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Convergent Synthesis of (2*R*,3*R*,8*R*,9*R*)-*N*-Boc-ADDA

Sebastien Meiries and Rodolfo Marquez*,†

WestCHEM, University of Glasgow, Joseph Black Building, University Avenue, Glasgow G12 8QQ, U.K.

r.marquez@chem.gla.ac.uk

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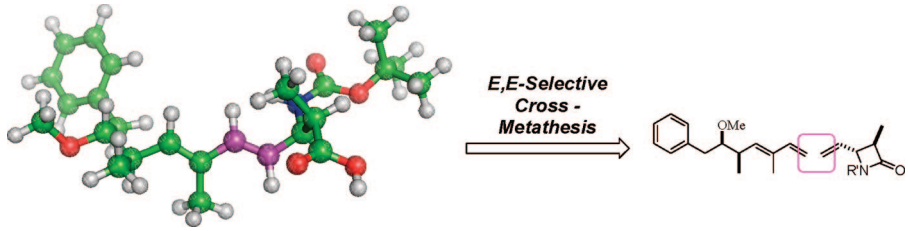

The convergent synthesis of *N*-Boc-(2*R*,3*R*,8*R*,9*R*,4*E*,6*E*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldecadenoic acid (*enantio*-*N*-Boc-ADDA) is reported. Our flexible approach takes advantage of highly efficient non-aldol aldol and cross-metathesis methodologies.

Introduction

Protein phosphatases (PPs) are a crucial group of proteins involved in a variety of processes including cell division, neurotransmission, memory, and learning. Some of the most important PPs are the serine-threonine phosphatases 1, 2A/B, and 4 (PP1, PP2A/B, and PP4), which have been shown to have significant roles in signal transduction pathways.[1] Unfortunately, despite extensive testing, our understanding of the relative pharmacological functions of the various phosphatases remains fairly limited due to their structural similarity and the lack of selective inhibitors.[2]

Motuporin **1**, nodularin **2**, and the microcystins (i.e., microcystin LA, **3**) (Figure 1) are macrocyclic peptides of marine origin (the microcystins and nodularin were isolated from cyanobacteria while motuporin was isolated from the marine sponge *Theonella swinhoei*).[3,4] Although all of them exhibit biological activity as protein phosphatase inhibitors, their toxicity has kept them from being developed as potential therapeutic leads.[5]

Structurally, the microcystins nodularin and motuporin share the unusual β-amino acid unit (2*S*,3*S*,8*S*,9*S*,4*E*,6*E*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldecadenoic acid **4** ("ADDA") which upon truncation causes the PP inhibitory activity of the macrocyclic peptides to cease. The unique structure of ADDA as well as its biological relevance has inspired a number of synthetic approaches developed to date.[6]

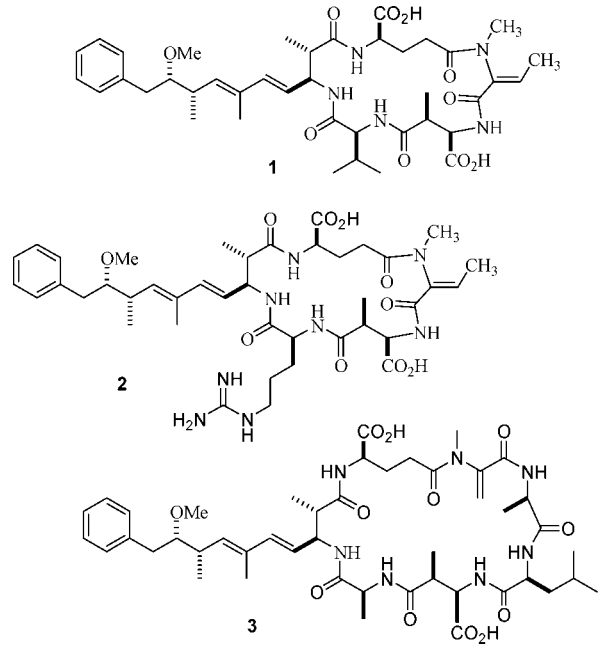

FIGURE 1. Motuporin **1**, nodularin **2**, and microcystin LA**3**.

Reports by Chamberlin and co-workers have demonstrated that microcystin analogues **5** incorporating the *N*-acylated ADDA chain and a single amino acid retain moderate activity

† Ian Sword Lecturer of Organic Chemistry.

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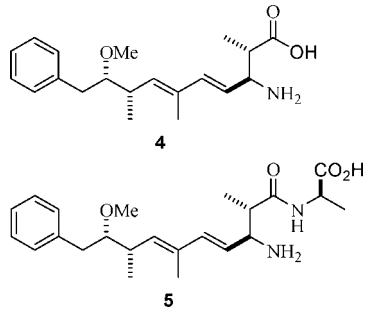


FIGURE 2. ADDA **4** and ADDA analogue **5**.

as PP1/PP2A inhibitors (Figure 2).[7,8] Interestingly, naturally occurring 6*Z*-ADDA[3] nodularin and microcystin analogues display none of the toxicity associated with the parent compounds.[9]

Iso-Motuporin **6** was recently isolated from the marine sponge *T. swinhoei*, showcasing a structurally novel *iso*-ADDA fragment (Figure 3).[10] This discovery, together with the previously reported biological activity of the 6*Z*-ADDA[3] derivates raise the possibility that stereoisomeric forms of the ADDA scaffold (and conversely microcystin, motuporin, and nodularin) provide an alternative starting point for the development of novel biological chemical probes to study and dissect phosphatase activity.

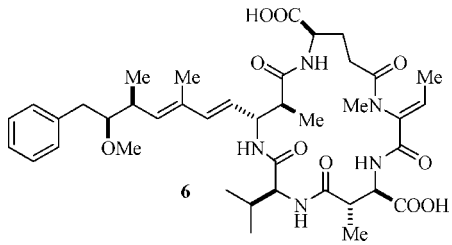
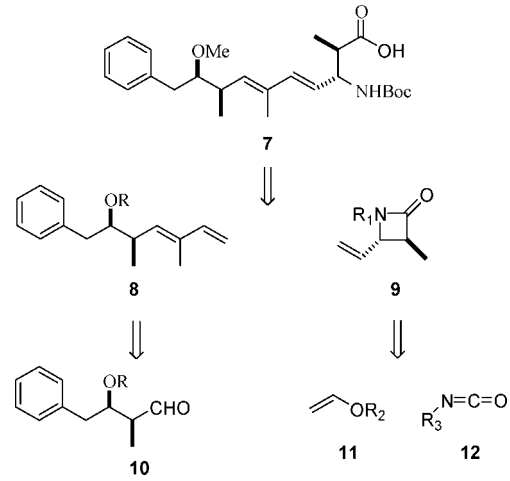


FIGURE 3. *Iso*-Motuporin **6** bearing the previously unidentified *iso*-ADDA chain.

As part of our efforts toward the generation of novel ADDA isoforms, we would like to report the first convergent synthesis of *enantio-N*-Boc-ADDA which takes advantage of a key *E,E*-selective diene cross-metathesis coupling to introduce the core diene unit. An efficient synthesis of *enantio*-ADDA would not only provide a proof of concept for our synthetic approach but also allow us to determine the effect of ADDA's absolute stereochemistry on its biological activity both on its own and when attached to other naturally occurring macrocyclic peptides.

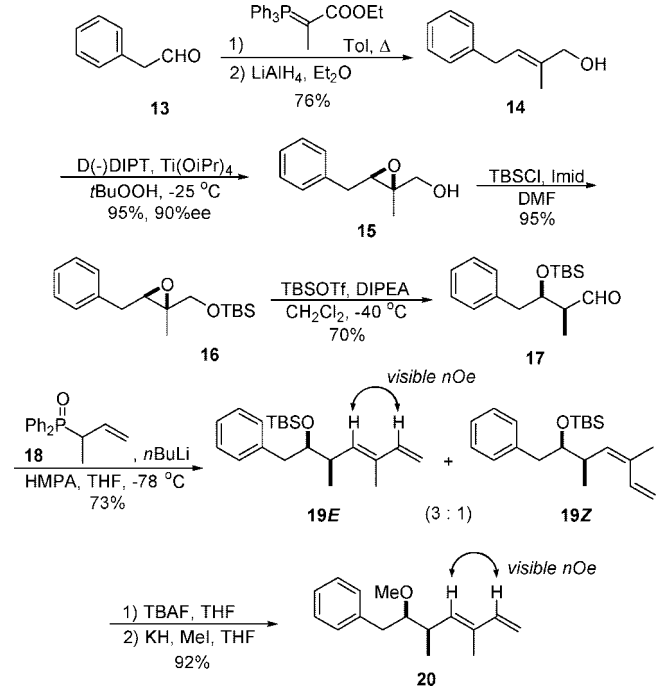
SCHEME 1. Retrosynthetic Analysis



Retrosynthetically, we envisioned *enantio-N*-Boc-ADDA **7** as having originated through the convergent cross-metathesis coupling of diene **8** with vinyl lactam **9**. Diene **8** could be readily secured through the olefination of aldehyde **10**, in turn easily accessible through Jung's non-aldol aldol methodology.[11] The β-lactam coupling partner on the other hand, could be accessed through the condensation of vinyl enol ether **11** and a suitably protected isocyanate **12** (Scheme 1).

Our synthesis began with phenylacetaldehyde **13** which was olefinated and reduced to afford the desired allylic alcohol **14** in excellent yield and with complete *E* selectivity. A Sharpless reagent-controlled epoxidation of alkenol **14** then generated the desired epoxide **15** in high yield and good enantiomeric excess (Scheme 2).

SCHEME 2. Non-aldol Aldol Approach to Diene Unit



Protection of alcohol **15** proceeded in near-quantitative yield to afford the TBS silyl ether **16**, which under Jung's non-aldol

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aldol conditions generated propionate **17** in high yield and as a single diastereomer. Olefination of aldehyde **17** with phosphine oxide **18**[12] afforded the desired diene **19** as mixture of isomers in which the major component exhibited the required internal *E* double-bond geometry. The double-bond geometry was corroborated through ^{1}H NMR and NOE analysis.

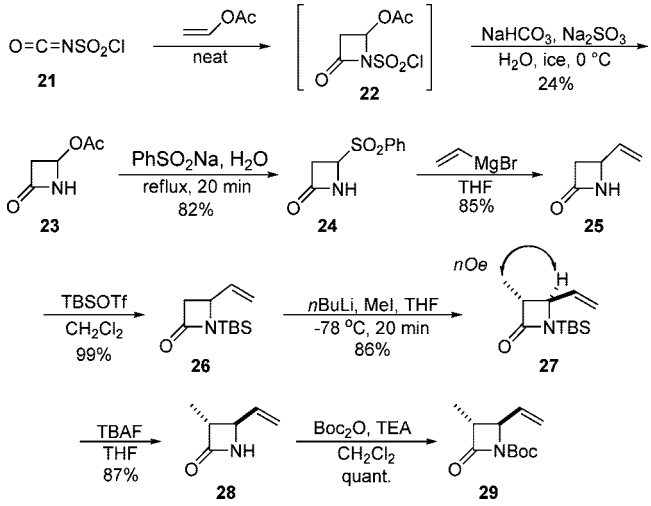
Efficient desilylation of diene **19*E*** followed by methylation of the resulting free hydroxyl group completed the synthesis of the *enantio*-ADDA unit's left-hand side **20** (Scheme 2).

The synthesis of the desired β-lactam coupling partner began with the careful treatment of vinyl acetate with chlorosulfonyl isocyanate **21** to generate the crude acetoxyazetidinone **23** in moderate yield (Scheme 3).[13] Acetoxyazetidinone **23** was then converted to sulfone **24** which upon treatment with vinylmagnesium bromide afforded the vinyl azetidinone **25** in good overall yield.[14]

Protection of vinyl azetidinone **25** proceeded in near-quantitative yield to generate the *N*-TBS silyl amide **26**. Enolization and methylation of lactam **26** completed the synthesis of the required β-lactam core unit **27** in good yield and as a single diastereomer. The relative configuration was corroborated through ^{1}H NMR and NOE analysis.

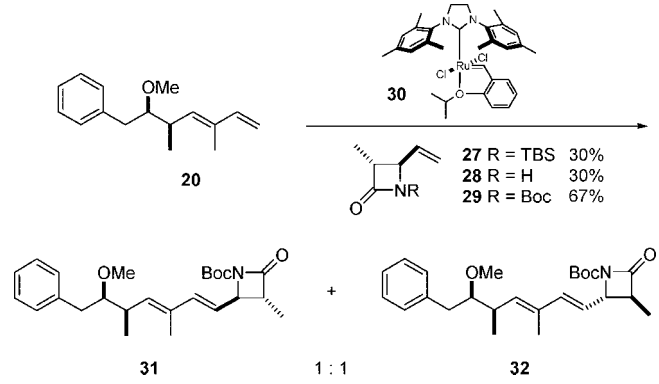
Introduction of the Boc protecting group proceeded in quantitative yield to afford the required carbamate unit **29** (Scheme 3).

SCHEME 3. Synthesis of β-Lactam Coupling Partner



Having successfully achieved the synthesis of both the left and right-hand side units, the crucial cross-metathesis couplings were attempted.[15] After extensive catalyst screening under a wide range of experimental conditions, the desired cross-metathesis was successfully achieved between diene **20** and β-lactams **27**−**29** to generate the desired product as a single *E*,*E*-diene and a 1:1 mixture of diastereomers. The cross-metathesis was only successful in the presence of the second generation Hoveyda−Grubbs catalyst **30** (Scheme 4), and the yield was greatly improved through the use of the Boc-protected lactam **29**. To the best of our knowledge, this is the first example of a diene−alkene cross-metathesis reaction involving two electron-rich species.[16]

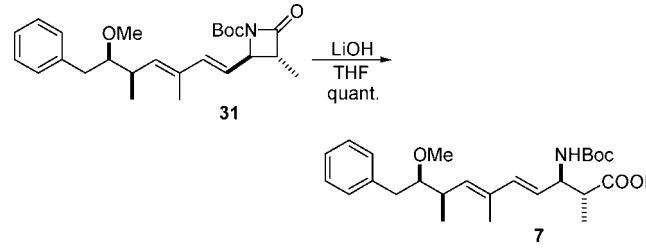
SCHEME 4. Diene−Alkene Cross-Methatesis



Separation of the diastereomeric mixture through the use of semi-preparative HPLC under reversed-phase conditions allowed the isolation of compound **31** with near-quantitative efficiency. The undetected compound **32** appears to have decomposed under the HPLC separation conditions.

Finally, a near-quantitative base-promoted ring opening of lactam **31** then completed our efficient and convergent synthesis of *enantio-N*-Boc-ADDA **7** (Scheme 5). The spectral data of *enantio-N*-Boc-ADDA matched that reported for *N*-Boc-ADDA. As expected, *enantio-N*-Boc-ADDA had almost the exact opposite optical rotation $[\alpha]^{23}_D$ +15.1 (c = 1.0, $CHCl_3$) to that reported for *N*-Boc-ADDA $[\alpha]^{23}_D$ −15.7 (c = 1.0, $CHCl_3$).[6d]

SCHEME 5. Completion of the Synthesis of *enantio-N*-Boc ADDA



In conclusion, we have completed the efficient and convergent synthesis of (2*R*,3*R*,8*R*,9*R*)-*N*-Boc-ADDA taking advantage of non-aldol aldol and cross-metathesis methodologies to introduce the key functionality.

Our efficient approach can be easily scaled up and compares favorably with the other approaches reported for the synthesis of ADDA in terms of convergence and flexibility despite the generation of the mixture of diastereomers during the cross-metathesis step (10 steps starting from phenyl acetaldehyde **13** and 10% overall yield). Furthermore, in most steps, the intermediate compounds can be taken on crude to subsequent steps in similar or better yields.

We are currently in the process of evaluating *enantio-N*-Boc ADDA's full biological profile, while simultaneously developing new potential phosphatase inhibitors using this synthetic approach.

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Experimental Section

(*E*)-2-Methyl-4-phenylbut-2-en-1-ol, 14. To a stirred solution of commercially available phenylacetaldehyde **13** (6.05 g, 504 mmol) in dry benzene (120 mL) was added (1-ethoxycarbonylethylidene)triphenylphosphorane (23.93 g, 660 mmol), and the resultant solution was refluxed overnight. The reaction mixture was concentrated under reduced pressure, and the resultant yellow residue was washed with petroleum ether (5 × 150 mL) to crush out triphenylphosphine oxide. After filtrations, the combined washings were concentrated under vacuum to give a crude residue (9.34 g) which was purified by column chromatography (silica gel, 1−2% diethyl ether in 40−60 petroleum ether) to afford (*E*)-ethyl 2-methyl-4-phenylbut-2-enoate (8.64 g, 84%) as a clear and colorless viscous oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (3H, t, J = 7.1 Hz), 2.00 (3H, appq, J = 1.4 Hz), 3.57 (2H, d, J = 7.6 Hz), 4.23 (2H, q, J = 7.1 Hz), 6.96 (1H, tq, J = 7.6, 1.4 Hz), 7.22−7.37 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.6, 14.3, 34.9, 60.6, 126.4, 128.5, 128.6, 128.7, 139.1, 140.0, 168.1; IR (thin film) ν_{max} = 3029, 2981, 2932, 1710, 1255, 742, 699 cm^{-1}; HRMS (EI) obsd M$^+$ 204.1152, calcd for $C_{13}H_{16}O_2$ 204.1150.

To a stirred solution of (*E*)-ethyl 2-methyl-4-phenylbut-2-enoate (2.11 g, 103 mmol) in anhydrous diethyl ether (40 mL) was added $LiAlH_4$ dropwise (1.0 M in hexanes, 10.0 mL, 10.0 mmol) at 0 °C. The reaction was allowed to warm to room temperature until completion as indicated by TLC (4 h). The reaction mixture was quenched at 0 °C by addition of water (2 mL) and aq sodium hydroxide (20%, 1 mL). The workup was continued by the further addition of water (40 mL) and aq sodium hydroxide (20%, 20 mL). The mixture was stirred for 30 min, after which the mineral solid precipitate was filtrated and washed with diethyl ether (120 mL). The organic extracts were dried over anhydrous sodium sulfate and concentrated under vacuum to give a crude residue (1.71 g). Flash column chromatography (silica gel, 60% diethyl ether in 40−60 petroleum ether) provided the desired alcohol **14** (1.51 g, 90%) as a clear and colorless viscous oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80 (3H, s), 1.98 (1H, bs), 3.42 (2H, d, J = 7.4 Hz), 4.04 (2H, s), 5.64 (1H, tq, J = 7.4, 1.4 Hz), 7.23−7.33 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 33.9, 68.6, 124.6, 126.0, 128.4, 128.6, 135.7, 141.0; IR (thin film) ν_{max} = 3324, 3027, 2915, 2860, 1493, 1453, 1016, 741, 698 cm^{-1}; HRMS (EI) obsd M$^+$ 162.1043, calcd for $C_{11}H_{14}O$ 162.1045.

((2*R*,3*R*)-3-Benzyl-2-methyloxiran-2-yl)methanol, 15. To flame-dried 4 Å molecular sieves (32 g in powder) in a round-bottom flask was added dry dichloromethane (250 mL) followed by freshly distilled D-(−)-DIPT (13.55 mL, 14.95 g, 63.80 mmol). After the mixture was cooled to −30 °C, freshly distilled $Ti(OiPr)_4$ (17.82 mL, 17.11 g, 60.19 mmol) was added, and the reaction was allowed to stir at −30 °C for 30 min. After the addition of *t*-BuOOH (5.5 M in decanes, 64.0 mL, 352 mmol) at −25 °C, the solution was allowed to stir for a further 1 h at −30 °C before being treated with a solution of alcohol **14** (27.70 g, 171 mmol) in anhydrous dichloromethane (250 mL). The reaction was stirred for 1 h at −30 °C and then allowed to warm slowly to room temperature overnight. The reaction was quenched by addition of water (800 mL) followed by an aq sodium hydroxide solution (30%) saturated with NaCl (175 mL total volume). The resultant milky mixture was filtrated through cotton wool and sand (2 kg) and then washed with diethyl ether (1000 mL) and dichloromethane (1000 mL). The phases were separated, and the aqueous layer was washed with dichloromethane (250 mL). The organic extracts were combined, dried over anhydrous sodium sulfate, and concentrated under vacuum to afford a viscous oil (51.28 g). Purification of the resulting crude residue by flash column chromatography (silica gel, 30% ethyl acetate in 40−60 petroleum ether) afforded the pure desired epoxide **15** (28.7 g, 95%, ee = 90%) as a clear and colorless viscous oil. The enantiomeric excess was determined through HPLC analysis with a chiral column using hexanes/2-propanol (99:1) at a flow rate of 0.75 mL/min: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (3H, s), 2.06 (1H, bs), 2.90 (1H, dd, J = 14.7, 6.2 Hz), 3.00 (1H, dd, J = 14.7, 6.4 Hz), 3.33 (1H, t, J = 6.3 Hz), 3.61 (1H, d, J = 12.3 Hz), 3.73 (1H, d, J = 12.3 Hz), 7.26−7.38 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 34.7, 60.3, 61.4, 65.3, 126.7, 128.7, 128.8, 137.6; $[\alpha]^{25}_D$ +23.2 (c = 1.0, $CHCl_3$); IR (thin film) ν_{max} = 3419, 3029, 2965, 2926, 2870, 1496, 1454, 1038, 742, 700 cm^{-1}; HRMS (EI) obsd M$^+$ 178.0995, calcd for $C_{11}H_{14}O_2$ 178.0994.

(((2*R*,3*R*)-3-Benzyl-2-methyloxiran-2-yl)methoxy)(*tert*-butyl)dimethylsilane, 16. A solution of epoxide **15** (207 mg, 1.16 mmol) in anhydrous *N,N*-dimethylformamide (6 mL) was treated with imidazole (237 mg, 3.48 mmol) and stirred until homogeneous. The reaction mixture was treated with TBSCl (277 mg, 1.84 mmol) and stirred under argon until completion as indicated by TLC analysis (2 h). The reaction was quenched by the addition of a 1:1 mixture of diethyl ether/water (14 mL total volume). The mixture was then slightly acidified by addition of aq HCl (1.0 M, 1.5 mL) before the two phases were separated. The organic extracts were washed with water (10 mL) and brine (10 mL). The combined ether extracts were dried over anhydrous sodium sulfate and concentrated under vacuum to yield a dark yellow crude oil (331 mg). Flash column chromatography (silica gel, 30% ethyl acetate in hexane) gave the desired silyl protected epoxide **16** (325 mg, 95%) as a clear and colorless viscous oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.03 (3H, s), 0.00 (3H, s), 0.84 (9H, s), δ 1.36 (3H, s), 2.78 (1H, dd, J = 14.8, 6.7 Hz), 2.93 (1H, dd, J = 14.8, 6.0 Hz), 3.09 (1H, appt, J = 6.3 Hz,), 3.52 (1H, d, J = 11.1 Hz), 3.57 (1H, d, J = 11.1 Hz), 7.18−7.28 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4, 14.4, 18.3, 25.9, 34.7, 61.2, 61.3, 68.0, 126.5, 128.6, 128.7, 137.8; $[\alpha]^{25}_D$ −2.5 (c = 1.0, $CHCl_3$); IR (thin film) ν_{max} = 2929, 2857, 1689, 1471, 1461, 1255, 1096, 837 cm^{-1}; HRMS (CI) obsd (M + H)$^+$ 293.1935, calcd for $C_{17}H_{29}O_2Si$ 293.1937.

(2*S*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)-2-methyl-4-phenylbutanal, 17. A −78 °C solution of the epoxy alcohol **16** (1.35 g, 4.60 mmol) in anhydrous dichloromethane (125 mL) was sequentially treated with anhydrous DIPEA (2.42 mL, 1.80 g, 13.89 mmol) and TBSOTf (3.19 mL, 3.67 g, 13.89 mmol). The mixture was then slowly allowed to warm to −45 °C and stirred until completion as indicated by TLC analysis (3 h). The cold mixture was then cooled once again to −78 °C before being poured into a separating funnel containing a 1:1 mixture of diethyl ether and 1 M aq $NaHPO_4$ (100 mL total volume). The phases were separated, and the organic layer was then successively washed with water (2 × 50 mL) and aq $NaHPO_4$ (1.0 M, 50 mL). The combined aqueous fractions were extracted with diethyl ether (20 mL), and the organic extracts were combined and dried over anhydrous sodium sulfate. The solvents were evaporated under reduced pressure to provide a light yellow crude oil (3.25 g) which was purified by flash chromatography (silica gel, 1% TEA, 20% dichloromethane in 40−60 petroleum ether) to afford the pure aldehyde **17** as a clear and colorless viscous oil (948 mg, 70%). The aldehyde proved unstable upon standing, and it could not be stored for any periods of time without decomposition being observed: ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.14 (3H, s), 0.00 (3H, s), 0.85 (9H, s), 1.15 (3H, d, J = 7.0 Hz), 2.35 (1H, qd, J = 6.9, 3.0 Hz), 2.80 (2H, d, J = 7.0 Hz), 4.39 (1H, td, J = 7.0, 3.0 Hz), 7.16−7.32 (5H, m), 9.70 (1H, bs); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.7, 7.3, 18.0, 25.7, 41.2, 50.5, 73.2, 126.6, 128.5, 129.4, 138.0, 204.9; $[\alpha]^{25}_D$ +37.0 (c = 1.0, $CHCl_3$); IR (thin film) ν_{max} = 3028, 2954, 2929, 2710, 1727, 1254, 1104, 1032, 837, 777, 700 cm^{-1}; HRMS (CI) obsd (M + H)$^+$ 293.1938, calcd for $C_{17}H_{29}O_2Si$ 293.1937.

***tert*-Butyl ((2*R*,3*R*,4*E*)-3,5-Dimethyl-1-phenylhepta-4,6-dien-2-yloxy)dimethylsilane, 19*E*, and *tert*-Butyl ((2*R*,3*R*,4*Z*)-3,5-Dimethyl-1-phenylhepta-4,6-dien-2-yloxy)dimethylsilane, 19*Z*.** A −78 °C solution of phosphine oxide **18** (1.20 g, 4.68 mmol) in anhydrous THF (16 mL) was treated with the dropwise addition of *n*-butyllithium (2.5 M in hexanes, 1.80 mL, 4.50 mmol). The reaction was stirred for 20 min at −78 °C before a solution of freshly distilled HMPA (1.65 mL, 1.70 g, 9.48 mmol) in dry THF (5 mL) was incorporated. A solution of aldehyde **17** (913 mg, 3.11

mmol) in anhydrous THF (5 mL) was then added dropwise, and the reaction mixture was stirred at −78 °C until completion as indicated by TLC analysis (15 min). The reaction was quenched with water (20 mL), and the two phases were separated. The organic layer was sequentially washed with water (2 × 20 mL) and satd aq LiBr (2 × 20 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo to give a viscous yellow oil (1.69 g) which was then purified by flash chromatography (silica gel, 1% TEA in 40−60 petroleum ether) to afford 565 mg of the pure TBS-protected diene **19*E*** and 188 mg of the minor diene **19*Z*** as colorless, clear, and viscous oils (753 mg, 73% overall yield).

19*E*: ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.26 (3H, s), 0.02 (3H, s), 0.87 (9H, s), 1.00 (3H, d, J = 6.8 Hz), 1.56 (3H, d, J = 1.2 Hz), 2.45−2.54 (1H, m), 2.69 (1H, dd, J = 13.6, 6.4 Hz), 2.82 (1H, dd, J = 13.6, 6.0 Hz), 3.78 (1H, appq, J = 6.2 Hz), 4.93 (1H, d, J = 10.8 Hz), 5.07 (1H, d, J = 17.4 Hz), 5.42 (1H, d, J = 9.7 Hz), 6.34 (1H, ddd, J = 17.4, 10.7, 0.4 Hz), 7.15−7.28 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.5, 11.8, 15.2, 18.1, 25.9, 37.1, 41.7, 77.3, 110.7, 126.0, 128.1, 129.7, 132.9, 136.9, 139.1, 141.8; $[\alpha]^{20}_D$ +23.0 (c = 1.0, $CHCl_3$); IR (thin film) ν_{max} = 3027, 2956, 2928, 2856, 1254, 1100, 1085, 835, 774, 699 cm^{-1}.

19*Z*: ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.15 (3H, s), 0.00 (3H, s), 0.87 (9H, s), 0.98 (3H, d, J = 6.8 Hz), 1.68 (3H, s), 2.51−2.56 (1H, m), 2.65 (2H, dd, J = 8.4, 1.3 Hz), 3.76−3.80 (1H, m), 4.96 (1H, d, J = 10.7 Hz), 5.11 (1H, d, J = 17.4 Hz), 5.58 (1H, d, J = 9.6 Hz), 6.44 (1H, dd, J = 17.4, 10.7 Hz), 7.06−7.28 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.6, 12.1, 16.9, 18.1, 25.9, 37.2, 41.3, 77.4, 110.7, 126.0, 128.2, 129.7, 133.9, 134.8, 139.4, 142.0; $[\alpha]^{25}_D$ −11.8 (c = 1.0, $CHCl_3$). IR (thin film) ν_{max} = 3027, 2956, 2928, 2856, 1254, 1100, 1085, 835, 774, 699 cm^{-1}.

((2*R*,3*R*,4*E*)-2-Methoxy-3,5-dimethylhepta-4,6-dienyl)benzene, 20. A solution of TBS-protected diene **19*E*** (544 mg, 1.65 mmol) in anhydrous THF (30 mL) was transferred into a round-bottom flask containing flame-activated powdered 4 Å molecular sieves (2 g). The suspension was treated with tetrabutylammonium fluoride (1.0 M in THF, 4.90 mL, 4.90 mmol), and the resulting mixture was stirred at room temperature until completion as indicated by TLC analysis (15 min). The mixture was then quenched with water (40 mL) and the reaction extracted with ethyl acetate (2 × 20 mL). The organic extracts were combined and dried over anhydrous sodium sulfate, and the solvents were removed under vacuum. The resulting brown oil (447 mg) was then taken on crude to the next reaction without any further purification.

Neat KH (1.20 g, 30 mmol) was mixed with anhydrous THF (90 mL), and the resulting suspension was treated with the crude dienol at 0 °C. The reaction mixture was then stirred under argon at 0 °C for 20 min, and iodomethane (1.60 mL, 3.65 g, 25.70 mmol) was incorporated through a small pad of basic alumina. The reaction mixture was then allowed to slowly warm to room temperature. The reaction was stirred at room temperature until completion (2−3 h) and carefully quenched by the slow addition of a satd aq $NaHCO_3$ (70 mL). The phases were separated, and the aqueous layer was extracted with diethyl ether (30 mL). The organic extract was dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The crude yellow oil (433 mg) obtained was then purified by flash chromatography (silica gel, 70% toluene in 40−60 petroleum ether) to afford diene **20** as a colorless and clear viscous oil (347 mg, 92% over two steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (3H, d, J = 6.7 Hz), 1.65 (3H, d, J = 1.2 Hz), 2.57−2.66 (1H, m), 2.70 (1H, dd, J = 13.9, 7.4 Hz), 2.83 (1H, dd, J = 13.9, 4.5 Hz), 3.19−3.23 (1H, m), 3.24 (3H, s), 4.97 (1H, d, J = 10.7 Hz), 5.11 (2H, dd, J = 17.4, 0.3 Hz), 5.41 (1H, d, J = 9.8 Hz), 6.38 (1H, ddd, J = 17.4, 10.6, 0.6 Hz), 7.17−7.30 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9, 16.2, 36.6, 38.2, 58.6, 86.9, 111.1, 125.9, 128.1, 129.4, 133.7, 135.8, 139.4, 141.6; $[\alpha]^{25}_D$ −2.6 (c = 1.0, $CHCl_3$); IR (thin film) ν_{max} = 3027, 2955, 2928, 2871, 1454, 1096, 700 cm^{-1}; HRMS (CI) obsd (M + H)$^+$ 231.1745, calcd for $C_{16}H_{23}O$ 231.1749.

4-Acetoxyazetidinone, 23. Freshly distilled vinyl acetate (286 mL, 267.1 g, 3.10 mol) was treated with chlorosulfonyl isocyanate (50 mL, 81.3 g, 574 mmol) at 0 °C. The reaction was followed by ^{1}H NMR, and the maximum conversion was obtained after 1 h, when the reaction mixture started to turn yellow. The reaction was then cooled to −78 °C and cannulated into a 2 L conical flask containing a previously made mixture of sodium bicarbonate (130 g, 1.54 mol), sodium sulfite (90 g, 714 mmol), ice (250 g, 13.88 mol), and water (250 g, 13.88 mol) under stirring and open to the air. It was imperative that the temperature of the conical flask was not allowed to warm up above 0 °C throughout the transfer. The mixture was then stirred until the bubbling ceased (1 h) and was then poured into a separating funnel. The phases were separated, and the organic layer was extracted with water (5 × 150 mL). The combined aqueous extracts were then extracted with dichloromethane (3 × 150 mL) followed by saturation of the aqueous phase with sodium chloride. The saturated aqueous solution was then extracted with dichloromethane (2 × 150 mL) and ethyl acetate (150 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated at 30 °C under reduced pressure to give the desired azetidinone **23** as viscous light yellow oil which was pure by ^{1}H NMR analysis and was used in the next step without any further purification (17.8 g, 24%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.05 (3H, s), 2.94 (1H, ddd, J = 15.2, 1.4, 0.5 Hz), 3.20 (1H, ddd, J = 15.2, 4.1, 2.6 Hz), 5.76 (1H, dd, J = 4.1, 1.4 Hz), 6.82 (1H, s).

4-(Phenylsulfonyl)azetidin-2-one, 24. Acetoxyazetidinone **23** (27.14 g, 210 mmol) was dissolved in water (110 mL) and treated with sodium phenyl sulfinate (35.0 g, 213.2 mmol). The mixture was refluxed for 20 min, and the yellow reaction mixture was then cooled to room temperature. The reaction was then extracted with dichloromethane (5 × 150 mL), the combined extracts were dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to give the pure sulfone **24** as a white powder (36.56 g, 173 mmol, 82%). The sulfone **24** was used in the next reaction without any further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.22 (1H, dd, J = 15.5, 2.3 Hz), 3.31 (1H, dd, J = 15.5, 5.0 Hz), 4.73 (1H, dd, J = 5.0, 2.3 Hz), 6.47 (1H, bs), 7.62−7.66 (2H, m), 7.73−7.78 (1H, m) 7.93−7.96 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.6, 64.8, 129.3, 129.7, 134.6, 135.0, 164.4; IR (thin film) ν_{max} = 3490, 3253, 3017, 2923, 2852, 1769, 1313, 1148 cm^{-1}; HRMS (CI) obsd (M + H)$^+$ 212.0374, calcd for $C_9H_{10}O_3NS$ 212.0381.

4-Vinylazetidin-2-one, 25. A −78 °C solution of sulfone **24** (36.56 g, 172 mmol) in anhydrous THF (620 mL) was treated with vinylmagnesium bromide (1.0 M in THF, 426 mL, 426 mmol), and the reaction was vigorously stirred at −78 °C for 30 min. The mixture was then consequently allowed to warm to 0 °C and stirred for 50 min. The reaction was then warmed to room temperature and stirred for 2 h. The reaction was quenched with satd aq ammonium chloride (185 mL) and stirred for a further 15 min. The crude mixture was then filtered through cotton wool, the two resulting phases were separated, and the aqueous layer was extracted with dichloromethane (3 × 500 mL). The combined organic extracts were collected and dried over anhydrous sodium sulfate and the solvents evaporated under vacuum to give the crude product as an orange/brown oil. The crude product was purified by flash chromatography (silica gel, 50% ethyl acetate in 40−60 petroleum ether) to give the pure vinylazetidinone **25** as a colorless and slightly viscous oil (14.98 g, 90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.67 (1H, dq, J = 14.8, 1.3 Hz), 3.17 (1H, ddd, J = 14.8, 5.2, 2.0 Hz), 4.07−4.11 (1H, m), 5.14 (1H, dt, J = 10.2, 0.9 Hz), 5.28 (1H, dt, J = 17.0, 1.0 Hz), 5.88 (1H, ddd, J = 17.0, 10.2, 7.0 Hz), 6.68 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.9, 49.4, 116.9, 137.5, 168.1; IR (thin film) ν_{max} = 3471, 3263, 2986, 2924, 1761 cm^{-1}; LRMS (CI) (M + H)$^+$ 98.18 (100).

1-(*tert*-Butyldimethylsilyl)-4-vinylazetidin-2-one, 26. A solution of vinylazetidinone **25** (100 mg, 1.03 mmol) in dry dichloromethane

(10 mL) was treated with anhydrous triethylamine (215 μL, 156 μg, 1.54 mmol), and TBSOTf (409 mg, 336 μL, 1.55 mmol) was added slowly to the resulting solution. The reaction mixture was stirred for 10 min, and the solvent was evaporated under reduced pressure. The crude orange oil was immediately purified by flash chromatography (silica gel, 10% ethyl acetate in 40−60 petroleum ether) to afford the desired *N*-TBS-protected azetidinone **26** as a clear, colorless, and slightly viscous oil (215 mg, 99%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.17 (3H, s), 0.21 (3H, s), 0.94 (9H, s), 2.75 (1H, dd, J = 15.4, 2.8 Hz), 3.29 (1H, dd, J = 15.4, 5.6 Hz), 3.99 (1H, ddd, J = 8.8, 5.6, 2.8 Hz), 5.16 (1H, dd, J = 10.0, 0.8 Hz), 5.27 (1H, dq, J = 17.1, 0.7 Hz), 5.84 (1H, ddd, J = 17.1, 10.1, 8.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.7, −5.5, 18.9, 26.2, 45.4, 51.7, 117.5, 139.7, 172.3; IR (thin film) ν_{max} = 3475, 3084, 2954, 2929, 2858, 1749 cm^{-1}; HRMS (CI) obsd (M + H)$^+$ 212.1468, calcd for $C_{11}H_{22}ONSi$ 212.1471.

1-(*tert*-Butyldimethylsilyl)-3-methyl-4-vinylazetidin-2-one, 27. A −78 °C solution of *N*-TBS-protected azetidinone **26** (7.73 g, 36.4 mmol) in anhydrous THF (400 mL) was treated with the slow addition of *n*-BuLi (2.5 M, 28.4 mL, 710 mmol). The reaction was then stirred for 10 min at −78 °C and was then quenched by addition of iodomethane previously filtered through basic alumina (7.52 mL, 17.2 g, 120.8 mmol). The reaction mixture was stirred at −78 °C for a further 10 min and then worked up by the sequential addition of methanol (12.9 mL) and satd aq ammonium chloride (168.6 mL). The crude mixture was then filtered through a pad of Celite and washed with diethyl ether (400 mL). The solvent was removed under vacuum, and the crude yellow oil (16.97 g) was purified by flash chromatography (silica gel, 10% ethyl acetate in 40−60 petroleum ether) to provide the pure methylated azetidinone **27** as a clear, colorless, and slightly viscous oil (6.43 g, 28.43 mmol, 78%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.14 (3H, s), 0.21 (3H, s), 0.93 (9H, s), 1.28 (3H, d, J = 7.4 Hz), 2.88 (1H, qd, J = 7.4, 2.5 Hz), 3.56 (1H, dd, J = 8.9, 2.5 Hz), 5.13 (1H, dd, J = 10.1, 1.0 Hz), 5.24 (1H, dq, J = 17.6, 0.6 Hz), 5.82 (1H, ddd, J = 17.6, 10.1, 8.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.6, −5.5, 13.2, 18.3, 26.2, 53.2, 60.7, 117.3, 139.2, 176.1; IR (thin film) ν_{max} = 3474, 3084, 2958, 2929, 2858, 1744 cm^{-1}; HRMS (CI) obsd (M + H)$^+$ 226.1626, calcd for $C_{12}H_{24}ONSi$ 226.1627.

3-Methyl-4-vinylazetidin-2-one, 28. A solution of *N*-TBS-protected vinylazetidinone **27** (8.78 g, 38.95 mmol) in methanol (300 mL) was treated by the slow addition of potassium fluoride (4.22 g, 72.63 mmol) at 0 °C. The reaction mixture was stirred for 10 min, and the solvent was evaporated under reduced pressure to yield a crude orange/brown oil (5.57 g) which was purified by flash chromatography (silica gel, 50% ethyl acetate in 40−60 petroleum ether) to afford the pure desired azetidinone **28** as a clear, colorless, and slightly viscous oil (3.77 g, 33.0 mmol 87%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (3H, d, J = 7.4 Hz), 2.92 (1H, qdd, J = 7.4, 2.3, 1.0 Hz), 3.72 (1H, dm, J = 7.2 Hz), 5.17 (1H, dappt, J = 10.2, 0.9 Hz), 5.30 (1H, dappt, J = 17.1, 1.0 Hz), 5.92 (1H, ddd, J = 17.1, 10.2, 7.1 Hz), 6.12 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7, 53.3, 58.2, 116.9, 137.1, 171.3; IR (thin film) ν_{max} = 3471, 3253, 3087, 3008, 2968, 2931, 2873, 1750, 1644, 1176, 926 cm^{-1}; HRMS (CI) obsd (M + H)$^+$ 112.0760, calcd for $C_6H_{10}ON$ 112.0762.

(3*R*,4*R*)-3-Methyl-2-oxo-4-vinylazetidine-1-carboxylic Acid *tert*-Butyl Ester, 29. A solution of lactam **28** (47 mg, 0.423 mmol) in anhydrous dichloromethane at room temperature (10 mL) was sequentially treated with anhydrous triethylamine (56 μL, 40.6 μg, 0.40 μmol), DMAP (50 mg, 0.41 mmol), and $(Boc)_2O$ (96 mg, 0.44 mmol). The resulting reaction mixture was stirred overnight and then concentrated under reduced pressure. The resulting crude yellow oil (151 mg) was purified by flash chromatography (silica gel, 0.5% TEA, 10% ethyl acetate in 40−60 petroleum ether to give the pure desired *N*-Boc-protected lactam **29** as a clear and colorless viscous oil (89 mg, 100%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (3H, d, J = 7.5 Hz), 1.48 (9H, s), 2.91 (1H, qd, J = 7.5, 3.0 Hz), 3.96 (1H, dd, J = 7.7, 3.0 Hz), 5.27 (1H, d, J = 10.3 Hz), 5.36 (1H, d, J = 17.1 Hz), 5.86 (1H, ddd, J = 17.1, 10.3, 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 27.9, 51.1, 61.2, 83.1, 118.7, 134.7, 147.8, 168.1; IR (thin film) ν_{max} = 3086, 2979, 2934, 1808, 1724, 1339, 1156 cm^{-1}; HRMS (CI) obsd (M + H)$^+$ 212.1283, calcd for $C_{11}H_{18}O_3N$ 212.1287.

(2*S*,3*S*)-*tert*-Butyl 2-((1*E*,3*E*,5*R*,6*R*)-6-methoxy-3,5-dimethyl-7-phenylhepta-1,3-dienyl)-3-methyl-4-oxoazetidine-1-carboxylate, 31, and (2*R*,3*R*)-*tert*-Butyl 2-((1*E*,3*E*,5*R*,6*R*)-6-methoxy-3,5-dimethyl-7-phenylhepta-1,3-dienyl)-3-methyl-4-oxoazetidine-1-carboxylate, 32. A solution of freshly purified methoxy diene **20** (40 mg, 0.174 mmol) and *N*-Boc-protected vinylazetidinone **29** (65 mg, 0.308 mmol) in dry toluene (2.5 mL) was treated with second-generation Hoveyda−Grubbs catalyst **30** (23 mg, 20 mol%). The resulting mixture was then refluxed for 22 h under anhydrous conditions. The solvent was evaporated under reduced pressure to yield a crude black viscous oil (130 mg) which was purified by flash chromatography (silica gel, 0.5% TEA, 0−20% ethyl acetate in 40−60 petroleum ether) to afford the desired heterodimers as a 1:1 mixture of diastereomers as a clear and very viscous yellowish oil (50 mg, 67%).

The diastereomeric mixture (50 mg) was then loaded onto a semipreparative HPLC under reversed-phase conditions as a DMSO stock solution (C18 column, 65:35 acetonitrile/water) to attempt the separation of the diastereomers. Compound **31** was isolated with near-quantitative efficiency after 53 min (254 nm optimized wavelength) (25 mg, 32% from diene **20**). Compound **32** appears to have decomposed as it was not detected either through the use of automatic multiwavelength detectors or TLC analysis of individual fractions (75 min run time).

31: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (3H, d, J = 6.7 Hz), 1.36 (3H, d, J = 7.5 Hz), 1.48 (9H, s), 1.66 (3H, d, J = 1.2 Hz), 2.60 (1H, m), 2.66 (1H, d, J = 7.5 Hz), 2.81 (1H, d, J = 4.6 Hz), 2.95 (1H, m), 3.19 (1H, m), 3.24 (3H, s), 4.03 (1H, dd, J = 8.1, 3.0 Hz), 5.45 (1H, d, J = 9.7 Hz), 5.54 (1H, dd, J = 15.4, 8.1 Hz), 6.33 (1H, d, J = 15.5 Hz), 7.17−7.29 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.3, 16.0, 28.0, 36.7, 38.2, 51.7, 58.7, 61.3, 77.2, 82.9, 86.8, 123.1, 126.0, 128.2, 129.4, 132.1, 137.4, 139.1, 139.2, 147.9, 168.5; IR (thin film) ν_{max} = 3422, 3029, 2976, 2931, 2875, 2362, 2342, 1810, 1723, 1333, 1157, 1104 cm^{-1}; HRMS (CI) obsd (M + H)$^+$ 212.1283, calcd for $C_{11}H_{18}O_3N$ 212.1287.

32: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (3H, d, J = 6.7 Hz), 1.35 (3H, d, J = 7.4 Hz), 1.49 (9H, s), 1.64 (3H, d, J = 1.2 Hz), 2.61 (1H, m), 2.69 (1H, d, J = 7.5 Hz), 2.80 (1H, d, J = 4.6 Hz), 2.94 (1H, m), 3.19 (1H, m), 3.23 (3H, s), 4.03 (1H, dd, J = 8.1, 3.0 Hz), 5.46 (1H, d, J = 9.8 Hz), 5.55 (1H, dd, J = 15.4, 8.1 Hz), 6.34 (1H, d, J = 15.5), 7.17−7.29 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7, 16.1, 28.0, 36.6, 38.1, 51.6, 58.6, 61.4, 77.3, 82.9, 86.9, 123.0, 126.1, 128.1, 129.3, 132.2, 137.2, 139.2, 147.8, 147.9, 168.4; IR (thin film) ν_{max} = 3422, 3029, 2976, 2931, 2875, 2362, 2342, 1810, 1723, 1333, 1157, 1104 cm^{-1}; HRMS (CI) obsd (M + H)$^+$ 212.1283, calcd for $C_{11}H_{18}O_3N$ 212.1287.

(2*S*,3*S*,4*E*,6*E*,8*R*,9*R*)-3-(*tert*-Butoxycarbonylamino)-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic Acid (*enantio*-*N*-Boc-ADDA), 7. A solution of *N*-Boc-protected lactam **31** (55 mg, 0.133 mmol) in THF (3 mL) was treated with aq LiOH (1.0 M, 0.60 mL, 0.60 mmol) at room temperature. The reaction was stirred at room temperature until completion (5 h) and then quenched by the sequential addition of water (2.4 mL) and glacial acetic acid (0.3 mL). The resulting mixture was extracted with diethyl ether (3 × 20 mL), and the combined organics were dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give a yellow oil (70 mg) which was purified by flash chromatography (silica gel, 0−10% MeOH in DCM) to give *enantio*-*N*-Boc-ADDA **7** as a clear and very viscous light yellowish oil (58 mg, 100%). The spectral data for *enantio*-*N*-Boc ADDA matched that reported for *N*-Boc ADDA: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (3H, d, J = 6.7 Hz), 1.04 (3H, d, J = 6.7 Hz), 1.25 (3H, d, J = 7.4 Hz), 1.45 (3H, s), 1.61 (3H, s), 2.57−2.81 (4H,

m), 3.19 (1H, m), 3.23 (3H, s), 4.39 (1H, bs), 5.25 (1H, bs), 5.39 (1H, d, $J = 9.8$ Hz), 5.48 (1H, dd, $J = 15.7$, 6.1 Hz), 6.20 (1H, d, $J = 15.6$ Hz), 7.17−7.29 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7, 14.6, 16.2, 28.4, 36.7, 38.3, 44.1, 54.1, 58.6, 79.8, 87.0, 125.1, 125.9, 128.2, 129.4, 132.5, 135.9, 136.5, 139.2, 139.4, 155.5, 179.4; $[\alpha]^{23}_{D}$ +15.1 ($c = 1.0$, $CHCl_3$); IR (thin film) $\nu_{max} = 3419$, 3334, 3029, 2972, 2929, 2605, 2534, 1709, 1169, 740, 701 cm^{-1}; HRMS (CI) obsd $(M + H)^+$ 432.2749, calcd for $C_{25}H_{38}O_5N$ 432.2750.

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Supporting Information Available: Spectral data of the described compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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