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Synthesis of Orthogonally Protected (2*S*)-2-Amino-adipic Acid (α-AAA) and (2*S*,4*R*)-2-Amino-4-hydroxyadipic Acid (Ahad)

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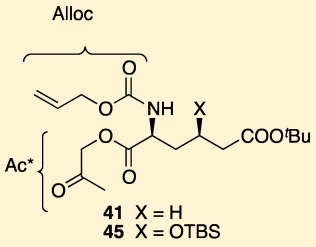
Supporting Information

ABSTRACT: (2*S*,4*R*)-2-Amino-4-hydroxyadipic acid (Ahad) building block **45** was synthesized in 11 steps and 6.5% overall yield from commercially available materials. Key steps in stereocontrol were an asymmetric conjugate addition employing a proline-based catalyst and a *syn*-selective intramolecular-conjugate addition of an oxygen nucleophile to an α,β-unsaturated ester. To enable incorporation of α-amino-adipic acid (α-AAA) and Ahad into peptides, a truly orthogonal protecting group scheme was developed, encompassing an allyloxycarbonyl (Alloc) carbamate for *N*α, a *tert*-butyl ester for the δ-COOH, an acetol ester for the α-COOH, and a *tert*-butyldimethylsilyl ether for the γ-hydroxy group of Ahad.



BACKGROUND AND INTRODUCTION

(2*S*,4*R*)-2-Amino-4-hydroxyadipic acid (Ahad) is a constituent amino acid of theonellamides A–F (Figure 1), bicyclic peptides isolated by Fusetani's group.[1] These compounds have been shown to inhibit the growth of prototypical fungi and cancer cell lines. Watabe et al. reported that theonellamide F induced vacuole formation in 3Y1 rat embryonic fibroblasts;[2] this is the first low molecular weight compound demonstrated to induce extraordinarily large vacuoles without causing cell death, suggesting potential as good molecular probes to investigate intracellular membrane structures.[3]

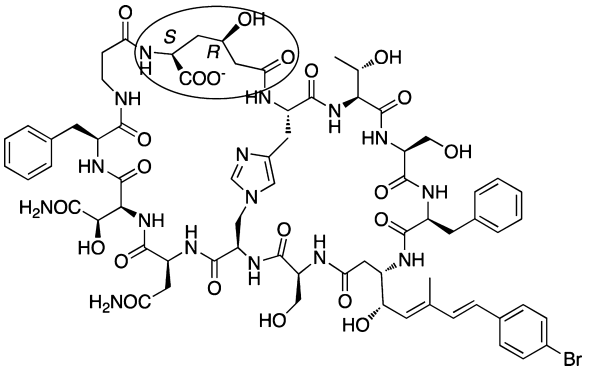
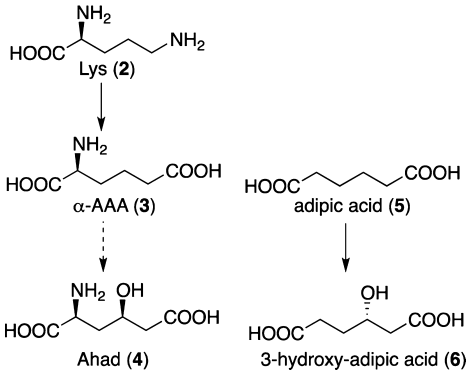


Figure 1. Theonellamide C (**1**) with the Ahad residue circled.

(2*S*)-α-Amino-adipic acid (α-AAA, **3**, Scheme 1), which lacks the γ-hydroxy group, occurs in theonegramide[4] and theopalauamide,[5] bicyclic compounds closely related to the theonellamides. Theopalauamide was shown to be produced by symbiotic, filamentous bacteria living within sponges of the *Theonella* genus.[6] Theopalauamide was recently demonstrated to inhibit the growth of *Saccharomyces cerevisaie* at 0.4 nM, and the molecular target was shown to be ergosterol.[7,8]

(3*S*)-3-Hydroxyadipic acid (**6**) is an oxidative degradation product of adipic acid (**5**) (Scheme 1) and is excreted in urine,[9]

Scheme 1. Biogenesis of Adipic Acids



while α-AAA (**3**) is a normal metabolite in the degradation of lysine (**2**).[10] Aside from the appearance of Ahad in the theonellamides (*vide supra*) the only other report of this amino acid was from Blass and Macheboeuf who proposed, without spectroscopic evidence, the occurrence of Ahad in cultures of *Vibrio cholerae*.[11] This α-amino-γ-hydroxy acid would appear to be of novel or mixed biogenesis.

Kristensen et al. reported the synthesis of a mixture of all four stereoisomers of Ahad in 1980,[12] as analytical standards for analysis. The synthesis was performed by analogy to Benoiton's protocol[13] for the synthesis of γ-hydroxyglutamic acids (Scheme 2). Condensation of the anion of ethyl acetamidocyanoacetate (**7**) with 3-acetoxy-4-chlorobutyronitrile (**8**), followed by hydrolysis and decarboxylation, yielded a mixture of four isomers; the two racemates were separated by ion exchange chromatography. In 1994, Tohdo, Hamada, and Shioiri reported the synthesis of Ahad in the context of their efforts toward theonellamide F.[14] They made intelligent use of the chiral pool, employing aspartic acid as the source of the Cα

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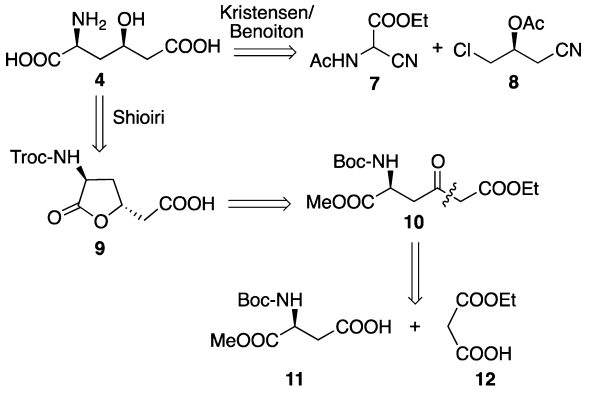
Scheme 2. Previous Syntheses of Ahad



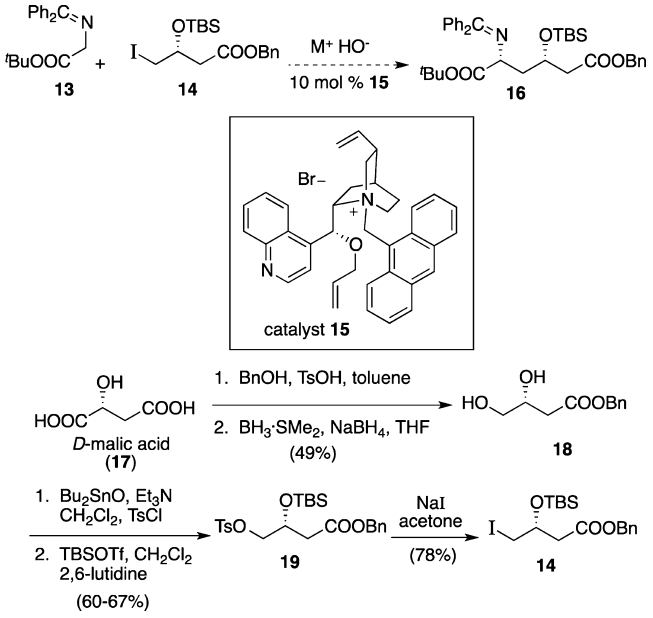
stereocenter. The acyl imidazole generated from the free acid in compound **11** was used to acylate the magnesium enolate of the malonate half ester **12**. The ketone was then reduced stereoselectively by hydrogenation under high pressure with Ru-(*R*)-BINAP. Unfortunately, upon generation of the secondary alcohol, spontaneous cyclization occurs to give a γ-lactone (*cf.*, **9**) which is ultimately not a useful intermediate in peptide synthesis (*vide infra*).

It is important to note that Ahad and α-AAA are incorporated into the cyclic peptides via their α-amino (*N*α) and the side chain carboxylate (δ-COOH). The α-carboxylic acid is not part of the peptide backbone and may be important for stabilization of an imidazolium cation in the natural products (Figure 1). During acidic degradation of the theonellamides, Ahad was isolated as the corresponding γ-lactone. As described above, Tohdo et al. used the γ-lactone functionality as "intramolecular protection" in building block **9**. On the basis of our experience with 4,5-dihydroxyleucine,[15] we believe that it would have been impossible to open the γ-lactone without epimerization at *C*α. Michl had shown earlier that *N*α-acyl and *N*α-carbamoyl γ-lactones are susceptible to epimerization, most likely via an oxazolone.[16] We therefore sought to avoid the γ-lactone moiety during our synthesis. The development of a sophistocated protecting group scheme that would support theonellamide synthesis became an integral goal of this work.

RESULTS AND DISCUSSION

For the synthesis of Ahad, we initially explored an approach based on the Corey–Lygo protocol wherein a glycine enolate is alkylated in the presence of the cinchona alkaloid-derived phase transfer catalyst **15** (Scheme 3).[17] While we were able to reproduce alkylations, as reported in the literature, for allyl bromide and *n*-butyl iodide, we were never able to isolate any alkylation product for reaction with electrophile **14**. It seems that the best electrophiles are allylic or benzylic and used in 5-fold excess. Electrophile **14** was synthesized in five steps from D-malic acid according to Scheme 3. Formation of the dibenzyl ester according to Lee et al.[18] was followed by chemoselective reduction of the α-hydroxyester[19] to give **18**. Selective tosylation of the primary alcohol under standard conditions[20] was not very rewarding, but was successfully achieved via the stannylene acetal.[21] Protection of the remaining secondary alcohol gave **19**. The tosylate was readily converted to iodide **14**. Even with suitable excesses of **14**, no alkylation was observed, under a variety of reaction conditions. We are forced to conclude that this is due to low reactivity in combination

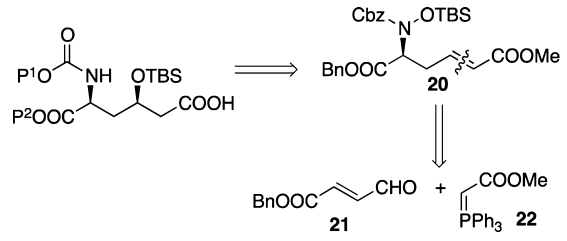
Scheme 3



with the steric hindrance of the center undergoing nucleophilic attack in **14** and related electrophiles that we investigated.

We next turned to the generation of the *syn*-1,3-amino-alcohol following an approach reported by MacMillan and co-workers in the context of their enantioselective organocatalytic amine conjugate additions.[22] According to Scheme 4, the γ-

Scheme 4



hydroxy group would be installed intramolecularly; exposure to a source of fluoride ion would generate an oxyanion from compound **20** that would add in a conjugate manner to the α,β-unsaturated ester. Conjugate addition of Cbz-NHOTBS to a chiral iminium ion generated from aldehyde **21** would occur enantioselectively to generate the first stereocenter. Wittig homologation with commerically available **22** would convert the aldehyde to the α,β-unsaturated ester **20**. We opted to perform the reactions implied in Scheme 4 using commercially available hydroxycarbamate and phosphorane reagents, cognizant of the fact that this would require some protecting group manipulations at a later stage. As noted previously, Ahad is incorporated into the cyclic peptides via the side chain carboxylate. Thus, the free acid depicted in the generic structure (Scheme 4) would ultimately be coupled with the appropriate amine of the bridging τ-histidinoalanine residue. Our theonellamide synthetic strategy involves a final global deprotection using fluoride, hence our choice of the TBS ether for the γ-hydroxy group. Candidates for temporary protection of the α-amino and δ-carboxy groups will be discussed in due course.

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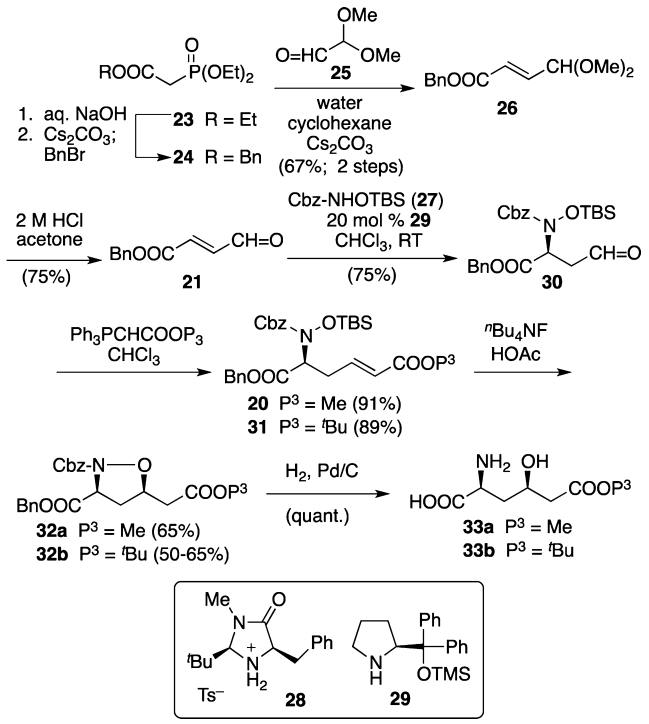
The execution of this plan is illustrated in Scheme 5. Diethyl (benzyloxycarbonylmethyl)phosphonate was prepared by

Scheme 5



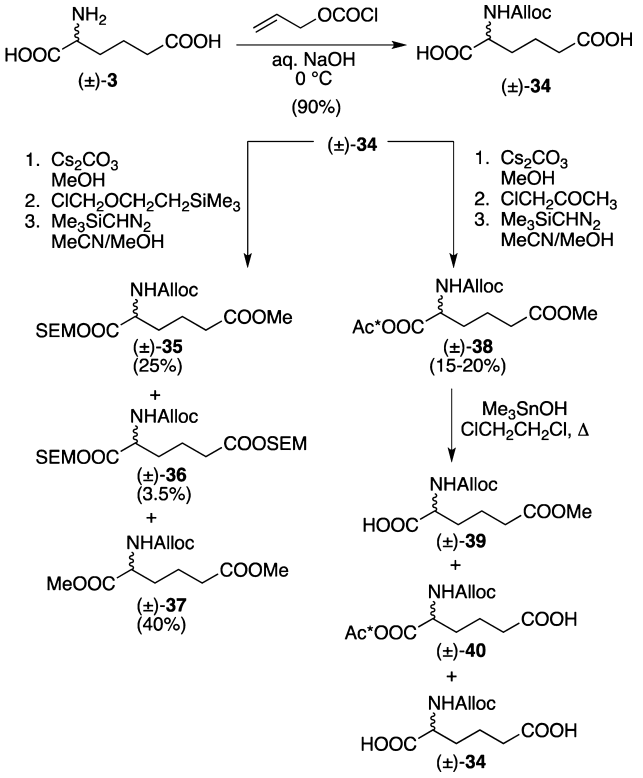
hydrolysis of the carboxylate ester of triethylphosphonoacetate (**23**) and conversion to the benzyl ester **24**. A Horner–Emmons reaction was conducted in a biphasic reaction mixture of cyclohexane and an aqueous solution of glyoxal dimethyl acetal (**25**) afforded *E*-**26**.[23] Hydrolysis of the dimethyl acetal to give aldehyde **21** was best accomplished according to Iesce et al.;[24] other conditions led to isolation of the hydrate. Conjugate addition of CbzNHOTBS (**27**) to (*E*)-benzyl 4-oxobut-2-enote (**21**) in the presence of catalyst **28** led to no isolable product. Fortunately, employing catalyst **29**, according to Córdova et al.,[25] afforded **30** in good yield that was then subjected to a Wittig reaction to obtain **20**. In practice, direct addition of the phosphorane to the reaction mixture containing **30** led to **20** directly in good overall yield. Treatment of compound **20** with fluoride ion facilitated silyl group removal with concomitant, intramolecular oxy-Michael addition to afford isooxazolidine **32a**.

While MacMillan and co-workers had employed samarium diiodide to reductively cleave the N–O bond in a compound analogous to **29**, we anticipated that exposure of **29** to standard hydrogenolysis conditions would simultaneously remove the Cbz and benzyl ester protecting groups, along with cleavage of the N–O bond.[26] This was borne out by experiment to give **33a** ready for introduction of a suitable suite of protecting groups.

We began our search for a combination of protecting groups that might be compatible with the total synthesis of a theonellamide, with α-AAA, as this congener is not hydroxylated at Cγ. Acetol[27] and 2-(trimethylsilyl)ethoxymethyl (SEM)[28] esters were entertained as possible protective groups for the α-carboxylate, as these functionalities appear likely to survive the various reaction conditions in the synthesis and have been shown to be cleaved using tetrabutylammonium fluoride.

Racemic α-AAA (±)-**3** was protected as its allyloxycarbamate[29] by analogy to a procedure for the Cbz-protection of adipic acid by Hachisako et al. (Scheme 6).[30] We explored a

Scheme 6



number of strategies to selectively protect one of the carboxylic acids in α-AAA, including the intermediacy of copper(II) complexes.[31] The approach that was most fruitful was based on the observation of Baldwin and others who have demonstrated that it is possible to selectively esterify the α-carboxylic acid of adipic acid,[32] since its pK_a is about one unit lower than that of the δ-carboxylic acid. Regioselective esterification of the α-acid in compound **34** was attempted by the addition of 0.5 equiv of cesium carbonate to form the putative monocesium carboxylate salt and reacting with SEM-Cl. The product mixture (without any purification) was subjected to trimethylsilyldiazomethane to afford a mixture of compounds **35**–**37** from which **35** could be isolated by flash chromatography. A low yield of compound **35** was obtained due to poor regioselectivity and the inability to purify the intermediate acid by flash chromatography due to its high polarity. Acetol ester **38** was obtained via an analogous series of reactions, in similarly low yield.

Nicolaou reported the impressive chemoselectivity of trimethyltin hydroxide for the hydrolysis of methyl esters, even in the presence of ethyl esters.[33] We hoped we would similarly be able to cleave the methyl esters in compounds **35** and **38**, in the presence of acetol and SEM esters respectively. When compound **38** was treated with Me_3SnOH, complex product mixtures were obtained, regardless of the number of equivalents of reagent and reaction temperature. Analysis of the product mixture by LCMS showed that the major product arose from hydrolysis of the acetol ester (giving compound **39**) instead of the methyl ester (minor product **40**). The starting

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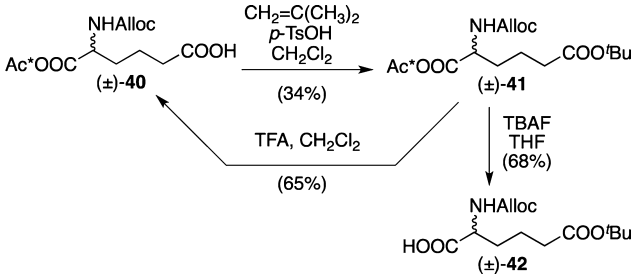
diester **38** and diacid **34** were also observed, revealing a reaction that is not synthetically useful. Similar results were obtained upon attempted hydrolysis of the SEM group from **35**.

We decided to substitute a *tert*-butyl ester for the ill-fated methyl ester. Cognizant of the acid lability of SEM esters, the acetol ester now became the clear choice. Thus, a mixture containing acid (±)-**40** was treated with isobutylene under acidic conditions to give diester (±)-**41** (Scheme 7). The

Scheme 7

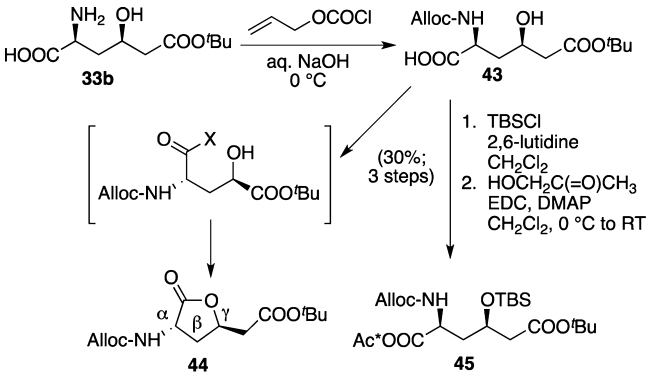


selective cleavage of the *tert*-butyl ester and the acetol ester were demonstrated using TFA and TBAF respectively (Scheme 7). Optically active (−)-**41** was prepared from L-α-amino-adipic acid.

Following these protecting group studies with α-AAA, Ahad building block **33b**, bearing a δ-COO^{t}Bu group, was synthesized via analogous reactions to those described earlier for the δ-COOMe building block **33a** (Scheme 5). The *tert*-butyl ester was introduced using commercially available (*tert*-butoxycarbonylmethylene)-triphenylphosphorane during the Wittig reaction to produce **31**. Chiral HPLC analysis showed that compound **31** was obtained in 87.4% ee. We base our assignment of the *S*-configuration at Cα on the transition-state model of Córdova and co-workers in which the amine nucleophile attacks the face of the conjugated pyrrolidinium ion opposite the bulky $CPh_2(OTMS)$ substituent.[25] Their model was vindicated by the conversion of some intermediates to known compounds for comparison. Treatment of compound **31** with the fluoride ion facilitated cyclization at room temperature to afford isooxazolidine **32b** in a 3.8:1.0 dr favoring the *syn* diastereomer. In attempts to improve the diastereoselectivity of the conjugate addition, we conducted the reaction at lower temperatures. For example, at 0 °C, a 10% yield of isooxazolidine **32b** was obtained with 4.2:1.0 dr. Confirmation of the *syn* relative stereochemistry was confirmed by a NOESY experiment that showed a cross peak between the Hα and Hγ protons of **32b** (5.6% NOE). The *syn* diastereomer could be further purified by normal phase HPLC, although in practice the minor diastereomer was gradually removed during chromatography following the next few reaction steps.

The free amine **33b** was protected as its allyloxycarbamate **43** (Scheme 8) by analogy to the procedure for α-AAA. Esterification of the α-acid was attempted in two ways: first, via reaction of the cesium salt with chloroacetone; and second, via coupling to acetol in the presence of activating agents. The only product isolated from various reaction conditions was the lactone **44** (Scheme 8). This undesired product afforded further confirmation of the 2*S*,4*R* stereochemistry since the Hβ protons gave rise to a multiplet at 2.4−2.8 ppm, consistent with a *trans*-1,4-disubstituted γ-lactone.[34] Various activated acyl species, including the acetol ester, were susceptible to

Scheme 8



nucleophilic attack by the γ-OH, mandating that we protect the secondary alcohol before the carboxylic acid.

Lajoie and co-workers had shown that a free alcohol can be masked as a TBS ether in the presence of free amine and free acid functional groups.[35] We applied their conditions, involving stoichiometric TBSCl and 2,6-lutidine, to compound **43**. Carbodiimide-mediated coupling of the resulting crude acid with acetol gave rise to **45** in reasonable overall yield. We expect this building block to be useful in the synthesis of theonellamides. The scope for chemoselective cleavage of the *tert*-butyl ester with *tert*-butyldimethylsilyl triflate,[36] liberation of the α-NH_2 with palladium(0), and ultimately cleavage of the silyl ether and acetol ester side chain protecting groups with fluoride provides an adaptable building block.

CONCLUSION

In summary, a robust, stereoselective synthesis of orthogonally protected (2*S*,4*R*)-α-amino-χ-hydroxyadipic acid has been developed starting from commercially available triethylphosphonoacetate (**23**), glyoxal dimethyl acetal (**25**), benzyl *N*-hydroxycarbamate, and (*tert*-butoxycarbonylmethylene)-triphenylphosphorane. The two stereoselective conjugate addition reactions represent a potentially general approach to 1,3-*syn* aminoalcohols. Incorporation of the α-AAA and Ahad building blocks, described herein, into the western hemisphere of theonellamides is currently underway in our laboratory.

EXPERIMENTAL PROCEDURES

(*S*)-Benzyl 3,4-Dihydroxybutanoate (18). *(a). (S)-Dibenzyl 2-Hydroxysuccinate.* Benzyl alcohol (1.50 mL, 1.61 g, 14.90 mmol) and *p*-toluenesulfonic acid monohydrate (14 mg, 0.074 mmol) were added to a solution of D-malic acid (**17**) (1.00 g, 7.46 mmol) in dry toluene (12 mL). The reaction mixture was heated under reflux with a Dean−Stark apparatus to effect the azeotropic removal of water. When no more water appeared in the distillate, the mixture was allowed to cool to rt and washed with saturated aqueous $NaHCO_3$ (25 mL) and brine (25 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by flash column chromatography on silica gel with Hex/EtOAc (4:1) as eluent to give the dibenzyl ester as a colorless oil (80%). R_f 0.42 (4:1 Hex−EtOAc). $[\alpha]_D^{25}$ +42.98 (*c* 2.5, $CHCl_3$) [Lit.[18] $[\alpha]_D^{25}$ +18.2 (*c* 2, $CHCl_3$)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.80 (dd, *J* = 16.4, 6.1 Hz, 1H), 2.86 (dd, *J* = 16.4, 4.7 Hz, 1H), 3.41 (br s, 1H), 4.52 (dd, *J* = 5.9, 4.8 Hz, 1H), 5.06 (s, 2H), 5.13 (s, 2H), 7.24−7.33 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 38.8, 66.8, 67.5, 67.6, 128.3, 128.4, 128.5, 128.6, 128.7, 135.2, 135.6, 170.3, 173.2. HRMS (ESI-TOF) calcd for $C_{18}H_{19}O_5$ $(M+H)^+$ 315.1227, obsd 315.1220.

(b). (S)-Benzyl 3,4-Dihydroxybutanoate. Borane-dimethylsulfide complex (175 μL, 0.350 mmol, 2.0 M solution in THF, 1.1 equiv) was added dropwise over 15 min to a solution of (*S*)-dibenzyl-2-

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hydroxysuccinate (100 mg, 0.318 mmol, 1 equiv) in dry THF (1 mL) at 0 °C under N_2. After 1 h of stirring, sodium borohydride (0.6 mg, 0.016 mmol, 0.05 equiv) was added, and the mixture was stirred overnight at rt. The mixture was quenched by the addition of methanol (1.5 mL), and stirring continued for 30 min. The solvent was evaporated, and the residue was purified by column chromatography on silica gel (1:1 Hex−EtOAc) to obtain diol **18** as a colorless oil (41 mg, 61%). R_f 0.31 (1:1 Hex−EtOAc). $[\alpha]_D^{25}$ +18.84 (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.49 (dd, *J* = 16.3, 4.3 Hz, 1H) 2.55 (dd, *J* = 16.3, 8.4 Hz, 1H), 3.35 (br s, 2H) 3.48 (dd, *J* = 11.4, 6.4 Hz, 1H) 3.62 (dd, *J* = 11.4, 3.5 Hz, 1H), 4.08−4.17 (m, 1H), 5.13 (s, 1H), 7.30−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 37.8, 65.7, 66.7, 68.6, 128.3, 128.4, 128.6, 135.6, 172.3. HRMS (ESI-TOF) calcd for $C_{11}H_{14}NaO_4$ $(M+Na)^+$ 233.0784, obsd 233.0793.

(*S*)-Benzyl 3-[(*tert*-Butyldimethylsilyl)oxy]-4-(tosyloxy)-butanoate (19). *(a). (S)-Benzyl 3-Hydroxy-4-(tosyloxy)butanoate.* To a solution of diol **18** (200.0 mg, 0.95 mmol, 1.00 equiv) in dry CH_2Cl_2 (2.5 mL) were added successively ^{n}Bu_2SnO (7.0 mg, 0.03 mmol, 0.03 equiv), a solution of Et_3N (135 μL, 98.4 mg, 0.97 mmol, 1.02 equiv) in dry CH_2Cl_2 (2.5 mL), and *p*-toluenesulfonyl chloride (190.7 mg, 0.97 mmol, 1.02 equiv) at rt. The mixture was stirred for 6 h and then treated with brine (10 mL). The aqueous layer was extracted with CH_2Cl_2 (4 × 15 mL). The combined organic layers were dried with anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (2:1 Hex−EtOAc) to obtain the tosylate (222 mg, 64%). R_f 0.43 (1:1 Hex−EtOAc). $[\alpha]_D^{25}$ +7.34 (*c* 1.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.00 (bs, 1H), 2.45 (s, 3H), 2.53 (dd, *J* = 16.6, 4.8 Hz, 1H), 2.62 (dd, *J* = 16.7, 7.5 Hz, 1H), 4.04 (d, *J* = 8.3 Hz, 2H), 4.25−4.28 (m, 1 H), 5.14 (s, 2H), 7.26−7.39 (m, 7H), 7.78 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.7, 37.4, 66.0, 66.9, 71.9, 128.0, 128.2, 128.5, 128.7, 130.0, 132.5, 135.3, 145.2, 171.4. HRMS (ESI-TOF) calcd for $C_{18}H_{21}O_6S$ $(M+H)^+$ 365.1053, obsd 365.1043.

(b). (S)-Benzyl 3-[(tert-Butyldimethylsilyl)oxy]-4-(tosyloxy)-butanoate (19). 2,6-Lutidine (178 μL, 163 mg, 1.5 mmol, 3.0 equiv) was added dropwise to a solution of (*S*)-benzyl 3-hydroxy-4-(tosyloxy)butanoate (185 mg, 0.5 mmol, 1.0 equiv) in dry CH_2Cl_2 (7.5 mL) under N_2 at rt. The mixture was stirred for 30 min before the dropwise addition of TBDMSOTf (140 μL, 161 mg, 0.6 mmol, 1.2 equiv). The mixture was stirred overnight, the solvent was evaporated, and the residue was purified by silica gel chromatography, eluting with 2:1→1:1 Hex−EtOAc, to give the TBS ether **19** (206 mg, 85%). R_f 0.38 (1:1 Hex−EtOAc). $[\alpha]_D^{25}$ +8.01 (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.02 (s, 3H), 0.03 (s, 3H), 0.81 (s, 9H), 2.45 (s, 3H), 2.49 (dd, *J* = 15.4, 6.9 Hz, 1H), 2.56 (dd, *J* = 15.4, 5.2 Hz, 1H), 3.93−4.00 (m, 2H), 4.3−4.35 (m, 1H), 5.06 (d, *J* = 12.3 Hz, 1H), 5.12 (d, *J* = 12.3 Hz, 1H), 7.32−7.38 (m, 5H), 7.77−7.79 (m, 4H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.1, −4.7, 17.9, 21.6, 25.6, 39.5, 66.5, 67.2, 72.3, 128.0, 128.2, 128.3, 128.6, 129.9, 132.8, 135.6, 144.9, 170.3. HRMS (ESI-TOF) calcd for $C_{24}H_{35}O_6SSi$ $(M+H)^+$ 479.1918, obsd 479.1925.

(*S*)-Benzyl 3-[(*tert*-Butyldimethylsilyl)oxy]-4-iodobutanoate (14). Sodium iodide (392 mg, 2.08 mmol, 8.0 equiv) was added to a solution of (*S*)-benzyl 3-[(*tert*-butyldimethylsilyl)oxy]-4-(tosyloxy)-butanoate (**19**) (125 mg, 0.26 mmol, 1.0 equiv) in acetone (5 mL). The mixture was stirred and heated at reflux overnight. Saturated aqueous $NaHCO_3$ (10 mL) was added, and the mixture was extracted with diethyl ether (5 × 15 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography on silica gel (Hex−EtOAc 5:1) afforded **14** as a brownish yellow oil (88 mg, 78%). R_f 0.58 (2:1 Hex−EtOAc). $[\alpha]_D^{25}$ +10.01 (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.04 (s, 3H), 0.11 (s, 3H), 0.87 (s, 9H), 2.60 (dd, *J* = 15.4, 7.1 Hz, 1H), 2.73 (dd, *J* = 15.4, 4.9 Hz, 1H), 3.21−3.30 (m, 2H), 4.05 (app. pent, *J* = 5.5 Hz, 1H), 5.09 (d, *J* = 12.3 Hz, 1H), 5.14 (d, *J* = 12.3 Hz, 1H), 7.25−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.9, −4.5, 12.8, 17.9, 25.7, 42.6, 66.5, 68.4, 128.3, 128.4, 128.6, 135.7, 170.7. HRMS (ESI-TOF) calcd for $C_{17}H_{28}IO_3Si$ $(M+H)^+$ 435.0847, obsd 435.0831.

Benzyl 2-(Diethoxyphosphoryl)acetate (24). Triethylphosphonoacetate (500 μL, 560 mg, 2.49 mmol, 1.00 equiv) was dissolved in 1 M NaOH (1 mL, 2.49 mmol, 1.00 equiv) and stirred at 60 °C overnight. The ethanol formed in the reaction was evaporated, and the aqueous layer was acidified to pH 2 with 10% $KHSO_4$. The aqueous layer was extracted with CH_2Cl_2 (4 × 15 mL) and dried over $MgSO_4$, filtered, and concentrated to give the carboxylic acid (373 mg) which was dissolved in dry MeOH (5 mL). Cesium carbonate (310 mg, 0.95 mmol, 0.5 equiv) was added, and the mixture was stirred for 2 h under N_2. The mixture was concentrated, dissolved in DMF (5 mL), and cooled to 0 °C. Benzyl bromide (274 μL, 391 mg, 2.28 mmol, 1.2 equiv) was added, and the mixture was warmed to rt, stirred overnight, diluted with EtOAc (10 mL), and washed with water (15 mL) and brine (15 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. Flash chromatography on silica gel (EtOAc−Hex 1:1→2:1) afforded **24** as a colorless oil (536 mg, 75%). R_f 0.48 (EtOAc−Hex 2:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.29 (t, *J* = 7.1 Hz, 6H), 2.99 (d, $^3J_{H-P}$ = 21.5 Hz, 2H), 4.09−4.16 (m, 4H), 5.18 (s, 2H), 7.30−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.3 (^3J = 16.3 Hz), 34.4 ($^1J_{C-P}$ = 134.2 Hz), 62.7 (^2J = 6.3 Hz), 67.3, 128.3, 128.4, 128.5, 135.4, 165.6. HRMS (ESI, −ve, TOF) calcd for $C_{13}H_{18}O_5P$ $(M-H)^-$ 285.0897, obsd 285.0897.

(2*E*)-Benzyl 4,4-Dimethoxybut-2-enoate (26). Cesium carbonate (2.20 g, 6.75 mmol, 1.5 equiv) was added to a solution of benzyl 2-(diethoxyphosphoryl)acetate **24** (1.28 g, 4.5 mmol, 1.0 equiv) in cyclohexane (20 mL). The suspension was heated to 65 °C, and then 2,2-dimethoxyacetaldehyde **25** (15.6 mL of a 60 wt % solution in H_2O, 937 mg, 9.0 mmol, 2.0 equiv) was added. The biphasic mixture became clear pale yellow and was stirred for 2 h at 65 °C. Saturated aqueous NH_4Cl (25 mL) was added, and the mixture was extracted with EtOAc (4 × 25 mL). The combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography on silica gel (Hex−EtOAc 2:1) afforded the dimethyl acetal **26** as a colorless oil (947 mg, 89%). R_f 0.56 (1:1 Hex−EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.32 (s, 6H), 4.94 (d, *J* = 3.0, 1H), 5.19 (s, 2H), 6.19 (d, *J* = 15.9 Hz, 1 H), 6.81 (dd, *J* = 15.8, 3.9 Hz, 1H), 7.30−7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 52.8, 66.4, 100.5, 124.4, 128.2, 128.3, 128.6, 135.8, 143.2, 165.6. HRMS (ESI-TOF) calcd for $C_{13}H_{17}O_4$ $(M+H)^+$ 237.1160, obsd 237.1153.

(*E*)-Benzyl 4-Oxobut-2-enoate (21). A solution of **26** (150 mg, 0.635 mmol) in acetone (30 mL) was treated with 2 M HCl (0.3 mL) and stirred at rt for 2 d. The acetone was evaporated, and residue was treated with water (5 mL) and extracted with $CHCl_3$ (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography on silica gel (Hex−EtOAc 2:1) afforded aldehyde **21** as a colorless oil (90 mg, 75%). R_f 0.46 (1:1 Hex−EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.26 (s, 2H), 6.74 (d, *J* = 15.9 Hz, 1H), 6.98 (dd, *J* = 15.9, 7.6 Hz, 1H), 7.32−7.39 (m, 5H), 9.72 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 67.5, 128.5, 128.7, 135.0, 140.0, 140.6, 164.7, 192.43. HRMS (ESI-TOF) calcd for $C_{11}H_{11}O_3$ $(M+H)^+$ 191.0712, obsd 191.0719.

Benzyl (*tert*-Butyldimethylsilyl)oxycarbamate (27). Triethylamine (249 μL, 181 mg, 1.79 mmol, 1.2 equiv) was added to a solution of benzyl-*N*-hydroxycarbamate (250 mg, 1.49 mmol, 1 equiv) in dry CH_2Cl_2 (5 mL) under N_2. The mixture was cooled to 0 °C, and TBSCl (270 mg, 1.79 mmol, 1.2 equiv) was added. The reaction mixture was warmed to rt and stirred overnight. The mixture was washed with water (5 mL) and brine (5 mL), and the organic layer was dried over $MgSO_4$, filtered, and concentrated. Flash chromatography on silica gel (Hex−EtOAc 4:1→1:2) afforded **27** as a clear oil (321 mg, 77%). R_f 0.66 (2:1 Hex−EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.15 (s, 6H), 0.94 (s, 9H), 5.16 (s, 2H), 7.02 (s, 1H), 7.30−7.35 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.8, 18.0, 25.9, 67.6, 128.3, 128.4, 128.5, 135.7, 158.6. HRMS (ESI-TOF) calcd for $C_{14}H_{24}NO_3Si$ $(M+H)^+$ 282.1520, obsd 282.1516.

(*S*)-Benzyl 2-[(Benzyloxycarbonyl)(*tert*-butyldimethylsilyloxy)]amino-4-oxo-butanoate (30). A solution of benzyl (*tert*-butyldimethylsilyl)oxycarbamate (**27**) (207.0 mg, 0.736 mmol, 1.4 equiv) in chloroform (1 mL) was treated with (*S*)-2-{diphenyl-[(trimethylsilyl)oxy]methyl}pyrrolidine (34.0 mg, 0.105 mmol, 0.2

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equiv) and acetic acid (9 μL, 9.4 mg, 0.105 mmol, 0.2 equiv) and stirred for 10 min at rt. Benzyl 4-oxo-but-2-enoate (**21**) (100.0 mg, 0.525 mmol, 1.0 equiv) was added, and the reaction mixture was stirred for 3.5 h at rt and concentrated. The residue was subjected to silica gel chromatography (Hex−EtOAc 5:1) providing the aldehyde **30** as a colorless oil (239 mg, 69%). R_f 0.30 (2:1 Hex−EtOAc). $[\alpha]_D^{25}$ −13.5 (*c* 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.08 (s, 3H), 0.12 (s, 3H), 0.87 (s, 9H), 2.87 (dd, *J* = 17.7, 5.8 Hz, 1H), 3.26 (dd, *J* = 17.7, 5.7 Hz, 1H), 5.07−5.18 (m, 5H), 7.26−7.40 (m, 10H), 9.81 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.8, −4.7, 18.1, 25.8, 42.7, 60.1, 67.5, 68.6, 128.1, 128.3, 128.5, 128.5, 128.6, 135.3, 159.2, 169.1, 198.2. HRMS (ESI-TOF) calcd for $C_{25}H_{34}NO_6Si$ $(M+H)^+$ 472.215, obsd 472.2139.

(2*S*,4*E*)-1-Benzyl-2-[(benzyloxycarbonyl)(*tert*-butyldimethylsilyloxy)-amino]-6-methyl-hex-4-enedioate (20) from 30. A solution of aldehyde **30** (137.0 mg, 0.290 mmol, 1.0 equiv) in chloroform (2.5 mL) was treated with methyl (triphenylphosphorylidine)acetate (164.0 mg, 0.435 mmol, 1.5 equiv) at 0 °C and allowed to warm to rt. The reaction mixture was stirred for 1.5 h and concentrated to a viscous oil. Flash chromatography on silica gel (Hex−EtOAc 5:1) afforded the α,β-unsaturated ester as colorless oil **20** (140 mg, 91%). R_f 0.30 (2:1 Hex−EtOAc); $[\alpha]_D^{25}$ −41.2 (*c* 0.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.07 (s, 3H), 0.09 (s, 3H), 0.85 (s, 9H), 2.78−2.93 (m, 2H), 3.73 (s, 3H), 4.64 (dd, *J* = 8.9, 6.1 Hz, 1H), 5.07 (d, *J* = 12.0 Hz, 1H), 5.10 (d, *J* = 12.2 Hz, 1H), 5.12 (d, *J* = 12.0 Hz, 1H), 5.16 (d, *J* = 12.0 Hz, 1H), 5.94 (d, *J* = 15.7 Hz, 1H), 6.97 (dt, *J* = 15.7, 7.0 Hz, 1H), 7.26−7.40 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.8, −4.7, 18.1, 25.8, 31.1, 51.5, 64.2, 67.2, 68.5, 123.6, 128.2, 128.3, 128.4, 128.5, 128.5, 128.6, 135.2, 144.3, 159.2, 166.1, 168.8. HRMS (ESI-TOF) calcd for $C_{28}H_{38}NO_7Si$ $(M+H)^+$ 528.2412, obsd 528.2420.

(2*S*,4*E*)-1-Benzyl-2-[(benzyloxycarbonyl)(*tert*-butyldimethylsilyloxy)-amino]-6-methyl-hex-4-enedioate (20): One-Pot Procedure from 21. A solution of benzyl (*tert*-butyldimethylsilyl)oxycarbamate (305.00 mg, 1.05 mmol, 1.4 equiv) in chloroform (1 mL) was treated with (*S*)-2-{diphenyl[(trimethylsilyl)-oxy]methyl}-pyrrolidine (50.35 mg, 0.15 mmol, 0.2 equiv), followed by the addition of acetic acid (10 μL, 9.28 mg, 0.15 mmol, 0.2 equiv) and stirred for 10 min at rt. Benzyl 4-oxo-but-2-enoate (**21**) (147.20 mg, 0.77 mmol, 1.0 equiv) was added, and the reaction mixture was stirred for 3.5 h at rt. Upon completion (determined by TLC), methyl (triphenylphosphorylidine)acetate (357.00 mg, 0.75 mmol, 1.5 equiv) was added in one portion. The reaction mixture was stirred for 2.5 h and then concentrated to afford a viscous oil. Flash chromatography on silica gel (Hex−EtOAc 5:1) afforded the α,β-unsaturated ester **20** as a colorless oil (280 mg, 71%). R_f 0.30 (2:1 Hex−EtOAc). NMR data were identical to those obtained via the two-step procedure.

(2*S*,4*E*)-1-Benzyl-2-[(benzyloxycarbonyl)(*tert*-butyldimethylsilyloxy)-amino]-6-*tert*-butyl-hex-4-enedioate (31). A solution of benzyl (*tert*-butyldimethylsilyl)oxycarbamate (**27**) (250.0 mg, 0.88 mmol, 1.4 equiv) in chloroform (1 mL) was treated with (*S*)-2-{diphenyl[(trimethylsilyl)oxy]methyl}pyrrolidine (41.0 mg, 0.12 mmol, 0.2 equiv), followed by the addition of acetic acid (7 μL, 7.5 mg, 0.12 mmol, 0.2 equiv), and stirred for 10 min at rt. Benzyl 4-oxo-but-2-enoate (**21**) (121.0 mg, 0.63 mmol, 1.0 equiv) was added, and the reaction mixture was stirred for 3.5 h at rt. Upon completion (determined by TLC), *tert*-butyl-2-(triphenylphosphoranylidene)-acetate (237.0 mg, 0.63 mmol, 1.0 equiv) was added in one portion. The reaction mixture was stirred for 1.5 h and then concentrated to a viscous oil. The triphenylphosphine oxide byproduct was precipitated by the addition of Et_2O. The solid was removed by filtration, and the filtrate was concentrated. Flash chromatography on silica gel (Hex−EtOAc 8:1→4:1) afforded the α,β-unsaturated ester **31** as colorless oil (354 mg, 70%). R_f 0.30 (2:1 Hex−EtOAc). $[\alpha]_D^{25}$ −37.2 (*c* 0.5, $CHCl_3$). The enantiomeric excess was determined on a Chiracel OD-H column (4.6 cm × 25 cm), eluting with 95% hexane, 5% isopropanol, at a flow rate of 0.5 mL min^{-1}, with detection at 218 nm. R_T (major) 21 min (93.7%); R_T (minor) 36 min (6.3%) for an ee of 87.4%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.08 (s, 3H), 0.10 (s, 3H), 0.85 (s, 9H), 1.47 (s, 9H), 2.76−2.91 (m, 2H), 4.57 (dd, *J* = 8.7, 6.2 Hz, 1H), 5.06−5.18 (m, 4H), 5.84 (d, *J* = 15.6 Hz, 1H), 6.86 (dt, *J* = 7.0, 15.6 Hz, 1H), 7.26−7.36 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.8, −4.7, 18.1, 25.8, 28.1, 31.2, 64.5, 67.2, 68.4, 80.3, 125.8, 128.1, 128.2, 128.4, 128.5, 128.5, 128.6, 135.3, 142.6, 159.1, 165.4, 168.9. HRMS (ESI-TOF) calcd for $C_{31}H_{44}NO_7Si$ $(M+H)^+$ 570.2412, obsd 570.2420.

(3*S*,5*R*)-Benzyl-5-[(methoxycarbonyl)methyl]-3-benzyloxycarbonyl-isooxazolidine-2-carboxylate (32a). To a solution of compound **20** (105 mg, 0.198 mmol, 1.0 equiv) in $CHCl_3$ (1 mL) was added acetic acid (17 μL, 17 mg, 0.297 mmol, 1.5 equiv). The mixture was cooled to 0 °C, and TBAF (297 μL, 1 M in THF with 5% H_2O, 0.297 mmol, 1.5 equiv) was added. The reaction was allowed to stir at 0 °C for 4 d. The reaction was monitored by TLC, and upon completion, the reaction mixture was concentrated and applied directly to a flash column, eluting with 4:1→2:1 Hex−EtOAc, to obtain compound **32a** (50 mg, 65%); R_f 0.23 (2:1 Hex−EtOAc). $[\alpha]_D^{25}$ −33.9 (*c* 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.23 (ddt, *J* = 12.8, 7.9, 4.8 Hz, 1H), 2.60 (dd, *J* = 16.4, 7.8 Hz, 1H), 2.83−2.93 (m, 2H), 3.68 (s, 3H), 4.35 (app. p, *J* = 7.1 Hz, 1H), 4.88 (dd, *J* = 9.5, 5.7 Hz, 1H), 5.19 (dd, *J* = 2.4 Hz, 2 H), 5.21 (s, 2H), 7.33−7.36 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.9, 37.9, 52.0, 60.6, 67.4, 68.4, 128.1, 128.2, 128.4, 128.5, 128.5, 128.6, 135.2, 135.5, 156.9, 170.0. HRMS (ESI-TOF) calcd for $C_{22}H_{24}NO_7$ $(M+H)^+$ 414.1547, obsd 414.1548.

(3*S*,5*R*)-Benzyl-5-[(*tert*-butoxycarbonyl)methyl]-3-benzyloxycarbonyl-isooxazolidine-2-carboxylate (32b). To a solution of compound **31** (500.0 mg, 0.88 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) was added acetic acid (0.078 mL, 78.9 mg, 1.32 mmol, 1.5 equiv). The mixture was cooled to 0 °C, and TBAF (1.3 mL, 1 M in THF, 1.32 mmol, 1.5 equiv) was added and allowed to stir at 0 °C for 30 min. The reaction mixture was warmed to rt and monitored by TLC. Upon completion (2.5 d) the mixture was concentrated and applied directly to a flash column, eluting with 4:1 Hex−EtOAc, and then the *syn* diastereomer was further purified by normal phase HPLC {(on a 25 mm × 10 mm Altima 10 μ silica column), with 5% EtOAc, 95% hexanes at 3 mL min^{-1} and dual wavelength detection at 218 and 254 nm} to obtain compound **32b** (344 mg, 55%). R_f 0.25 (2:1 Hex−EtOAc). $[\alpha]_D^{25}$ −23.25 (*c* 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 9H), 2.20 (ddt, *J* = 12.7, 9.1, 5.9 Hz, 1 H), 2.48 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.77−2.88 (m, 2H), 4.24−4.31 (m, 1H), 4.86 (dd, *J* = 9.6, 5.9 Hz, 1H), 5.16 (d, *J* = 4.9 Hz, 1 H), 5.18 (d, *J* = 2.0 Hz, 1 H), 5.19 (d, *J* = 1.0 Hz, 1 H), 5.22 (d, *J* = 4.0 Hz, 1 H), 7.26−7.37 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ28.0, 38.0, 38.4, 60.6, 67.4, 68.4, 81.5, 128.2, 128.3, 128.4, 128.5, 128.6, 135.2, 135.5, 157.0, 168.8, 170.1. HRMS (ESI-TOF) calcd for $C_{25}H_{30}NO_7$ $(M+H)^+$ 456.5547, obsd 456.5548.

2-(Allyloxycarbonylamino)adipic Acid (34). Racemic α-aminoadipic acid (250 mg, 1.55 mmol, 1.0 equiv) was added to a solution of sodium hydroxide (223 mg, 5.60 mmol, 3.6 equiv) in water (12.5 mL) at 0 °C. Allyl chloroformate (247 μL, 281 mg, 2.35 mmol, 1.5 equiv) was added dropwise over 30 min, and stirring continued for 4 h in an ice bath. The mixture was washed with diethyl ether (20 mL). The aqueous layer was acidified to pH 2 by the addition of conc. HCl and extracted with EtOAc (4 × 20 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated to give (±)-*N*-allyloxycarbonyl-2-amino-adipic acid (**34**) (350 mg, 92%). L-2-Amino-adipic acid (100 mg) was subjected to the same procedure to give (L)-*N*-allyloxycarbonyl-2-amino-adipic acid (−)-**34** (130 mg, 89%). $[\alpha]_D^{25}$ −7.82 (*c* 1.0, MeOH). The following data were obtained for the racemic compound: R_f 0.29 (6:4:1 $CHCl_3$−MeOH−H_2O). ^{1}H NMR (CD_3OD, 400 MHz) δ 1.67−1.74 (m, 3H), 1.87−190 (m, 1H), 2.33 (t, *J* = 6.8 Hz, 2H), 4.14 (dd, *J* = 8.0, 4.4 Hz, 1H), 4.54 (d, *J* = 5.3 Hz, 2H), 4.97 (br s, 1H), 5.18 (dd, *J* = 10.5, 1.4 Hz, 1H), 5.31 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.93 (ddt, *J* = 15.9, 10.6, 5.3 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 19.4, 29.1, 31.2, 52.0, 63.5, 114.5, 131.3, 155.6, 172.7, 174.0. HRMS (ESI-TOF) calcd for $C_{10}H_{15}NNaO_6$ $(M+Na)^+$ 268.0792, obsd 268.0786.

(±)-2-(Allyloxycarbonylamino)-6-methyl-1-(2-trimethylsilyl-ethoxy-methyl)-adipate (35) and other products. Cesium carbonate (173 mg, 0.53 mmol, 0.5 equiv) was added to a solution

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of (±)-2-(allyloxycarbonylamino)adipic acid (**34**) (261 mg, 1.10 mmol, 1.0 equiv) in dry MeOH (3 mL). The mixture was stirred for 2.5 h under N_2 at rt. The mixture was concentrated, and the residue dissolved in DMF (3 mL) and cooled to 0 °C. 2-(Trimethylsilyl)-ethoxymethyl chloride (226 μL, 213 mg, 1.30 mmol, 1.2 equiv) was added, and the mixture was warmed to rt, stirred overnight, and partitioned between brine (20 mL) and EtOAc (25 mL). The brine was further extracted with EtOAc (3 × 25 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give a colorless oil that was dissolved in acetonitrile (2.5 mL) and methanol (250 μL). Trimethylsilyldiazomethane (900 μL, 2 M solution in Et_2O, 1.80 mmol, 1.6 equiv) was added dropwise, and the mixture was stirred for 2.45 h at rt under N_2. The mixture was concentrated, applied to a flash column, and eluted with 3:1 hexanes−EtOAc to give di-SEM ester (**36**) (R_f 0.62, 2:1 hexanes−EtOAc) (19 mg, 3.5%), mixed ester **35** (R_f 0.49, 2:1 hexanes−EtOAc) (99 mg, 25%), and dimethyl ester **37** (R_f 0.33, 2:1 hexanes−EtOAc) (116 mg, 40%). Data for (±)-**35**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.01 (s, 9H) 0.95 (app.t, *J* = 8.4 Hz, 2H), 1.68−1.73 (m, 3H), 1.87−1.92 (m, 1H), 2.31−2.38 (m, 2H), 3.65 (s, 3H), 3.66−3.73 (m, 2H), 4.35−4.38 (m, 1H), 4.56 (d, *J* = 5.4 Hz, 2H), 5.20 (dd, *J* = 10.4, 1.3 Hz, 2H), 5.26−5.36 (m, 3H), 5.90 (ddt, *J* = 16.1, 10.6, 5.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −1.5, 18.0, 20.6, 31.8, 33.3, 51.6, 53.6, 65.8, 68.2, 89.9, 117.8, 132.6, 155.8, 171.9, 173.3. HRMS (ESI-TOF) calcd for $C_{17}H_{31}NNaO_7Si$ $(M+Na)^+$ 412.1762, obsd 412.1748.

(±)-2-(Allyloxycarbonylamino)-6-methyl-1-(2-oxopropyl)-adipate (38). *(a). 2-(Allyloxycarbonylamino)-1-(2-oxopropyl)-adipic acid.* Cesium carbonate (166 mg, 0.51 mmol, 0.5 equiv) was added to a solution of (±)-2-(allyloxycarbonylamino)-adipic acid (**34**) (250 mg, 1.02 mmol, 1.0 equiv) in dry MeOH (1 mL). The mixture was stirred for 2 h under N_2 at rt. The mixture was concentrated, dissolved in DMF (2 mL), and cooled to 0 °C. Chloroacetone (97 μL, 113 mg, 1.22 mmol, 1.2 equiv) was added, and the mixture was warmed to rt, stirred overnight, diluted with H_2O (15 mL), and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give a colorless oil (300 mg).

*(b). 2-(Allyloxycarbonylamino)-6-methyl-1-(2-oxopropyl)-adipate (**38**).* The oil was dissolved in acetonitrile (3 mL) and methanol (300 μL). Trimethylsilyldiazomethane (498 μL, 2 M solution in Et_2O, 0.99 mmol, 1.1 equiv) was added dropwise, and the mixture stirred for 2.5 h at rt under N_2. The mixture was concentrated and applied to a flash column. Elution with a gradient of 3:1→1:1 Hex−EtOAc gave compound **38** as a colorless oil (64 mg, 20%). R_f 0.40 (2:1 EtOAc−Hex). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.73−1.82 (m, 3H), 1.97−2.02 (m, 1H), 2.15 (s, 3H), 2.37 (t, *J* = 6.4 Hz, 2H), 3.66 (s, 3H), 4.42−4.46 (m, 1H), 4.56 (d, *J* = 5.5 Hz, 2H), 4.63 (d, *J* = 16.8 Hz, 1H), 4.88 (d, *J* = 16.8 Hz, 1H), 5.21 (dd, *J* = 10.4, 1.3 Hz, 2H), 5.28−5.35 (m, 2H), 5.90 (ddt, *J* = 16.1, 10.5, 5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.5, 26.0, 31.7, 33.3, 51.6, 53.5, 65.9, 68.7, 117.9, 132.5, 155.8, 171.7, 173.5, 200.6. HRMS (ESI-TOF) calcd for $C_{14}H_{21}NNaO_7$ $(M+Na)^+$ 338.1216, obsd 338.1220.

(±)-2-(Allyloxycarbonylamino)-6-(*tert*-butyl)-1-(2-oxopropyl)-adipate (41). *(a). (±)-2-(Allyloxycarbonylamino)-1-(2-oxopropyl)-adipate.* Cesium carbonate (332 mg, 1.02 mmol, 0.5 equiv) was added to a solution of (±)-2-(allyloxycarbonylamino)-adipic acid **34** (500 mg, 2.04 mmol, 1.0 equiv) in dry MeOH (4 mL). The mixture was stirred for 2 h under N_2 at rt. The mixture was concentrated, dissolved in DMF (5 mL), and cooled to 0 °C. Chloroacetone (194 μL, 226 mg, 2.44 mmol, 1.2 equiv) was added, and the mixture was warmed to rt, stirred overnight, diluted with H_2O (30 mL), and extracted with EtOAc (3 × 40 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give a colorless oil (500 mg).

*(b). (±)-2-(Allyloxycarbonylamino)-6-(tert-butyl)-1-(2-oxopropyl)-adipate (**41**).* The oil was dissolved in CH_2Cl_2 (10 mL) and added to condensed isobutylene (10 mL) and *p*-TsOH (663 mg, 3.49 mmol, 2.1 equiv). The flask was stoppered, and the mixture was stirred at rt for 3 d, diluted with CH_2Cl_2 (20 mL), and washed with sat'd aq. $NaHCO_3$ (25 mL). The aqueous layer was further extracted with CH_2Cl_2 (2 × 30 mL), and the combined organic layers were dried over $MgSO_4$, filtered, concentrated, and applied to a flash column, eluting with a gradient of 3:1→1:1 Hex−EtOAc, which gave compound **41** as a colorless oil (198 mg, 34%). R_f 0.32 (2:1 EtOAc−Hex). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41 (s, 9H), 1.64−1.79 (m, 2H), 1.91−2.02 (m, 2H), 2.14 (s, 3H) 2.25 (t, *J* = 6.9 Hz, 2H), 4.42 (dd, *J* = 12.4, 7.4 Hz, 1H), 4.55 (d, *J* = 5.4 Hz, 2H), 4.62 (d, *J* = 16.8 Hz, 1H), 4.75 (d, *J* = 16.8 Hz, 1H), 5.19 (dd, *J* = 10.4, 1.2 Hz, 1H), 5.26−5.39 (m, 1H), 5.89 (ddt, *J* = 16.2, 10.6, 5.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.7, 26.0, 28.1, 31.6, 34.7, 53.4, 65.9, 68.7, 80.4, 117.8, 132.6, 155.8, 171.8, 172.4. HRMS (ESI-TOF) calcd for $C_{17}H_{28}NO_7$ $(M+H)^+$ 358.1820, obsd 358.1826.

(L)-*N*-Allyloxycarbonyl-2-amino-adipic acid (50 mg) was subjected to the same procedures to give (−)-**41** (20 mg, 30% over two steps). $[\alpha]_D^{25}$ −7.75 (*c* 1.0, MeOH).

2-(Allyloxycarbonylamino)-1-(2-oxopropyl)-adipic Acid (40). To a solution of diester **41** (25 mg, 0.069 mmol, 1.0 equiv) in dry CH_2Cl_2 (2 mL) was added trifluoroacetic acid (2 mL) at 0 °C and allowed to stir at 0 °C for 1 h. The reaction mixture was warmed to rt and stirred overnight, concentrated, and applied to a flash column. Elution with a gradient of 3:1→4:1 EtOAc−Hex gave compound **40** (15 mg, 65%). R_f 0.23 (3:1 EtOAc−Hex). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.20−1.29 (m, 2H), 1.78−1.84 (m, 2H), 2.17 (s, 3H), 2.43 (t, *J* = 7.1 Hz, 2H), 4.43−4.50 (m, 1H), 4.58 (d, *J* = 5.0 Hz, 2H), 4.65 (d, *J* = 16.8 Hz, 1H), 4.80 (d, *J* = 16.8 Hz, 1H), 5.22 (dd, *J* = 10.4, 1.1 Hz, 1H), 5.29 (d, *J* = 2.6 Hz, 1H), 5.34 (s, 1H), 5.91 (ddt, *J* = 16.2, 10.7, 5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.4, 26.0, 31.7, 32.9, 53.4, 66.0, 68.7, 118.0, 132.5, 155.9, 171.6, 176.6. HRMS (ESI-TOF) calcd for $C_{13}H_{19}NNaO_7$ $(M+Na)^+$ 324.1054, obsd 324.1054.

2-(Allyloxycarbonylamino)-6-(*tert*-butyl)adipate (42). TBAF (111 μL, 1 M in THF, 0.112 mmol, 2.0 equiv) was added to a solution of compound **41** (20 mg, 0.056 mmol, 1.0 equiv) in dry THF (1 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h, warmed to rt, and stirred overnight. The mixture was concentrated and applied to a flash column, eluting with a gradient of 3:1→4:1 EtOAc−Hex to give compound **42** (11 mg, 68%). R_f 0.25 (2:1 EtOAc−Hex). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41 (s, 9H), 1.64−1.79 (m, 2H), 1.91−2.02 (m, 2H), 2.25 (t, *J* = 6.9 Hz, 2H), 4.42 (dd, *J* = 12.4, 7.4 Hz, 1H), 4.55 (d, *J* = 5.4 Hz, 2H), 5.19 (dd, *J* = 10.4, 1.2 Hz, 1H), 5.26−5.39 (m, 1H), 5.89 (ddt, *J* = 16.2, 10.6, 5.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.7, 28.1, 31.6, 34.7, 53.4, 65.9, 80.4, 117.8, 132.6, 155.8, 171.8, 172.4. HRMS (ESI-TOF) calcd for $C_{14}H_{23}NNaO_6$ $(M+Na)^+$ 324.1424, obsd 324.1418.

(3*S*,5*R*)-3-(Allyloxycarbonylamino)-5-[(*tert*-butoxycarbonyl)-methyl]-2-oxo-tetrahydrofuran (44). *(a). (2S,4R)-2-Amino-6-tert-butyl-4-hydroxyadipic Acid (**33b**).* Compound **32b** (100 mg, 0.219 mmol, 1.0 equiv) was dissolved in dry MeOH (2 mL), and 10% Pd−C (93 mg, 0.879 mmol, 4.0 equiv) was added. The suspension was stirred at rt overnight under an atmosphere of H_2. The reaction mixture was filtered through Celite, and the filtrate was concentrated to give the amino acid **33b** as a colorless oil (40 mg). R_f 0.56 (6:4:1 $CHCl_3$−MeOH−H_2O).

*(b). (2S,4R)-2-(Allyloxycarbonylamino)-6-tert-butyl-4-hydroxy-adipic Acid (**43**).* The amino acid **33b** was dissolved in a solution of sodium hydroxide (32 mg, 0.788 mmol, 3.6 equiv) in water (2 mL) at 0 °C and followed by dropwise addition of allyl chloroformate (28 μL, 32 mg, 0.263 mmol, 1.2 equiv) at 0 °C. The mixture was stirred an additional 1 h at 0 °C and then warmed to rt and stirred overnight. The reaction mixture was washed with diethyl ether (5 mL) to remove unreacted allylchloroformate. The aqueous layer was cooled to 0 °C and then acidified to ∼pH 4 by the dropwise addition of 0.5 M HCl. The aqueous layer was extracted with EtOAc (5 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to obtain compound **43**. R_f 0.54 (9:1 CH_2Cl_2−MeOH).

*(c). (3S,5R)-3-(Allyloxycarbonylamino)-5-[(tert-Butoxycarbonyl)-methyl]-2-oxo-tetrahydrofuran (**44**).* Cesium carbonate (36 mg, 0.109 mmol, 0.5 equiv) was added to a solution of acid **43** in dry MeOH (4 mL). The mixture was stirred for 2 h under N_2 at rt. The mixture was concentrated, dissolved in DMF (5 mL), and cooled to 0 °C. Chloroacetone (21 μL, 24 mg, 0.263 mmol, 1.2 equiv) was added,

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and the mixture was warmed to rt, stirred overnight, diluted with H_2O (5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give a colorless oil that was dissolved in CH_2Cl_2 (2 mL) and added 2,6-lutidine (254 μL, 235 mg, 2.190 mmol, 10.0 equiv) and TBSOTf (402 μL, 463 mg, 1.752 mmol, 8.0 equiv). The reaction mixture was stirred and concentrated to remove the CH_2Cl_2. Water (2 mL) was added to the reaction mixture which was then cooled to 0 °C and acidified to ~pH 4 by the dropwise addition of 0.5 M HCl. The acidic solution was then extracted with EtOAc (4 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and then concentrated to afford a viscous oil. Flash chromatography on silica gel (Hex−EtOAc 3:1) afforded the lactone **44** as a colorless oil (57 mg, 45% over four steps). R_f 0.54 (1:1 Hex−EtOAc). $[\alpha]_D^{25}$ −8.47 (*c* 2.5, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 1.45 (s, 9H), 2.14−2.17 (m, 1H), 2.38−2.79 (m, 3H), 4.48 (dd, *J* = 16.1, 9.3 Hz, 1H), 4.58 (d, *J* = 5.3 Hz, 2H), 4.98 (dd, *J* = 16.1, 9.3 Hz, 1H), 5.22 (app. d, *J* = 10.4 Hz, 1H), 5.30 (app. d, *J* = 16.4 Hz, 1H), 5.46 (d, *J* = 5.7 Hz, 1H), 5.90 (ddt, *J* = 16.4, 10.8, 5.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.0, 33.6, 40.6, 49.5, 66.2, 74.2, 81.9, 118.2, 132.3, 155.9, 168.5, 174.6. HRMS (ESI-TOF) calcd for $C_{14}H_{21}NNaO_6$ $(M+Na)^+$ 322.1261, obsd 322.1270.

(2*S*,4*R*)-2-(Allyloxycarbonylamino)-6-(*tert*-butyl)-4-(*tert*-butyldimethylsilyloxy)-1-(2-oxopropyl)-adipic acid (45). *(a). (2S,4R)-2-(Allyloxycarbonylamino)-6-(tert-butyl)-4-(tert-butyldimethylsilyloxy)-adipic acid (45).* Compound **32b** (80 mg, 0.176 mmol, 1.0 equiv) was converted to compound **43** as described in steps (a) and (b) of the preceding procedure. 2,6-Lutidine (51 μL, 47 mg, 0.44 mmol, 2.5 equiv) and TBSCl (66 mg, 0.44 mmol, 2.5 equiv) were added sequentially to a solution of acid **43** in dry CH_2Cl_2 (2 mL) at rt under N_2. The reaction mixture was stirred and concentrated to remove the CH_2Cl_2. Water (2 mL) was added to the reaction mixture which was then cooled to 0 °C and acidified to ~pH 4 by the dropwise addition of 0.5 M HCl. The acidic solution was then extracted with EtOAc (4 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give the carboxylic acid that was used directly in the next step without further purification. R_f 0.61 (95:5 CH_2Cl_2−MeOH).

(b). (2S,4R)-2-(Allyloxycarbonylamino)-6-(tert-butyl)-4-(tert-butyldimethylsilyloxy)-1-(2-oxopropyl)-adipic Acid (45). The carboxylic acid was dissolved in dry CH_2Cl_2 (2 mL) and cooled to 0 °C under a N_2 atmosphere. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide) (EDC) (68 mg, 0.352 mmol, 2.0 equiv) was added, followed by DMAP (6 mg, 0.0528 mmol, 0.3 equiv) and acetol (36 μL, 39 mg, 0.528 mmol, 3.0 equiv) at 0 °C. The reaction mixture was warmed to rt, stirred overnight, and then concentrated to afford a viscous oil. Flash chromatography on silica gel (Hex−EtOAc 3:1) afforded the compound **45** as a colorless oil (25 mg, 30% over four steps). R_f 0.60 (1:1 Hex−EtOAc). $[\alpha]_D^{25}$ −13.25 (*c* 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 0.08 (s, 3H), 0.09 (s, 3H), 0.89 (s, 9H), 1.45 (s, 9H), 1.93−1.99 (m, 1H), 2.17 (s, 3H), 2.30−2.51 (m, 3H), 4.29 (app. pent. *J* = 5.9 Hz, 1H), 4.50 (ddd, *J* = 12.4, 7.7, 4.8 Hz, 1H), 4.57−4.78 (m, 4H), 5.20 (d, *J* = 10.5 Hz, 1H), 5.30 (d, *J* = 16.0 Hz, 1H), 5.62 (d, *J* = 7.1 Hz, 1H), 5.90 (ddt, *J* = 16.0, 10.7, 5.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.6, −4.7, 17.9, 26.1, 27.9, 28.1, 38.3, 43.1, 51.4, 65.9. 67.2, 68.7, 80.9, 117.7, 132.7, 155.9, 171.7, 173.5, 201.0. HRMS (ESI-TOF) calcd for $C_{23}H_{42}NO_8Si$ $(M+H)^+$ 488.2674, obsd 488.2684.

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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