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A Unified Strategy for Kainoid Synthesis

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A unified strategy for kainoid synthesis was developed. The key features of the strategy involve a Claisen–Ireland rearrangement to construct the contiguous stereogenic centers and a palladium-catalyzed formation of the pyrrolidine ring with complete stereoselectivity. The present protocol has enabled rapid access to a wide range of kainoids with diverse types of substituents (alkenyl, aryl, and alkyl groups) at the 4-position of the pyrrolidie ring, starting from the common intermediate and appropriate acetic acid derivatives. To test the generality of the strategy, we have accomplished the syntheses of kainic acid, *o*-methoxyphenyl derivative (MFPA), and a novel cyclopropyl derivative (CPKA), using 3-methylbut-3-enoic acid, 2-(2-methoxyphenyl)acetic acid, and 2-cyclopropylacetic acid, respectively.

Introduction

The kainoids (**1**) are 2,3,4-trisubstituted pyrrolidine derivatives that contain a glutamic acid moiety and various substituents at the 4-position of the pyrrolidine ring (Figure 1).[1] Kainic acid (**2**), the parent member of the kainoids, was first isolated in 1953 from the Japanese marine alga *Digenea simplex*.[2] Since then, **2** has been found in another alga (*Centrocerus clavulatum*) and a moss (*Alsidium helminthocorton*).[3] As well as showing potent anthelmintic properties,[4] **2** acts as an excitatory amino-acid-receptor agonist, and it is widely used as a tool in neuropharmacology to stimulate nerve cells and mimic disease states, such as epilepsy,[5] Alzheimer's disease, and Huntington's chorea.[6]

Other natural kainoids, domoic acid[7] and isodomoic acids,[8] isolated from another Japanese alga *Chondria armata*, as well as acromelic acids A and B, isolated from the Japanese mushroom *Clitocybe acromelalga*,[9] also show potent neuroexcitatory activities. It has been reported that domoic acid (**3**) and acromelic acid A (**5**) are approximately 10 and 100 times more potent than kainic acid, respectively.[10] A variety of unnatural kainoids have also been synthesized in attempts to find new neuroexcitatory agents.[11] For example, Shirahama and co-workers prepared the *o*-methoxyphenyl derivative MFPA (**6**), which is more potent than natural kainoids.[11i,11j]

Synthetic routes to the kainoids have been extensively explored, not only as a result of their importance in the field of neuroscience, but also due to their unique structures.[12–14] To date, more than 50 syntheses of kainic acid, and several syntheses of domoic acid,[15] the isodomoic acids,[16] and the acromelic acids,[9a,17] have been reported. These synthetic approaches, and also those directed at unnatural analogs,[18] are specifically designed to synthesize the respective target kainoid. To the best of our knowledge, there seems to be no versatile route that can prepare any type of kainoids, including alkenyl (e.g., kainic acid, domoic acid), aryl (e.g., acromelic acids, MFPA), and alkyl analogs. A unified synthetic strategy for a variety of kainoids would effectively provide new analogs with potential neuroexcitatory activities. In this paper, we disclose syntheses of kainic acid (**2**), MFPA (**6**), and a new cyclopropyl analog of kainic acid (CPKA, **7**) by means of a unified strategy, featuring a Claisen–Ireland rearrangement[19] and a palladium-mediated pyrrolidine-ring formation.

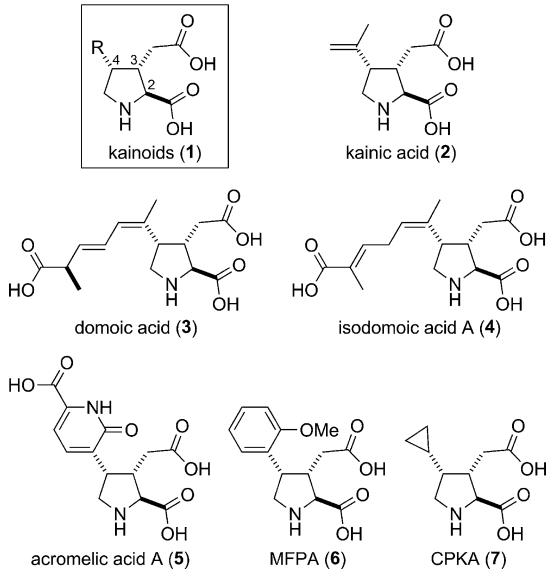

Figure 1. Structures of kainoids.

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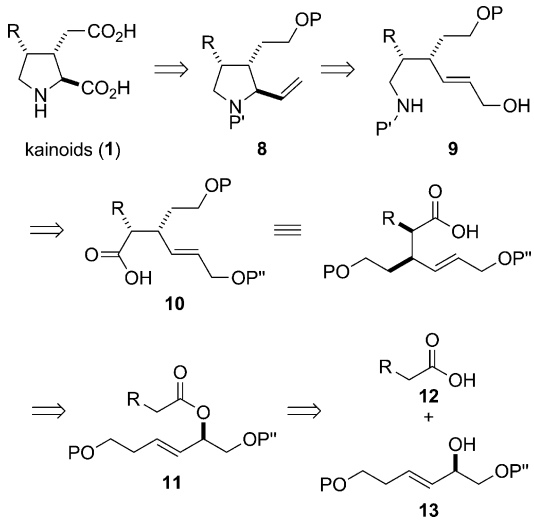
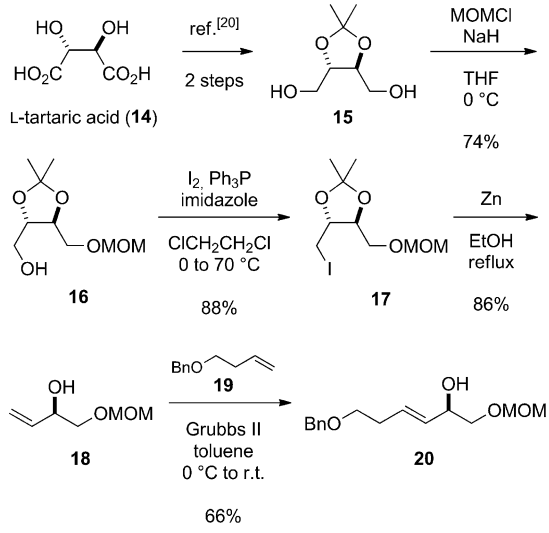
Results and Discussion

Our retrosynthetic analysis is shown in Scheme 1. We envisioned that the pyrrolidine ring could be effectively formed by palladium-catalyzed cyclization of allylic alcohol **9**. The amino group in **9** could be introduced using the carboxylic acid moiety in **10**. To control the contiguous stereogenic centers in **10**, which correspond to those at the 3- and 4-positions of the pyrrolidine ring, we decided to use the Claisen–Ireland rearrangement of chiral allylic ester **11**. Condensation of 2-substituted acetic acid **12** and allylic alcohol **13** could give **11**. According to this strategy, selection of appropriate acetic acid derivatives could introduce a variety of substituents at the 4-position of the kainoid products (R in **1**).



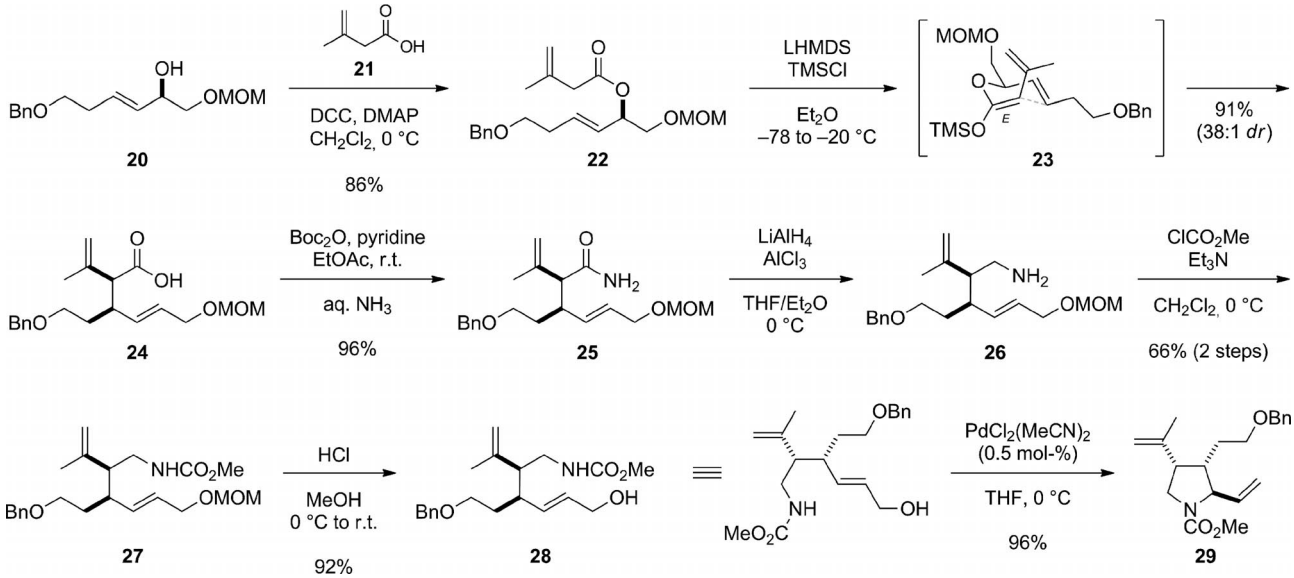
Scheme 1. Retrosynthetic analysis.

Our synthesis commenced with the preparation of the common synthetic intermediate, allylic alcohol **20** (Scheme 2). According to a known procedure,[20] L-tartaric acid (**14**) was converted into diol **15**. Selective protection of one of the hydroxy groups in **15** and iodination of the resulting alcohol (i.e., **16**) gave iodide **17**. Reduction of the vicinal iodohydrin moiety in **17** with zinc in refluxing ethanol gave olefin **18** in good yield. Homologation of **18** by a cross-metathesis reaction with olefin **19** gave the desired allylic alcohol (i.e., **20**).[21]



Scheme 2. Synthesis of common synthetic intermediate **20**; Bn = benzyl, MOM = methoxymethyl.

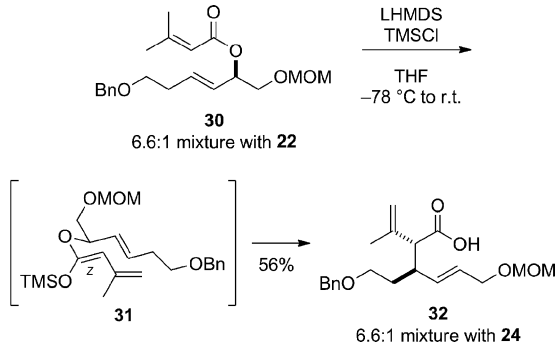
With the key intermediate in hand, we aimed at synthesizing kainic acid through the crucial Claisen–Ireland rearrangement (Scheme 3). After condensation of **20** with 3-methylbut-3-enoic acid (**21**),[22] the resulting ester (i.e., **22**)



Scheme 3. Synthesis of kainic acid; Boc = *tert*-butoxycarbonyl, DCC = *N*,*N*′-dicyclohexylcarbodiimide, DMAP = 4-(dimethylamino)-pyridine, LHMDS = lithium hexamethyldisilazide, TMS = trimethylsilyl.

was treated with LHMDS in the presence of TMSCl at –78 °C to form (*E*)-silyl enolate **23**, which, upon warming to –20 °C, underwent a [3,3]-sigmatropic rearrangement via a chair-like transition state to give **24** in 91% yield, with a high diastereoselectivity (38:1).[23]

It is noteworthy that the Claisen–Ireland rearrangement of the corresponding 3-methylcrotonate (i.e., **30**) produced **32**, a diastereomer of **24**, as a major product (Scheme 4). This was attributed to the formation of (*Z*)-silyl enolate **31** from 3-methylcrotonate,[24] followed by a subsequent [3,3]-sigmatropic rearrangement via a chair-like transition state.



Scheme 4. Claisen–Ireland rearrangement using 3-methylcrotonate.

Next, we focused on the construction of the pyrrolidine ring. The carboxylic acid in **24** was converted into the primary amine (in **26**) by first forming primary amide **25** via a mixed anhydride,[25] followed by reduction with AlH_3. Protection of the amine in **26** and subsequent cleavage of the MOM group gave **28**. Upon treatment with $PdCl_2(MeCN)_2$ (0.5 mol-%) in THF at 0 °C,[26] **28** underwent exceptionally facile cyclization to give **29** stereoselectively. NOESY experiments on **29** indicated that the product had all the required stereochemistry for the synthesis of kainic acid.

The stereoselective formation of **29** can be explained in terms of transition state geometries (Figure 2). In the cyclization step, the π-bond in the allylic alcohol and the lone pair on the nitrogen atom in the carbamate must overlap sufficiently. With this restriction, there are two plausible transition states: **A** and **B**. Transition state **A**, which leads to the formation of **29**, is more energetically favorable because it has a conformation where the $A^{1,3}$-strain is minimized, whereas steric repulsion exists between the allylic alcohol moiety and the alkyl chains in transition state **B**.

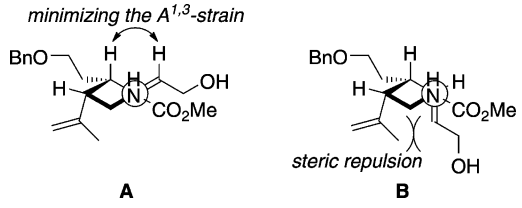
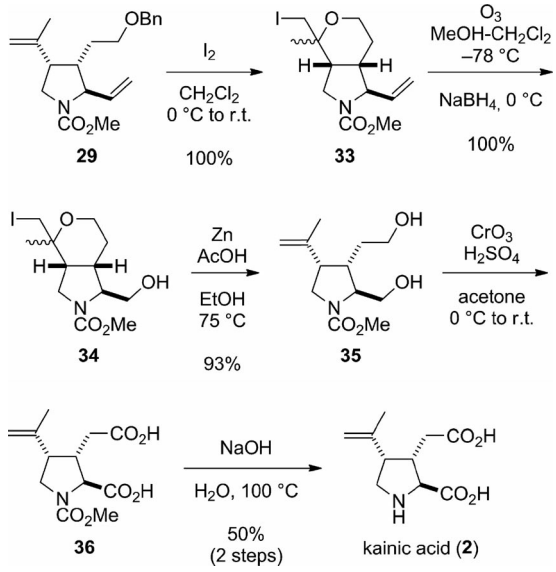


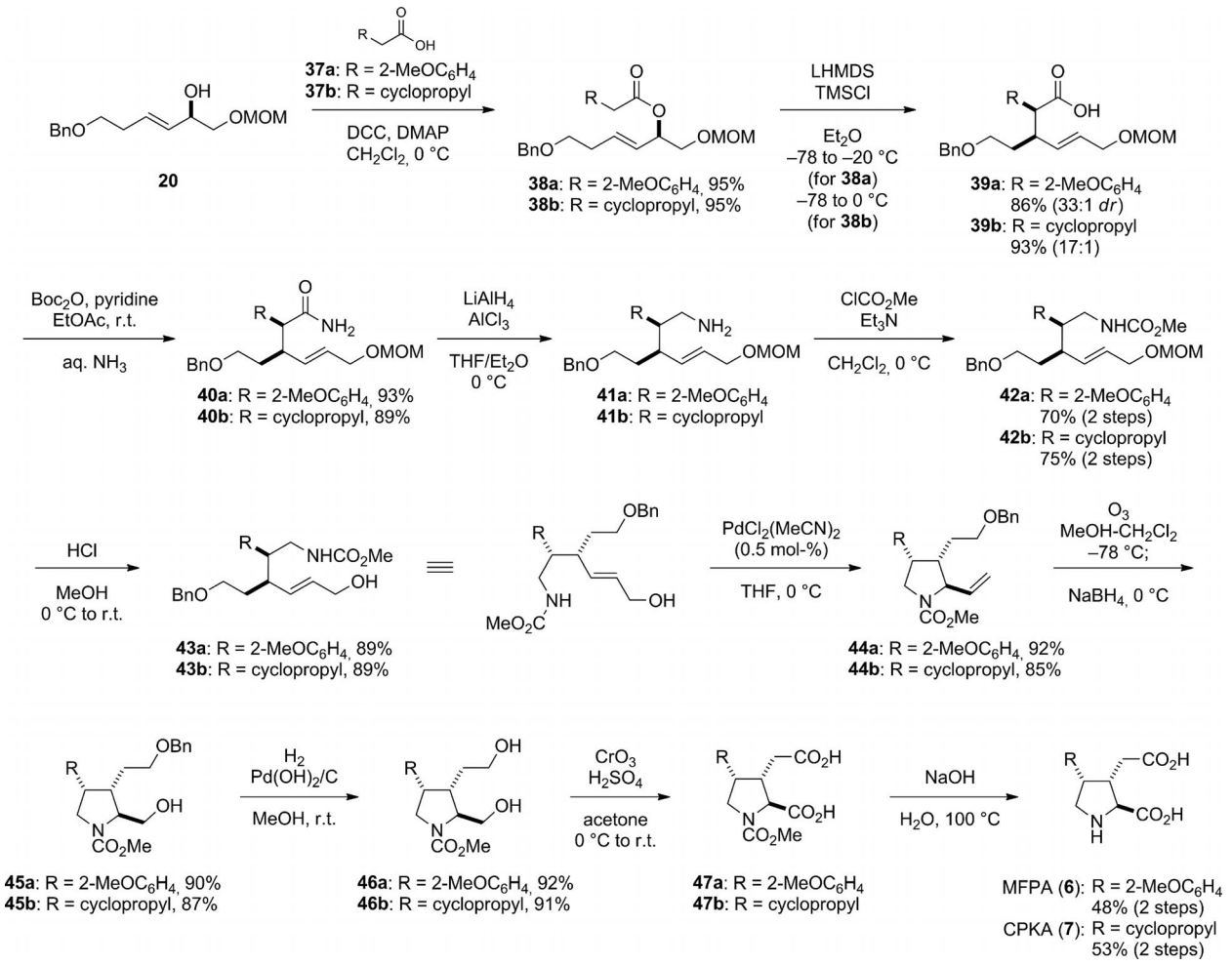
Figure 2. Rationale for the stereoselective cyclization.

Completion of the synthesis of kainic acid required oxidative cleavage of the vinyl group (Scheme 5). However, oxidation of **29** with OsO_4 or ozone resulted in the preferential oxidation of the isopropenyl group. This preference in the oxidation could be utilized for protection of the isopropenyl group. Upon treatment with iodine, **29** underwent iodoetherification with concomitant cleavage of the benzyl group to give **33** as a mixture of diastereomers. Ozonolysis of **33** proceeded smoothly, and after reduction with sodium borohydride, alcohol **34** was obtained in excellent yield. Reductive cleavage of the cyclic ether by treatment with zinc gave diol **35**, which was then subjected to Jones oxidation to give dicarboxylic acid **36**. Finally, alkaline hydrolysis of the methyl carbamate moiety gave kainic acid (**2**).



Scheme 5. Completion of the synthesis.

Having established a synthetic route to kainic acid, we next attempted to synthesize an unnatural kainoid, MFPA (**6**), in order to verify the general applicability of our strategy. In this synthesis, 2-(2-methoxylphenyl)acetic acid (**37a**), instead of 3-methylbut-3-enoic acid (**21**), was used as the coupling partner (Scheme 6). The condensation reaction between **20** and **37a** gave **38a** in 95% yield. The crucial Claisen–Ireland rearrangement, introduction of the amine moiety, and palladium-catalyzed formation of the pyrrolidine ring proceeded uneventfully to give **44a** in good yield. Ozonolysis of the vinyl group in **44a** followed by reduction with $NaBH_4$ gave **45a**. Cleavage of the benzyl ether by hydrogenolysis gave diol **46a**, which could be converted into MFPA (**6**) by Jones oxidation and alkaline hydrolysis. The established transformations were also successfully used for the synthesis of a new cyclopropyl analog of kainic acid (CPKA, **7**),[27] starting from 2-cyclopropylacetic acid (**37b**) as the coupling partner.



Scheme 6. Synthesis of analogs of kainic acid.

Conclusions

In summary, syntheses of kainic acid (**2**), MFPA (**6**), and CPKA (**7**) have been accomplished from a common intermediate **20** by means of a unified strategy featuring a Claisen–Ireland rearrangement to construct the contiguous stereogenic centers and palladium-catalyzed formation of the pyrrolidine ring with complete stereoselectivity. This strategy can be used for the synthesis of a wide range of kainoids with diverse types of substituents at the 4-position of the pyrrolidine ring. Further application of this unified strategy to the synthesis of more complex kainoids is currently underway in our laboratories.

Experimental Section

General Remarks: Nuclear magnetic resonance [^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz)] spectra were determined with a JEOL-ECS400 instrument unless otherwise noted. Chemical shifts for ^{1}H NMR spectra are reported in parts per million (ppm) downfield from tetramethylsilane and coupling constants are given in Hertz (Hz). Tetramethylsilane and/or residual solvents were used as internal standards. The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Chemical shifts for ^{13}C NMR spectra are reported in ppm. The center line of the triplet at δ = 77.16 ppm for deuteriochloroform was used as an internal standard. Spectra in D_2O were calibrated using the signal at δ = 30.9 ppm for acetone. Infrared (IR) spectra were recorded with a JASCO FTIR-410 Fourier Transform Infrared Spectrophotometer, and the data are reported in wavenumbers (cm^{-1}). High-resolution mass spectra (HRMS) were obtained with a JEOL JMS-T100LP AccuTOF LC-plus instrument using either the positive electrospray ionization (ESI) method or the positive direct analysis in real time (DART) ionization method, with PEG as the internal standard. Optical rotations were measured with a JASCO P-2200 Digital Polarimeter at room temperature, using the sodium D line. Melting points (m.p.) were determined with a Yanaco Micro Melting Point Apparatus. Analytical thin-layer chromatography (TLC) was carried out on Merck analytical plates, 0.25 mm thick, precoated with silica gel 60 F_{254}. Preparative TLC separations were carried out on Merck analytical plates (0.25 or 0.50 mm thick) precoated with silica gel 60 F_{254}. Reverse-phase preparative TLC separations were carried out on Merck analytical plates precoated with silica gel 60 RP-18 F_{254} S. Flash chromatography separations were carried out on Kanto Chemicals Silica Gel 60 (spherical, 40–100 mesh). Reverse-phase chromatography separations were carried out on Kanto Chemicals Silica Gel 120 RP-18 (spherical, 40–50 μm particle size). Reagents were commercial grade and were used without any purification. Anhydrous tetrahydrofuran, diethyl ether, toluene, and dichloromethane were purchased from Kanto Chemicals Co., Inc.,

and were purified using a Glass Contour Solvent System. Anhydrous benzene and *N*,*N*-dimethylformamide were purchased from Kanto Chemicals Co., Inc. and stored over activated MS (4Å). Anhydrous methanol, ethanol, and acetonitrile were also purchased from Kanto Chemicals Co., Inc. and stored over activated MS (3Å). All reactions sensitive to oxygen or moisture were carried out under an argon atmosphere.

{(4*S*,5*S*)-5-[(Methoxymethoxy)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}methanol (16): NaH (60% in mineral oil; 2.74 g, 68.5 mmol) was added to a solution of [(4*S*,5*S*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl]dimethanol[20] (**15**; 10.1 g, 62.3 mmol) in tetrahydrofuran (250 mL) at 0 °C. The mixture was stirred for 30 min at 0 °C, then MOMCl (5.20 mL, 68.5 mmol) was added dropwise. The mixture was stirred for an additional 2.5 h at 0 °C, then it was quenched with saturated aqueous NH_4Cl. The organic solvent was removed under reduced pressure, and the aqueous mixture was extracted with ethyl acetate (3×). The combined organic extracts were washed with brine, dried with anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 1:3 to 3:2) to give **16** (9.46 g, 73.6%) as a colorless oil. $[\alpha]_D^{23}$ = +1.26 (*c* = 1.00, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3477, 2987, 2935, 2886, 2826, 1456, 1372, 1215, 1153, 1041, 919, 847, 802 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.67 (s, 2 H), 4.08 (ddd, *J* = 8.3, 5.5, 5.0 Hz, 1 H), 3.95 (ddd, *J* = 8.3, 4.1, 4.1 Hz, 1 H), 3.85–3.78 (m, 1 H), 3.73–3.65 (m, 1 H), 3.70 (dd, *J* = 10.5, 5.5 Hz, 1 H), 3.66 (dd, *J* = 10.5, 5.0 Hz, 1 H), 3.38 (s, 3 H), 2.30 (m, 1 H), 1.44 (s, 3 H), 1.43 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 109.6 (C), 96.8 (CH_2), 79.3 (CH), 76.4 (CH), 67.9 (CH_2), 62.4 (CH_2), 55.5 (CH_3), 27.1 (CH_3), 27.1 (CH_3) ppm. HRMS ($DART^+$): calcd. for $C_9H_{19}O_5$ $[M + H]^+$ 207.1233; found 207.1225.

(4*R*,5*S*)-4-(Iodomethyl)-5-[(methoxymethoxy)methyl]-2,2-dimethyl-1,3-dioxolane (17): Imidazole (9.37 g, 138 mmol), Ph_3P (15.6 g, 59.6 mmol) and iodine (14.0 g, 55.0 mmol) were added to a solution of {(4*S*,5*S*)-5-[(methoxymethoxy)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}methanol (**16**; 9.46 g, 45.9 mmol) in dichloroethane (200 mL) at 0 °C. The mixture was stirred for 10 min, then it was warmed to 70 °C. After 5 h, the reaction mixture was cooled to 0 °C and quenched with saturated aqueous $Na_2S_2O_3$. The mixture was extracted with dichloromethane (3×), and the combined organic extracts were washed with saturated aqueous $Na_2S_2O_3$, saturated aqueous NH_4Cl, and brine. The resulting organic layer was dried with anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 1:9 to 1:4) to give **17** (12.8 g, 88.3%) as a colorless oil. $[\alpha]_D^{24}$ = –17.1 (*c* = 1.00, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2987, 2934, 2886, 2823, 1455, 1380, 1371, 1239, 1215, 1151, 1111, 1040 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.67 (s, 2 H), 3.98 (ddd, *J* = 7.3, 5.5, 4.5 Hz, 1 H), 3.89 (ddd, *J* = 7.3, 5.5, 5.5 Hz, 1 H), 3.75 (dd, *J* = 10.5, 4.5 Hz, 1 H), 3.70 (dd, *J* = 10.5, 5.5 Hz, 1 H), 3.39 (s, 3 H), 3.35 (dd, *J* = 10.5, 5.5 Hz, 1 H), 3.31 (dd, *J* = 10.5, 5.5 Hz, 1 H), 1.48 (s, 3 H), 1.43 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 110.0 (C), 96.8 (CH_2), 80.3 (CH), 77.5 (CH), 68.1 (CH_2), 55.5 (CH_3), 27.5 (CH_3), 27.4 (CH_3), 6.3 (CH_2) ppm. HRMS ($DART^+$): calcd. for $C_9H_{18}IO_5$ $[M + H]^+$ 317.0250; found 317.0263.

(*R*)-1-(Methoxymethoxy)but-3-en-2-ol (18): Dibromoethane (1.00 mL, 11.6 mmol) and TMSCl (650 μL, 5.15 mmol) were added to a suspension of zinc (39.29 g, 601 mmol) in ethanol (400 mL). The mixture was stirred at reflux for 10 min, then (4*R*,5*S*)-4-(iodomethyl)-5-[(methoxymethoxy)methyl]-2,2-dimethyl-1,3-dioxolane (**17**; 19.0 g, 60.1 mmol) was added dropwise. The mixture was stirred for an additional 1.5 h at reflux, then it was cooled to room temperature. The resulting mixture was filtered through a Celite pad, and the filter cake was rinsed with methanol. The organic solvent was removed under reduced pressure, and the residue was diluted with brine and saturated aqueous NH_4Cl. The aqueous mixture was extracted with diethyl ether (5×), and the combined organic extracts were dried with anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by distillation (92 to 94 °C, 25 Torr) to give **18** (6.83 g, 86.0%) as a colorless oil. $[\alpha]_D^{25}$ = 6.1 (*c* = 1.00, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3443, 2946, 2888, 2826, 1644, 1442, 1037, 927 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 5.86 (ddd, *J* = 17.3, 10.5, 5.5 Hz, 1 H), 5.39 (ddd, *J* = 17.3, 1.5, 1.5 Hz, 1 H), 5.22 (ddd, *J* = 10.5, 1.5, 1.5 Hz, 1 H), 4.69 (d, *J* = 6.7 Hz, 1 H), 4.67 (d, *J* = 6.7 Hz, 1 H), 4.35–4.29 (m, 1 H), 3.68 (dd, *J* = 10.5, 3.2 Hz, 1 H), 3.48 (dd, *J* = 10.5, 7.3 Hz, 1 H), 3.40 (s, 3 H), 2.72 (d, *J* = 4.1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 136.8 (CH), 116.5 (CH_2), 97.1 (CH_2), 72.8 (CH_2), 71.7 (CH), 55.6 (CH_3) ppm. HRMS ($DART^+$): calcd. for $C_6H_{13}O_3$ $[M + H]^+$ 133.0865; found 133.0859.

(*R*,*E*)-6-(Benzyloxy)-1-(methoxymethoxy)hex-3-en-2-ol (20): Grubbs catalyst 2nd generation (64.2 mg, 0.0756 mmol) was added to a solution of (*R*)-1-(methoxymethoxy)but-3-en-2-ol (**18**; 1.00 g, 7.57 mmol) and [(but-3-en-1-yloxy)methyl]benzene[28] (**19**; 6.14 g, 37.8 mmol) in toluene (50 mL) at 0 °C. The mixture was stirred for 15 min, then further Grubbs catalyst (64.2 mg, 0.0756 mmol) was added. The reaction mixture was gradually warmed to room temperature over 1 h, where it was stirred for another 2 h. Then, additional [(but-3-en-1-yloxy)methyl]benzene (1.23 g, 7.57 mmol) and Grubbs catalyst (64.2 mg, 0.0756 mmol) were added at room temperature. The mixture was stirred for an additional 9 h, then the reaction was quenched with dimethyl sulfoxide (200 μL), and the mixture was stirred for 12 h. Activated carbon (400 mg) was added, and the mixture was stirred for 2 h. The resulting mixture was filtered through a Celite pad, and the filter cake was rinsed with dichloromethane. The organic solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane, 1:2) to give **20** (1.32 g, 65.5%) as a pale yellow oil. $[\alpha]_D^{25}$ = –9.4 (*c* = 1.00, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3451, 2933, 2863, 1454, 1362, 1111, 1036 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.38–7.26 (m, 5 H), 5.82 (dt, *J* = 15.0, 7.3 Hz, 1 H), 5.55 (dd, *J* = 15.0, 7.0 Hz, 1 H), 4.68 (d, *J* = 6.4 Hz, 1 H), 4.66 (d, *J* = 6.4 Hz, 1 H), 4.51 (s, 2 H), 4.31–4.25 (m, 1 H), 3.62 (dd, *J* = 10.5, 3.2 Hz, 1 H), 3.52 (t, *J* = 6.9 Hz, 1 H), 3.44 (dd, *J* = 10.5, 7.8 Hz, 1 H), 3.39 (s, 3 H), 2.63 (d, *J* = 3.2 Hz, 1 H), 2.38 (dt, *J* = 7.3, 6.9 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 138.5 (C), 130.3 (CH), 129.9 (CH), 128.5 (CH), 127.8 (CH), 127.7 (CH), 97.1 (CH_2), 73.0 (CH_2), 73.0 (CH_2), 71.5 (CH), 69.7 (CH_2), 55.5 (CH_3), 32.9 (CH_2) ppm. HRMS (ESI^+): calcd. for $C_{15}H_{23}O_4$ $[M + H]^+$ 289.1416; found 289.1408.

(*R*,*E*)-6-(Benzyloxy)-1-(methoxymethoxy)hex-3-en-2-yl 3-Methylbut-3-enoate (22): 3-Methylbut-3-enoic acid[22a] (**21**; 1.34 g, 13.4 mmol), *N*,*N*′-dicyclohexylcarbodiimide (2.44 g, 11.8 mmol), and 4-(dimethylamino)pyridine (289 mg, 2.37 mmol) were added to a solution of (*R*,*E*)-6-(benzyloxy)-1-(methoxymethoxy)hex-3-en-2-ol (**20**; 2.10 g, 7.88 mmol) in dichloromethane (80 mL) at 0 °C. The mixture was stirred for 40 min, then further *N*,*N*′-dicyclohexylcarbodiimide (1.12 g, 5.43 mmol) and 3-methylbut-3-enoic acid (1.00 g, 9.99 mmol) were added. The mixture was stirred for an additional 4.5 h at 0 °C, then it was quenched with saturated aqueous NH_4Cl. The resulting suspension was filtered through a Celite pad, and the filter cake was rinsed with dichloromethane. The filtrate was extracted with dichloromethane (4×), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$,

saturated aqueous NH_4Cl, and brine. The resulting organic phase was dried with anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 1:9 to 1:3) to give **22** (2.36 g, 85.9%) as a colorless oil. $[\alpha]_D^{25}$ = –121 (*c* = 0.50, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2932, 1739, 1651, 1454, 1243, 1152, 1112, 1030, 968 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.38–7.26 (m, 5 H), 5.84 (dt, *J* = 15.1, 6.8 Hz, 1 H), 5.54 (dd, *J* = 15.1, 6.9 Hz, 1 H), 5.45 (dt, *J* = 6.9, 5.0 Hz, 1 H), 4.90 (s, 1 H), 4.85 (s, 1 H), 4.63 (d, *J* = 6.9 Hz, 1 H), 4.61 (d, *J* = 6.9 Hz, 1 H), 4.50 (s, 2 H), 3.62 (d, *J* = 5.0 Hz, 2 H), 3.50 (t, *J* = 6.7 Hz, 2 H), 3.34 (s, 3 H), 3.06 (s, 2 H), 2.37 (dt, *J* = 6.7, 6.8 Hz, 2 H), 1.80 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 170.6 (C), 138.6 (C), 138.5 (C), 132.2 (CH), 128.5 (CH), 127.7 (CH), 127.7 (CH), 126.8 (CH), 114.8 (CH_2), 96.5 (CH_2), 73.4 (CH), 73.0 (CH_2), 69.5 (CH_2), 69.0 (CH_2), 55.4 (CH_3), 43.8 (CH_2), 32.9 (CH_2), 22.5 (CH_3) ppm. HRMS (ESI^+): calcd. for $C_{20}H_{28}NaO_5$ $[M + Na]^+$ 371.1834; found 371.1842.

(2*S*,3*R*,*E*)-3-[2-(Benzyloxy)ethyl]-6-(methoxymethoxy)-2-(prop-1-en-2-yl)hex-4-enoic Acid (24): (*R*,*E*)-6-(Benzyloxy)-1-(methoxymethoxy)hex-3-en-2-yl 3-methylbut-3-enoate (**22**; 2.26 g, 6.49 mmol) was dissolved in diethyl ether (100 mL) and the solution was cooled to –78 °C. Lithium bis(trimethylsilyl)amide (1.17 M in tetrahydrofuran; 11.1 mL, 13.0 mmol) was added over 10 min, and then chlorotrimethylsilane (1.64 mL, 13.0 mmol) was added dropwise. The mixture was stirred for 15 min, then it was warmed to –20 °C. The mixture was stirred for an additional 2.5 h, then it was quenched with saturated aqueous NH_4Cl. The mixture was extracted with ethyl acetate (4×), and the combined organic extracts were washed with brine. The resulting organic phase was dried with anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 2:3, then methanol/dichloromethane, 1:9) to give **24** (2.05 g, 90.7%) as a pale yellow oil. This material was obtained as a 38:1 mixture of diastereomers. $[\alpha]_D^{25}$ = +47.4 (*c* = 0.50, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2938, 1731, 1705, 1644, 1454, 1376, 1213, 1150, 1102, 1029, 975, 903 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.36–7.25 (m, 5 H), 5.52 (dt, *J* = 15.4, 6.0 Hz, 1 H), 5.31 (dd, *J* = 15.4, 9.6 Hz, 1 H), 4.93 (s, 1 H), 4.91 (s, 1 H), 4.58 (d, *J* = 6.4 Hz, 1 H), 4.56 (d, *J* = 6.4 Hz, 1 H), 4.51 (d, *J* = 11.9 Hz, 1 H), 4.44 (d, *J* = 11.9 Hz, 1 H), 3.97 (d, *J* = 5.9 Hz, 2 H), 3.52–3.41 (m, 2 H), 3.34 (s, 3 H), 3.03 (d, *J* = 10.6 Hz, 1 H), 2.74 (dddd, *J* = 10.6, 10.2, 9.6, 3.0 Hz, 1 H), 1.94–1.85 (m, 1 H), 1.72 (s, 3 H), 1.56–1.45 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 180.0 (C), 141.0 (C), 138.4 (C), 133.5 (CH), 128.4 (CH), 128.4 (CH), 127.9 (CH), 127.7 (CH), 116.2 (CH_2), 95.0 (CH_2), 72.9 (CH_2), 67.9 (CH_2), 67.2 (CH_2), 58.5 (CH), 55.3 (CH_3), 39.7 (CH), 32.9 (CH_2), 20.0 (CH_3) ppm. HRMS (ESI^+): calcd. for $C_{20}H_{28}NaO_5$ $[M + Na]^+$ 371.1834; found 371.1818.

(2*S*,3*R*,*E*)-3-[2-(Benzyloxy)ethyl]-6-(methoxymethoxy)-2-(prop-1-en-2-yl)hex-4-enamide (25):[125] Di-*tert*-butyl dicarbonate (2.40 g, 11.0 mmol) and pyridine (574 μL, 7.15 mmol) were added to a solution of (2*S*,3*R*,*E*)-3-[2-(benzyloxy)ethyl]-6-(methoxymethoxy)-2-(prop-1-en-2-yl)hex-4-enoic acid (**24**; 1.92 g, 5.51 mmol) in ethyl acetate (19 mL) at room temperature. The mixture was stirred for 3 h, then aqueous ammonia (14 M solution; 983 μL, 13.8 mmol) was added. The mixture was stirred for an additional 2 h, then it was quenched with HCl (1 M aqueous), then neutralized with saturated aqueous $NaHCO_3$. The mixture was extracted with ethyl acetate (5×), and the combined organic extracts were washed with brine. The resulting organic phase was dried with anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 1:1 to 1:0) to give **25** (1.83 g, 95.5%) as a pale yellow oil. $[\alpha]_D^{26}$ = +62.7 (*c* = 0.50, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3330, 3196, 2934, 1669, 1454, 1375, 1211, 1150, 1102, 1030, 974, 920 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.47–7.25 (m, 5 H), 5.57 (br. s, 1 H), 5.52 (dt, *J* = 15.4, 6.0 Hz, 1 H), 5.35 (dd, *J* = 15.4, 9.4 Hz, 1 H), 5.28 (br. s, 1 H), 4.87 (s, 1 H), 4.86 (m, 1 H), 4.58 (d, *J* = 6.4 Hz, 1 H), 4.56 (d, *J* = 6.4 Hz, 1 H), 4.51 (d, *J* = 11.7 Hz, 1 H), 4.44 (d, *J* = 11.7 Hz, 1 H), 3.97 (d, *J* = 6.0 Hz, 2 H), 3.53–3.43 (m, 2 H), 3.34 (s, 3 H), 2.86 (d, *J* = 10.6 Hz, 1 H), 2.77 (dddd, *J* = 10.6, 10.2, 9.4, 3.0 Hz, 1 H), 1.98–1.89 (m, 1 H), 1.69 (s, 3 H), 1.54–1.44 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 174.4 (C), 143.2 (C), 138.6 (C), 134.3 (CH), 128.4 (CH), 127.9 (CH), 127.9 (CH), 127.6 (CH), 115.1 (CH_2), 95.0 (CH_2), 72.9 (CH_2), 68.1 (CH_2), 67.3 (CH_2), 59.6 (CH), 55.2 (CH_3), 39.1 (CH), 33.1 (CH_2), 19.7 (CH_3) ppm. HRMS (ESI^+): calcd. for $C_{20}H_{29}NaNO_4$ $[M + Na]^+$ 370.1994; found 370.1995.

Methyl {(2*S*,3*R*,*E*)-3-[2-(Benzyloxy)ethyl]-6-(methoxymethoxy)-2-(prop-1-en-2-yl)hex-4-en-1-yl}carbamate (27): Aluminium chloride (3.97 g, 29.8 mmol) was added to a stirred suspension of lithium aluminium hydride (3.40 g, 89.6 mmol) in diethyl ether (150 mL) at 0 °C, and the suspension was stirred for 30 min. The supernatant solution was added to a stirred solution of (2*S*,3*R*,*E*)-3-[2-(benzyloxy)ethyl]-6-(methoxymethoxy)-2-(prop-1-en-2-yl)hex-4-enamide (**25**; 1.00 g, 2.88 mmol) in tetrahydrofuran (25 mL) at 0 °C. The solution was stirred for 12 h, then the reaction was quenched with Rochelle salt (30% aqueous solution), and the mixture was stirred for 12 h. The mixture was then extracted with the mixed solvent (methanol/dichloromethane, 1:9; 4×), and the combined organic extracts were washed with Rochelle salt (30% aqueous solution) and brine. The resulting organic phase was dried with anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to give a crude primary amine.

The crude amine was dissolved in dichloromethane (40 mL) and triethylamine (803 μL, 5.78 mmol) and methyl chloroformate (287 μL, 3.74 mmol) were added at 0 °C. The mixture was stirred for 2 h, then it was quenched with water and HCl (3 M aqueous). The mixture was extracted with dichloromethane (3×), and the combined organic extracts were washed with brine. The resulting organic phase was dried with anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 1:4 to 2:3) to give **27** (747 mg, 66.2%) as a colorless oil. $[\alpha]_D^{26}$ = –41.3 (*c* = 0.50, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3346, 2945, 2882, 1726, 1644, 1531, 1454, 1375, 1254, 1150, 1102, 1031, 976, 921 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.37–7.26 (m, 5 H), 5.47 (dt, *J* = 15.3, 5.5 Hz, 1 H), 5.39 (dd, *J* = 15.3, 8.5 Hz, 1 H), 4.89 (s, 1 H), 4.73 (s, 1 H), 4.62 (m, 1 H), 4.59 (d, *J* = 7.1 Hz, 1 H), 4.57 (d, *J* = 7.1 Hz, 1 H), 4.49 (d, *J* = 12.2 Hz, 1 H), 4.43 (d, *J* = 12.2 Hz, 1 H), 3.97 (d, *J* = 5.5 Hz, 2 H), 3.64 (s, 3 H), 3.52–3.43 (m, 2 H), 3.43–3.36 (m, 1 H), 3.36 (s, 3 H), 3.06–2.96 (m, 1 H), 2.35–2.24 (m, 1 H), 2.24–2.13 (m, 1 H), 1.96–1.86 (m, 1 H), 1.62 (s, 3 H), 1.50–1.40 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 156.8 (C), 143.9 (C), 138.5 (C), 134.7 (CH), 128.3 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 114.8 (CH_2), 95.0 (CH_2), 72.9 (CH_2), 67.9 (CH_2), 67.3 (CH_2), 55.1 (CH_3), 51.9 (CH_3), 51.3 (CH), 41.1 (CH_2), 40.3 (CH), 32.2 (CH_2), 19.9 (CH_3) ppm. HRMS (ESI^+): calcd. for $C_{22}H_{33}NaNO_5$ $[M + Na]^+$ 414.2256; found 414.2257.

Methyl {(2*S*,3*R*,*E*)-3-[2-(Benzyloxy)ethyl]-6-hydroxy-2-(prop-1-en-2-yl)hex-4-en-1-yl}carbamate (28): A solution of hydrogen chloride in methanol (5–10%; 10 mL) was added to a flask containing methyl {(2*S*,3*R*,*E*)-3-[2-(benzyloxy)ethyl]-6-(methoxymethoxy)-2-(prop-1-en-2-yl)hex-4-en-1-yl}carbamate (**27**; 747 mg, 1.91 mmol)

at 0 °C. The mixture was stirred for 10 min, then it was warmed to room temperature. The mixture was stirred for an additional 9 h, then it was cooled to 0 °C, and quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with ethyl acetate (3×), and the combined organic extracts were washed with brine. The resulting organic phase was dried with anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 1:2 to 1:0) to give **28** (608 mg, 91.7%) as a pale yellow oil. $[\alpha]_D^{26}$ = –46.2 (*c* = 0.50, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3423, 3342, 2942, 2864, 1704, 1538, 1454, 1366, 1260, 1097, 979, 897 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.37–7.25 (m, 5 H), 5.55 (dt, *J* = 15.2, 5.4 Hz, 1 H), 5.39 (dd, *J* = 15.2, 9.2 Hz, 1 H), 4.89 (s, 1 H), 4.72 (s, 1 H), 4.64 (m, 1 H), 4.50 (d, *J* = 11.9 Hz, 1 H), 4.43 (d, *J* = 11.9 Hz, 1 H), 4.03 (m, 2 H), 3.64 (s, 3 H), 3.55–3.35 (m, 3 H), 3.05–2.95 (m, 1 H), 2.34–2.24 (m, 1 H), 2.22–2.14 (m, 1 H), 1.95–1.85 (m, 1 H), 1.63 (s, 3 H), 1.49–1.38 (m, 1 H), 1.28 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 156.9 (C), 143.9 (C), 138.4 (C), 132.6 (CH), 130.9 (CH), 128.3 (CH), 127.7 (CH), 127.5 (CH), 114.6 (CH_2), 72.8 (CH_2), 67.9 (CH_2), 63.0 (CH_2), 52.0 (CH_3), 51.2 (CH), 41.1 (CH_2), 39.9 (CH), 31.9 (CH_2), 20.3 (CH_3) ppm. HRMS (ESI^+): calcd. for $C_{20}H_{29}NaNO_4$ $[M + Na]^+$ 370.1994; found 370.1990.

Methyl (2*R*,3*S*,4*S*)-3-[2-(Benzyloxy)ethyl]-4-(prop-1-en-2-yl)-2-vinylpyrrolidine-1-carboxylate (29): Bis(acetonitrile)dichloropalladium(II) (1.90 mg, 7.34 μmol) was added to a solution of methyl {(2*S*,3*R*,*E*)-3-[2-(benzyloxy)ethyl]-6-hydroxy-2-(prop-1-en-2-yl)hex-4-en-1-yl}carbamate (**28**; 510 mg, 1.47 mmol) in tetrahydrofuran (10 mL) at 0 °C. The mixture was stirred for 2 h, then it was quenched with water. The mixture was extracted with ethyl acetate (3×), and the combined organic extracts were washed with water and brine. The resulting organic phase was dried with anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 1:4) to give **29** (466 mg, 96.4%) as a colorless oil. $[\alpha]_D^{23}$ = –33.8 (*c* = 0.50, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3084, 2949, 2861, 1704, 1644, 1450, 1382, 1194, 1114 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 60 °C): δ = 7.36–7.24 (m, 5 H), 5.78 (ddd, *J* = 17.0, 10.3, 5.1 Hz, 1 H), 5.10 (m, 2 H), 4.89 (m, 1 H), 4.66 (s, 1 H), 4.50 (d, *J* = 12.4 Hz, 1 H), 4.46 (d, *J* = 12.4 Hz, 1 H), 4.28–4.18 (m, 1 H), 3.68 (s, 3 H), 3.56–3.41 (m, 4 H), 2.92–2.82 (m, 1 H), 2.20–2.13 (m, 1 H), 1.70 (s, 3 H), 1.65–1.53 (m, 1 H), 1.40–1.28 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C; this material was observed as a mixture of two rotamers): δ = 156.0 (C), 155.6 (C), 142.3 (C), 142.1 (C), 138.4 (2 C), 138.2 (CH), 137.7 (CH), 128.3 (2 CH), 127.5 (2 CH), 127.5 (2 CH), 114.7 (CH_2), 114.3 (CH_2), 112.1 (CH_2), 112.0 (CH_2), 73.0 (CH_2), 72.9 (CH_2), 68.5 (CH_2), 68.3 (CH_2), 64.3 (CH), 63.9 (CH), 52.3 (2 CH_3), 47.5 (CH_2), 47.3 (CH_2), 45.4 (CH), 44.5 (CH), 43.1 (CH), 42.0 (CH), 27.2 (2 CH_2), 22.6 (2 CH_3) ppm. HRMS (ESI^+): calcd. for $C_{20}H_{27}NaNO_3$ $[M + Na]^+$ 352.1889; found 352.1881.

Methyl (1*R*,3a*R*,7a*S*)-4-(Iodomethyl)-4-methyl-1-vinylhexahydropyrano[3,4-*c*]pyrrole-2(3*H*)-carboxylate (33): Iodine (200 mg, 0.789 mmol) was added to a solution of methyl (2*R*,3*S*,4*S*)-3-[2-(benzyloxy)ethyl]-4-(prop-1-en-2-yl)-2-vinylpyrrolidine-1-carboxylate (**29**; 173 mg, 0.526 mmol) in dichloromethane (5 mL) at 0 °C. The solution was gradually warmed to room temperature over 4 h, and then the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$. The mixture was extracted with ethyl acetate (3×), and the combined organic extracts were washed with water and brine. The resulting organic phase was dried with anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 3:10) to give **33** (191 mg, 99.6%) as a pale yellow oil. This material was obtained as a mixture of two diastereomers. $[\alpha]_D^{26}$ = 46.1 (*c* = 0.50, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2979, 2949, 2888, 1701, 1451, 1385, 1083 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C; this material was observed as a mixture of two rotamers for each diastereomer): δ = 5.83–5.70 (m, 1 H), 5.18–5.02 (m, 2 H), 4.20–4.16 [m, (1/2)1 H], 4.09–4.04 [m, (1/2)1 H], 3.82–3.41 [m, 2 H + (1/2)1 H], 3.72 [s, (1/2)3 H], 3.68 [s, (1/2)3 H], 3.27 [dd, *J* = 11.0, 2.3 Hz, (1/2)1 H], 3.17 [dd, *J* = 10.1, 6.9 Hz, (1/2)1 H], 3.07 [dd, *J* = 10.1, 9.6 Hz, (1/2)1 H], 2.47–2.27 (m, 1 H), 2.22–2.06 (m, 1 H), 1.61–1.45 (m, 2 H), 1.49 [s, (1/2)2 H], 1.41 [s, (1/4)3 H], 1.41 [s, (1/4)3 H], 1.26 [s, (1/2)2 H], 1.22 [s, (1/4)3 H], 1.21 [s, (1/4) 3 H] ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C; this material was observed as a mixture of two rotamers for each diastereomer): δ = 156.0 (C), 156.0 (C), 155.8 (C), 155.8 (C), 136.8 (CH), 136.7 (CH), 136.2 (CH), 136.2 (CH), 115.1 (CH_2), 115.1 (CH_2), 114.8 (CH_2), 114.8 (CH_2), 71.7 (2 C), 70.6 (2 C), 66.0 (CH), 65.8 (CH), 65.7 (CH), 65.5 (CH), 61.2 (CH_2), 61.1 (CH_2), 59.9 (CH_2), 59.8 (CH_2), 52.5 (2 CH_3), 52.5 (2 CH_3), 46.4 (CH_2), 46.0 (CH_2), 44.6 (CH_2), 44.2 (CH_2), 40.5 (CH), 39.5 (CH), 39.5 (CH), 38.8 (CH), 38.7 (CH), 38.5 (CH), 37.8 (CH), 37.7 (CH), 26.3 (2 CH_3), 26.1 (CH_2), 26.0 (CH_2), 25.4 (CH_2), 25.3 (CH_2), 23.1 (CH_3), 23.1 (CH_3), 15.8 (CH_2), 15.7 (CH_2), 15.0 (CH_2), 14.9 (CH_2) ppm. HRMS (ESI^+): calcd. for $C_{13}H_{20}INaNO_3$ $[M + Na]^+$ 388.0386; found 388.0376.

Methyl (1*S*,3a*R*,7a*S*)-1-(Hydroxymethyl)-4-(iodomethyl)-4-methylhexahydropyrano[3,4-*c*]pyrrole-2(3*H*)-carboxylate (34): Dichloromethane saturated with ozone was added to a solution of methyl (1*R*,3a*R*,7a*S*)-4-(iodomethyl)-4-methyl-1-vinylhexahydropyrano-[3,4-*c*]pyrrole-2(3*H*)-carboxylate (**33**; 119 mg, 0.326 mmol, a mixture of two diastereomers) in methanol (2 mL) at –78 °C. After TLC indicated the complete consumption of starting material, argon was passed through the reaction mixture, and then sodium borohydride (123 mg, 3.26 mmol) was added. Then, the resulting suspension was warmed to 0 °C, and stirred for an additional 30 min. The reaction mixture was quenched with saturated aqueous NH_4Cl. The mixture was extracted with ethyl acetate (3×), and the combined organic extracts were washed with saturated aqueous NH_4Cl and brine. The resulting organic phase was dried with anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 3:1) to give **34** (120 mg, 100%) as a white foam. This material was obtained as a mixture of two diastereomers. $[\alpha]_D^{26}$ = 25.9 (*c* = 0.68, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3437, 2951, 2876, 1686, 1455, 1389, 1081 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C; this material was observed as a mixture of two rotamers for each diastereomer): δ = 3.82–3.40 [m, 4 H + (1/2)1 H], 3.74 (s, 3 H), 3.30 [d, *J* = 11.0 Hz, (1/2)1 H], 3.25–3.00 (m, 2 H), 2.53–2.15 (m, 2 H), 1.67–1.43 (m, 4 H), 1.44 [s, (1/2)3 H], 1.20 [s, (1/2)3 H] ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C; this material was observed as a mixture of two rotamers for each diastereomer): δ = 157.6 (C), 157.4 (C), 156.0 (2 C), 71.6 (2 C), 70.4 (2 C), 66.9 (CH), 66.7 (CH), 65.9 (CH), 65.7 (CH), 64.5 (CH_2), 64.4 (CH_2), 62.9 (2 CH_2), 61.3 (2 CH_2), 60.0 (2 CH_2), 52.9 (2 CH_3), 52.6 (2 CH_3), 46.9 (CH_2), 46.5 (CH_2), 45.0 (CH_2), 44.7 (CH_2), 41.3 (CH), 40.2 (CH), 39.7 (CH), 38.6 (CH), 36.3 (CH), 35.8 (CH), 35.5 (CH), 35.0 (CH), 26.5 (CH_2), 26.3 (CH_2), 26.2 (2 CH_3), 25.7 (CH_2), 25.6 (CH_2), 23.3 (CH_3), 23.1 (CH_3), 15.8 (CH_2), 15.5 (CH_2), 15.3 (CH_2), 15.0 (CH_2) ppm. HRMS (ESI^+): calcd. for $C_{12}H_{20}INaNO_4$ $[M + Na]^+$ 392.0335; found 392.0332.

Methyl (2*S*,3*S*,4*S*)-3-(2-Hydroxyethyl)-2-(hydroxymethyl)-4-(prop-1-en-2-yl)pyrrolidine-1-carboxylate (35): Methyl (1*S*,3a*R*,7a*S*)-1-(hydroxymethyl)-4-(iodomethyl)-4-methylhexahydropyrano[3,4-*c*]-pyrrole-2(3*H*)-carboxylate (**34**; 91.0 mg, 0.246 mmol, a mixture of

two diasteromers) was dissolved in ethanol (0.8 mL), and a suspension of zinc in ethanol (3 mL) was added at 75 °C [the zinc was preliminarily activated with dibromoethane (6 μL) and chlorotrimethylsilane (9 μL) in ethanol suspension at 75 °C]. The mixture was stirred for 5 min, and then acetic acid (300 μL, 5.24 mmol) was added. The mixture was stirred for an additional 2 h at 75 °C, then it was filtered through a Celite pad, and the filter cake was rinsed with methanol. The filtrate was evaporated under reduced pressure to give the crude diol. The crude product was purified by silica gel column chromatography (methanol/dichloromethane, 1:25) to give **35** (56.0 mg, 93.4%) as a pale yellow oil. $[\alpha]_D^{26}$ = –31.6 (*c* = 0.30, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3382, 2950, 2888, 1677, 1460, 1394 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.95 (br. s, 1 H), 4.91 (s, 1 H), 4.66 (s, 1 H), 4.05–3.97 (m, 1 H), 3.85–3.68 (m, 4 H), 3.76 (s, 3 H), 3.55–3.42 (m, 2 H), 2.95–2.85 (m, 1 H), 2.70 (br. s, 1 H), 2.35–2.25 (m, 1 H), 1.74 (s, 3 H), 1.60–1.50 (m, 1 H), 1.44–1.32 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 157.6 (C), 142.1 (C), 112.6 (CH_2), 64.8 (CH_2), 64.4 (CH), 61.0 (CH_2), 53.3 (CH_3), 48.2 (CH_2), 46.0 (CH), 38.8 (CH), 30.0 (CH_2), 22.6 (CH_3) ppm. HRMS (ESI^+): calcd. for $C_{12}H_{21}NaNO_4$ $[M + Na]^+$ 266.1368; found 266.1374.

Kainic Acid (2): Jones reagent[29] (8 N; 84 μL, 0.670 mmol) was added to a solution of methyl (2*S*,3*S*,4*S*)-3-(2-hydroxyethyl)-2-(hydroxymethyl)-4-(prop-1-en-2-yl)pyrrolidine-1-carboxylate (**35**; 16.3 mg, 0.0670 mmol) in acetone at 0 °C. The mixture was stirred for 10 min, then water (160 μL) was added. The mixture was stirred for an additional 20 min, then it was warmed to room temperature. After 90 min, additional Jones reagent (8 N; 42 μL, 0.335 mmol) was added. The mixture was stirred for another 50 min, then water (500 μL) was added, and it was stirred for an additional 40 min. The reaction mixture was quenched with isopropyl alcohol (300 μL), and then it was saturated with NaCl (ca. 230 mg). The aqueous layer was extracted with ethyl acetate (5 ×). The combined organic extracts were evaporated under reduced pressure. The residue was dissolved in NaOH solution (8% aq.; 2 mL), and this solution was washed with diethyl ether (2 ×). The aqueous phase was stirred at 100 °C for 17.5 h, and then cooled to room temperature. The crude suspension was then filtered through two separate columns of ion-exchange resin[30] [Amberlyst A-26 (OH^- form; water, then 5% aqueous HCO_2H) and DOWEX 50WX8 (H^+ form, 200–400 mesh; water, then 3% aqueous NH_3)] to give a pale yellow solid. This material was purified by reverse-phase preparative TLC (methanol/water, 3:97) to give **2** (7.2 mg, 50.4%) as a white solid. m.p. 241–245 °C (decomp.). $[\alpha]_D^{24}$ = –14.4 (*c* = 0.36, H_2O). IR (film): $\tilde{\nu}$ = 3411, 2971, 1624, 1588, 1399, 886 cm^{-1}. ^1H NMR (400 MHz, D_2O, 25 °C): δ = 5.04 (s, 1 H), 4.76 (s, 1 H), 4.10 (d, *J* = 3.2 Hz, 1 H), 3.64 (dd, *J* = 11.9, 7.3 Hz, 1 H), 3.44 (dd, *J* = 11.9, 11.0 Hz, 1 H) 3.12–2.96 (m, 2 H), 2.45 (dd, *J* = 16.5, 6.4 Hz, 1 H), 2.35 (dd, *J* = 16.5, 8.3 Hz, 1 H), 1.77 (s, 3 H) ppm. ^{13}C NMR (100 MHz, D_2O, 25 °C): δ = 180.5 (C), 174.3 (C), 140.9 (C), 113.6 (CH_2), 66.6 (CH), 47.0 (CH_2), 46.5 (CH), 42.6 (CH), 36.8 (CH_2), 22.8 (CH_3) ppm. HRMS (ESI^+): calcd. for $C_{10}H_{15}NaNO_4$ $[M + Na]^+$ 236.0899; found 236.0898.

(*R*,*E*)-6-(Benzyloxy)-1-(methoxymethoxy)hex-3-en-2-yl 2-(2-Methoxyphenyl)acetate (38a): 2-Methoxyphenylacetic acid (**37a**; 1.54 g, 9.28 mmol), *N*,*N*′-dicyclohexylcarbodiimide (2.17 g, 10.5 mmol), and 4-(dimethylamino)pyridine (227 mg, 1.86 mmol) were added to a solution of (*R*,*E*)-6-(benzyloxy)-1-(methoxymethoxy)hex-3-en-2-ol (**20**; 1.65 g, 6.19 mmol) in dichloromethane (80 mL) at 0 °C. The mixture was stirred for 3 h, then it was quenched with saturated aqueous NH_4Cl. The resulting suspension was filtered through a Celite pad, and the filter cake was rinsed with dichloromethane. The filtrate was extracted with dichloromethane (3 ×), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine. The resulting organic phase was dried with anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 1/4) to give **38a** (2.44 g, 95.1%) as a pale red oil. $[\alpha]_D^{26}$ = –19.4 (*c* = 0.50, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2936, 1738, 1603, 1496, 1464, 1249, 1153, 1113, 1030, 969 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.36–7.21 (m, 6 H), 7.17 (dd, *J* = 7.5, 1.6 Hz, 1 H), 6.89 (ddd, *J* = 7.5, 7.2, 0.9 Hz, 1 H), 6.84 (dd, *J* = 8.2, 0.9 Hz, 1 H), 5.78 (dt, *J* = 15.3, 7.2 Hz, 1 H), 5.53 (dd, *J* = 15.3, 6.9 Hz, 1 H), 5.45 (dt, *J* = 6.9, 5.5 Hz, 1 H), 4.59 (d, *J* = 6.6 Hz, 1 H), 4.57 (d, *J* = 6.6 Hz, 1 H), 4.50 (s, 2 H), 3.77 (s, 3 H), 3.65 (s, 2 H), 3.60 (d, *J* = 5.5 Hz, 2 H), 3.49 (t, *J* = 6.9 Hz, 2 H), 3.31 (s, 3 H), 2.36 (dt, *J* = 7.0, 5.3 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 171.1 (C), 157.6 (C), 138.5 (C), 131.6 (CH), 130.9 (CH), 128.6 (CH), 128.5 (CH), 127.7 (CH), 127.7 (CH), 127.0 (CH), 123.2 (C), 120.5 (CH), 110.4 (CH), 96.5 (CH_2), 73.3 (CH), 73.0 (CH_2), 69.5 (CH_2), 69.0 (CH_2), 55.4 (CH_3), 55.3 (CH_3), 36.2 (CH_2), 32.9 (CH_2) ppm. HRMS (ESI^+): calcd. for $C_{24}H_{30}NaO_6$ $[M + Na]^+$ 437.1940; found 437.1956.

(2*S*,3*R*,*E*)-3-[2-(Benzyloxy)ethyl]-6-(methoxymethoxy)-2-(2-methoxyphenyl)hex-4-enoic Acid (39a): (*R*,*E*)-6-(Benzyloxy)-1-(methoxymethoxy)hex-3-en-2-yl 2-(2-methoxyphenyl)acetate (**38a**; 2.43 g, 5.86 mmol) was dissolved in diethyl ether (75 mL), and the solution was cooled to –78 °C. Lithium bis(trimethylsilyl)amide (1.17 M in tetrahydrofuran; 10.0 mL, 11.7 mmol) was added over 15 min, and then chlorotrimethylsilane (1.48 mL, 11.7 mmol) was added dropwise. The mixture was stirred for 15 min, then it was warmed to –20 °C. The mixture was stirred for another 2.5 h, then it was quenched with saturated aqueous NH_4Cl. The mixture was extracted with ethyl acetate (4 ×), and the combined organic extracts were washed with brine. The resulting organic phase was dried with anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 2:1) to give **39a** (2.10 g, 86.3%) as a pale yellow oil. This material was obtained as a 33:1 mixture of diastereomers. $[\alpha]_D^{26}$ = +19.2 (*c* = 0.50, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2940, 1731, 1705, 1599, 1494, 1464, 1246, 1149, 1103, 1029 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.37–7.16 (m, 6 H), 7.19 (dd, *J* = 8.2, 7.4 Hz, 1 H), 6.89 (dd, *J* = 7.4, 7.3 Hz, 1 H), 6.82 (d, *J* = 8.2 Hz, 1 H), 5.30 (d, *J* = 15.6 Hz, 1 H), 5.25 (d, *J* = 15.6 Hz, 1 H), 4.50 (d, *J* = 11.9 Hz, 1 H), 4.43 (d, *J* = 11.9 Hz, 1 H), 4.30 (d, *J* = 6.2 Hz, 1 H), 4.23 (d, *J* = 6.2 Hz, 1 H), 4.17 (d, *J* = 9.6 Hz, 1 H), 3.83–3.74 (m, 2 H), 3.79 (s, 3 H), 3.54–3.43 (m, 2 H), 3.23 (s, 3 H), 3.01–2.89 (m, 1 H), 2.07–1.97 (m, 1 H), 1.67–1.56 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 178.2 (C), 157.1 (C), 138.6 (C), 134.1 (CH), 129.3 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 127.9 (CH), 127.6 (CH), 125.7 (C), 120.8 (CH), 110.9 (CH), 94.5 (CH_2), 72.9 (CH_2), 68.3 (CH_2), 67.0 (CH_2), 55.7 (CH_3), 55.2 (CH_3), 47.8 (CH), 42.4 (CH), 33.1 (CH_2) ppm. HRMS (ESI^+): calcd. for $C_{24}H_{30}NaO_6$ $[M + Na]^+$ 437.1940; found 437.1935.

(2*S*,3*R*,*E*)-3-[2-(Benzyloxy)ethyl]-6-(methoxymethoxy)-2-(2-methoxyphenyl)hex-4-enamide (40a): Di-*tert*-butyl dicarbonate (1.52 g, 6.96 mmol) and pyridine (483 μL, 6.01 mmol) were added to a solution of (2*S*,3*R*,*E*)-3-[2-(benzyloxy)ethyl]-6-(methoxymethoxy)-2-(2-methoxyphenyl)hex-4-enoic acid (**39a**; 1.92 g, 4.63 mmol) in ethyl acetate (20 mL) at room temperature. The mixture was stirred for 3.5 h, then aqueous ammonia (14 M solution; 728 μL, 10.2 mmol) was added. The mixture was stirred for an additional 1 h, then it was quenched with HCl (1 M aqueous), and then neutralized with saturated aqueous $NaHCO_3$. The mixture was extracted with ethyl acetate (5 ×), and the combined organic extracts were washed with

saturated aqueous NH_4Cl and brine. The resulting organic phase was dried with anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 1:1 to 2:1) to give **40a** (1.79 g, 93.4%) as a pale yellow oil. $[\alpha]_D^{26}$ = +41.8 (*c* = 0.50, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2939, 2868, 1680, 1491, 1244, 1102 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.38–7.21 (m, 6 H), 7.17 (ddd, *J* = 8.2, 7.4, 1.8 Hz, 1 H), 6.91 (ddd, *J* = 7.7, 7.4, 0.9 Hz, 1 H), 6.84 (dd, *J* = 8.2, 0.9 Hz, 1 H), 5.76 (br. s, 1 H), 5.33 (dt, *J* = 15.1, 6.0 Hz, 1 H), 5.25 (dd, *J* = 15.1, 9.2 Hz, 1 H), 5.19 (br. s, 1 H), 4.52 (d, *J* = 11.9 Hz, 1 H), 4.46 (d, *J* = 11.9 Hz, 1 H), 4.28 (d, *J* = 6.4 Hz, 1 H), 4.20 (d, *J* = 6.4 Hz, 1 H), 3.95 (d, *J* = 10.5 Hz, 1 H), 3.83 (s, 3 H), 3.78 (m, 2 H), 3.57–3.49 (m, 2 H), 3.22 (s, 3 H), 3.16–3.06 (m, 1 H), 2.12–2.03 (m, 1 H), 1.67–1.55 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 175.2 (C), 156.7 (C), 138.7 (C), 134.8 (CH), 129.5 (CH), 128.4 (CH), 128.2 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 126.6 (C), 121.1 (CH), 110.6 (CH), 94.4 (CH_2), 72.9 (CH_2), 68.4 (CH_2), 67.1 (CH_2), 55.6 (CH_3), 55.2 (CH_3), 48.9 (CH), 41.1 (CH), 33.2 (CH_2) ppm. HRMS (ESI^+): calcd. for $C_{24}H_{31}NaNO_5$ $[M + Na]^+$ 436.2100; found 436. 2082.

Methyl {(2*S*,3*R*,*E*)-3-[2-(Benzyloxy)ethyl]-6-(methoxymethoxy)-2-(2-methoxyphenyl)hex-4-en-1-yl}carbamate (42a): Aluminium chloride (5.74 g, 43.1 mmol) was added to a stirred suspension of lithium aluminium hydride (4.98 g, 131 mmol) in diethyl ether (450 mL) at 0 °C, and the resulting suspension was stirred for 30 min. The supernatant solution was added to a stirred solution of (2*S*,3*R*,*E*)-3-[2-(benzyloxy)ethyl]-6-(methoxymethoxy)-2-(2-methoxyphenyl)hex-4-enamide (**40a**; 1.78 g, 4.31 mmol) in tetrahydrofuran (70 mL) at 0 °C. The solution was stirred for 21 h, then the reaction was quenched with Rochelle salt (30% aqueous solution), and the mixture was stirred for 8 h. The mixture was extracted with ethyl acetate (5×), then with the mixed solvent (methanol/dichloromethane, 1:9; 3×), and the combined organic extracts were washed with Rochelle salt (30% aqueous solution) and brine. The resulting organic phase was dried with anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to give a crude primary amine.

The crude amine was dissolved in dichloromethane (50 mL) and triethylamine (1.20 mL, 8.61 mmol) and methyl chloroformate (562 µL, 7.32 mmol) were added at 0 °C. The mixture was stirred for 1 h, then it was quenched with saturated aqueous NH_4Cl. The mixture was extracted with ethyl acetate (3×), and the combined organic extracts were washed with Rochelle salt (30% aqueous solution) and brine. The resulting organic phase was dried with anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 1:4 to 1:2) to give **42a** (1.37 g, 69.5%) as a colorless oil. $[\alpha]_D^{26}$ = –61.2 (*c* = 0.50, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3341, 2942, 2882, 1725, 1523, 1494, 1456, 1244, 1102, 1030 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.37–7.26 (m, 5 H), 7.18 (ddd, *J* = 8.3, 7.3, 1.4 Hz, 1 H), 7.04 (dd, *J* = 7.3, 1.4 Hz, 1 H), 6.89 (dd, *J* = 7.3, 7.3 Hz, 1 H), 6.84 (d, *J* = 8.3 Hz, 1 H), 5.42 (dt, *J* = 15.2, 5.7 Hz, 1 H), 5.31 (dd, *J* = 15.2, 9.4 Hz, 1 H), 4.49 (m, 1 H), 4.47 (d, *J* = 11.9 Hz, 1 H), 4.45 (d, *J* = 6.9 Hz, 1 H), 4.41 (d, *J* = 11.9 Hz, 1 H), 4.40 (d, *J* = 6.9 Hz, 1 H), 3.90 (d, *J* = 5.7 Hz, 2 H), 3.77 (s, 3 H), 3.70–3.55 (m, 1 H), 3.59 (s, 3 H), 3.49–3.32 (m, 4 H), 3.30 (s, 3 H), 2.64–2.55 (m, 1 H), 1.99–1.89 (m, 1 H), 1.44–1.32 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 158.1 (C), 157.0 (C), 138.7 (C), 135.0 (CH), 129.1 (CH), 128.4 (CH), 128.3 (C), 128.0 (CH), 127.8 (CH), 127.8 (CH), 127.6 (CH), 120.5 (CH), 110.8 (CH), 94.9 (CH_2), 73.0 (CH_2), 68.4 (CH_2), 67.4 (CH_2), 55.3 (CH_3), 55.2 (CH_3), 52.0 (CH_3), 43.2 (CH_2), 42.1 (CH), 41.9 (CH), 32.2 (CH_2) ppm. HRMS (ESI^+): calcd. for $C_{26}H_{35}NaNO_6$ $[M + Na]^+$ 480.2362; found 480. 2384.

Methyl {(2*S*,3*R*,*E*)-3-[2-(Benzyloxy)ethyl]-6-hydroxy-2-(2-methoxyphenyl)hex-4-en-1-yl}carbamate (43a): A solution of hydrogen chloride in methanol [prepared from acetyl chloride (4 mL) and methanol (25 mL)] was added to a flask containing methyl {(2*S*,3*R*,*E*)-3-[2-(benzyloxy)ethyl]-6-(methoxymethoxy)-2-(2-methoxyphenyl)hex-4-en-1-yl}carbamate (**42a**; 1.32 g, 2.88 mmol) at 0 °C. The mixture was gradually warmed to room temperature over 1.5 h. The mixture was stirred for an additional 6.5 h, then it was cooled to 0 °C, and quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with ethyl acetate (4×), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine. The resulting organic phase was dried with anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 1:2 to 4:1) to give **43a** (1.06 g, 88.9%) as a colorless oil. $[\alpha]_D^{26}$ = –61.7 (*c* = 0.50, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3414, 2941, 2863, 1703, 1526, 1493, 1456, 1244 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.37–7.25 (m, 5 H), 7.19 (dd, *J* = 8.2, 7.4 Hz, 1 H), 7.05 (d, *J* = 7.2 Hz, 1 H), 6.90 (dd, *J* = 7.4, 7.2 Hz, 1 H), 6.84 (d, *J* = 8.2 Hz, 1 H), 5.48 (dt, *J* = 15.2, 6.0 Hz, 1 H), 5.31 (dd, *J* = 15.2, 9.4 Hz, 1 H), 4.52 (m, 1 H), 4.47 (d, *J* = 12.1 Hz, 1 H), 4.40 (d, *J* = 12.1 Hz, 1 H), 3.96–3.89 (m, 2 H), 3.78 (s, 3 H), 3.76–3.63 (m, 1 H), 3.60 (s, 3 H), 3.47–3.40 (m, 1 H), 3.40–3.30 (m, 3 H), 2.61–2.53 (m, 1 H), 2.00–1.89 (m, 1 H), 1.43–1.32 (m, 1 H), 1.05 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 158.0 (C), 157.1 (C), 138.6 (C), 133.4 (CH), 131.3 (CH), 129.1 (CH), 128.4 (CH), 128.3 (C), 127.8 (CH), 127.8 (CH), 127.6 (CH), 120.5 (CH), 110.7 (CH), 72.9 (CH_2), 68.3 (CH_2), 63.4 (CH_2), 55.3 (CH_3), 52.0 (CH_3), 42.9 (CH_2), 42.1 (CH), 41.7 (CH), 32.0 (CH_2) ppm. HRMS (ESI^+): calcd. for $C_{24}H_{31}NaNO_5$ $[M + Na]^+$ 436.2100; found 436.2108.

Methyl (2*R*,3*S*,4*S*)-3-[2-(Benzyloxy)ethyl]-4-(2-methoxyphenyl)-2-vinylpyrrolidine-1-carboxylate (44a): Bis(acetonitrile)dichloropalladium(II) (3.11 mg, 0.0120 mmol) was added to a solution of methyl {(2*S*,3*R*,*E*)-3-[2-(benzyloxy)ethyl]-6-hydroxy-2-(2-methoxyphenyl)hex-4-en-1-yl}carbamate (**43a**; 990 mg, 2.39 mmol) in tetrahydrofuran (20 mL) at 0 °C. The mixture was stirred for 1.5 h, then it was quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with ethyl acetate (3×), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine. The resulting organic phase was dried with anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 1:9 to 1:4) to give **44a** (870 mg, 91.9%) as a colorless oil. $[\alpha]_D^{26}$ = –53.1 (*c* = 0.50, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2951, 2862, 1699, 1601, 1585, 1495, 1449, 1385, 1245, 1120, 1029, 919 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 60 °C): δ = 7.33–7.23 (m, 5 H), 7.20 (dd, *J* = 7.7, 7.4 Hz, 1 H), 7.05 (d, *J* = 7.4 Hz, 1 H), 6.89 (dd, *J* = 7.8, 7.7 Hz, 1 H), 6.83 (d, *J* = 7.8 Hz, 1 H), 5.88 (ddd, *J* = 16.8, 10.6, 6.1 Hz, 1 H), 5.16 (d, *J* = 16.8 Hz, 1 H), 5.14 (d, *J* = 10.6 Hz, 1 H), 4.36 (s, 2 H), 4.27–4.21 (m, 1 H), 3.90 (m, 1 H), 3.85–3.66 (m, 2 H), 3.75 (s, 3 H), 3.71 (s, 3 H), 3.36 (t, *J* = 6.6 Hz, 2 H), 2.54–2.46 (m, 1 H), 1.45–1.24 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C; this material was observed as a mixture of two rotamers): δ = 157.4 (2 C), 156.2 (C), 155.7 (C), 138.6 (CH), 138.5 (2 C), 138.1 (CH), 128.4 (2 CH), 127.8 (2 CH), 127.7 (2 CH), 127.7 (2 CH), 127.6 (2 CH), 127.3 (C), 127.0 (C), 120.1 (2 CH), 115.2 (CH_2), 114.5 (CH_2), 110.3 (2 CH), 72.8 (2 CH_2), 68.9 (CH_2), 68.6 (CH_2), 64.7 (CH), 64.3 (CH_2), 55.3 (2 CH_3), 52.4 (2 CH_3), 49.0 (CH_2), 48.8 (CH_2), 44.1 (CH), 43.3 (CH), 38.1 (CH), 37.5 (CH),

27.9 (2 CH_2) ppm. HRMS (ESI$^+$): calcd. for $C_{24}H_{29}NaNO_4$ [M + Na]$^+$ 418.1994; found 418.1988.

Methyl (2*S*,3*S*,4*S*)-3-[2-(Benzyloxy)ethyl]-2-(hydroxymethyl)-4-(2-methoxyphenyl)pyrrolidine-1-carboxylate (45a): Dichloromethane saturated with ozone was added to a solution of methyl (2*R*,3*S*,4*S*)-3-[2-(benzyloxy)ethyl]-4-(2-methoxyphenyl)-2-vinylpyrrolidine-1-carboxylate (**44a**; 143 mg, 0.362 mmol) in methanol (1 mL) at –78 °C. After TLC indicated the complete consumption of the starting material, argon was passed through the reaction mixture, and then sodium borohydride (137 mg, 3.62 mmol) was added. The resulting suspension was warmed to 0 °C, and then stirred for an additional 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl. The mixture was extracted with dichloromethane (3×), and the combined organic extracts were washed with saturated aqueous NH_4Cl and brine. The resulting organic phase was dried with anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 1:1) to give **45a** (131 mg, 90.3%) as a colorless oil. $[\alpha]_D^{26}$ = –47.8 (*c* = 1.39, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3446, 2951, 2873, 1683, 1495, 1456, 1389, 1241, 1122 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.35–7.25 (m, 5 H), 7.22 (dd, *J* = 7.3, 7.3 Hz, 1 H), 6.98 (d, *J* = 7.3 Hz, 1 H), 6.90 (dd, *J* = 7.8, 7.3 Hz, 1 H), 6.84 (d, *J* = 7.8 Hz, 1 H), 4.40 (s, 2 H), 4.33 (m, 1 H), 3.96–3.70 (m, 5 H), 3.76 (s, 3 H), 3.76 (s, 3 H), 3.67 (dd, *J* = 10.6, 7.4 Hz, 1 H), 3.43–3.33 (m, 2 H), 2.48–2.37 (m, 1 H), 1.46–1.22 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 158.1 (C), 157.3 (C), 138.4 (C), 128.5 (CH), 128.0 (CH), 127.8 (CH), 127.8 (CH), 127.7 (C), 127.7 (CH), 120.8 (CH), 110.4 (CH), 73.0 (CH_2), 68.5 (CH_2), 67.3 (CH_2), 65.6 (CH), 55.3 (CH_3), 53.1 (CH_3), 50.7 (CH_2), 40.9 (CH), 38.3 (CH), 28.6 (CH_2) ppm. HRMS (ESI$^+$): calcd. for $C_{23}H_{29}NaNO_5$ [M + Na]$^+$ 422.1943; found 422.1932.

Methyl (2*S*,3*S*,4*S*)-3-(2-Hydroxyethyl)-2-(hydroxymethyl)-4-(2-methoxyphenyl)pyrrolidine-1-carboxylate (46a): Palladium hydroxide (20% on carbon; wetted with ca. 50% water; 12.6 mg, 9.03 μmol) was added to a solution of methyl (2*S*,3*S*,4*S*)-3-[2-(benzyloxy)ethyl]-2-(hydroxymethyl)-4-(2-methoxyphenyl) pyrrolidine-1-carboxylate (**45a**; 120 mg, 0.301 mmol) in methanol (10 mL). The flask was charged with hydrogen gas (1 atm) at room temperature. The mixture was stirred for 1.5 h at room temperature, then it was filtered through a Celite pad, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 7:3, then methanol/dichloromethane, 1:9) to give **46a** (85.9 mg, 92.2%) as a pale yellow oil. $[\alpha]_D^{26}$ = –79.1 (*c* = 0.63, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3402, 2952, 1679, 1494, 1461, 1391, 1244, 1123, 1051 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.24 (dd, *J* = 7.6, 7.6 Hz, 1 H), 7.00 (d, *J* = 7.6 Hz, 1 H), 6.92 (dd, *J* = 7.6, 7.6 Hz, 1 H), 6.88 (d, *J* = 7.6 Hz, 1 H), 4.30 (m, 1 H), 3.96–3.73 (m, 5 H), 3.83 (s, 3 H), 3.77 (s, 3 H), 3.69 (dd, *J* = 10.6, 6.9 Hz, 1 H), 3.64–3.52 (m, 2 H), 2.48–2.38 (m, 1 H), 1.55 (br. s, 1 H), 1.40–1.17 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 157.7 (C), 157.2 (C), 128.1 (CH), 127.6 (CH), 127.6 (C), 120.8 (CH), 110.5 (CH), 66.2 (CH_2), 65.2 (CH), 61.0 (CH_2), 55.5 (CH_3), 53.0 (CH_3), 50.5 (CH_2), 40.7 (CH), 38.3 (CH), 31.3 (CH_2) ppm. HRMS (ESI$^+$): calcd. for $C_{16}H_{23}NaNO_5$ [M + Na]$^+$ 332.1474; found 332.1466.

MFPA (6): A solution of methyl (2*S*,3*S*,4*S*)-3-(2-hydroxyethyl)-2-(hydroxymethyl)-4-(2-methoxyphenyl) pyrrolidine-1-carboxylate (**46a**; 57.0 mg, 0.184 mmol) in acetone (2 mL) was added dropwise to a solution of Jones reagent (8 N; 230 μL, 1.84 mmol) in acetone (0.5 mL) at 0 °C. The mixture was stirred for 10 min, then it was warmed to room temperature, and water (30 μL) was added. The mixture was stirred for 1.5 h, then it was quenched with isopropyl alcohol (300 μL). The mixture was extracted with diethyl ether (5×), and the combined organic extracts were evaporated under reduced pressure. The residue was dissolved in NaOH solution (8% aq.; 5 mL), and this solution was washed with diethyl ether (2×). The aqueous phase was stirred at 100 °C for 5 h, and then cooled to room temperature. The crude suspension was then filtered through two separate columns of ion-exchange resin [Amberlyst A-26 (OH^- form; water, then 5% aqueous HCO_2H) and DOWEX 50WX8 (H^+ form, 200–400 mesh; water, then 3% aqueous NH_3)] to give a pale yellow solid. This material was purified by reverse-phase silica gel column chromatography (only water to methanol/water, 1:4) to give **6** (24.5 mg, 47.6%) as a white solid. m.p. 230–232 °C (decomp.). $[\alpha]_D^{23}$ = +5.94 (*c* = 1.05, H_2O). IR (film): $\tilde{\nu}$ = 3415, 3066, 1623, 1584, 1396, 1248 cm^{-1}. ^{1}H NMR (400 MHz, D_2O, 25 °C): δ = 7.38 (dd, *J* = 7.8, 7.8 Hz, 1 H), 7.12 (d, *J* = 7.8 Hz, 1 H), 7.08 (d, *J* = 8.2 Hz, 1 H), 7.00 (dd, *J* = 7.3, 7.3 Hz, 1 H), 4.08 (d, *J* = 7.4 Hz, 1 H), 3.96 (ddd, *J* = 8.3, 8.0, 8.0 Hz, 1 H), 3.87 (s, 3 H), 3.83 (dd, *J* = 12.2, 8.0 Hz, 1 H), 3.74 (dd, *J* = 12.2, 8.0 Hz, 1 H), 3.19–3.11 (m, 1 H), 2.36 (dd, *J* = 16.0, 5.5 Hz, 1 H), 1.90 (dd, *J* = 16.0, 9.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, D_2O, 25 °C): δ = 179.4 (C), 174.5 (C), 157.9 (C), 130.5 (CH), 129.9 (CH), 125.1 (C), 121.4 (CH), 111.9 (CH), 66.3 (CH), 55.9 (CH_3), 48.5 (CH_2), 43.7 (CH), 42.2 (CH), 36.9 (CH_2) ppm. HRMS (ESI$^+$): calcd. for $C_{14}H_{17}NaNO_5$ [M + Na]$^+$ 302.1004; found 302.1014.

(*R*,*E*)-6-(Benzyloxy)-1-(methoxymethoxy)hex-3-en-2-yl 2-Cyclopropylacetate (38b): Cyclopropylacetic acid (**37b**; 439 mg, 4.39 mmol), *N*,*N*′-dicyclohexylcarbodiimide (969 mg, 4.698 mmol), and 4-(dimethylamino)pyridine (115 mg, 0.940 mmol) were added to a solution of (*R*,*E*)-6-(benzyloxy)-1-(methoxymethoxy)hex-3-en-2-ol (**20**; 834 mg, 3.13 mmol) in dichloromethane (40 mL) at 0 °C. The mixture was stirred for 7.5 h, then it was quenched with saturated aqueous NH_4Cl. The resulting suspension was filtered through a Celite pad, and the filter cake was rinsed with dichloromethane. The filtrate was extracted with dichloromethane (3×), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine. The resulting organic phase was dried with anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 1:9 to 1:4) to give **38b** (1.04 g, 95.4%) as a colorless oil. $[\alpha]_D^{24}$ = –20.9 (*c* = 0.50, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2934, 2881, 2855, 1953, 1112, 1038 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.38–7.24 (m, 5 H), 5.84 (dt, *J* = 15.6, 6.6 Hz, 1 H), 5.55 (dd, *J* = 15.6, 6.8 Hz, 1 H), 5.46 (dt, *J* = 6.8, 5.3 Hz, 1 H), 4.64 (d, *J* = 6.4 Hz, 1 H), 4.62 (d, *J* = 6.4 Hz, 1 H), 4.50 (s, 2 H), 3.62 (m, 2 H), 3.51 (t, *J* = 6.6 Hz, 2 H), 3.35 (s, 3 H), 2.38 (dt, *J* = 6.6, 6.6 Hz, 2 H), 2.24 (d, *J* = 7.3 Hz, 2 H), 1.10–1.00 (m, 1 H), 0.56–0.50 (m, 2 H), 0.18–0.12 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 172.5 (C), 138.4 (C), 131.8 (CH), 128.5 (CH), 127.7 (CH), 127.7 (CH), 127.0 (CH), 96.5 (CH_2), 73.0 (CH), 73.0 (CH_2), 69.5 (CH_2), 69.1 (CH_2), 55.4 (CH_3), 39.6 (CH_2), 32.9 (CH_2), 7.0 (CH), 4.5 (CH_2), 4.4 (CH_2) ppm. HRMS (ESI$^+$): calcd. for $C_{20}H_{28}NaO_5$ [M + Na]$^+$ 371.1834; found 371.1827.

(2*R*,3*R*,*E*)-3-[2-(Benzyloxy)ethyl]-2-cyclopropyl-6-(methoxymethoxy)hex-4-enoic Acid (39b): (*R*,*E*)-6-(Benzyloxy)-1-(methoxymethoxy)hex-3-en-2-yl 2-cyclopropylacetate (**38b**; 1.02 g, 2.91 mmol) was dissolved in diethyl ether (35 mL), and the solution was cooled to –78 °C. Lithium bis(trimethylsilyl)amide (1.17 M in tetrahydrofuran; 5.28 mL, 6.17 mmol) was added over 10 min, and then chlorotrimethylsilane (780 μL, 6.17 mmol) was added dropwise. The mixture was stirred for 10 min, then it was warmed to 0 °C. The mixture was stirred for another 4.5 h, and then it was quenched with saturated aqueous NH_4Cl. The mixture was ex-

tracted with ethyl acetate (4 ×), and the combined organic extracts were washed with brine. The resulting organic phase was dried with anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (two separate columns: methanol/dichloromethane, 1:99 to 1:9, then ethyl acetate/hexane, 1:2 to 1:0) to give **39b** (949 mg, 93.4%) as a pale yellow oil. This material was obtained as a 17:1 mixture of diastereomers. $[\alpha]_D^{24}$ = –1.39 (*c* = 0.50, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3070, 2936, 1731, 1704, 1454, 1366, 1104 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.37–7.26 (m, 5 H), 5.61 (dt, *J* = 15.6, 5.5 Hz, 1 H), 5.53 (dd, *J* = 15.6, 9.2 Hz, 1 H), 4.62 (d, *J* = 6.4 Hz, 1 H), 4.60 (d, *J* = 6.4 Hz, 1 H), 4.50 (d, *J* = 11.9 Hz, 1 H), 4.44 (d, *J* = 11.9 Hz, 1 H), 4.02 (d, *J* = 5.5 Hz, 2 H), 3.54–3.40 (m, 2 H), 3.36 (s, 3 H), 2.78–2.67 (m, 1 H), 1.95–1.85 (m, 1 H), 1.70–1.58 (m, 1 H), 1.62 (dd, *J* = 10.1, 7.8 Hz, 1 H), 0.96–0.86 (m, 1 H), 0.65–0.55 (m, 1 H), 0.55–0.45 (m, 1 H), 0.27–0.20 (m, 1 H), 0.20–0.13 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 180.4 (C), 138.4 (C), 134.2 (CH), 128.6 (CH), 128.4 (CH), 127.9 (CH), 127.7 (CH), 95.3 (CH_2), 73.0 (CH_2), 68.2 (CH_2), 67.5 (CH_2), 55.5 (CH), 55.3 (CH_3), 42.7 (CH), 32.6 (CH_2), 11.7 (CH), 6.5 (CH_2), 2.9 (CH_2) ppm. HRMS (ESI^+): calcd. for $C_{20}H_{28}NaO_5$ $[M + Na]^+$ 371.1834; found 371.1852.

(2*R*,3*R*,*E*)-3-[2-(Benzyloxy)ethyl]-2-cyclopropyl-6-(methoxymethoxy)hex-4-enamide (40b): Di-*tert*-butyl dicarbonate (1.10 g, 5.03 mmol) and pyridine (242 μL, 3.02 mmol) were added to a solution of (2*R*,3*R*,*E*)-3-[2-(benzyloxy)ethyl]-2-cyclopropyl-6-(methoxymethoxy)hex-4-enoic acid (**39b**; 876 mg, 2.51 mmol) in ethyl acetate (10 mL) at room temperature. The mixture was stirred for 3.5 h, then aqueous ammonia (14 M solution; 359 μL, 5.03 mmol) was added. The mixture was stirred for another 1.5 h, then additional aqueous ammonia (14 M solution; 180 μL, 2.52 mmol) was added. The mixture was stirred for 2.5 h, thn the reaction mixture was quenched with saturated aqueous NH_4Cl, and then neutralized with saturated aqueous $NaHCO_3$. The mixture was extracted with ethyl acetate (4 ×), and the combined organic extracts were washed with brine. The resulting organic phase was dried with anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 1:2 to 1:0) to give **40b** (778 mg, 89.1%) as a white solid. m.p. 80.5–82.3 °C. $[\alpha]_D^{25}$ = +6.84 (*c* = 0.50, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3378, 3187, 2930, 2895, 2865, 1652, 1118 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.37–7.25 (m, 5 H), 5.74 (br. s, 1 H), 5.68–5.56 (m, 2 H), 5.41 (br. s, 1 H), 4.62 (d, *J* = 6.2 Hz, 1 H), 4.60 (d, *J* = 6.2 Hz, 1 H), 4.49 (d, *J* = 11.9 Hz, 1 H), 4.44 (d, *J* = 11.9 Hz,1 H), 4.02 (d, *J* = 4.2 Hz, 2 H), 3.55–3.39 (m, 2 H), 3.35 (s, 3 H), 2.80–2.73 (m, 1 H), 1.94–1.85 (m, 1 H), 1.78–1.67 (m, 1 H), 1.49 (dd, *J* = 10.1, 6.4 Hz, 1 H), 0.92–0.82 (m, 1 H), 0.68–0.60 (m, 1 H), 0.57–0.47 (m, 1 H), 0.27–0.13 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 176.9 (C), 138.5 (C), 134.4 (CH), 128.4 (CH), 127.8 (CH), 127.8 (CH), 127.6 (CH), 95.4 (CH_2), 73.0 (CH_2), 68.4 (CH_2), 67.7 (CH_2), 56.4 (CH), 55.3 (CH_3), 42.6 (CH), 32.6 (CH_2), 11.2 (CH), 6.6 (CH_2), 3.1 (CH_2) ppm. HRMS (ESI^+): calcd. for $C_{20}H_{29}NaNO_4$ $[M + Na]^+$ 370.1994; found 370.1991.

Methyl {(2*R*,3*R*,*E*)-3-[2-(Benzyloxy)ethyl]-2-cyclopropyl-6-(methoxymethoxy)hex-4-en-1-yl}carbamate (42b): Aluminium chloride (2.00 g, 15.0 mmol) was added to a stirred suspension of lithium aluminium hydride (1.74 g, 45.8 mmol) in diethyl ether (250 mL) at 0 °C, and the suspension was stirred for 70 min. The supernatant solution was added to a stirred solution of (2*R*,3*R*,*E*)-3-[2-(benzyloxy)ethyl]-2-cyclopropyl-6-(methoxymethoxy)hex-4-enamide (**40b**; 748 mg, 2.15 mmol) in tetrahydrofuran (30 mL) at 0 °C. The solution was stirred for 16.5 h, then the reaction was quenched with ammonia (7 N aqueous), and the mixture was stirred for 6 h. The mixture was extracted with the mixed solvent (methanol/dichloromethane, 1:9; 5 ×), and the combined organic extracts were washed with Rochelle salt (30% aqueous solution) and brine. The resulting organic phase was dried with anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to give a crude primary amine.

The crude amine was dissolved in dichloromethane (20 mL), and triethylamine (600 μL, 4.31 mmol) and methyl chloroformate (281 μL, 3.66 mmol) were added at 0 °C. The mixture was stirred for 100 min, then the mixture was quenched with saturated aqueous NH_4Cl. The mixture was extracted with dichloromethane (4 ×), and the combined organic extracts were washed with brine. The resulting organic phase was dried with anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 1:4 to 1:2) to give **42b** (635 mg, 75.3%) as a colorless oil. $[\alpha]_D^{25}$ = –10.6 (*c* = 0.53, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3347, 2940, 2879, 1726, 1531, 1258, 1103, 1030 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.37–7.25 (m, 5 H), 5.63, (dd, *J* = 15.6, 9.2 Hz, 1 H), 5.54 (dt, *J* = 15.6, 5.5 Hz, 1 H), 4.84 (m, 1 H), 4.62 (s, 2 H), 4.50 (d, *J* = 11.9 Hz, 1 H), 4.44 (d, *J* = 11.9 Hz, 1 H), 4.02 (d, *J* = 5.5 Hz, 2 H), 3.65 (s, 3 H), 3.50–3.35 (m, 2 H), 3.36 (s, 3 H), 3.28–3.13 (m, 2 H), 2.44–2.36 (m, 1 H), 1.84–1.76 (m, 2 H), 0.87–0.77 (m, 1 H), 0.58–0.40 (m, 3 H), 0.23–0.15 (m, 1 H), 0.15–0.05 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 157.1 (C), 138.6 (C), 134.5 (CH), 128.6 (CH), 128.4 (CH), 127.8 (CH), 127.6 (CH), 95.5 (CH_2), 73.1 (CH_2), 68.7 (CH_2), 67.8 (CH_2), 55.3 (CH_3), 52.1 (CH_3), 48.1 (CH), 44.5 (CH_2), 41.8 (CH), 32.8 (CH_2), 10.6 (CH), 4.8 (CH_2), 2.9 (CH_2) ppm. HRMS (ESI^+): calcd. for $C_{22}H_{33}NaNO_5$ $[M + Na]^+$ 414.2256; found 414.2243.

Methyl {(2*R*,3*R*,*E*)-3-[2-(Benzyloxy)ethyl]-2-cyclopropyl-6-hydroxyhex-4-en-1-yl}carbamate (43b): A solution of hydrogen chloride in methanol [prepared from acetyl chloride (3 mL) and methanol (15 mL)] was added to a flask containing methyl {(2*R*,3*R*,*E*)-3-[2-(benzyloxy)ethyl]-2-cyclopropyl-6-(methoxymethoxy)hex-4-en-1-yl}carbamate (**42b**; 604 mg, 1.54 mmol) at 0 °C. The mixture was gradually warmed to room temperature over 2 h. The mixture was stirred for an additional 5 h, then it was cooled to 0 °C and quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with ethyl acetate (3 ×), then the aqueous layer was saturated with NaCl, and then extracted again with ethyl acetate (2 ×). The resulting organic phase was dried with anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 1:2 to 4:1) to give **43b** (477 mg, 88.9%) as a colorless oil. $[\alpha]_D^{25}$ = –13.4 (*c* = 0.54, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3339, 3000, 2937, 2866, 1703, 1535, 1264, 1099 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.36–7.24 (m, 5 H), 5.66–5.54 (m, 2 H), 4.76 (m, 1 H), 4.50 (d, *J* = 12.2 Hz, 1 H), 4.44 (d, *J* = 12.2 Hz, 1 H), 4.10–4.04 (m, 2 H), 3.65 (s, 3 H), 3.50–3.35 (m, 2 H), 3.30–3.15 (m, 2 H), 2.46–2.36 (m, 1 H), 1.83–1.73 (m, 2 H), 1.60–1.50 (m, 1 H), 0.85–0.77 (m, 1 H), 0.55–0.42 (m, 3 H), 0.22–0.14 (m, 1 H), 0.12–0.06 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 157.2 (C), 138.5 (C), 132.5 (CH), 131.8 (CH), 128.4 (CH), 127.8 (CH), 127.6 (CH), 73.0 (CH_2), 68.6 (CH_2), 63.4 (CH_2), 52.1 (CH_3), 48.1 (CH), 44.2 (CH_2), 41.5 (CH), 32.6 (CH_2), 10.4 (CH), 4.8 (CH_2), 2.9 (CH_2) ppm. HRMS (ESI^+): calcd. for $C_{20}H_{29}NaNO_4$ $[M + Na]^+$ 370.1994; found 370.1988.

Methyl (2*R*,3*S*,4*R*)-3-[2-(Benzyloxy)ethyl]-4-cyclopropyl-2-vinylpyrrolidine-1-carboxylate (44b): Bis(acetonitrile)dichloropalladium(II) (1.50 mg, 5.79 μmol) was added to a solution of methyl

{(2*R*,3*R*,*E*)-3-[2-(benzyloxy)ethyl]-2-cyclopropyl-6-hydroxyhex-4-en-1-yl}carbamate (**43b**; 453 mg, 1.16 mmol) in tetrahydrofuran (8 mL) at 0 °C. The mixture was stirred for 1.5 h, then it was quenched with H_2O. The mixture was extracted with ethyl acetate (3 ×), and the combined organic extracts were washed with brine (2 ×). The resulting organic phase was dried with anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 1:4) to give **44b** (363 mg, 84.5%) as a colorless oil. $[\alpha]_D^{25}$ = –2.90 (*c* = 0.49, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3079, 2949, 2868, 1704, 1449, 1384, 1105 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 60 °C): δ = 7.37–7.24 (m, 5 H), 5.69 (ddd, *J* = 17.4, 10.1, 6.0 Hz, 1 H), 5.14–5.00 (m, 2 H), 4.50 (s, 2 H), 4.16–4.06 (m, 1 H), 3.66 (s, 3 H), 3.58–3.52 (m, 2 H), 3.50–3.42 (m, 1 H), 3.42–3.30 (m, 1 H), 2.05–1.95 (m, 2 H), 1.68–1.56 (m, 1 H), 1.52–1.42 (m, 1 H), 0.65–0.55 (m, 1 H), 0.55–0.42 (m, 2 H), 0.12–0.03 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C; this material was observed as a mixture of two rotamers): δ = 155.8 (C), 155.4 (C), 138.4 (CH), 138.2 (2 C), 137.9 (CH), 128.2 (2 CH), 127.5 (2 CH), 127.4 (2 CH), 114.8 (CH_2), 114.2 (CH_2), 72.8 (2 CH_2), 68.6 (CH_2), 68.5 (CH_2), 64.0 (CH), 63.7 (CH), 52.0 (2 CH_3), 50.8 (CH_2), 50.6 (CH_2), 44.8 (2 CH), 43.9 (CH), 43.8 (CH), 27.5 (2 CH_2), 9.4 (2 CH), 4.0 (2 CH_2), 3.6 (2 CH_2) ppm. HRMS (ESI^+): calcd. for $C_{20}H_{27}NaNO_3$ $[M + Na]^+$ 352.1889; found 352.1880.

Methyl (2*S*,3*S*,4*R*)-3-[2-(Benzyloxy)ethyl]-4-cyclopropyl-2-(hydroxymethyl)pyrrolidine-1-carboxylate (45b): Dichloromethane saturated with ozone was added to a solution of methyl (2*R*,3*S*,4*R*)-3-[2-(benzyloxy)ethyl]-4-cyclopropyl-2-vinylpyrrolidine-1-carboxylate (**44b**; 152 mg, 0.460 mmol) in methanol (1 mL) at –78 °C. After TLC indicated complete consumption of the starting material, argon was passed through the reaction mixture, and then sodium borohydride (87.0 mg, 2.30 mmol) was added. Then, the resulting suspension was warmed to 0 °C, and stirred for an additional 1.5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and brine. The mixture was extracted with dichloromethane (3 ×), and the combined organic extracts were washed with brine (2 ×). The resulting organic phase was dried with anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 1:2 to 2:1) to give **45b** (133 mg, 86.8%) as a colorless oil. $[\alpha]_D^{21}$ = –7.04 (*c* = 0.50, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3437, 2947, 2871, 1699, 1680, 1454, 1389, 1110 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.37–7.25 (m, 5 H), 4.51 (s, 2 H), 4.37 (dd, *J* = 8.2, 2.3 Hz, 1 H), 3.82–3.75 (m, 1 H), 3.75–3.67 (m, 1 H), 3.73 (s, 3 H), 3.63–3.52 (m, 3 H), 3.44 (dd, *J* = 10.5, 5.0 Hz, 1 H), 3.38 (dd, *J* = 10.5, 6.1 Hz, 1 H), 2.12–2.02 (m, 1 H), 2.04–1.94 (m, 1 H), 1.76–1.66 (m, 1 H), 1.42–1.34 (m, 1 H), 0.64–0.51 (m, 2 H), 0.51–0.42 (m, 1 H), 0.17–0.10 (m, 1 H), 0.08–0.01 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 158.0 (C), 138.3 (C), 128.5 (CH), 127.8 (CH), 127.8 (CH), 73.1 (CH_2), 68.7 (CH_2), 66.9 (CH_2), 64.9 (CH), 52.9 (CH_3), 52.1 (CH_2), 45.2 (CH), 41.2 (CH), 28.3 (CH_2), 10.1 (CH), 5.1 (CH_2), 3.4 (CH_2) ppm. HRMS (ESI^+): calcd. for $C_{19}H_{27}NaNO_4$ $[M + Na]^+$ 356.1838; found 356.1825.

Methyl (2*S*,3*S*,4*R*)-4-Cyclopropyl-3-(2-hydroxyethyl)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (46b): Palladium hydroxide (20% on carbon; wetted with ca. 50% water; 14.8 mg, 10.6 μmol) was added to a solution of methyl (2*S*,3*S*,4*R*)-3-[2-(benzyloxy)ethyl]-4-cyclopropyl-2-(hydroxymethyl)pyrrolidine-1-carboxylate (**45b**; 118 mg, 0.353 mmol) in methanol (10 mL). The flask was put under hydrogen gas (1 atm) at room temperature. The mixture was stirred for 2 h at room temperature, then it was filtered through a Celite pad, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 2:1, then methanol/dichloromethane, 3:37) to give **46b** (77.9 mg, 90.8%) as a colorless oil. $[\alpha]_D^{26}$ = –8.08 (*c* = 0.54, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3403, 2945, 2878, 1681, 1457, 1390 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.29 (br. s, 1 H), 3.84–3.60 (m, 5 H), 3.73 (s, 3 H), 3.48–3.38 (m, 2 H), 2.10–2.00 (m, 2 H), 1.70–1.53 (m, 2 H), 1.52–1.40 (m, 1 H), 0.67–0.53 (m, 2 H), 0.53–0.43 (m, 1 H), 0.24–0.12 (m, 1 H), 0.12–0.03 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 157.6 (C), 65.5 (CH_2), 64.4 (CH), 60.9 (CH_2), 52.8 (CH_3), 51.8 (CH_2), 45.2 (CH), 40.4 (CH), 30.9 (CH_2), 10.0 (CH), 4.8 (CH_2), 3.6 (CH_2) ppm. HRMS (ESI^+): calcd. for $C_{12}H_{21}NaNO_4$ $[M + Na]^+$ 266.1368; found 266.1377.

CPKA (7): Jones reagent (8 N; 114 μL, 0.913 mmol) was added to a solution of methyl (2*S*,3*S*,4*R*)-4-cyclopropyl-3-(2-hydroxyethyl)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (**46b**; 22.2 mg, 0.0912 mmol) in acetone (2 mL) at 0 °C. The mixture was stirred for 5 min, then water (240 μL) was added, and the mixture was warmed to room temperature. After 2.3 h, additional Jones reagent (8 N; 57.0 μL, 0.456 mmol) and water (800 μL) were added. The mixture was stirred for 1 h, then it was quenched with isopropyl alcohol (500 μL). The aqueous mixture was saturated with NaCl (ca. 450 mg), then extracted with ethyl acetate (5 ×), and the combined organic extracts were evaporated under reduced pressure. The residue was dissolved in NaOH solution (12% aq.; 2 mL), and the resulting solution was washed with diethyl ether (2 ×). The aqueous phase was stirred at 100 °C for 21.5 h, and then cooled to room temperature. The crude suspension was then filtered through two separate columns of ion-exchange resin [Amberlyst A-26 (OH^- form; water, then 5% aqueous HCO_2H) and DOWEX 50WX8 (H^+ form, 200–400 mesh; water, then 3% aqueous NH_3)] to give a pale yellow solid. This material was purified by reverse-phase preparative TLC (methanol/water, 3:97) to give **7** (10.4 mg, 53.3%) as a white solid. m.p. 252–254 °C (decomp.). $[\alpha]_D^{24}$ = 23.1 (*c* = 0.46, H_2O). IR (film): $\tilde{\nu}$ = 3402, 3003, 1714, 1623, 1400 cm^{-1}. ^1H NMR (400 MHz, D_2O, 25 °C): δ = 3.95 (d, *J* = 8.3 Hz, 1 H), 3.58 (dd, *J* = 11.8, 6.9 Hz, 1 H), 3.38 (dd, *J* = 11.8, 4.3 Hz, 1 H), 2.97–2.77 (m, 3 H), 1.88–1.75 (m, 1 H), 0.73–0.60 (m, 2 H), 0.60–0.50 (m, 1 H), 0.24–0.10 (m, 2 H) ppm. ^{13}C NMR (100 MHz, D_2O, 25 °C): δ = 177.3 (C), 174.1 (C), 64.5 (CH), 50.9 (CH_2), 46.3 (CH), 43.2 (CH), 34.4 (CH_2), 9.7 (CH), 5.5 (CH_2), 2.9 (CH_2) ppm. HRMS (ESI^+): calcd. for $C_{10}H_{15}NaNO_4$ $[M + Na]^+$ 236.0899; found 236.0897.

(*R*,*E*)-6-(Benzyloxy)-1-(methoxymethoxy)hex-3-en-2-yl 3-Methylbut-2-enoate (30): Sodium hydride (60% in mineral oil; 6.4 mg, 0.160 mmol) was added to a solution of (*R*,*E*)-6-(benzyloxy)-1-(methoxymethoxy)hex-3-en-2-ol (**20**; 32.8 mg, 0.123 mmol) in tetrahydrofuran (1.0 mL) at 0 °C. The mixture was stirred for 30 min, then pentafluorophenyl 3-methylcrotonate[31] (98.4 mg, 0.370 mmol) was added. The mixture was stirred for an additional 45 min at 0 °C, then it was quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with ethyl acetate (3 ×), and the combined organic extracts were dried with anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 1:9 to 1:4) to give **30** (containing **22** as a 6.6:1 mixture; 32.5 mg, 75.6%) as a colorless oil. $[\alpha]_D^{23}$ = –20.3 (*c* = 0.31, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2935, 1718, 1562, 1517, 1454, 1277, 1147 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.36–7.26 (m, 5 H), 5.83 (dt, *J* = 15.3, 7.3 Hz, 1 H), 5.72 (s, 1 H), 5.56 (dd, *J* = 15.3, 6.9 Hz, 1 H), 5.46 (dt, *J* = 6.5, 5.5 Hz, 1 H), 4.64 (d, *J* = 6.8 Hz, 1 H), 4.62 (d, *J* = 6.8 Hz, 1 H), 4.50 (s, 2 H), 3.64 (d, *J* = 5.5 Hz, 2 H), 3.51 (t, *J* = 6.6 Hz, 2 H), 3.34 (s, 3 H), 3.05 (s, 2 H), 2.37 (dt, *J* = 7.3, 6.6 Hz, 2 H), 2.16 (s, 3 H), 1.89 (s, 3 H) ppm. ^{13}C

NMR (100 MHz, $CDCl_3$, 25 °C): δ = 165.9 (C), 157.4 (C), 138.5 (C), 131.5 (CH), 128.5 (CH), 127.8 (CH), 127.7 (CH), 127.4 (CH), 116.2 (CH), 96.5 (CH_2), 73.0 (CH_2), 72.2 (CH), 69.5 (CH_2), 69.2 (CH_2), 55.4 (CH_3), 32.9 (CH_2), 27.6 (CH_3), 20.4 (CH_3) ppm. HRMS (ESI^+): calcd. for $C_{20}H_{28}NaO_5$ $[M + Na]^+$ 371.1834; found 371.1819.

(2*R*,3*R*,*E*)-3-[2-(Benzyloxy)ethyl]-6-(methoxymethoxy)-2-(prop-1-en-2-yl)hex-4-enoic Acid (32): (*R*,*E*)-6-(Benzyloxy)-1-(methoxymethoxy)hex-3-en-2-yl 3-methylbut-2-enoate [**30**; 12.3 mg, 0.0353 mmol; prepared as a 6.6:1 mixture with (*R*,*E*)-6-(benzyloxy)-1-(methoxymethoxy)hex-3-en-2-yl 3-methylbut-3-enoate (**22**)] was dissolved in tetrahydrofuran (0.5 mL), and the solution was cooled to –78 °C. Lithium bis(trimethylsilyl)amide (1.17 M in tetrahydrofuran; 60.3 μL, 0.0706 mmol) was added over 10 min, and then chlorotrimethylsilane (8.91 μL, 0.0706 mmol) was added. The mixture was stirred for 10 min, then it was warmed to room temperature. The mixture was stirred for an additional 4.5 h, then it was quenched with saturated aqueous NH_4Cl. The mixture was extracted with ethyl acetate (4×), and the combined organic extracts were dried with anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by preparative thin-layer chromatography (methanol/dichloromethane, 1:19) to give **32** (containing **24** as a 6.6:1 mixture; 6.9 mg, 56%) as a colorless oil. $[\alpha]_D^{25}$ = –60.3 (*c* = 0.35, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2944, 2864, 1732, 1708, 1454, 1151, 1102, 1030 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.36–7.26 (m, 5 H), 5.60 (dt, *J* = 15.6, 6.9 Hz, 1 H), 5.46 (dd, *J* = 15.6, 9.2 Hz, 1 H), 4.99 (s, 2 H), 4.58 (d, *J* = 6.7 Hz, 1 H), 4.56 (d, *J* = 6.7 Hz, 1 H), 4.50 (d, *J* = 11.9 Hz, 1 H), 4.43 (d, *J* = 11.9 Hz, 1 H), 3.98 (d, *J* = 6.0 Hz, 2 H), 3.51–3.36 (m, 2 H), 3.33 (s, 3 H), 2.98 (d, *J* = 10.5 Hz, 1 H), 2.71 (dddd, *J* = 10.5, 9.2, 9.0, 2.8 Hz, 1 H), 1.90–1.82 (m, 1 H), 1.81 (s, 3 H), 1.38–1.24 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 176.7 (C), 140.5 (C), 138.6 (C), 134.1 (CH), 129.3 (CH), 128.5 (CH), 127.8 (CH), 127.7 (CH), 116.7 (CH_2), 95.2 (CH_2), 73.1 (CH_2), 68.0 (CH_2), 67.5 (CH_2), 58.7 (CH), 55.3 (CH_3), 39.5 (CH), 31.7 (CH_2), 20.0 (CH_3) ppm. HRMS (ESI^+): calcd. for $C_{20}H_{28}NaO_5$ $[M + Na]^+$ 371.1834; found 371.1839.

Supporting Information (see footnote on the first page of this article): Copies of the ^1H and ^{13}C NMR spectra for all key intermediates and final products.

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[1] a) M. G. Moloney, *Nat. Prod. Rep.* **2002**, *19*, 597–616; b) M. G. Moloney, *Nat. Prod. Rep.* **1999**, *16*, 485–498; c) M. G. Moloney, *Nat. Prod. Rep.* **1998**, *15*, 205–219; d) A. F. Parsons, *Tetrahedron* **1996**, *52*, 4149–4174; e) K. Hashimoto, H. Shirahama, *J. Synth. Org. Chem. Jpn.* **1989**, *47*, 212–223.

[2] S. Murakami, T. Takemoto, Z. Shimizu, *J. Pharm. Soc. Jpn.* **1953**, *73*, 1026–1028.

[3] a) G. Balansard, M. Pellegrini, C. Cavalli, P. Timon-David, M. Gasquet, *Ann. Pharm. Fr.* **1983**, *41*, 77–86; b) G. Balansard, A. Gayte-Sorbier, C. Cavalli, *Ann. Pharm. Fr.* **1982**, *40*, 527–534; c) G. Impellizzeri, S. Mangiafico, G. Oriente, M. Piattelli, S. Sciuto, E. Fattorusso, S. Magno, C. Santacroce, D. Sica, *Phytochemistry* **1975**, *14*, 1549–1557.

[4] I. Nitta, H. Watase, Y. Tomiie, *Nature* **1958**, *181*, 761–762.

[5] G. Sperk, *Prog. Neurobiol.* **1994**, *42*, 1–32.

[6] J. T. Coyle, R. Schwarcz, *Nature* **1976**, *263*, 244–246.

[7] a) T. Takemoto, K. Daigo, *Chem. Pharm. Bull.* **1958**, *6*, 578–580; b) K. Daigo, *J. Pharm. Soc. Jpn.* **1959**, *79*, 356; c) K. Daigo, *J. Pharm. Soc. Jpn.* **1959**, *79*, 353–356; d) K. Daigo, *J. Pharm. Soc. Jpn.* **1959**, *79*, 350–353.

[8] a) L. Zaman, O. Arakawa, A. Shimosu, Y. Onoue, S. Nishio, *Toxicon* **1997**, *35*, 205–212; b) J. L. C. Wright, M. Falk, A. G. Mcinnes, J. A. Walter, *Can. J. Chem.* **1990**, *68*, 22–25; c) M. Maeda, T. Kodama, T. Tanaka, H. Yoshizumi, T. Takemoto, K. Nomoto, T. Fujita, *Chem. Pharm. Bull.* **1986**, *34*, 4892–4895.

[9] a) K. Konno, K. Hashimoto, Y. Ohfune, H. Shirahama, T. Matsumoto, *J. Am. Chem. Soc.* **1988**, *110*, 4807–4815; b) K. Konno, H. Shirahama, T. Matsumoto, *Tetrahedron Lett.* **1983**, *24*, 939–942.

[10] a) H. Shinozaki, *Prog. Neurobiol.* **1988**, *30*, 399–435; b) M. Ishida, H. Shinozaki, *Brain Res.* **1988**, *474*, 386–389; c) H. Shinozaki, M. Ishida, T. Okamoto, *Brain Res.* **1986**, *399*, 395–398.

[11] a) K. Furuta, G. X. Wang, T. Minami, M. Nishizawa, S. Ito, M. Suzuki, *Tetrahedron Lett.* **2004**, *45*, 3933–3936; b) J. E. Baldwin, A. M. Fryer, G. J. Pritchard, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 309–311; c) I. Collado, J. Ezquerra, A. I. Mateo, A. Rubio, *J. Org. Chem.* **1998**, *63*, 1995–2001; d) H. Baumgartner, A. C. O'Sullivan, *Tetrahedron* **1997**, *53*, 2775–2784; e) M. Hashimoto, K. Hashimoto, H. Shirahama, *Tetrahedron* **1996**, *52*, 1931–1942; f) S. Hanessian, S. Ninkovic, U. Reinhold, *Tetrahedron Lett.* **1996**, *37*, 8971–8974; g) K. Konno, K. Hashimoto, H. Shirahama, *Heterocycles* **1992**, *33*, 303–311; h) K. Hashimoto, M. Horikawa, M. Ishida, H. Shinozaki, H. Shirahama, *Bioorg. Med. Chem. Lett.* **1992**, *2*, 743–746; i) K. Hashimoto, H. Shirahama, *Tetrahedron Lett.* **1991**, *32*, 2625–2628; j) K. Hashimoto, M. Horikawa, H. Shirahama, *Tetrahedron Lett.* **1990**, *31*, 7047–7050.

[12] C. I. Stathakis, E. G. Yioti, J. K. Gallos, *Eur. J. Org. Chem.* **2012**, 4661–4673.

[13] For recent examples, see: a) K. Oe, Y. Ohfune, T. Shinada, *Org. Lett.* **2014**, DOI: 10.1021/ol5009526; b) N. K. Reddy, S. Chandrasekhar, *J. Org. Chem.* **2013**, *78*, 3355–3360; c) C. Bhat, S. G. Tilve, *Tetrahedron Lett.* **2013**, *54*, 245–248; d) A. Orellana, S. K. Pandey, S. Carret, A. E. Greene, J.-F. Poisson, *J. Org. Chem.* **2012**, *77*, 5286–5296; e) Z. Luo, B. Zhou, Y. Li, *Org. Lett.* **2012**, *14*, 2540–2543; f) K. Kitamoto, Y. Nakayama, M. Sampei, M. Ichiki, N. Furuya, T. Sato, N. Chida, *Eur. J. Org. Chem.* **2012**, 4217–4231; g) P. A. Evans, P. A. Inglesby, *J. Am. Chem. Soc.* **2012**, *134*, 3635–3638; h) H.-J. Yu, C. Shao, Z. Cui, C.-G. Feng, G.-Q. Lin, *Chem. Eur. J.* **2012**, *18*, 13274–13278; i) G. Wei, J. M. Chalker, T. Cohen, *J. Org. Chem.* **2011**, *76*, 7912–7917; j) S. Takita, S. Yokoshima, T. Fukuyama, *Org. Lett.* **2011**, *13*, 2068–2070; k) M. A. Lowe, M. Ostovar, S. Ferrini, C. C. Chen, P. G. Lawrence, F. Fontana, A. A. Calabrese, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2011**, *50*, 6370–6374; *Angew. Chem.* **2011**, *123*, 6494–6498; l) T. Kamon, Y. Irifune, T. Tanaka, T. Yoshimitsu, *Org. Lett.* **2011**, *13*, 2674–2677; m) A. Farwick, J. U. Engelhart, O. Tverskoy, C. Welter, Q. A. Umlauf, F. Rominger, W. J. Kerr, G. Helmchen, *Adv. Synth. Catal.* **2011**, *353*, 349–370; n) P. J. Parsons, S. P. G. Rushton, R. R. Panta, A. J. Murray, M. P. Coles, J. Lai, *Tetrahedron* **2011**, *67*, 10267–10273; o) G. Lemière, S. Sedehizadeh, J. Toueg, N. Fleary-Roberts, J. Clayden, *Chem. Commun.* **2011**, *47*, 3745–3747; p) K. Kitamoto, M. Sampei, Y. Nakayama, T. Sato, N. Chida, *Org. Lett.* **2010**, *12*, 5756–5759; q) A. Farwick, G. Helmchen, *Org. Lett.* **2010**, *12*, 1108–1111.

[14] G. Arena, C. C. Chen, D. Leonori, V. K. Aggarwal, *Org. Lett.* **2013**, *15*, 4250–4253.

[15] Y. Ohfune, M. Tomita, *J. Am. Chem. Soc.* **1982**, *104*, 3511–3513.

[16] a) S. E. Denmark, J. H.-C. Liu, J. M. Muhuhi, *J. Org. Chem.* **2011**, *76*, 201–215; b) Y. Ni, R. M. Kassab, M. V. Chevliakov, J. Montgomery, *J. Am. Chem. Soc.* **2009**, *131*, 17714–17718; c) S. E. Denmark, J. H.-C. Liu, J. M. Muhuhi, *J. Am. Chem. Soc.* **2009**, *131*, 14188–14189; d) J. Clayden, F. E. Knowles, I. R. Baldwin, *J. Am. Chem. Soc.* **2005**, *127*, 2412–2413; e) Y. Ni, K. K. D. Amarasinghe, B. Ksebati, J. Montgomery, *Org. Lett.* **2003**, *5*, 3771–3773.

[17] a) H. Ouchi, A. Asahina, T. Asakawa, M. Inai, Y. Hamashima, T. Kan, *Org. Lett.* **2014**, *16*, 1980–1983; b) J. E. Baldwin, A. M. Fryer, G. J. Pritchard, M. R. Spyvee, R. C. Whitehead, M. E. Wood, *Tetrahedron Lett.* **1998**, *39*, 707–710; c) J. E. Baldwin, A. M. Fryer, G. J. Pritchard, M. R. Spyvee, R. C. Whitehead, M. E. Wood, *Tetrahedron* **1998**, *54*, 7465–7484; d) M. Horikawa, K. Hashimoto, H. Shirahama, *Tetrahedron Lett.* **1993**, *34*, 331–334; e) A. Barco, S. Benetti, G. P. Pollini, G. Spalluto, V. Zanirato, *Gazz. Chim. Ital.* **1993**, *123*, 185–188; f) S. Takano, S. Tomita, Y. Iwabuchi, K. Ogasawara, *Heterocycles* **1989**, *29*, 1473–1476; g) J. E. Baldwin, C.-S. Li, *J. Chem. Soc., Chem. Commun.* **1988**, 261–263; h) S. Takano, Y. Iwabuchi, K. Ogasawara, *J. Am. Chem. Soc.* **1987**, *109*, 5523–5524; i) K. Konno, K. Hashimoto, Y. Ohfune, H. Shirahama, T. Matsumoto, *Tetrahedron Lett.* **1986**, *27*, 607–610; j) K. Hashimoto, K. Konno, H. Shirahama, T. Matsumoto, *Chem. Lett.* **1986**, 1399–1400.

[18] a) S. Sasaki, H. Suzuki, H. Ouchi, T. Asakawa, M. Inai, R. Sakai, K. Shimamoto, Y. Hamashima, T. Kan, *Org. Lett.* **2014**, *16*, 564–567; b) T. Higashi, Y. Isobe, H. Ouchi, H. Suzuki, Y. Okazaki, T. Asakawa, T. Furuta, T. Wakimoto, T. Kan, *Org. Lett.* **2011**, *13*, 1089–1091; c) A. Nakamura, S. Lectard, D. Hashizume, Y. Hamashima, M. Sodeoka, *J. Am. Chem. Soc.* **2010**, *132*, 4036–4037; d) K. Peixoto Da Silva, M. N. Godoi, C. R. D. Correia, *Org. Lett.* **2007**, *9*, 2815–2818; e) M. Kamabe, T. Miyazaki, K. Hashimoto, H. Shirahama, *Heterocycles* **2002**, *56*, 105–111; f) S. Itadani, S. Takai, C. Tanigawa, K. Hashimoto, H. Shirahama, *Tetrahedron Lett.* **2002**, *43*, 7777–7780; g) A. Ahmed, R. A. Bragg, J. Clayden, K. Tchabanenko, *Tetrahedron Lett.* **2001**, *42*, 3407–3410; h) D. S. Matteson, R. P. Singh, J. Lu, J. Yang, P. S. Pharazyn, *Polyhedron* **2000**, *19*, 587–589; i) M.-R. Schneider, P. Klotz, I. Ungureanu, A. Mann, C.-G. Wermuth, *Tetrahedron Lett.* **1999**, *40*, 3873–3876; j) H. Maeda, N. Selvakumar, G. A. Kraus, *Tetrahedron* **1999**, *55*, 943–954; k) J. S. Bryans, J. M. Large, A. F. Parsons, *J. Chem. Soc. Perkin Trans. 1* **1999**, 2905–2910; l) H. Maeda, G. A. Kraus, *J. Org. Chem.* **1997**, *62*, 2314–2315; m) J. E. Baldwin, S. J. Bamford, A. M. Fryer, M. P. W. Rudolph, M. E. Wood, *Tetrahedron* **1997**, *53*, 5255–5272; n) M. Horikawa, H. Shirahama, *Synlett* **1996**, 95–96; o) T. Sato, K. Matsubayashi, K. Yamamoto, H. Ishikawa, H. Ishibashi, M. Ikeda, *Heterocycles* **1995**, *40*, 261–270; p) M. Horikawa, Y. Shima, K. Hashimoto, H. Shirahama, *Heterocycles* **1995**, *40*, 1009–1014; q) J. E. Baldwin, S. J. Bamford, A. M. Fryer, M. E. Wood, *Tetrahedron Lett.* **1995**, *36*, 4869–4872; r) J. E. Baldwin, M. Rudolph, *Tetrahedron Lett.* **1994**, *35*, 6163–6166.

[19] Independent from our research, Reddy and Chandrasekhar recently synthesized kainic acid using a Claisen–Ireland rearrangement to control the stereochemistries at the 3- and 4-positions of the pyrrolidine ring; see ref.[13b]

[20] E. A. Mash, K. A. Nelson, S. V. Deusen, S. B. Hemperly, *Org. Synth.* **1990**, *68*, 92–98.

[21] a) M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953–956; b) A. K. Chatterjee, T.-L. Choi, D. P. Sanders, R. H. Grubbs, *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.

[22] a) P. R. Andreana, J. S. McLellan, Y. Chen, P. G. Wang, *Org. Lett.* **2002**, *4*, 3875–3878; b) W. Oppolzer, E. P. Kündig, P. M. Bishop, C. Perret, *Tetrahedron Lett.* **1982**, *23*, 3901–3904.

[23] a) R. E. Ireland, P. Wipf, J. D. Armstrong, *J. Org. Chem.* **1991**, *56*, 650–657; b) R. E. Ireland, P. Wipf, J. Xiang, *J. Org. Chem.* **1991**, *56*, 3572–3582; c) R. E. Ireland, R. H. Mueller, A. K. Willard, *J. Am. Chem. Soc.* **1976**, *98*, 2868–2877.

[24] S. E. Denmark, G. L. Beutner, T. Wynn, M. D. Eastgate, *J. Am. Chem. Soc.* **2005**, *127*, 3774–3789.

[25] D. E. Patterson, J. D. Powers, M. LeBlanc, T. Sharkey, E. Boehler, E. Irdam, M. H. Osterhout, *Org. Process Res. Dev.* **2009**, *13*, 900–906.

[26] a) H. Yokoyama, Y. Hirai, *Heterocycles* **2008**, *75*, 2133–2153; b) Y. Hirai, T. Terada, Y. Amemiya, T. Momose, *Tetrahedron Lett.* **1992**, *33*, 7893–7894.

[27] To facilitate the Claisen–Ireland rearrangement (**38b**→**39b**), the reaction mixture was warmed to 0 °C after the formation of the silyl enolate.

[28] J. R. Cochrane, C. S. P. McErlean, K. A. Jolliffe, *Org. Lett.* **2010**, *12*, 3394–3397.

[29] B. M. Trost, M. T. Rudd, *Org. Lett.* **2003**, *5*, 1467–1470.

[30] The purification method was inspired by the following report: S. Takano, T. Sugihara, S. Satoh, K. Ogasawara, *J. Am. Chem. Soc.* **1988**, *110*, 6467–6471.

[31] The ester was prepared from 3-methylcrotonic acid according to the reported procedure: N. S. Sheikh, C. J. Bataille, T. J. Luker, R. C. D. Brown, *Org. Lett.* **2010**, *12*, 2468–2471.

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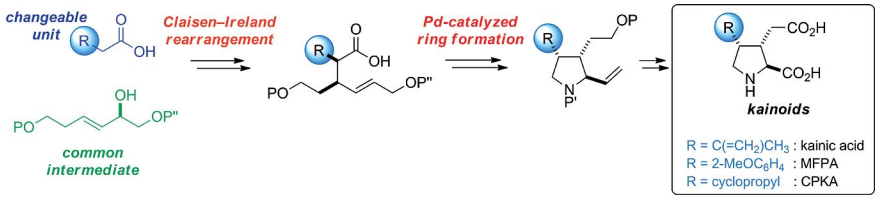

The syntheses of kainic acid, MFPA, and a cyclopropyl analog of kainic acid (CPKA) have been accomplished from a common intermediate. A unified strategy was used, featuring a Claisen–Ireland rearrangement to construct the contiguous stereogenic centers, and a palladium-catalyzed formation of the pyrrolidine ring with complete stereoselectivity.

Keywords: Synthesis design / Total synthesis / Natural products / Alkaloids / Cyclization / Rearrangement

