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Hetero-Diels–Alder and pyroglutamate approaches to (2*S*,4*R*)-2-methylamino-5-hydroxy-4-methylpentanoic acid

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Abstract—The stereoselective syntheses of fully protected (2*S*,4*R*)-2-methylamino-5-hydroxy-4-methylpentanoic acid, a non-coded amino acid of cyclomarin A, and its diastereomer are reported. A pyroglutamate template was employed in the key diastereoselective alkylation used for introducing the 4-methyl stereochemistry. In addition, the first diastereoselective intramolecular hetero-Diels–Alder of a 2-cyano-1-azadiene with an electron deficient dienophile is described.

1. Introduction

Cyclomarin A (**1**, Fig. 1) is a potent anti-inflammatory agent[1] that has been a recent target of interest in several research laboratories,[2,3] including our own.[4–7] The non-coded amino acid constituents of cyclomarin A provide a wealth of structural diversity and challenges which require extension of the scope of existing methods or development of new strategies for synthesizing these compounds. In our continuing efforts to complete both novel and efficient syntheses of these amino acids, we have investigated the use of a hetero-Diels–Alder reaction employing a 2-cyano-1-azadiene to prepare the fully protected (2*S*,4*R*)-2-methylamino-5-hydroxy-4-methylpentanoic acid fragment of cyclomarin A. We also report the completed synthesis of this fragment and its diastereomer (2*S*,4*S*)-2-methylamino-5-hydroxy-4-methylpentanoic acid, using a pyroglutamate framework for the establishment of stereochemistry.

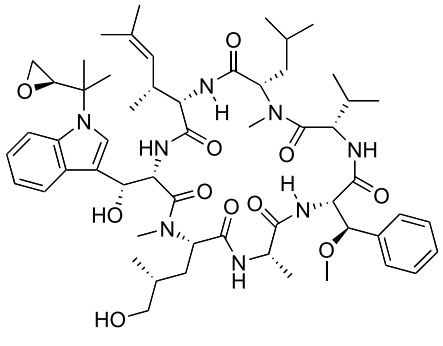

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Figure 1. Cyclomarin A.

2. Results

The initial strategy used for making the (2*S*,4*R*)-2-methylamino-5-hydroxy-4-methylpentanoic acid fragment utilized a hetero-Diels–Alder reaction that allowed for stereochemical control at both the 2- and 4-positions in one step. The hydroxyl and *N*-methyl functionalities would be introduced by oxidation of the olefin and reduction of the resultant formyl groups. Azadienes have been used previously in Diels–Alder (DA) reactions and their application and scope have been reviewed thoroughly.[8,9] Since the nitrogen of 1-azadienes renders the pi system more electron deficient, its ability to undergo a Type I Diels–Alder reaction is diminished. Most reported examples of hetero-DA reactions with 1-azadienes occur via an inverse electron demand (Type II) mechanism.[8,9] If there are enolizable protons at the 4-position, tautomerization may occur to generate an enamine which can undergo the DA reaction more easily with an electron deficient dienophile[8] (Fig. 2). Other factors contributing to the low yields of hetero-DA reactions using 1-azadienes include competitive imine [2+2] cycloadditions and the instability of the enamine products. The low reactivity and product instability may be reduced by the use of substrates with *N*-acyl,[10] *N*,*N*-sulfonyl[8] or *N*,*N*-dialkylamino[11] substitution

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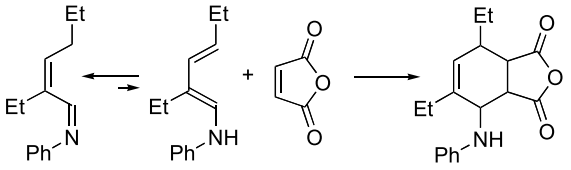


Figure 2. 1-Azadienes can undergo tautomerization to enamides.

on the nitrogen. It is believed that the acyl and sulfonyl substitution stabilize the enamine products; the dialkyl group increases the electron density in the system. It has also been observed that a methoxy or cyano group at the 2-position on the azadiene improves the DA reaction[10,12,13] (Fig. 3).

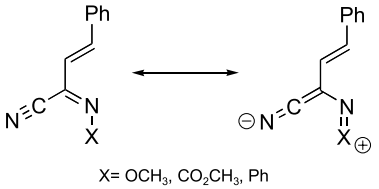


Figure 3. Electronic stabilizing groups for 1-azadienes.

Motorina and Grierson have extensively investigated the use of 2-cyano-1-azadienes in DA or intramolecular DA (IMDA) reactions.[14] The authors observed that 2-cyano-1-azadienes may undergo DA type reactions in a regiocontrolled fashion with moderate stereocontrol. We expected that existing chirality in the diene or dienophile in our system would induce asymmetry to the remote methyl center. It was believed that this effect could be enhanced if the reaction was run in an intramolecular fashion. In addition, the regiochemistry of the DA reaction could be controlled by the tether restriction. The most accessible location for the chiral auxiliary would be attached to the nitrogen at the 1-position, though it would reduce the reactivity of the diene itself. It was hoped that this deficiency could be overcome by the addition of a cyano or methoxy group at the 2-position on the diene (Fig. 4). It was predicted that the proposed synthon would lead to the undesired (2*S*,4*S*)-diastereomer (Fig. 5); however, there was reason to believe that the desired compound could be produced by modification of the chiral auxiliary or epimerization.

The synthesis (Scheme 1) began with *S*-phenylglycinol, which is available from Aldrich or from a borohydride reduction of phenylglycine ethyl ester hydrochloride salt.[15,16] The amino alcohol was treated with *trans*-crotonyl chloride and 2 N sodium carbonate under biphasic conditions to give the crotonamide **2** in 97% yield.[17] The subsequent esterification step was achieved by treating the crotonamide with acryloyl chloride under phase transfer conditions in 93% yield.[18] The enamide **3** was then treated with Hunig's base and triflic anhydride at −60 °C, followed by displacement of the vinyl triflate by lithium cyanide and 12-crown-4 complex to provide the 2-cyano-1-azadiene **4** in low yield. This triene was heated to 110 °C in benzene for 48 h, yielding an unstable bicyclic compound **5** the structure and stereochemistry of which were determined by spectroscopic methods to be those of a single diastereomer. Despite the low yield, this reaction represents the first example of remote asymmetric induction with either intermolecular or intramolecular DA reactions of 2-cyano-1-azadienes.[4] It is also the first example of a diastereoselective intramolecular DA reaction of a 2-cyano-1-azadiene with an electron deficient dienophile. Unfortunately, treatment of the unstable cycloadduct with ozone led to decomposition.

Given the difficulties encountered in formation of the cyanoazadiene and its low reactivity, other methods were investigated (Scheme 2). The effect of an electron donating substituent in the diene system was probed by the addition of a 2-alkoxy group, employing imidoesters and an oxazoline. The methyl imido ester was formed by treatment of the enamide **3** with methyl triflate, but heating this unstable compound (**7**) in a sealed tube yielded only decomposition products. Use of a microwave reactor gave the same results.

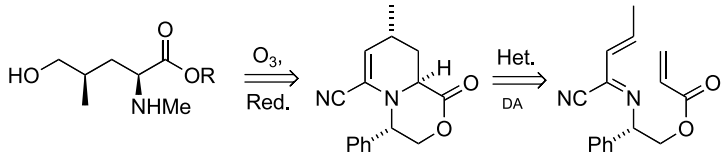


Figure 4. Hetero-Diels–Alder disconnections.

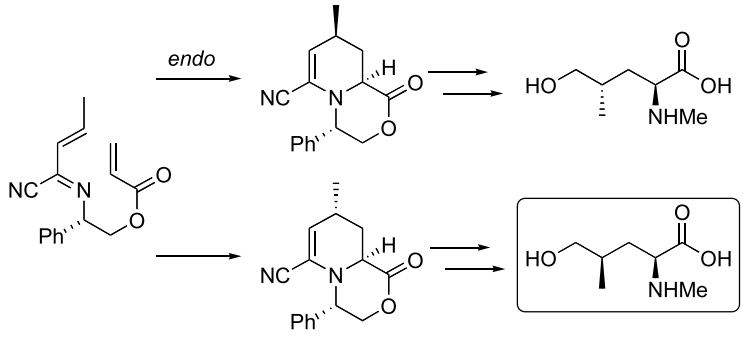
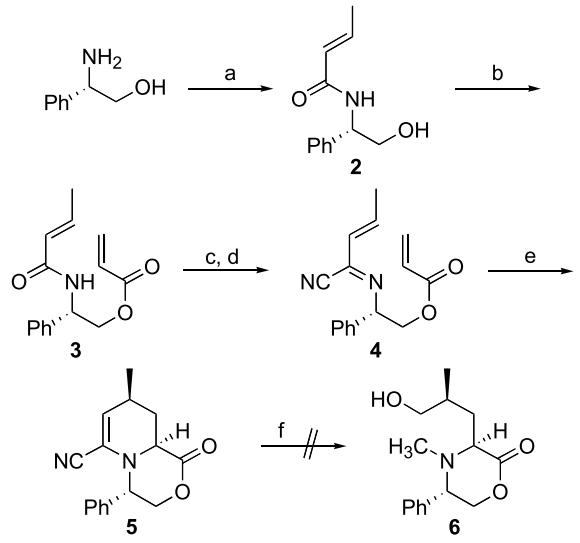


Figure 5. 2-Methylamino-5-hydroxy-4-methylpentanoic acid stereochemistry for both possible Diels–Alder adducts.

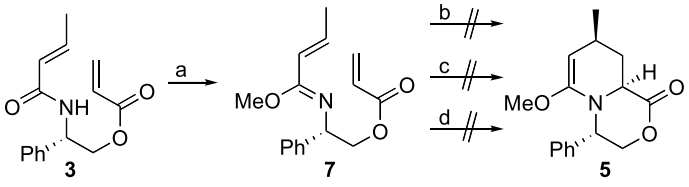


Scheme 1. Reagents and conditions: (a) *trans*-crotonyl chloride, aq Na_2CO_3, CH_2Cl_2, 97%; (b) 30% aq KOH, CH_2Cl_2, acryloyl chloride, TBAI, 0 °C, 93%; (c) DIEA, Tf_2O, CH_2Cl_2, −60 °C; (d) 12-crown-4, LiCN, THF, −60 °C, 24% over 2 steps; (e) toluene, 120 °C, 48 h, 9%; (f) ozone, CH_2Cl_2, −78 °C; $NaBH_4$, MeOH.

conditions having previously used TMSCl, $ZnCl_2$ and TEA in toluene at high temperature[20] to effect the DA reaction of enamides with α,β-unsaturated esters.[21] Using TBSOTf or TMSCl/$ZnCl_2$ and TEA, attempts were made to form the azadiene in situ at both ambient and elevated temperature. Both reactions resulted either in recovery of starting material or decomposition. In an effort to improve the electronic alignment, an electron-withdrawing group was installed on the terminus of the acrylate functionality. The expectation was that even if the DA reaction did not occur, maybe a degenerate mechanism, such as a base-mediated tandem conjugate addition would allow generation of the desired product. However, after many variations of the hetero-Diels–Alder route were attempted with no significant improvement, this approach was eventually abandoned for a more favorable one.[5]

3. Discussion

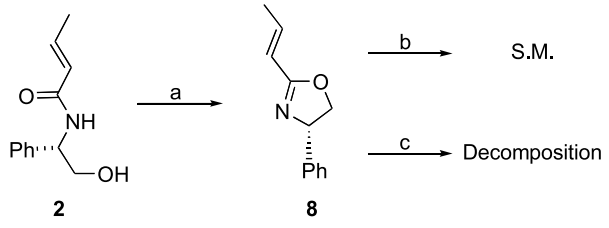
The pyroglutamate moiety is a powerful synthetic building block that has been previously used to prepare glutamic acid and leucine derivatives.[22,23] Its versatility and high functional group density allows it to be used for a variety of



Scheme 2. Reagents and conditions: (a) MeOTf, CH_2Cl_2; (b) 150 °C, 12 h, neat; (c) benzene, 110 °C, 4d; (d) 5 M ether–$LiClO_4$, 5 days.

Treatment of alcohol **2** with tosyl chloride and triethylamine produced oxazoline **8** in 63% yield (Scheme 3).[17] This compound was then treated with several conditions including various dienophiles, but no reaction was observed except decomposition in certain instances. The lack of reactivity was attributed to the preferred *s-trans* conformation of the pi system when the diene's 4-position is substituted.

Huang and co-workers reported intramolecular DA reactions with 1-azadiene substrates that were formed in situ for

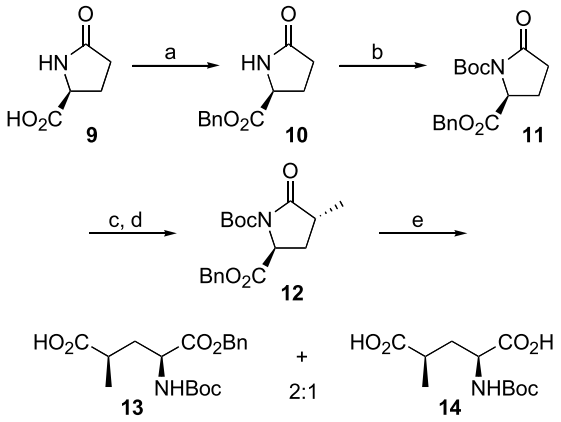


Scheme 3. Reagents and conditions: (a) TsCl, TEA, CH_2Cl_2, 2d, 63%; (b) maleic anhydride, 110–115 °C; (c) diethyl acetylene dicarboxylate.

the construction of heterocyclic ring systems.[19] The advantages of these reactions were the mild conditions (trialkylsilyl chlorides and triethylamine) under which they proceeded. Fukomoto and co-workers used the milder trialkylsilyl trifluoromethanesulfonates and triethylamine targets.[24] It was envisioned that using a stereoselective alkylation at the α-position of the amide followed by inversion would afford the product with the desired stereochemistry (Fig. 6). Investigations by several groups[24–28] had validated the feasibility of this approach, but conflicting results were obtained with regard to the *cis*:*trans* selectivity of the alkylation depending on the substrate, base and electrophile.[25,27–30] Young and co-workers found that the major product of alkylation mixtures was the *cis* product.[29,30] Furthermore, they were able to improve both the yield and stereoselectivity of the reaction to 70% and a 17:1 *cis*:*trans* ratio[29] if lithium hexamethyldisilazide was used as the base and methyl triflate as the electrophile.

Figure 6. Pyroglutamic acid disconnection.

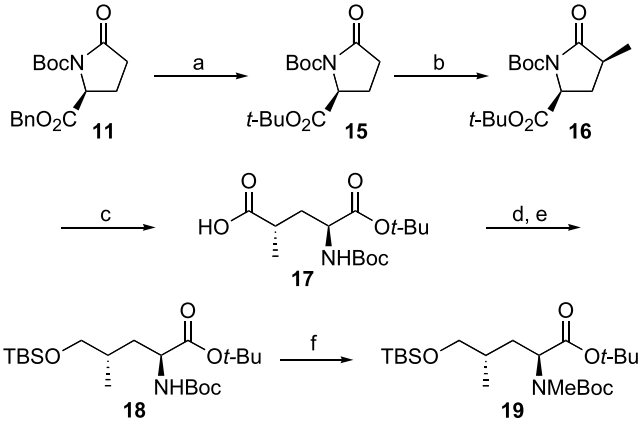
In our system, the original protecting group was a benzyl ester, with the hope that upon lithium hydroxide opening of the lactam ring little or no hydrolysis of the ester would occur. The synthesis (Scheme 4) proceeded in good yield following the procedure of Young and co-workers to afford the fully protected pyroglutamate **11**.[22] The stereoselective alkylation using LiHMDS and methyl triflate followed by



Scheme 4. Reagents and conditions: (a) TEA, benzyl chloride, acetone, 85%; (b) Boc_2O, DMAP, CH_3CN, 73%; (c) LiHMDS, MeOTf, Toluene, −78 °C; (d) LiHMDS, 2,6-di-*t*-butylphenol, Toluene, −78 °C, 34% over 2 steps; (e) 1 M LiOH, THF, 30 min, 0 °C, 54%.

inversion using LiHMDS and ammonium chloride proceeded with a *cis*:*trans* ratio of 1:4 in 34% yield over two steps. The lithium hydroxide ring opening did not proceed as well as planned and generated what was believed to be the desired benzyl ester **13** as well as the free carboxylic acid **14**, but never in isolable yields. A modification of the protecting group scheme was required and we investigated the use of a *tert*-butyl group instead of a benzyl moiety.

The *tert*-butyl ester allowed for opening of the lactam ring without hydrolysis of the ester.[22] Beginning with fully protected pyroglutamate **11**, the ester was deprotected using standard hydrogenation conditions and protected as the *tert*-butyl ester **15** using Boc_2O, TEA, and DMAP in acetonitrile in an 83% yield over 2 steps (Scheme 5). The stereoselective alkylation proceeded in 70% yield with a 7:1 ratio of *cis* **16**:*trans*. The lithium hydroxide opening proceeded in quantitative yield, and subsequent reduction of the mixed anhydride produced the alcohol in 69% yield.[22,31] The resulting alcohol was to be protected as its TBS ether. Standard conditions of TBSCl and imidazole in methylene chloride led to consistently low yields. Variation of the base-catalyst system (imidazole, 2,6-lutidine and TEA/DMAP) did not increase the yield. Eventually, changing the solvent to DMF and using TBSCl with the TEA/DMAP system successfully provided TBS ether **18** in 91% yield.

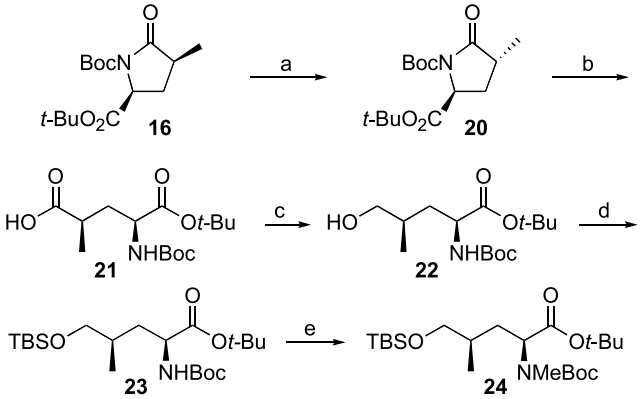


Scheme 5. Reagents and conditions: (a) (i) H_2, Pd/C, EtOAc; (ii) Boc_2O, DMAP, TEA, MeCN, 83%; (b) (i) LiHMDS, THF, −78 °C; (ii) MeOTf, 70% 7:1; (c) LiOH, THF, 0 °C to rt, quant; (d) (i) *i*-BuOCOCl, TEA, THF, −40 °C; (ii) $NaBH_4$, H_2O, 0 °C, 69%; (e) TBSCl, DMAP, TEA, DMF, 91%; (f) (i) NaHMDS, THF, 0 °C to rt; (ii) MeI, 70%.

N-Boc protected nitrogens have been previously methylated using NaH or KH[32] though in this particular case both reagents met with limited success. Using NaHMDS as the base[33] provided methylated product **19** in 36% yield. In an effort to improve the methylation, carbamate **18** was treated with Ag_2O and MeI,[34] which led to a clean product in 50% yield. The nitrogen was methylated in 70% yield using optimized conditions of NaHMDS (2.5 equiv) and MeI (10 equiv), to provide the fully protected unnatural diastereomer of (2*S*,4*S*)-2-methylamino-5-hydroxy-4-methylpentanoic acid **19** with the same stereochemistry as the product obtained in the hetero-DA reaction.

The stereoselective alkylation of the protected pyroglutamate yielded two diastereomers, the major product being the undesired *cis* product **16**, but the products were separable by column chromatography. The *cis* product had been isomerized previously by Ezquerra and co-workers, using 1 equiv of KCN in DMF over 4 days to give a final ratio of 33:67 of *cis*:*trans* product.[27,26] Conditions which would allow for faster reaction time while maintaining a similar yield and product ratio were desired.

Initial studies with the benzyl ester indicated that use of LiHMDS and a kinetic quench with ammonium chloride would give a *cis*:*trans* ratio of 1:4; however, this result did not translate to the *tert*-butyl ester series. Despite numerous trials with various conditions, products were obtained which consisted primarily of the *cis* isomer. Use of KHMDS and ammonium chloride led to decomposition, while NaHMDS with ammonium chloride led to more successful inversion (1:2 *cis*:*trans*), but in reduced yield. Using acetic acid to quench the isomerization after enolization with NaHMDS[23] led to recovery of starting material. The next bases tried were DABCO and DBU; DABCO produced no reaction and led only to the isolation of starting material. However, the use of 4 equiv of DBU in methylene chloride over 2 days consistently gave primarily inverted product **20** in a 3:1 ratio and in high yields (Scheme 6). With epimerization achieved, the lactam ring was hydrolyzed selectively with



Scheme 6. Reagents and conditions: (a) 4 equiv DBU, CH_2Cl_2, 0 °C to rt, 86%, 3.1:1; (b) LiOH, THF, 0 °C to rt, 78%; (c) (i) *i*-BuOCOCl, TEA, THF, −40 °C; (ii) $NaBH_4$, H_2O, 0 °C, 67%; (d) TBSCl, DMAP, TEA, DMF, 93%; (e) (i) NaHMDS, THF, 0 °C to rt; (ii) MeI, 57%.

lithium hydroxide. Mixed anhydride reduction of the resulting acid **21** proceeded in 67% yield to afford the primary alcohol **22**. The TBS protection and subsequent *N*-methylation proceeded in 93 and 57% yields, respectively, using conditions developed during synthesis of the unnatural diastereomer to give fully protected (2*S*,4*R*)-2-methylamino-5-hydroxy-4-methylpentanoic acid **24**.

4. Conclusions

The synthesis of the fully protected (2*S*,4*R*)-2-methylamino-5-hydroxy-4-methylpentanoic acid fragment of cyclomarin A was accomplished in 8 steps and 14% overall yield. In addition, we have synthesized (2*S*,4*S*)-2-methylamino-5-hydroxy-4-methylpentanoic acid in 7 steps and 26% overall yield. We also have reported the first example of a diastereoselective intramolecular Diels–Alder reaction of a 2-cyano-1-azadiene with an electron deficient dienophile.

5. Experimental

5.1. General

All reactions were performed under argon. THF was distilled over sodium-benzophenone, while CH_2Cl_2 and toluene were distilled over calcium hydride. Flash column chromatography was carried out on E. Merck silica gel 60 (240–400 mesh) using the solvent systems listed under individual experiments. Proton and carbon magnetic resonance spectra were recorded on a Bruker AM-500 Fourier transform spectrometer. Infrared spectra (IR) were obtained on a Perkin–Elmer Model 1600 FT-IT spectrophotometer. Optical rotations were recorded on a Perkin–Elmer Model 341 polarimeter at the sodium D line. Melting points were obtained on a Thomas Hoover Uni-melt apparatus and are uncorrected.

5.1.1. (*S*)-Acrylic acid 2-but-2-enoylamino-2-phenylethyl ester 3. To a cold (0 °C) solution of alcohol **2** (2.29 g, 11.0 mol) in CH_2Cl_2 (20 mL) was added 30:70 KOH solution (20 mL) and tetrabutylammonium iodide (TBAI, 0.406 g, 1.1 mmol). To the reaction mixture was added acryloyl chloride (1.3 mL, 15.6 mmol) in CH_2Cl_2 (3 mL) via an addition funnel at 0 °C. After 20 min, the organic layer was separated. The organic layer was then washed with water (3×10 mL) until the aqueous layer was neutral. The organic phase was dried (Na_2SO_4) and concentrated to yield an orange oil. Column chromatography (20% acetone/hexanes) afforded a clear white glass (2.65 g, 93%). (**3**): R_f 0.25 (30% acetone/hexanes, $KMnO_4$ stain); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27–7.35 (m, 5H), 6.79–6.89 (m, 1H), 6.55–6.62 (m, 1H), 6.49 (dd, J=17.4, 1.2 Hz, 1H), 6.10 (dd, J=17.3, 10.4 Hz, 1H), 5.80–5.89 (m, 2H), 5.36–5.45 (m, 1H), 4.51 (dd, J=11.4, 7.5 Hz, 1H), 4.37 (dd, J=11.5, 6.7 Hz, 1H), 1.83 (dd, J=6.9, 1.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 165.5, 140.3, 138.4, 131.4, 128.6, 127.8, 127.8, 126.7, 124.8, 66.1, 52.4, 17.6; IR (neat) 3282, 3064, 1726, 1670, 1633, 1541, 1446, 1408, 1294, 1269, 1188, 1060, 968, 810, 700 cm^{-1}; HRMS *m*/*z* calculated for $C_{15}H_{17}NO_3Na$ $(M+Na)^+$282.1106, found 282.1093; $[\alpha]_D^{25}$+56.4 (*c* 3.63, $CHCl_3$).

5.1.2. (*S*)-Acrylic acid 2-(1-cyano-but-2-enylidene-amino)-2-phenylethyl ester 4. A cold (−60 °C) solution of acrylate **3** (0.500 g, 1.93 mmol) and diisopropylethyl amine (0.5 mL, 2.89 mmol) in CH_2Cl_2 (6.5 mL) was stirred for 1 h. Triflic anhydride (freshly opened bottle) was added dropwise. The reaction was allowed to stir 2 h during which time it turned to a brown solution. To this reaction mixture was added a suspension of (89 mg, 2.72 mmol) LiCN (dried over P_2O_5 under vacuum at 80 °C for 4 h) and 12-crown-4 (30 μL, 0.19 mmol) in THF (6 mL) at −73 °C via cannula syringe and then warmed to −60 °C for 1.5 h. After that time, the reaction was warmed to −20 °C over 30 min and water (6 mL) was added. The reaction was diluted with ether while warming to room temperature. The layers formed were separated and the aqueous layer was extracted with ether (2×10 mL). The combined organic layers were washed with water (10 mL), dried (Na_2SO_4) and concentrated to a brown oil. Column chromatography (5% acetone/hexanes to 8% acetone/hexanes) afforded a yellow oil (0.111 g, 21%). (**4**): R_f 0.65 (30% acetone/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27–7.52 (m, 5H), 6.71–6.78 (m, 1H), 6.37–6.41 (m, 2H), 6.09 (dd, J=17.4, 10.4 Hz, 1H), 5.83 (dd, J=10.5, 1.3 Hz, 1H), 5.08–5.13 (m, 1H), 4.50 (dd, J=11.1, 3.9 Hz, 1H), 4.40 (dd, J=11.1, 9.2 Hz, 1H), 1.96 (dd, J=6.9, 1.6 Hz, 3H); HRMS (CI) *m*/*z* calculated for $C_{16}H_{17}N_2O_2$ $(M+H)^+$269.1284, found 269.1284. Product was too unstable for further characterization.

5.1.3. (4*S*,8*S*,10*S*)-8-Methyl-1-oxo-4-phenyl-1,3,4,8,9,9a-hexahydropyrido[2,1-*c*][1,4]oxazine-6-carbonitrile 5. Azadiene **4** (164 mg, 0.61 mmol) was dissolved in toluene (12 mL), placed in a sealed tube and charged with a magnetic stirrer. The reaction was heated to 130 °C for 50 h. The compound was concentrated and purified by column chromatography (2% ethyl acetate/hexanes to 8% ethyl acetate/hexanes) to afford the product as a brown oil, (14 mg, 9%) and starting material, as a yellow oil, (39 mg, 24%). (**5**): R_f 0.54 (30% ethyl acetate/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.45 (m, 5H), 4.93 (t, J=3.8 Hz, 1H), 5.33 (s, 1H), 4.66–4.76 (m, 2H), 3.86 (dd, J=11.2, 3.1 Hz, 1H), 2.43–2.51 (m, 2H), 1.65 (quartet of doublets, J=12.1, 2.5 Hz, 1H), 1.08 (d, J=6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7, 135.4, 128.7, 127.9, 127.3, 123.2, 115.2, 70.6, 56.2, 54.1, 32.7, 29.7, 28.4, 20.3; HRMS (CI) *m*/*z* calculated for $C_{16}H_{17}N_2O_2$ $(M+H)^+$269.1284, found 269.1284. Product was too unstable for further characterization.

5.1.4. (*S*)-Acrylic acid 2-(1-methoxy-but-2-enylidene-amino)-2-phenylethyl ester 7. To a solution of amide **3** (1.67 g, 7.45 mmol) in CH_2Cl_2 (25 mL) was added methyl triflate (1.5 mL, 12.88 mmol) dropwise at room temperature. The reaction was allowed to stir for 96 h then diluted with CH_2Cl_2 (40 mL), washed with saturated sodium bicarbonate (30 mL) and dried (Na_2SO_4). The solution was concentrated in vacuo to a yellow oil. Column chromatography (10% acetone/hexanes to 20% acetone/hexanes) afforded the product as a yellow oil (0.844 g, 48%) as well as starting material (40%). (**7**): R_f 0.61 (30%

acetone/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (m, 2H), 7.32 (m, 2H), 7.25 (m, 1H), 6.54 (m, 1H), 6.35 (m, 1H), 6.08 (m, 2H), 5.78 (m, 1H), 4.90 (dd, J=8.1, 5.0 Hz, 1H), 4.35 (ddd, J=10.7, 5.1, 2.8 Hz, 1H), 4.25 (m, 1H), 3.75 (d, J=2.2 Hz, 3H), 1.80 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 158.5, 141.5, 137.7, 130.6, 128.5, 128.3, 127.3, 117.9, 117.8, 69.7, 69.5, 59.8, 52.4, 18.2; IR (neat) 3060, 3028, 2944, 2348, 2096, 17,225, 1673, 1621, 1492, 1437, 1406, 1377, 1287, 1265, 1182, 1098, 1044, 986, 963, 839 cm^{-1}; HRMS (CI) m/z calcd for $C_{16}H_{19}NO_2$ $(M+H)^+$: 274.1440, found 274.1435; $[\alpha]_D^{25}$ +5.9° (c 1.05, $CHCl_3$).

5.1.5. (2*S*,4*R*)-4-Methyl-5-oxo-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-*tert*-butyl ester, *trans*-12, and (2*S*,4*S*)-4-Methyl-5-oxo-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-*tert*-butyl ester, *cis*-12. To a cooled (−78 °C) solution of lactam **11** (1.00 g, 3.13 mmol) in anhydrous toluene (6 mL) was added 1 M LiHMDS solution in THF (3.6 mL, 3.60 mmol). After stirring for 1 h at the same temperature, methyl triflate (0.39 mL, 3.44 mmol) was added via syringe. After stirring for another 2 h at −78 °C, 1 M LiHMDS in THF (4.1 mL, 4.07 mmol) was added to the reaction mixture. Following another 2 h of stirring at −78 °C, the reaction was quenched with saturated ammonium chloride and allowed to warm to room temperature for 10 min before diluting it with ethyl acetate. The reaction was extracted into ethyl acetate (3× 25 mL), dried with sodium sulfate and concentrated to a yellow-tan foam. The crude residue was purified by column chromatography (5% ethyl acetate/hexanes to 30% ethyl acetate/hexanes) to afford 0.280 g (27%) of yellow oil *trans*-**12** and 0.070 g (7%) of yellow oil *cis*-**12**. (*trans*-**12**): R_f 0.70 (40% ethyl acetate/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26–7.41 (m, 5H), 5.25 (d, J=12.2 Hz, 1H), 5.20 (d, J=12.2 Hz, 1H), 4.62 (dd, J=9.6, 1.3 Hz, 1H), 2.55–2.73 (m, 1H), 2.14–2.35 (m, 1H), 1.80–2.00 (m, 1H), 1.46 (s, 9H), 1.23 (d, J=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 171.1, 149.5, 135.1, 128.7, 128.6, 128.4, 83.5, 67.3, 57.0, 36.5, 30.5, 27.8, 15.1; IR (neat) 3033, 2977, 2934, 2879, 2359, 1792, 1752, 1716, 1498, 1456, 1391, 1368, 1316, 11,284, 1251, 1185, 1153, 1120, 1100, 1061, 973, 014, 854, 776, 750, 699 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{23}NO_5$ $(M+Na)^+$: 356.1576, found 356.1484; $[\alpha]_D^{25}$ −18.0° (c 1.42, $CHCl_3$).

(*cis*-**12**): R_f 0.57 (40% ethyl acetate/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26–7.41 (m, 5H), 5.20 (d, J=12.1 Hz, 1H), 5.14 (d, J=12.1 Hz, 1H), 4.47–4.54 (m, 1H), 2.46–2.64 (m, 2H), 1.51–1.64 (m, 1H), 1.47 (s, 9H), 1.19 (d, J=6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 171.2, 149.3, 134.9, 128.5, 128.5, 128.4, 83.4, 67.1, 57.3, 37.3, 29.5, 27.7, 16.1, 14.1; IR (neat) 3033, 2978, 2934, 2878, 2360, 1790, 1751, 1716, 1498, 1456, 1392, 1369, 1318, 1292, 1259, 1176, 1154, 1124, 969, 913, 850, 784, 749, 699 cm^{-1}; HRMS (CI) m/z calcd for $C_{18}H_{23}NO_5$ $(M+H)^+$: 334.1654, found 334, 1656; $[\alpha]_D^{25}$ −43.9° (c 1.38, $CHCl_3$).

5.1.6. (2*S*,4*S*)-2-(*tert*-Butoxycarbonylmethylamino)-5-(*tert*-butyldimethylsilanyloxy)-4-methylpentanoic acid *tert*-butyl ester 19. To a solution of TBS ether **18** (0.0448 g, 0.107 mmol) in THF (0.8 mL) at 0 °C, NaHMDS (1.0 M in THF, 0.27 mL, 0.268 mmol) was added dropwise. The reaction stirred at 0 °C for 10 min and at room temperature for 30 min before iodomethane (0.07 mL, 1.07 mmol) was added dropwise. After 2 h, the reaction was quenched with the addition of saturated NH_4Cl and ether. The aqueous portion was extracted 3 times with ether and the combined organic portions were washed with water and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using 1% acetone in petroleum ether, which yielded **19** as a yellow oil (0.0326 g, 70%). (**19**): R_f 0.64 (5% acetone/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.75 (dd, J=11.8, 2.9 Hz, 0.5H), 4.51 (dd, J=11.7, 3.7 Hz, 0.5H), 3.43 (dd, J=9.7, 5.1 Hz, 1H), 3.35 (m, 1H), 2.73 (d, J=15.7, 3H), 1.90 (m, 1H), 1.51 (m, 1H), 1.47 (m, 1H), 1.43 (s, 9H), 1.42 (s, 9H), 0.87 (m, 3H), 0.86 (s, 9H), 0.01 (s, 6H); ^{1}H NMR (500 MHz, d_8-toluene, 363 K) δ 4.82 (m, 1H), 3.43 (m, 2H), 2.85 (s, 3H), 1.98 (m, 1H), 1.69 (m, 2H), 1.44 (s, 9H), 1.35 (s, 9H), 0.96 (d, J=2.9 Hz, 3H), 0.93 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 171.4, 156.4, 155.9, 81.1, 81.0, 79.9, 79.6, 68.3, 68.3, 57.2, 56.1, 32.2, 31.9, 30.1, 28.4, 28.0, 25.9, 18.3, 15.6, 15.5, −5.4; ^{13}C NMR (125 MHz, d_8-toluene, 363 K) δ 171.6, 156.5, 80.9, 79.7, 69.1, 58.1, 33.8, 33.4, 31.0, 30.8, 28.9, 28.5, 26.5, 18.9, 16.5, −5.0; IR (neat) 2956, 2930, 2857, 1737, 1700, 1472, 1391, 1367, 1324, 1254, 1154, 1093, 1034, 1007, 950, 912, 838, 776, 666 cm^{-1}; HRMS (ESI) m/z calcd for $C_{22}H_{45}NO_5Si$ $(M+Na)^+$: 454.3051, found 454.2944; $[\alpha]_D^{25}$ −16.8° (c 1.15, $CHCl_3$).

5.1.7. (2*S*,4*R*)-4-Methyl-5-oxopyrrolidine-1,2-dicarboxylic acid di-*tert*-butyl ester 20.[30] *cis*-Methylpyroglutamate **16** (0.1571 g, 0.525 mmol) was taken up in 4.1 mL CH_2Cl_2 and cooled to 0 °C. DBU (0.31 mL, 2.10 mmol) was added dropwise and the reaction stirred at 0 °C for 15 min and then at room temperature for 48 h. The reaction was diluted with CH_2Cl_2, washed twice with 10% HCl, and once each with water and brine. The organic portion was dried over Na_2SO_4, filtered and concentrated to give the crude product which was purified by flash chromatography using 5–10% ethyl acetate in petroleum ether yielding **20** as a clear colorless oil (0.1351 g, 86% in a 3.1:1 ratio of *trans*/*cis*). (**20**): R_f 0.65 (30% ethyl acetate/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.35 (dd, J=9.5, 1.1 Hz, 1H), 2.58 (m, 1H), 2.17 (ddd, J=13.2, 8.7, 1 Hz, 1H), 1.83 (m, 1H), 1.48 (s, 9H), 1.47 (s, 9H), 1.14 (d, J=7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 170.2, 149.4, 89.9, 82.1, 57.6, 36.4, 30.6, 27.8, 22.5, 15.1; IR (neat) 2977, 2934, 2359, 23,341, 1792, 1739, 1717, 1457, 1368, 1315, 1284, 1249, 1225, 1154, 1099, 973, 917, 884, 846, 813, 775 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{25}NO_5$ $(MH)^+$: 300.1811, found 300.1805; $[\alpha]_D^{25}$ −12.6° (c 1.11, $CHCl_3$).

5.1.8. (2*S*,4*R*)-2-*tert*-Butoxycarbonylamino-4-methylpentanedioic acid 1-*tert*-butyl ester 21. *trans*-Methylpyroglutamate **20** (0.1039 g, 0.347 mmol) was taken up in 1.8 mL THF and cooled to 0 °C. 0.42 mL 1 M LiOH (aqueous, 0.416 mmol) was added dropwise over 15 min, the reaction was stirred for 15 min and was the quenched by addition of a mixture of ethyl acetate (1 mL) and saturated sodium bicarbonate (1 mL). The layers were separated and the organic portion was extracted with saturated sodium bicarbonate. The aqueous portions were combined, cooled to 0 °C and acidified to pH 4 using 10% citric acid and

extracted 5 times with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered and concentrated yielding **21** as a white solid (0.0862 g, 78%). (**21**): mp 72–74 °C; R_f 0.54 (50% ethyl acetate/petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 10.42 (bs, 1H), 5.21 (d, J= 6.6 Hz, 1H), 5.01 (d, J=8.3 Hz, 1H), 2.56 (m, 1H), 2.17 (m, 1H), 1.64 (m, 1H), 1.43 (s, 9H), 1.40 (s, 9H), 1.20 (d, J= 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.3, 171.4, 155.8, 82.4, 80.2, 52.5, 36.8, 36.2, 28.2, 27.9, 17.4; IR (neat) 3330, 2978, 2931, 2359, 2340, 1714, 1508, 1455, 1396, 1368, 1255, 1154, 1061, 847, 669 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{27}NO_6$ $(M+Na)^+$: 340.1838, found 340.1731; $[\alpha]_D^{25}$ −23.4° (*c* 1.4, MeOH).

5.1.9. (2*S*,4*R*)-2-*tert*-Butoxycarbonylamino-5-hydroxy-4-methylpentanoic acid *tert*-butyl ester 22. To a solution of acid **21** (0.1429 g, 0.450 mmol) in 2.3 mL THF at −40 °C, Et_3N (0.08 mL, 0.585 mmol) was added dropwise. Isobutyl chloroformate (0.07 mL, 0.540 mmol) was added dropwise over 10 min, to give a yellow/orange color and the reaction was stirred at −40 °C for 2 h. The reaction was warmed to 0 °C, $NaBH_4$ (0.102 g, 2.70 mmol) in H_2O (2 mL) was added and the reaction stirred at 0 °C for 1 h and then warmed to room temperature. After stirring at room temperature for 3.5 h, the reaction was quenched with the addition of ethyl acetate and brine at 0 °C. The organic portion was washed with ice cold 10% citric acid 3 times, twice with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified using flash chromatography using 25% ethyl acetate/petroleum ether yielding **22** as a clear colorless oil (0.0913 g, 67%). (**22**): R_f 0.48 (30% ethyl acetate/petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 5.22 (d, J=6.8 Hz, 1H), 4.24 (d, J= 4.7 Hz, 1H), 3.48 (dd, J=10.7, 5.3 Hz, 1H), 3.41 (dd, J= 10.7, 6.3 Hz, 1H), 2.65 (bs, 1H), 1.75 (m, 2H), 1.44–1.35 (m, 1H), 1.40 (s, 9H), 1.38 (s, 9H), 0.90 (d, J=6.7, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 155.6, 81.8, 79.7, 67.7, 52.6, 37.7, 32.3, 28.2, 27.9, 17.4; IR (neat) 3364, 2976, 1712, 1511, 1455, 1390, 1367, 1251, 1154, 1046, 848 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{29}NO_5$ $(M+Na)^+$: 326.2045, found 326.1941; $[\alpha]_D^{25}$ +5.16° (*c* 1.03, $CHCl_3$).

5.1.10. (2*S*,4*R*)-2-*tert*-Butoxycarbonylamino-5-(*tert*-butyldimethylsilanyloxy)-4-methyl-pentanoic acid *tert*-butyl ester 23. Alcohol **22** (0.0857 g, 0.282 mmol) was dissolved in 0.7 mL DMF and TBS-Cl (0.128 g, 0.846 mmol) was added. The reaction was stirred for 10 min. DMAP (0.0345 g, 0.282 mmol) and Et_3N (0.24 mL, 1.69 mmol) were added and the solution was allowed to stir for 18 h. The reaction was quenched with the addition of brine and was extracted 3 times with ether. The organic portion was washed sequentially with H_2O (3 times), ice cold 10% HCl, brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using 10% ethyl acetate in petroleum ether, yielding **23** as a pale yellow oil (0.1093 g, 93%). (**23**): R_f 0.46 (5% acetone/petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 5.20 (d, J=7.7 Hz, 1H), 4.13 (m, 1H), 3.49 (dd, J=9.9, 5.1 Hz, 1H), 3.36 (dd, J=9.9, 5.8 Hz, 1H), 1.81 (m, 2H), 1.70 (m, 1H), 1.42 (s, 9H), 1.40 (s, 9H), 0.90 (d, J=6.9, 3H), 0.86 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 155.4, 81.4, 79.3, 67.1, 52.6, 36.2, 32.4, 28.3, 28.0, 25.9, 25.6, 17.3, −3.6, −5.5; IR (neat) 3359, 2956, 2930, 2857, 2348, 1718, 1501, 1472, 1392, 1366, 1252, 1154, 1093, 1049, 836, 776 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{21}H_{43}NO_5Si$ $(M+Na)^+$: 440.2910, found 440.2796; $[\alpha]_D^{25}$ −0.5° (*c* 1.09, $CHCl_3$).

5.1.11. (2*S*,4*R*)-2-(*tert*-Butoxycarbonylmethylamino)-5-(*tert*-butyldimethylsilanyloxy)-4-methylpentanoic acid *tert*-butyl ester 24. The procedure described above for compound **19** was followed, using TBS-ether **23** (0.1250 g, 0.299 mmol). Compound **24** was isolated as a pale yellow oil (0.0739 g, 57%). (**24**): R_f 0.59 (5% acetone/petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 4.67 (dd, J=10.2, 5.0 Hz, 0.5H), 4.40 (dd, J=10.1, 5.0 Hz, 0.5H), 3.43 (m, 2H), 2.76 (d, J=20.6 Hz, 3H), 1.92 (m, 1H), 1.56 (m, 1H), 1.44 (m, 1H), 1.42 (s, 9H), 1.41 (s, 9H), 0.92 (d, J=6.8 Hz, 3H), 0.86 (s, 9H), 0.01 (d, J=4.7 Hz, 6H); ^1H NMR (500 MHz, d_8-toluene, 363 K) δ 4.77 (m, 1H), 3.51 (d, J= 4.0 Hz, 2H), 2.84 (d, J=12.8 Hz, 3H), 1.69 (m, 1H), 1.53 (m, 2H), 1.48 (s, 9H), 1.41 (s, 9H), 0.98–0.94 (m, 3H), 0.97 (s, 9H), 0.08 (d, J=7.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 171.3, 156.2, 155.9, 81.1, 79.9, 79.6, 66.5, 57.9, 56.6, 32.3, 32.0, 30.5, 29.7, 28.4, 28.0, 25.9, 18.3, 17.7, 17.5, −5.4; ^{13}C NMR (125 MHz, d_8-toluene, 363 K) δ 171.5, 156.4, 80.8, 79.7, 67.7, 58.5, 33.7, 33.4, 31.0, 28.9, 28.5, 26.5, 18.9, 17.9, −5.0; IR (neat) 2956, 2930, 2857, 2350, 1737, 1700, 1472, 1391, 1367, 1323, 1254, 1148, 1096, 1045, 1006, 952, 910, 838, 776, 665 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{22}H_{45}NO_5Si$ $(M+Na)^+$: 454.3051, found 454.2977; $[\alpha]_D^{25}$ −18.4° (*c* 1.06, $CHCl_3$).

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