium fluoride buffered with acetic acid, producing alcohol **11** in 84% yield, presumably by simultaneous rearrangement of the initially formed lactone **10**. The structure and relative stereochemistry of alcohol **11** were verified by X-ray crystal diffraction.

With the hydroxyl group in the side chain rather than the ring in **11** in an exocyclic position, the outlook for the proposed ring opening improved, as free rotation would remove the rigid alignment requirement necessary for reductive fragmentation. In an attempt to install a reductive handle, alcohol **11** was treated with methanesulfonyl chloride and triethylamine, but neither the mesylate nor the chloride was obtained. As we might have expected, elimination product **12** was formed in good yield.

We believed that ring opening of such a system could be achieved by taking advantage of the nucleophilic nature of palladium(0) with allylic acetoxy groups. In this substrate, a hydride would be required for displacement of the intermediate (π-allyl)palladium complex. The use of polymethylhydrosiloxane (PMHS)[26] as a mild hydride donor for the displacement of allylic acetates has been reported.[27] However, the regioselectivity of the reduction of allylic acetates of disubstituted olefins was not predictable. Lautens and co-workers employed palladium-catalyzed formate reduction of allylic acetates in conjunction with ring-closing olefin metathesis substrates but also observed competitive β-hydride elimination, resulting in diene formation.[28] Mikami and co-workers reported the reduction of allylic acetates and phosphates using a $SmI_2-Pd(PPh_3)_4$ system in which regioselectivity was drastically affected by the proton source that was

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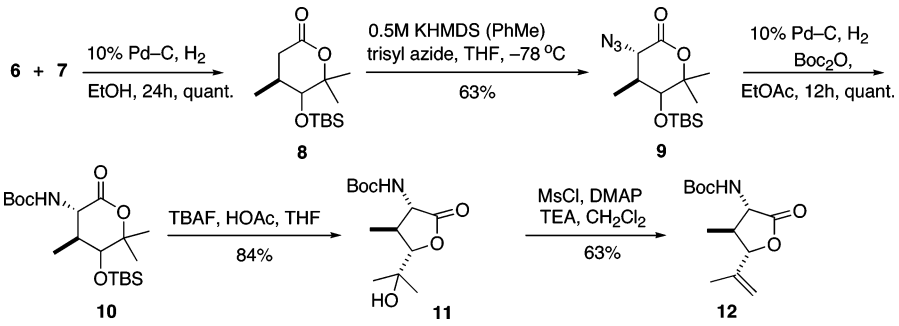
SCHEME 3



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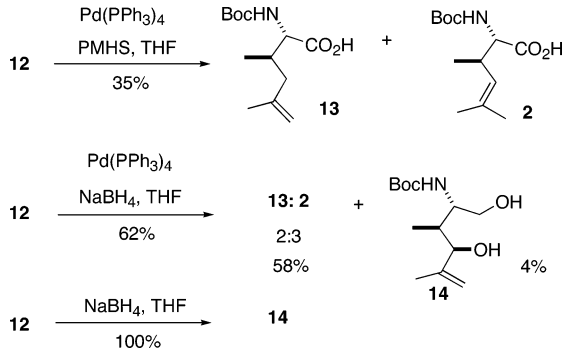

employed.[29] Hutchins and co-workers reported reduction of allylic acetates with palladium(0) and $NaBH_4$ or $NaBH_3CN$[30] and of various allylic oxgen, sulfur, and selenium functional groups with $Pd(PPh_3)_4$ and $LiBHEt_3$.[31] In this account, the authors suggested that poorer hydride transfer reagents such as $NaBH_4$ or $NaBH_3CN$ tend to attack the π-allyl system at the most electrophilic carbon, whereas potent hydride sources attack the carbon with greater steric accessibility to give the more highly substituted olefin products.[31] However, ammonium formate was exceptional in that it consistently provided the less-substituted olefin regardless of substrate.

In the case of substrate **12**, reductive ring opening using strong hydride sources such as LAH or $LiBHEt_3$ was not feasible because of the lability of the lactone. Reactions employing the ammonium formate also seemed unsuitable as the terminal olefin would likely be regenerated following ring fragmentation. Therefore, we chose to proceed with the PMHS/$NaBH_4$ system in the belief it might provide us with the more thermodynamically stable trisubstituted olefin **2**. We expected conversion to be a challenging issue in this case because of the favorable reversibility of the ring-closing event with the (π-allyl)palladium intermediate (Scheme 4).

Treatment of **12** with $(Ph_3P)_4Pd$ and PMHS successfully liberated the carboxylate ion, but hydride displacement of the palladium complex afforded the less-substituted olefin as the major product in low yield (35%). The product mixture revealed a 2.6:1 ratio of terminal olefin **13** and olefin **2**, as well as a significant quantity of starting material. This type of lactone opening has received very little attention to date. Treatment of **12** with sodium borohydride in the presence of palladium catalysis and in the absence of catalyst provided different results. As expected, reduction with $NaBH_4$ without catalyst resulted in quantitative formation of aminodiol **14.** However, when $NaBH_4$was used in conjunction with $(Ph_3P)_3Pd$ in THF, a mixture of compounds **13** and **2** was obtained in a 2:3 ratio in favor of the desired olefin and the total yield was improved to 58%. The diol **14** was also produced in 4% yield.

Conclusions

Racemic syntheses of the 2-amino-3,5-dimethylhex-4-enoic acid and 2-amino-3,5-dimethylhex-5-enoic acid were accomplished. This strategy complements the existing methods in the literature for synthesizing γ,δ-unsaturated amino acid substrates with steric demand or disubstitution at the δ-position. A new method for the synthesis of δ,ϵ-unsaturated amino acids is reported. The palladium-catalyzed reduction of allylic γ-lactone **12** with a variety of hydride sources represents one of the few examples of this type of reaction.

Experimental Section

General Methods.[32] **5-Hydroxy-4,6,6-trimethyl-5,6-dihydropyran-2-one[13] (5).** *Method A*: To a cold (0 °C) solution of enoate *E*/*Z*-**4** (3.0 g, 16.3 mmol) in HPLC EtOH (410 mL) was added 60% $HClO_4$ (45 mL, 0.41 mol) dropwise via an addition funnel over 20 min at 0 °C. After addition, the reaction was warmed to room temperature for 20 min and then cooled back to 0 °C to neutralize it with 4 N NaOH (100 mL). The reaction was concentrated in vacuo, then diluted with water (150 mL), and extracted with CH_2Cl_2 (2 × 250 mL). The combined organic phases were washed with brine until neutral, dried (Na_2SO_4), and concentrated. Purification by column chromatography (EtOAc−hexanes) yielded **5** as a yellow oil (1.37 g, 67%). *Method B*: To a cold (−40 °C) solution of enoate *E*/*Z*-**4** (3.00 g, 16.3 mmol) in CH_2Cl_2 (140 mL) was added CF_3SO_3H (1.44 mL, 16.3 mmol) in CH_2Cl_2 (40 mL) dropwise via an addition funnel. The reaction was stirred at −40 °C for 1 h and then warmed to −20 °C for 1 h. When starting material had disappeared as shown by TLC, 5%$NaHCO_3$ solution (50 mL) was added to quench the reaction at −20 °C. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL), and the combined organic phase was dried (Na_2SO_4) and concentrated to a yellow oil (2.94 g). The crude oil was purified by column chromatography (EtOAc−hexanes) to yield **5** as a yellow oil (1.95 g, 96%): R_f 0.11 (30:70 EtOAc−hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 1.39 (s, 3H), 1.44 (s, 3H), 2.06 (s, 3H), 3.86 (s, 1H), 5.81 (s, 1H); ^{13}C NMR (125 MHz,

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$CDCl_3$) δ 20.4, 22.2, 25.9, 71.5, 82.8, 116.2, 157.8, 164.3; IR (neat) 3406 (br), 2924 (m), 2900 (w), 2853 (w), 1715 (s), 1657 (w), 1443 (w), 1378 (m), 1298 (m), 1154 (s), 990 (m), 792 (w) cm^{-1}.

5-(*tert*-Butyldimethylsilanyloxy)-4,6,6-trimethyl-5,6-dihydropyran-2-one (6) and 5-(*tert*-Butyldimethylsilanyloxy)-6,6-dimethyl-4-methylene-tetrahydropyran-2-one (7). To a cold (−20 °C) solution of alcohol **5** (1.18 g, 7.56 mmol) and 2,6-lutidine (1.8 mL, 15.1 mmol) in CH_2Cl_2 (8 mL) was added TBDMSOTf (2.1 mL, 9.10 mmol) dropwise via a syringe over 20 min. The reaction was stirred 25 min more before being quenched with saturated $NaHCO_3$ (3 mL), then warmed to room temperature, and poured into saturated $NaHCO_3$ (40 mL). The mixture was shaken, and the layers were allowed to separate. The aqueous layer was extracted with Et_2O (3 × 50 mL), and the combined organic phase was washed with 1 N HCl (2 × 80 mL). The organic phase was dried (Na_2SO_4) and concentrated to a white solid. Purification by column chromatography (EtOAc−petroleum ether) yielded a white powder (1.33 g, 65%) as an inseparable 3:1 mixture of allylic TBDMS ethers **6** and **7**. Data for **6**: ^1H NMR (500 MHz, $CDCl_3$) δ 0.12 (s, 3H), 0.17 (s, 3H), 0.95 (s, 9H), 1.38 (s, 3H), 1.43 (s, 3H), 2.00 (s, 3H), 4.19 (s, 1H), 5.82 (s,1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.1, −3.8, 20.5, 21.3, 26.8, 73.3, 82.8, 116.5, 158.1, 169.1; IR (neat) 2927 (w), 2854 (w), 1711 (s), 1655 (w), 1472 (w), 1366 (w), 1310 (w), 1293 (w), 1252 (w), 1161 (m), 1071 (w), 994 (m), 836 (m), 776 (m), 603 (w) cm^{-1}; HRMS *m/z* calculated for $C_{14}H_{26}O_3SiNa$ $(M + Na)^+$ 293.1549, found 293.1537. Data for **7:** ^1H NMR (500 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.14 (s, 3H), 0.93 (s, 9H), 1.33 (s, 3H), 1.40 (s, 3H), 3.22 (doublet of triplets, J = 18.7, 1.3 Hz, 1H), 3.45 (doublet of triplets, J = 17.8, 2.2 Hz, 1H), 4.00 (s, 1H), 5.06 (d, J = 0.5 Hz, 1H), 5.12 (d, J = 1.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.1, −4.6, 18.1, 23.7, 35.2, 75.6, 83.7, 112.6, 139.3, 163.3; IR (neat) 2927 (w), 2854 (w), 1711 (s), 1655 (w), 1472 (w), 1366 (w), 1310 (w), 1293 (w), 1252 (w), 1161 (m), 1071 (w), 994 (m), 836 (m), 776 (m), 603 (w) cm^{-1}; HRMS *m/z* calculated for $C_{14}H_{26}O_3SiNa$ $(M + Na)^+$ 293.1549, found 293.1537.

***cis*-5-(*tert*-Butyldimethylsilanyloxy)-4,6,6-trimethyltetrahydropyran-2-one (8).** The 3:1 mixture of TBDMS ethers **6** and **7** (1.16 g, 4.29 mmol) was dissolved in absolute EtOH (25 mL), 10% Pd/C (225 mg) was added, and the mixture was stirred under a hydrogen atmosphere. After 22 h, the reaction mixture was filtered through a slurry of Celite, and EtOH was evaporated to dryness to obtain **8** as a white powder (1.18 g, 100%), which was used without further purification: mp 82−84 °C; R_f 0.24 (30:70 EtOAc−petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.88 (s, 9H), 0.97 (d, J = 6.1 Hz, 3H), 1.33 (s, 6H), 2.21−2.41 (m, 3H), 3.49 (s,1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −3.6, −3.4, 18.1, 18.3 25.9, 26.0, 26.6, 27.9, 28.5, 28.9, 32.2, 73.8, 85.1, 170.9; IR (neat) 2935 (m), 2855 (m), 1706 (s), 1472 (w), 1301 (s), 1136 (s), 775 (s) cm^{-1}; HRMS *m/z* calculated for $C_{14}H_{28}O_3SiNa$ $(M + Na)^+$ 295.1705, found 295.1705.

3-Azido-5-(*tert*-butyldimethylsilanyloxy)-4,6,6-trimethyltetrahydropyran-2-one (9). To a 0.5 M KHMDS solution in toluene (4.4 mL, 2.22 mmol) cooled to −78 °C was added lactone **8** (0.550 g, 2.02 mmol) in THF (9 mL) dropwise via a syringe. The reaction was stirred at −78 °C for 0.5 h and then transferred via a cannula to a cold (−78 °C) solution of 2,4,6-triisopropylbenzenesulfonyl azide (0.781 g, 2.53 mmol) in THF (9 mL). After 1−2 min HOAc was added to quench the reaction. The reaction was warmed to room temperature and allowed to stir for 18 h. The reaction was partitioned between brine (60 mL) and CH_2Cl_2 (140 mL) (note: major emulsions may form at this stage), and the organic layer was washed with saturated $NaHCO_3$, forming a creamy white organic phase. The organic phase was dried (Na_2SO_4) and concentrated to a yellow-white foam. Purification by column chromatography (EtOAc−petroleum ether) yielded **9** as a white solid (0.400 g, 63%): mp 99−101 °C; R_f 0.54 (30:70 EtOAc−petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.10 (s, 3H), 0.90 (s, 9H), 1.13 (d, J = 6.6 Hz, 3H), 1.35 (s, 3H), 1.37 (s, 3H), 2.11−2.26 (m, 1H), 3.56 (d, J = 1.7 Hz, 1H), 3.90 (d, J = 11.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −3.5, −3.4, 16.5, 18.4, 26.1, 26.3, 27.8, 35.1, 60.5, 75.0, 85.6, 168.9; IR (neat) 2954 (m), 2931 (m), 2112 (s), 1776 (w), 1735 (s), 1261 (s), 1110 (s), 834 (m), 777 (m) cm^{-1}; HRMS *m/z* calculated for $C_{14}H_{27}N_3O_3SiNa$ $(M + Na)^+$ 336.1719, found 336.1736.

[5-(*tert*-Butyldimethylsilanyloxy)-4,6,6-trimethyl-2-oxotetrahydropyran-3-yl]carbamic Acid *tert*-Butyl Ester (10). A flask containing a solution of azide **9** (0.203 g, 0.648 mmol), 10% Pd/C (52 mg), and Boc_2O (0.204 g, 0.933 mmol) in HPLC EtOAc (10 mL) was evacuated and then fitted with a balloon of H_2. The reaction was stirred for 12 h, and the palladium was removed by filtration. The filtrate was concentrated to a white solid. The crude solid was purified by column chromatography (petroleum ether to 20:80 EtOAc−petroleum ether) to give **10** as a white solid (0.236 g, 94%): mp 152−153 °C; R_f 0.21 (20:80 EtOAc−petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 0.09 (s, 3H), 0.11 (s, 3H), 0.92 (s, 9H), 1.07 (d, J = 6.7 Hz, 3H), 1.37 (s, 3H), 1.43 (s, 9H), 1.47 (s, 3H), 2.60−2.80 (m, 1H), 3.63 (d, J = 2.0 Hz, 1H), 3.77−3.98 (m, 1H), 4.83−5.03 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.7, −4.1, 9.8, 18.1, 25.8, 28.3, 29.7, 30.3, 36.6, 53.0, **f)** 74.9, 80.0, 86.9, 155.4, 169.9; IR (neat) 3409 (br), 2931 (m), 2856 (w), 1732 (s), 1715 (s), 1504 (m), 1366 (m), 1254 (s), 1159 (s), 1108 (s), 1043 (s), 833 (m), 776 (m) cm^{-1}; HRMS *m/z* calculated for $C_{19}H_{37}NO_5SiNa$ $(M + Na)^+$ 410.2339, found 410.2338.

[5-(1-Hydroxy-1-methylethyl)-4-methyl-2-oxotetrahydrofuran-3-yl]carbamic Acid *tert*-Butyl Ester (11). To a solution of TBDMS ether **10** (0.251 g, 0.648 mmol) in THF (6.4 mL) was added a 1.0 M TBAF solution in THF (1.8 mL) and acetic acid (0.02 mL). The reaction was stirred for 48 h and concentrated to dryness. Column chromatography (30:70 EtOAc−petroleum ether to 100% EtOAc) afforded **11** as a white solid (0.149 g, 84%): mp 165−166 °C; R_f 0.41 (50:50 EtOAc−hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 1.23 (s, 3H), 1.31 (d, J = 6.6 Hz, 3H), 1.33 (s, 3H), 1.45 (s, 9H), 1.88 (brs, 1H), 2.33−2.49 (m, 1H), 3.87 (d, J = 8.6 Hz, 1H), 4.04−4.20 (m,1H), 4.84−5.09 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.6, 25.0, 27.1, 28.3, 37.9, 57.8, 71.1, 80.4, 89.0, 155.7, 174.4; IR (neat) 3455 (w, br), 3277 (m), 2974 (w), 1788 (s), 1713 (s), 1362 (w), 1172 (m) cm^{-1}; HRMS (CI) *m/z* calculated for $C_{13}H_{23}NO_5$ $(M + H)^+$ 274.1654, found 274.1652.

(5-Isopropenyl-4-methyl-2-oxotetrahydrofuran-3-yl)-carbamic Acid *tert*-Butyl Ester (12). To a an ice-cooled solution of alcohol **11** (473 mg, 1.74 mmol) and triethylamine (2.9 mL, 20.9 mmol) in CH_2Cl_2 (0.5 mL) was added methanesulfonyl chloride (1.3 mL, 17.4 mmol) followed by DMAP (212 mg, 1.74 mmol). The reaction was warmed to room temperature and stirred for 48 h. The reaction was diluted with CH_2Cl_2 and washed with 10% HCl, saturated $NaHCO_3$ solution, and brine. The organic phase was dried (Na_2SO_4) and concentrated. The crude residue was purified by column chromatography (EtOAc−hexanes) to afford **12** as a clear foam (282 mg, 63%); R_f 0.73 (50:50 EtOAc−hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 1.17 (d, J = 6.5 Hz, 3H), 1.44 (s, 9H), 1.74 (s, 3H), 2.13−2.28 (m, 1H), 4.14 (brs, 1H), 4.34 (d, J = 10.1 Hz, 1H), 4.49 (m, 1H), 5.05 (s, 1H), 5.06 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 16.6, 28.2, 42.3, 57.5, 80.5, 86.7, 116.3, 139.5, 155.5, 174.2; IR (neat) 3338 (br), 2974 (w), 2930 (w), 1791 (s), 1700 (s), 1161 (s) cm^{-1}; HRMS (CI) *m/z* calculated for $C_{13}H_{21}NO_4Na$ $(M + Na)^+$ 278.1368, found 278.1381.

2-*tert*-Butoxycarbonylamino-3,5-dimethylhex-5-enoic Acid (13) and 2-*tert*-Butoxy-carbonylamino-3,5-dimethylhex-4-enoic Acid (2). To a solution of olefin **12** (22 mg, 86.2 μmol) and $Pd(PPh_3)_4$ (5 mg, 4.31 μmol) in THF (0.5 mL) was added poly(methylhydrosiloxane) (PMHS,15 mg, 224 μmol, 2.6 mequiv) in one portion. After 18 h, the reaction turned dark yellow and was diluted with dichloromethane and washed with 10% HCl, saturated $NaHCO_3$, and brine. The organic phase was dried (Na_2SO_4), concentrated, and purified by column chromatography (hexanes to 50:50 EtOAc−hexanes)

to afford a clear oil as 2.6:1 mixture of **13** and **2**. Data for **13**: R_f 0.16 (50:50 EtOAc−hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (d, J = 7.0 Hz, 3H), 1.43 (s, 9H), 1.70 (s, 3H), 1.90 (dd, J = 13.9,8.1 Hz, 1H), 2.14 (dd, J = 13.9,6.8 Hz, 1H), 2.25−2.39 (m, 1H), 4.30−4.43 (m, 1H), 4.72 (s, 1H), 4.81 (s, 1H), 4.97 (d, J = 9.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.4, 22.1, 28.3, 33.3, 41.8, 57.5, 80.5, 112.8, 124.4, 142.8, 174.2; IR (neat) 3337 (br), 2968 (m), 2917 (s), 2848 (w), 1714 (s), 1392 (m), 1367 (m), 1253 (m), 1163 (s), 1074 (m) cm^{-1}; HRMS *m*/*z* calculated for $C_{13}H_{24}NO_4$ $(M + H)^+$ 258.1705, found 258.1696. Data for **2**: R_f 0.16 (50:50 EtOAc−hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (d, J = 6.9 Hz, 3H), 1.45 (s, 9H), 1.62 (s, 3H), 1.69 (s, 3H), 2.82−2.96 (m, 1H), 4.09−4.25 (m, 1H), 4.96 (d, J = 9.6 Hz, 1H), 5.03 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.0, 25.9, 28.3, 29.7, 35.2, 41.8, 80.5, 112.8, 124.5, 142.8, 174.2; IR (neat) 3345 (br), 2973 (m), 2920 (m), 2360 (s), 2340 (s), 1680 (s), 1391 (m), 1366 (m), 1252 (m), 1168 (s), 1074 (m), 668 (s) cm^{-1}; HRMS *m*/*z* calculated for $C_{13}H_{24}NO_4$ $(M + H)^+$ 258.1705, found 258.1696.

(3-Hydroxy-1-hydroxymethyl-2,4-dimethylpent-4-enyl)carbamic Acid *tert*-Butyl Ester (14). To a solution of lactone **12** (24 mg, 94 μmol) in THF (1.5 mL) was added sodium borohydride (7 mg, 0.188 mmol) in one portion. After 24 h, the reaction was diluted with water and extracted with EtOAc (2 × 20 mL). The organic phase was dried over Na_2SO_4 and concentrated to afford **14** as a white foam (24 mg, 100%): R_f 0. 16 (50:50 EtOAc−hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.76 (d, J = 7.0 Hz, 3H), 1.47 (s, 9H), 1.70 (s, 3H), 1.78−1.91 (m, 1H), 3.67 (m, J = 4.7,1.1 Hz, 2H), 3.76 (d, J = 9.0 Hz, 1H), 3.92−4.06 (m, 1H), 4.88 (s, 1H), 4.89 (s, 1H), 5.05 (d, J = 7.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.3, 16.7, 28.4, 29.7, 37.9, 53.4, 64.4, 78.4, 80.3, 113.6, 145.4, 157.3; IR (neat) 3342 (br), 2971 (s), 2925 (s), 2247 (w), 1682 (s), 1516 (s), 1455 (m), 1366 (s), 1253 (s), 1173 (s), 1026 (m), 900 (m), 735 (w) cm^{-1}; HRMS *m*/*z* calculated for $C_{13}H_{25}NO_4Na$ $(M + Na)^+$ 282.1681, found 282.1675.

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Supporting Information Available: Experimental procedures for **3**, *E*-**4**, and *E*/*Z*-**4**; ^{1}H NMR and ^{13}C NMR spectra of all new compounds; and tables of X-ray structural data in CIF format and ORTEP diagrams for **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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