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Stereoconvergent Synthesis of (*2S,3S,8S,9S,4E,6E*)-*N*-Boc-ADDA Starting from (*S*)-Serine and (*S*)-Phenyllactic Acid

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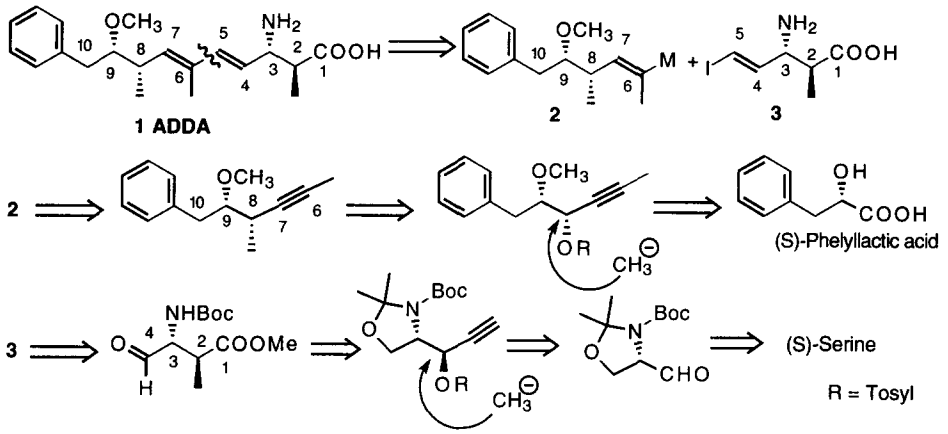
Abstract: *. The important naturally occurring β-amino acid N-Boc-ADDA is prepared following a disconnection of the C-C bond between the two E,E double bonds. The stereochemistry of the two synthons was controlled using the alkylation of chiral bromoallenes derived from naturally occurring (S)-serine and (S)-phenyllactic acid. The cupration of bromoallenes derived from (S)-serine also provides a general method for the synthesis of chiral β-alkylated aspartic acid derivatives.*

ADDA, (*2S,3S,8S,9S,4E,6E*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyl-4,6-decadienoic acid is an unusual amino acid present in several bioactive natural peptides such as microcystins, motopurin and nodularin.[1] Many of those peptides display inhibitory activity against different protein kinases and protein phosphatases. The reversible phosphorylation is now known to play a critical role in cellular signal transduction as protein phosphatase are able to revert the action of protein kinases. Phosphorylation of different serine and threonine residues in proteins participates in the control of a wide range of cell processes, including cell-cycle progression, cell proliferation, protein synthesis, transcriptional regulation and neurotransmission.[2] Recently the binding of mycrocistin with a protein phosphatase (PP-1) has been resolved by X-ray analysis showing that one of the binding domains is represented by the hydrophobic groove of ADDA.[3]

ADDA's unusual structure attracted the interest of synthetic organic chemists as testified by the recent publications of several different total syntheses. These papers report on the control of ADDA's relative and absolute stereochemistry, either starting from naturally occurring amino acids, as threonine[4] or aspartate,[5] starting from D-glucose[6], starting from resolved 3-pentyn-2-ol,[7] either through asymmetric syntheses based on Evans auxiliary [8]or Sharpless epoxidation.[9]

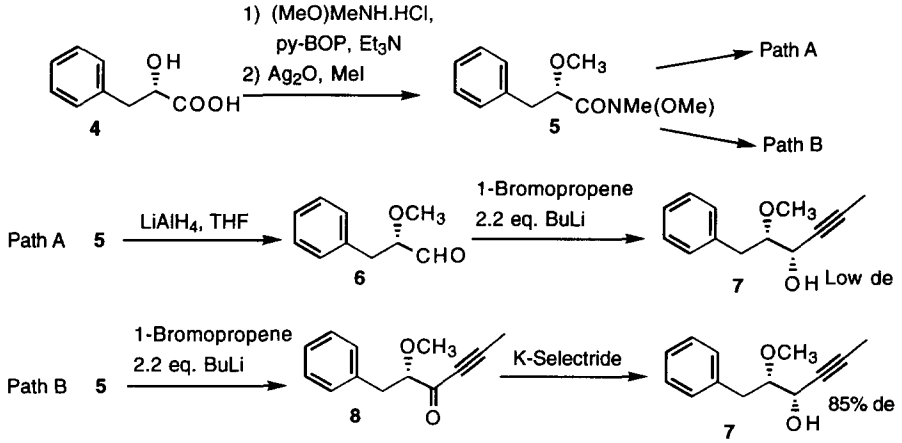
Our retrosynthetic approach divides[5] the molecule into two parts, the C^1-C^5 and the C^6-C^{10} fragments coupled through a stereoselective organometallic conjugate addition to an internal triple bond. The fragments **2** and **3** (scheme 1), each having two stereogenic centres, can be related to chiral propargylic alcohol tosylates through a formal *ipso* methylation with retention of configuration. In both cases the goal can be reached using

the technique of cupration of chiral bromoallenes derived from propargylic tosylates.[10] This convergent approach to **1** employs, as the key step, the same reaction on different substrates. With this strategy, the control of the sterochemistry turns out to be a problem of controlling the ethynylation of a chiral (enantiomerically pure) aldehyde.



Scheme 1

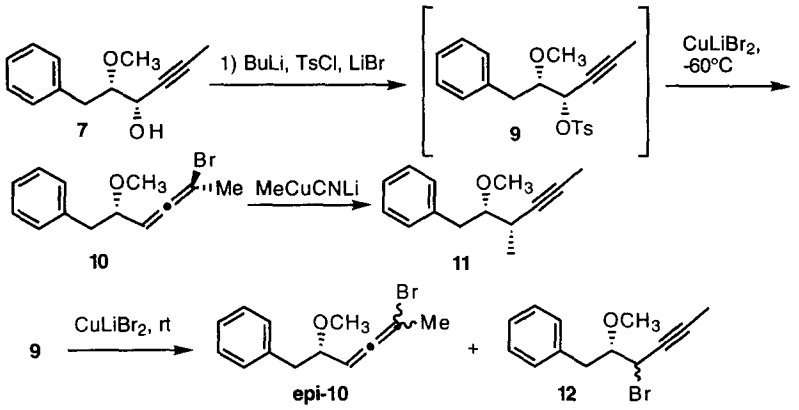
For the synthesis of the C^6-C^{10} fragment **2** we started from *(S)*-phenyllactic acid **4** which was transformed into the methoxy amide **5** (scheme 2). The methoxymethyl amide has the twofold function of protecting the carboxyl during the methylation of the alcohol and activating the carboxylic group for the next step. Between the two possible order of events relative to the transformation of the amide **5** into the *syn* alcohol **7**, reported in scheme 2, we chose path B that was expected to give the *syn* alcohol with a higher diastereoisomeric ratio.



Scheme 2

Reaction of **5** with 1-propynyllithium, generated from 1 bromopropene and 2.2 equivalents of BuLi,[11] yielded ketone **8** which was reduced using K-Selectride at -100°C in THF. The desired *syn* alcohol **7** was obtained in a 85% de and purified by column chromatography.

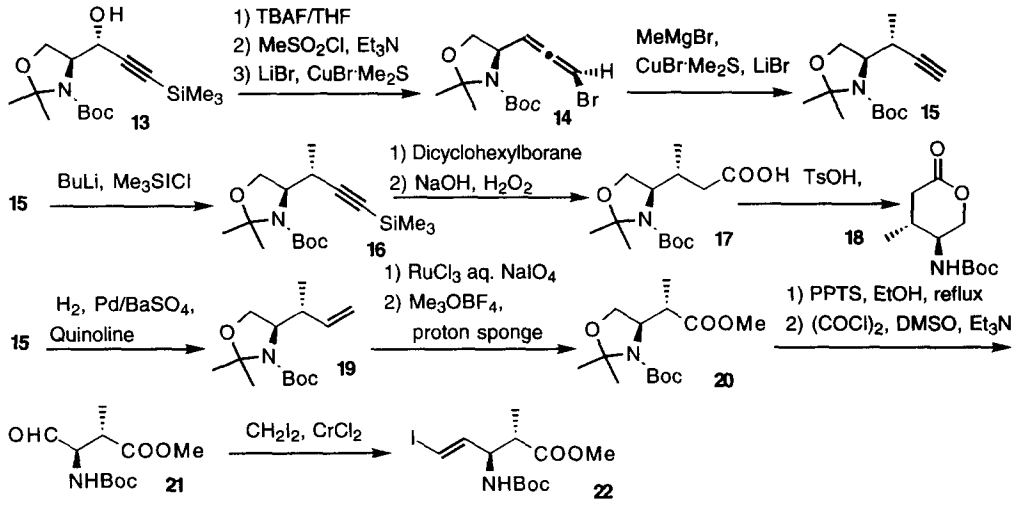
Alcohol **7** was transformed into the tosylate **9** using BuLi, TsCl and LiBr at -60°C.[12] This procedure avoid the possibility of racemisation of the alcohol and allows further reaction directly on the reaction mixture. SN2 reaction of $CuLiBr_2$ on tosylate **9** gave satisfactory results exclusively at -60°C. The previously reported conditions (reaction performed at room temperature or in refluxing THF),[13] applied to compound **9**, gave a mixture of epimeric allenes **10** and bromides **12**. (scheme 3)



Scheme 3

Compound **10** (together with less than 5% of the epimer) was alkylated with MeCuCNLi in THF giving the desired *syn* derivative in 76% yield after column chromatography on silica gel. No trace of the other possible isomers were detected by NMR analysis.

Analogously the stereoselective preparation of fragment C^1-C^5 was achieved through the reaction of the Gilman cuprate with a chiral bromoallene. Following a reported procedure[14] product **13** was obtained as a single diastereoisomer. After desilylation, the alcohol was submitted to the general procedure of mesylation and alkylation to give the propargylic derivative **15**. This compound is an ideal C^4-C^5 chiron for the preparation of β-alkylated aspartic or glutamic acid derivatives.

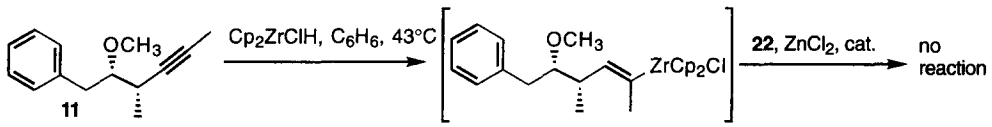


Scheme 4

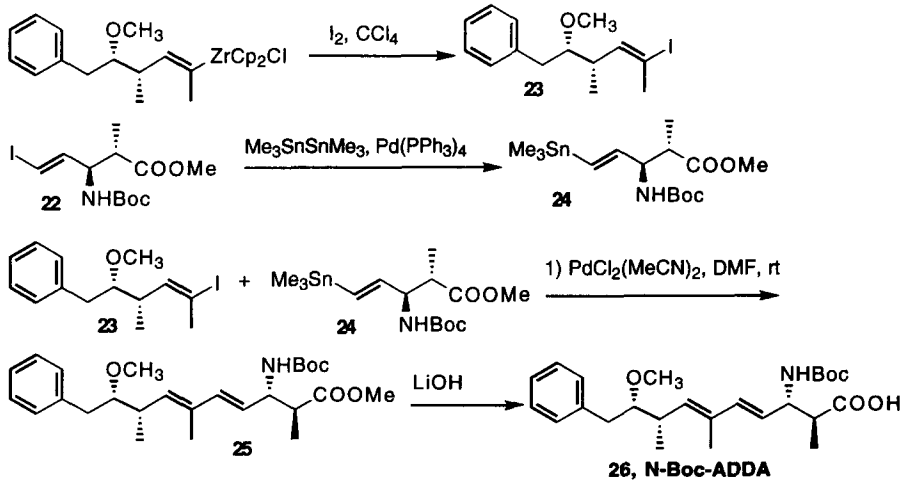
For the preparation of the β-alkylated glutamic derivative the alkyne needs to be oxidised at the terminal position. Silylation and subsequent oxidation of **16** with dicyclohexylborane and H_2O_2 gave the acid **17** which was further transformed into compound **18**, a well known precursor of β-glutamic acid derivatives.[15] On the other hand, the preparation of β-aspartic derivatives was accomplished sequentially by reduction of the triple bond to a double bond and oxidation with $NaIO_4$ in the presence of catalytic ruthenium tetroxide.

The esterification of the acid was difficult and several methods were explored. Finally, trimethyloxonium tetrafluoborate[16] in combination with proton sponge was found to be very suitable. Final ring opening of the oxazoline ring with PPTS in refluxing ethanol and subsequent oxidation with Swern reagent gave aldehyde in acceptable yields. The aldehyde was immediately treated with CH_2I_2 and dry $CrCl_2$ to give the E-iodide **22** required for the ADDA synthesis. (scheme 4)

Our first attempt at the coupling of the fragments **11** and **22** was carried out by hydrozirconation of **11** and Pd catalysed coupling with the vinyl iodide **22** (Negishi method).[17] Several reaction conditions were tried (see scheme 5) but with unsatisfactory results. The formation of the vinyl-zirconium intermediate was proved by quenching the reaction mixture resulting from the addition of the Schwartz reagent (Cp_2ZrClH) to the propargylic derivative **11** with iodine. The failure of further coupling with the vinyl iodide **22** can be attributed to the presence of the NHBoc that can interact with the $ZnCl_2$ present in the reaction medium. Possible options for the developments of this reaction are the use of an organometallic reagent containing a more electronegative metal core (Hg, Sn, Cu or B) or trying to invert the polarisation of the nucleophile-electrophile couple.



cat. employed: $Pd(PPh_3)_4$ at 25° and 50°C; $PdCl_2(PPh_3)_2$ + 2 eq. of DIBAL at 25°C and 50°C; $Ni(PPh_3)_4$ at 25 and 50°C



Scheme 5

We decided to follow this second route, employing the iodide **23**, previously prepared as proof of the formation of the zirconocene intermediate, and the vinylstannane **24** obtained from vinyl iodide **22** and hexamethyldistannane in the presence of $Pd(PPh_3)_4$.[18] The coupling carried under the classical Stille conditions,[19] gave the desired compound in 60% yield (after column chromatography) as a single diasteroisomer. Finally saponification of the methyl ester with LiOH gave the desired amino acid (**25, N-Boc-ADDA**) in a suitable form to be used in further syntheses of peptides employing ether liquid or solid phase techniques.

Experimental section

^1H and ^{13}C NMR were obtained at 200/300 MHz and 50/75 MHz respectively in $CDCl_3$ at room temperature (unless otherwise noted); coupling constants J values are in Hz. Mass spectra were recorded on a low-resolution instrument by EI at 70 eV, unless otherwise noted. IR spectra were recorded in CCl_4 and measured in cm^{-1}. Air- and/or moisture-sensitive reactions were conducted under an atmosphere of dry argon using oven-dried glassware and standard syringe/septum techniques. THF and ether were distilled from sodium-benzophenone, methylene chloride from CaH_2 prior to use. The organic extracts of crude products were dried over anhydrous Na_2SO_4. The organic solvents were removed by evaporation under reduced pressure with a rotary evaporator. The column chromatographies were performed by using the flash chromatography technique.

(2*S*)-*N*,2-Dimethoxy-*N*-methyl-3-phenylpropanamide, 5 . To a solution of (*S*)-phenyllactic acid **4** (1 g, 6.0 mmol) and triethylamine (0.84 mL, 6.0 mmol) in dichloromethane (50 mL), cooled to -20°C, was added N,O-dimethylhydroxylamine hydrochloride (1.2 g, 12.0 mmol), triethylamine (2 mL, 13.2 mmol), and benzotriazol-1-yloxy tripyrrolidino-phosphonium hexfluorophosphate (py-BOP) (2.6 g, 6.0 mmol). The solution was stirred for 30 min and then warmed to room temperature and stirred for 6 h. After dilution with dichloromethane (100 mL), the reaction mixture was washed three times with HCl 3N, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried and concentrated *in vacuo*. The crude product was purified by chromatography (hexane / ethyl acetate 50 / 50) to provide the amide (1 g, 81% yield), which was used directly in the next step. To a solution of the above alcohol (0.85 g, 4.1 mmol) in dry DMF (15 mL), were subsequently added Ag_2O (1.9 g, 8.2 mmol) and MeI (1.3 mL, 24.6 mmol). The reaction mixture was stirred at room temperature for 48 h, quenched with water (5 mL) and extracted with ether (50 mL). After drying and evaporation of the solvent, purification by chromatography (hexane / ethyl acetate 50 / 50) gave product **5** (0.805 g, 88% yield).^1H NMR δ : 2.99 (m, 2H), 3.20 (s, 3H), 3.32 (s, 3H), 3.58 (s, 3H), 4.34 (t, J = 6.4, 1H), 7.22-7.31 (m, 5H). ^{13}C NMR δ : 32.2, 38.6, 57.5, 61.3, 79.2, 126.5, 128.3, 129.4, 137.6, 172.8. MS *m/z* (%): 224 (M^+, 100), 191 (8), 135 (43), 131 (27), 104 (13).

(5*S*)-5-Methoxy-6-phenyl-2-hexyn-4-one, 8. To a stirred solution of (Z/E)-1-bromopropene (1.87 g, 15.5 mmol) in THF (10 mL) cooled to -78°C, BuLi (22 mmol from a 1.55 M solution in hexane) was slowly added over a period of 10 min. The resulting milky mixture was stirred at -78°C for an additional 2 h and a solution of the amide **5** (2.23 g, 10 mmol) in THF (5 mL) was slowly added at -78°C. The reaction mixture was maintained at -78°C for 1 h and then allowed to warm to room temperature. A saturated aqueous solution of NH_4Cl (10 mL) was added, and the product was extracted with Et_2O (3 x 30 mL). The organic layer was washed with brine (2 x 50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by chromatography (hexane / ether 90 / 10) afforded pure **8** in 89% yield. ^1H NMR (50°C) δ : 2.08 (s, 3H), 3.03 (ABX system, δ_A = 3.09, δ_B = 2.95, J_{AX} = 8.5, J_{BX} = 4.5, J_{AB} = 15 , 2H), 3.35 (s, 3H), 3.90 (X part of ABX system, J_{AX} = 8.5, J_{BX} = 4.5, 1H), 7.23-7.34 (m, 5H).^{13}C NMR (50°C) δ : 4.4, 38.3, 58.5, 78.4,

88.2, 94.90, 126.6, 128.3, 129.3, 136.7, 188.8..IR : 2260, 1671. MS *m/z* (%): 170 (17), 155 (3), 135 (100), 105 (15), 103 (46), 91 (25). $[\alpha]_D^{20}$ = -19.4 (c = 5.0, CH_2Cl_2). Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found C, 77.17; H, 6.91.

(4*S*,5*S*)-5-Methoxy-6-phenyl-2-hexyn-4-ol 7. To a solution of potassium tri-*sec*-butylborohydride (K-selectride) (1 M in THF, 6.5 mmol) in THF (20 mL) cooled to -100°C, was added a solution of ketone **8** (1.1 g, 5.4 mmol) in THF. The reaction mixture was stirred at -100°C for 2 h, quenched with a saturated aqueous solution of NH_4Cl (10 mL) and extracted with Et_2O (3 x 30 mL). After drying and evaporation of the solvent, purification by chromatography (hexane / ether 80 / 20) gave product **7** (0.79 g, 72% yield). ^1H NMR δ : 1.88 (d, J = 2, 3H), 2.54 (d, J = 5.1, 1H), 2.85 (dd, J = 6.9, J = 14, 1H), 2.99 (dd, J = 5, J= 14, 1H), 3.40 (s, 3H), 3.41-3.50 (m, 1H), 4.17-4.24 (m, 1H), 7.22-7.35 (m, 5H). ^{13}C NMR δ : 3.6, 36.6, 59.2, 63.9, 65.4, 82.4, 85.4, 126.2, 128.3, 129.5, 138.1. MS *m/z* : 204 (M^+, 0.4), 189 (0.6), 172 (4), 135 (100), 103 (34), 91 (24). IR: 3582, 3034, 2927, 2064, 1387, 1112. $[\alpha]_D^{20}$ = -22 (c = 1, $CHCl_3$). Anal. Calcd. for $C_{13}H_{16}O_2$: C, 75.08; H, 7.97. Found C, 74.99; H, 8.14.

(2*S*,5*S*)- 2-Bromo-5-methoxy-6-phenyl-2,3-hexadiene, 10. A solution of alcohol **7** (0.53 g, 2.6 mmol) and dry LiBr (0.22 g, 2.6 mmol) in THF (10 mL) cooled to -60°C, was treated dropwise with BuLi (2.6 mmol of a 1.57 M solution in hexane). After stirring for 30 min, p-toluenesulfonyl chloride (0.5 g, 2.6 mmol) was added. The reaction mixture was stirred for 15 min at -60°C, and 2 h at room temperature. The tosylate **9** was immediately used as a THF solution. After cooling to -60°C, a solution of dry LiBr (1.12 g, 13 mmol) and CuBr·Me_2S (2.66 g, 13 mmol) in THF (15 mL) was added. The mixture was stirred for 30 min at -60°C and then allowed to warm to room temperature. After stirring at room temperature overnight, the reaction was quenched with a saturated solution of NH_4Cl and extracted with ether (3 x 20 mL). The organic layer was washed with brine and dried. After evaporation of the solvent, column chromatography (hexane / ether 98 / 2) gave the final product **10** (0.6 g, 72% yield) contaminated with small amounts of the other diastereomer. The two diastereomers (ratio: 95 / 5) were not separable at this stage of the synthesis. ^1H NMR δ : 2.25 (d, J = 3, 3H), 2.82-3.03 (m, 2H), 3.34 (s, 3H), 3.93-4.04 (m, 1H), 5.10-5.18 (m, 1H), 7.18-7.35 (m, 5H). ^{13}C NMR δ : 25.2, 41.8, 56.8, 65.8, 79.8, 97.8, 126.3, 128.2, 129.4, 137.5, 203.3. IR: 3069, 2928, 1958, 1604, 1454, 1105. MS, *m/z* (%): 268 (M^+, 0.2), 186 (14), 175 (74), 155 (77), 135 (100), 103 (32), 91 (63), 77 (14). Anal. Calcd. for $C_{13}H_{15}BrO$: C, 58.44; H, 5.66. Found C, 58.13; H, 5.64.

(4*S*,5*S*)-5-Methoxy-4-methyl-6-phenyl-2-hexyne, 11. A suspension of copper(I) cyanide (1.2 g, 13.6 mmol) in dry ether (20 mL) at 0°C was treated dropwise with MeLi (13.6 mmol of a 1.6 M solution in ether). The mixture was stirred for 30 min at 0°C. After cooling to -78°C, a solution of bromoallene **10** (0.45 g, 1.7 mmol) in THF (10 mL) was added. The reaction mixture was stirred for 10 min at -78°C before being allowed to warm to room temperature. After stirring for 2 h at room temperature, the mixture was quenched with saturated NH_4Cl (20 mL) and extracted with ether (3 x 30 mL). The organic layer was dried and concentrated *in vacuo*. The crude product was purified by chromatography (hexane / ether 98 / 2) to provide product **11** (260 mg, 76% yield) as a single diastereomer. ^1H NMR δ : 1.19 (d, J = 7, 3H), 1.84 (d, J = 2.4, 3H), 2.52-2.60 (m, 1H), 2.80-3.04 (m, 2H), 3.21-3.33 (m, 1H), 3.28 (s, 3H), 7.20-7.30 (m, 5H). ^{13}C NMR δ : 3.6, 17.4, 30.1, 37.8, 58.4, 65.8, 81.0, 85.8, 126.0, 128.1, 129.5, 139.1. IR : 3034, 2926, 1939, 1453, 1119. MS *m/z* (%): 202 (M^+, 4), 170 (8), 155 (4), 135 (100), 111 (57), 103 (31), 91 (30), 77 (10). $[\alpha]_D^{20}$ = - 60 (c = 1, $CHCl_3$).

(4*S*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyl-[(3*R*)-3-bromo-1,2-propadien-1-yl]-1,3-oxazolidine, 14. To a solution of alcohol **13** (4.0 g, 12 mmol) in dry THF (50 mL) cooled to 0°C, TBAF (3.9 g, 15 mmol) was added and the mixture stirred at room temperature for 6 h. Ether (100 mL) was added followed by water (2 x 30 mL). The organic layer was dried and concentrated in vacuo. The crude was dissolved into dichloromethane (25 mL) and cooled to -50°C. Triethylamine (1.5 g, 15 mmol) was added

followed by methanesulfonyl chloride (1.7 g, 15 mmol). The mixture was allowed to warm to room temperature and, after stirring for 1 h, NH_4Cl (sat. solution) was added. The organic layer was separated, dried and the solvent evaporated. The crude was dissolved into ether (10 mL) and filterd through silica gel. The ether was additionally dried and evaporated. The crude (2.5 g) was dissolved in dry THF (30 mL) and a solution of dry LiBr (1.96 g, 22.6 mmol) and CuBr.Me_2S (4.6 g, 22.6 mmol) in dry THF (20 mL) was added and the mixture heated at 60°C for 6 h. After cooling, ether (150 mL) was added followed by NH_4Cl (sat. solution, 40 mL). The ethereal layer was separated, dried and the solvent evaporated. Column chromatography (hexane / ether 50 / 50) gave product **14** (1.4 g, 38% overall yield) as a yellow waxy material. ^1H NMR (50°C): δ 1.58 (s, 9H), 1.62 (s, 6H), 3.90 (dd, J= 2 , J= 9 2H), 4.05 (dd, J= 6 J= 9, 1H), 4.5 (m, 1H), 5.50 (t-like, 1H), 6.09 (dd, J= 6, J= 2, 1H). ^{13}C NMR (50°C): δ 23.3, 26.4, 28.2, 54.9, 67.5, 74.0, 80.6, 93.8, 100.1, 154.9, 200.1. IR: 2985, 1958, 1705. $[\alpha]_D^{25}$ = -311 (c = 1; $CHCl_3$). MS *m/z* (%): 261 (46), 246 (11), 203 (24), 57 (100).

(*4S*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyl-4-[(*2S*)-3-propyn-2-yl]-1,3-oxazolidine, 15. CuBr.Me_2S (3.23 g, 15.7 mmol) and dry LiBr (1.37 g, 15.7 mmol) were dissolved into dry THF (25 mL). The solution was cooled to 0°C and a solution of methylmagnesium bromide (5.2 mL of a 3M solution in ether, 15.7 mmol) was slowly added. After 30 min of stirring at 0°C (warning the mixture has to become clear),[20] this solution was transferred "via cannula" into a solution of bromoallene **14** (1 g, 3.1 mmol) in dry THF (20 mL) cooled to -78°C. The mixture was stirred for 30 min at -78°C and then warmed to room temperature. After quenching with NH_4Cl (sat solution, 10 mL) and extraction with ether, the organic layer was separed and dried. After evaporation of the solvent, column chromatography (hexane / ether 90 / 10) gave product **15** (0.63 g, 80% yield) containing 5% of the allenic derivative. ^1H NMR (50°C) δ 1.16 (d, J= 7, 3H), 1.50 (s, 9H), 1.61 (s, 6H), 2.02 (d, J= 2, 1H), 3.2 (m, 1H), 4.0 (m, 3H). ^{13}C NMR (50°C) δ 3.3, 14.6, 26.2, 27.9, 28.6, 59.9, 60.3, 64.2, 80.2, 81.2, 94.2, 154.6. IR: 3316, 2172, 1708. MS *m/z* (%): 254 (MH^+, 100), 239 (4), 200 (59), 154 (25). Anal. Calcd. for $C_{14}H_{23}NO_3$ C: 66.37; H: 9.15; N: 5.53. Found C: 66.29; H, 9.01; N, 65.60.

(*4S*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyl-4-[(*2S*)-4-trimethylsilyl-3-propyn-2-yl]-1,3-oxazolidine, 16. To a solution of product **15** (0.3 g, 1.17 mmol) in dry THF (15 mL), BuLi (1.2 mL of a 1.47 M solution in hexane, 1.74 mmol) was added and the mixture stirred at -78°C for 30 min and 1 h at room temperature. The mixture was cooled again to -78°C and chlorotrimethylsilane (0.4 mL, 2.94 mmol) was added with a syringe. After stirring for 12 h at room temperature NH_4Cl (sat. solution 10 mL) was added, the organic layer was separated, dried and the solvent evaporated. Column chromatography (hexane / ether 80 / 20) gave product **16** (0.22 g, 58% yield). ^1H NMR δ: 0.13 (s, 9H), 1.15 (d, J= 7, 3H), 1.46 (s, 9H), 1.52 (s, 3H), 1.6 (s, 3H), 3.1 (m, 1H), 3.8 (m, 1H), 3.91 (dd, J= 6, J= 9, 1H), 4.06 (dd, J= 3, J= 9, 1H).

(*4S,5S*)-5-(*tert*-Butoxycarbonyl)amino-4-methyl-tetrahydropyran-2-one, 18. Cyclohexene (0.08 mL, 0.8 mmol) and borane dimethylsulfide (0.2 mL of a 2M solution in THF, 0.4 mmol) were mixed at 0°C and stirred for 1h . The flask was cooled to -35°C and compound **16** (65 mg, 0.2 mmol) in dry THF (5 mL) was added. The mixture was stirred at 40°C for 12 h. Methanol (0.5 mL), NaOH (0.5 mL of a 3 M solution) and H_2O_2 (0.5 mL of a 30% solution) were subsequently added and the mixture stirred for 3 h at 40°C. The mixture was diluted with additional NaOH 1M and washed with ether. After acidification to pH 1, ethyl acetate was added and the organic layer separated and dried. After evaporation of the solvent the crude was dissolved in toluene (10 mL) in the presence of TsOH (50 mg) and the mixture refluxed for 3 h. After evaporation of the solvent, column chromatography (hexane / ether 50 / 50) gave product **18** (16 mg, 35% overall yield). ^1H NMR: δ 1.15 (d, J= 7, 3H), 1.5 (s, 9H), 1.8 (m, 1H), 2.25 (dd, J= 10, J= 17, 1H), 2.73 (dd, J= 6, J= 17, 1H), 3.7 (m, 1H), 4.07 (dd, J= 7, J= 12, 1H), 4.4 (dd, J= 4, J= 7, 1H), 4.6 (bs, 1H). Ms *m/z* (%): 229 (M^+, 100), 173 (25), 156 (57).

(*4S*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyl-4-[(*2S*)-3-propen-2-yl]-1,3-oxazolidine, 15. A solution of product **15** (1.0 g, 3.9 mmol) in ethyl acetate (15 mL) was added to a dispersion of Pd on barium sulfate (150 mg) and quinoline (1 mL) previously saturated with H_2. The mixture was stirred under an H_2 atmosphere (baloon) for 12 h. After filtration of the catalyst, washing of the organic layer with HCl (10 mL 5% solution) and drying, column chromatography (eluent hexane / ether 90 / 10) gave product **19** (0.85 g, 85%). ^{1}H NMR (50°C). δ: 1.26 (d, J= 7, 3H), 1.50 (s, 9H), 1.61 (s, 6H), 3.1 (m, 1H), 4.1 (m, 3H), 5.7 and 5.9 (m, 2H), 6.3 (m, 1H). ^{13}C NMR (50°C) δ: 8.6, 23.2, 27.9, 28.6, 31.5, 59.9, 60.3, 81.6, 94.2, 108.6, 124.4, 154.6. IR: 3316, 3010, 1708, 1650. MS *m/z* (%); 255 (M^+, 20), 241 (74).

(*4S*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyl-4-[(*2S*)-methyl-propan-2-yl]-1,3-oxazolidine, 20. $RuCl_3$ (20 mg) and $NaIO_4$ (0.8 g, 3.7 mmol) were stirred in a mixture of water (5 mL) and acetonitrile (5 mL). Product **19** (0.8 g, 3.1 mmol) in CCl_4 (5 mL) was added and the mixture stirred at room temperature for 6 h. Ethanol (3 mL) was added in order to destroy the excess of unreacted oxidizing agent, followed by ethyl acetate (30 mL) and water (15 mL). The organic layer was separated, dried and the solvent evaporated. The crude was dissolved into a solution of sodium carbonate (10 mL), the aqueous solution washed two times with ether, and after acidification to pH 1 with HCl, the crude acid was extracted with $CHCl_3$ (3 x 10 mL). After drying and evaporation of the solvent, the crude (0.7 g, 82%) was dissolved in CH_2Cl_2 (15 mL) and trimethyloxonium tetrafluoroborate (1.14 g, 7.7 mmol) was added followed by proton sponge (1.64 g, 7.7 mmol). The mixture was stirred at room temperature for 24 h. The solvent was removed in vacuo yielding a yellow solid which was purified by column chromatography (hexane / ethyl acetate 60 / 40) to give the methyl ester **20** (0.54 g, 61 % overall yield) as a waxy material. ^{1}H NMR (50°C) δ 0.98 (d, J= 7, 3H), 1.50 (s, 9H), 1.6 and 1.7 (two s, 6H), 1.9 (m, 1H), 3.5 (s, 3H), 3.8-4.3 (m, 3H). MS *m/z* (%): 287 (M^+, 60), 230 (50), 57 (100).

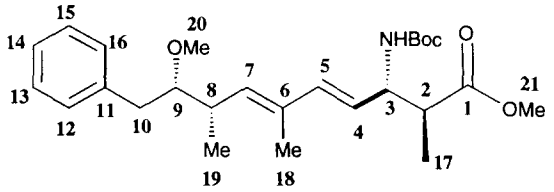
(2*R*,3*S*)-2-(*tert*-Butoxycarbonyl)amino-3-methoxycarbonyl-butanal (21). Oxazolidine **20** (0.5 g, 1.74 mmol) was dissolved in ethanol (25 mL) and PPTS (0.57 g, 2.2 mmol) added and the mixture refluxed for 4 h. The mixture was concentrated, dissolved in water and extracted three times with ethyl acetate. The organic layer was separated and dried. The solvent was evaporated in vacuo and the crude (0. 35 g, 70%) dissolved in dry CH_2Cl_2 (5 mL) and added to a solution of the Swern reagent, previously prepared from DMSO (0.2 g, 2.61 mmol), oxalyl chloride (0.33 g, 2.61 mmol) and triethylamine (0.3 g, 3.0 mmol), cooled to -78°C. After stiring at -78°C for 30 min and for 2 h at room temperature, water was added followed by ether. After separation and drying, evaporation and chromatography (hexane / ether 70 / 30) gave the aldehyde **21** (0.30 g, 85% yield). ^{1}H NMR δ : 1.27 (d, J = 7.4, 3H), 1.46 (s, 9H), 3.27-3.33 (m, 1H), 3.68 (s, 3H), 4.33 (dd, J = 3.4, J= 9, 1H), 5.60 (d, J = 9, 1H), 9.65 (s, 1H). ^{13}C NMR δ : 13.4, 28.1, 39.9, 52.1, 60.9, 80.2, 156.0, 174.5, 200.2. $[\alpha]_D^{23}$ = + 8 (c = 1, $CHCl_3$). Anal. Calcd. for $C_{11}H_{19}NO_5$: C, 53.86; H, 7.81; N, 5.71. Found C, 54.03; H, 7.90; N, 5.65.

(2*S*,3*R*,4*E*)-3-(*tert*-Butoxycarbonyl)amino-2-methyl-5-iodo-4-pentenoic acid methyl ester. 22. Anhydrous $CrCl_2$ (0.9 g, 7.3 mmoles) was suspended in dry THF (10 mL). A solution of aldehyde **21** (0.3 g, 1.2 mmol) and iodoform (0. 96 g, 2.4 mmol) in THF (10 mL) was added dropwise to the suspension at room temperature. After stirring in the dark for 7 h at room temperature, the reaction mixture was hydrolyzed with a saturated solution of NH_4Cl, and extracted with ether (3 x 20 mL). The combined extracts were dried over Na_2SO_4 and concentrated. Purification by chromatography (hexane / ether 80 / 20) gave **22** (0.33 g, 75% yield) as a single isomer. ^{1}H NMR δ : 1.23 (d, J = 7.4, 3H), 1.46 (s, 9H), 2.66-2.75 (m, 1H), 3.70 (s, 3H), 4.22-4.32 (m, 1H), 5.22 (d, J = 7.4 , 1H), 6.35 (d, J = 14 1H), 6.50 (dd, J = 5.8, J= 14, 1H). ^{13}C NMR δ : 14.4, 28.2, 42.7, 51.9, 56.8, 79.7, 142.3, 144.0, 155.2, 174.7. IR: 3445, 2984, 1728, 1486, 1169. $[\alpha]_D^{23}$ = + 18.9 (c = 1, $CHCl_3$). Anal. Calcd. for $C_{12}H_{20}INO_4$: C, 39.04; H, 5.46; N, 3.79. Found C, 39.27; H, 5.59; N, 3.74.

(2*S*,3*R*,4*E*)- 3-(*tert*-Butoxycarbonyl)amino-2-methyl-5-trimethylstannyl-4-pentenoic acid methyl ester (24) To a solution of vinyl iodide **22** (0.2 g, 0.54 mmol) in THF (10 mL) were subsequently added freshly prepared $Pd(PPh_3)_4$ (5%, 30 mg) and hexamethyldistannane (196 mg, 0.59 mmol). After stirring for 1 h at 50°C and evaporation of the solvent, column chromatography (hexane / ether 70 / 30) gave product **24** (0.16 g, 74% yield). ^1H NMR (50°C) δ : 0.09 (s , 9H), 1.19 (d, J = 7.1, 3H), 1.42 (s, 9H), 2.69-2.79 (m, 1H), 3.62 (s, 3H), 4.29-4.33 (m, 1H), 5.30 (d, J = 9.2, 1H), 5.85 (dd, J = 19 , J= 4.2, 1H), 6.15 (d, J = 19, 1H); ^{13}C NMR (50 °C) δ : -9.70 (m, JC-Sn = 173), 14.2, 28.2, 43.1, 51.4, 56.2, 79.2, 130.7, 145.2, 155.5, 175.2.

(4*S*,5*S*,2*E*)-2-Iodo-5-methoxy-4-methyl-6-phenyl-2-hexene 23. Cp_2ZrClH (120 mg, 0.4 mmol) and freshly distilled benzene (3 mL) were introduced into a flask in the dark and under argon. A solution of the alkyne **11** (40 mg, 0.2 mmol) in dry benzene (3 mL) was then added. The suspension was stirred for 2 h at 43°C. After cooling to room temperature, the reaction mixture was transferred *via cannula* into a solution of iodine (0.8 mmol) in CCl_4 (5 mL) and stirred at room temperature for 48 h. A saturated aqueous solution of NH_4Cl (5 mL) was added, and the product was extracted with Et_2O (3 x 10 mL). The organic layer was washed with brine, dried and concentrated *in vacuo*. Purification by chromatography (hexane / ether 95 / 5) afforded pure vinyl iodide **23** (45 mg, 70%), identified as the *E* isomer. ^1H NMR δ : 1.05 (d, J = 6.8, 3H), 2.26 (d, J = 1.4, 3H), 2.43-2.55 (m, 1H), 2.66-2.89 (m, 2H), 3.15-3.25 (m, 1H), 3.28 (s, 3H), 6.11 (dd, J = 1.4 Hz, J= 10, 1H), 7.18-7.35 (m, 5H). ^{13}C NMR δ : 15.4, 27.7, 37.7, 39.0, 58.5, 85.9, 94.1, 126.0, 128.2, 129.3, 138.8, 143.7. IR : 3033, 2933, 1635, 1454, 1100. $[\alpha]_D^{20}$ = - 48 (c = 1, $CHCl_3$).

(2*S*,3*S*,8*S*,9*S*,4*E*,6*E*)-3-(*tert*-Butoxycarbonyl)amino-9-methoxy-2,6,8-trimethyl-10-phenyl-4,6-decadienoic acid methyl ester, 25. Under a purge of argon, in a flame-dried flask were added the catalyst $PdCl_2(CH_3CN)_2$ (3 mg, 2% mol) and dry DMF (2 mL). The vinyl iodide **23** (40 mg, 0.12 mmol) was then added as a solution in dry DMF (2 mL) followed by vinylstannane **24** (90 mg, 0.2 mmol). After stirring for 4 h at room temperature, the reaction mixture was quenched with saturated NH_4Cl solution, extracted with ether and dried over Na_2SO_4. From the crude product, a mixture of *E,E* and *E,Z* isomers in a ratio of 90/10. Pure product (*E,E*) was obtained by chromatography (hexane / ether 95 / 5) in 58% yield.



^1H NMR (CD_3OD) δ : 1.01 (d, J = 6.8, 3H, CH_3-19), 1.11 (d, J = 7, 3H, CH_3-17), 1.43 (s, 9H, *t*-Bu), 1.60 (s, 3H, CH_3-18), 2.58 (m, J = 6.5, 9.8 and 6.8, 1H, CH-8), 2.64 (m, J = 10 and 7, 1H, CH-2), 2.66 (A part of ABX system , J_{AB} = 14, J_{AX} = 7, 1H of CH_2-10), 2.82 (B part of ABX system J_{BA} = 14, J_{BX} = 4.7, 1H of CH_2-10), 3.23 (s, 3H, CH_3-20), 3.23-3.26 (X part of ABX system, J_{XA} = 7, J_{XB} = 4.7, 1H, CH-9), 3.65 (s, 3H, CH_3-21), 4.26-4.46 (m, 1H, CH-3), 5.4 (d, J = 10.6, 1H, CH-7), 5.5 (dd, J = 15.6 and 7.5, 1H, CH-4), 6.2 (d, J = 15.6, 1H, CH-5), 7.16 (tt, J = 7.3 and 1.7, 1H, CH-14), 7.17 (dd, J = 7.3 and 1.7, 2H, CH-12 and CH-16), 7.24 (dt, J = 7.3 and 1.7, 2H, CH-13 et CH-15). ^{13}C NMR (CD_3OD) δ : 12.8 (CH_3-18), 14.3 (CH_3-17), 16.5 (CH_3-19), 28.7 ($3CH_3$, *t*-Bu), 37.69 (CH-8), 38.9 (CH_2-10), 45.6 (CH-2), 52.2 (CH_3-21), 56.5 (CH-3), 58.7 (CH_3-20), 81.2 (C-O of Boc), 88.4 (CH-9), 125.8 (CH-4), 127.0 (CH-14), 129.2 (CH-13 and CH-15), 130.5 (CH-12 and CH-16), 133.8 (C-6), 137.05 (CH-7), 138.0 (CH-5), 140.5 (C-11), 157.5 (C=O of Boc), 176.6 (O=C-1). IR : 3033, 2983, 2934, 2551, 1711, 1454, 1406, 1164, 1106. MS (IC)*m/z* :446(M^+, 83), 389 (52), 346 (56), 329 (68), 297 (75), 216 (7), 194 (100), 135 (77), 120 (18), 116 (30), 91 (8), 57 (2). $[\alpha]_D^{23}$ = - 24 (c = 1, $CHCl_3$). Anal. Calcd. for $C_{26}H_{39}NO_5$: C, 72.08; H, 8.82; N, 3.14. Found C, 72.27; H, 8.51; N, 3.34.

N-Boc-ADDA , 26. A solution of LiOH (30 mg, 1.3 mmol) in water (3 mL) was added to a solution of ester **13** (30 mg, 0.07 mmol) in 1,2-dimethoxyethane (3 mL). The mixture was stirred at room temperature for 5 h. The pH of the mixture was adjusted to 1 with 10% aqueous HCl, and then the mixture was extracted with ether (3 x 5 mL). After drying, evaporation of the solvent gave acid **26** in 66% yield. ^{1}H NMR δ : 1.02 (d, J = 6.8, 3H, CH_3-19), 1.2 (d, J = 7, 3H, CH_3-17), 1.45 (s, 9H, *t*-Bu), 1.65 (d, J = 1.2, 3H, CH_3-18), 2.59-2.81 (m, 4H, CH_2-10, CH-8 and CH-2), 3.16-3.24 (m, 1H, CH-9), 3.23 (s, 3H, CH_3-20), 4.23-4.41 (m, 1H, CH-3), 5.4 (d, J = 10.6, 1H, CH-7), 5.4-5.53 (m, 1H, CH-4), 6.2 (d, J = 15.6, 1H, CH-5), 7.16-7.23 (m, 5 aromatics H). $[\alpha]_D^{23}$ = - 15.7 (c = 1, $CHCl_3$). (lit.[8] -15.7 (c = 1, $CHCl_3$).

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20. Warning: the use in this reaction of synthesized methylmagnesium iodide always gave a cloudy cuprate solution and consequently poor yields of product **15**.

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