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Stereocontrolled Synthesis of γ-Branched Amino Acids. $TiCl_4$ Mediated Addition of (E)-Crotylsilane to N,O-Protected Serine Aldehyde

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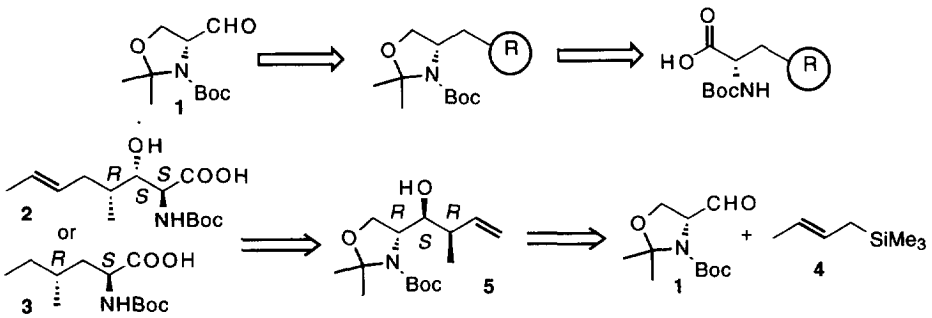
Abstract: The N-Boc derivatives of (2S,3S,4R,6E)-2-amino-3-hydroxy-4-methyl-6-octenoic acid and (2S,4R)-2-amino-4-methyl-hexanoic acid have been prepared using the acetonide of D-Serine aldehyde **1** as a formyl glycine equivalent. The stereochemistry of the y-branch was introduced by reaction of (E)-crotyltrimethylsilane with **1** in the presence of $TiCl_4$ followed by elaboration of the terminal double bond and further transformation of the Serine hydroxymethyl group into a carboxylic acid.

"Exotic" α-amino acids with unusual side chains exhibiting peculiar properties, once introduced into peptides and proteins, are nowadays one of the most popular targets for organic and medicinal chemists.[1] Their main applications are the introduction into peptides used as agonists, antagonists, enzyme inhibitors or for the preparation of chimeras. Amongst this family, γ-branched amino acids have been developed and mainly employed for their increased lipophilicity and their conformational restriction.[2]

The acetonide of D-Serine aldehydes (the so called Garner aldehyde **1**)[3] is a useful tool for the synthesis of differently functionalised amino acids.[1] A common strategy is the transformation of the aldehyde into the "exotic" side chain followed by deprotection and oxidation of the terminal CH_2OH group to COOH.[1,4] Within this approach, γ-branched amino acids could be prepared "via" a stereocontrolled addition of a crotyl type organometallic reagent to **1** and further elaboration of the double bond. Several stereoselective allylations of **1** have been reported using different allylic organometallic reagents.[5] Moreover a chiral crotyltitanium reagent has been used in reaction with (S)-**1** to prepare the homo allylic alcohol **5** with the (S,S,S) configuration,[6] whereas reaction of **1** with achiral (Z)-crotylboronate furnished the (S,R,S) isomer with 50% de.[7]

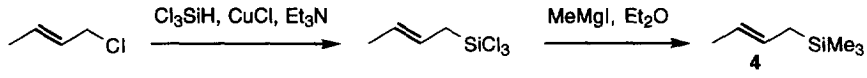


Scheme 1

We report here the synthesis of two γ-branched amino acids (**2** and **3**) present into immunosuppressive analogous of Cyclosporine A,[8] which employs, as the key step, the Lewis acid mediated addition of (E)-crotylsilane **4** to **1**. This approach should provide a stereoselective route to a common intermediate for the

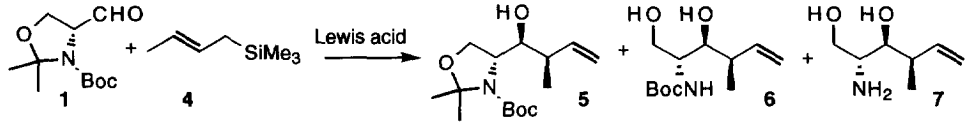
synthesis of the desired amino acid and should allow us to explore the diastereoselectivity of the reaction of crotylsilanes with a representative α-amino aldehyde.

Crotylsilanes are reported to react with aldehydes with syn stereoselectivity.[9] Therefore the control of the stereochemistry of the γ-methyl branch of the target amino acid could be achieved. Pure (E)-crotyltrimethylsilane was prepared by reaction of commercially available (E)-crotyl bromide with trichlorosilane in the presence of triethylamine and a catalytic amount of CuCl, followed by reaction with methylmagnesium iodide.



Scheme 2

The results of the reaction of this crotylsilane with the Garner aldehyde **1**, in the presence of different Lewis acid, are reported in scheme 3.



Entry	Lewis acid[a]	Reac. conditions	Ratio **5** / **6**/ **7**[b]	de of **5**[c]	Yields of **5**[e]
1	$TiCl_4$	CH_2Cl_2, -78°C, 2 h	8/ 2/ 0	90%	66%
2	$TiCl_4$	CH_2Cl_2, -78°C, 8 h	5/ 3/ 2	90%	25%
3	TiCl4 (2 eq.)	CH_2Cl_2, -78°C, 2 h	1/ 7/ 2	50%	(**6**: 45%)
4	$SnCl_4$	CH_2Cl_2, -78°C, 1 h	7/ 2/ 1	70%	41%
5	$SnCl_4$ (2 eq.)	CH_2Cl_2, -78°C, 1 h	1/ 8/ 1	(**5**, **6**: 60%)[d]	(**6**: 42%)
6	$BF_3.Et_2O$	$CHCl_3$, -60°C, 8 h	9 / 1/ 0	65%	74%
7	$ZnCl_2$	CH_2Cl_2, -78°C, 12 h	9 / 1/ 0	85%	25%[f]

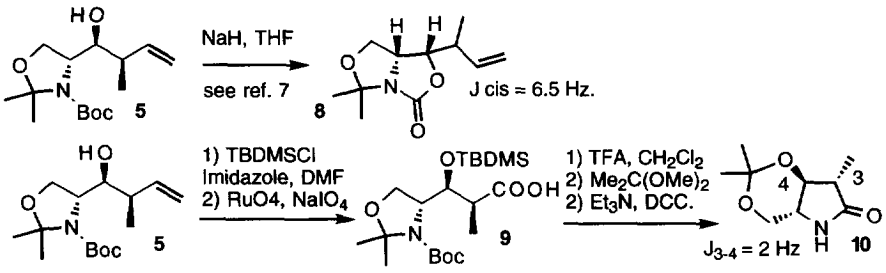
a) All the reactions (except for entries 3 and 5), were done using 1 eq of the Lewis acid and 2 eq of compound **4** respect to the aldehyde. b) Determined by glc analysis on the crude reaction mixture. c) Determined by glc analysis of compound **5** in the crude reaction mixture. d) Determined by 1H NMR analysis on **6** after column chromatography on silica gel. e) Yields of isolated and fully characterised compounds. f) 40% of the starting material was recovered .

Scheme 3

The ratio between the products **5** **6** and **7** was determined by glc analysis of the crude reaction mixture. A more accurate analysis of the GC peak attributed to compound **5** showed the presence of an additional signal which was attributed to a different diastereoisomer. Changing the chromatographic conditions we were able to separate this two peaks and to determine the diastereoisomeric excess of **5**. When the reaction was performed under the conditions described in entries 1, 2, 4 and 7, we were able to separate product **5** diastereoisomerically pure after column chromatography on silica gel.

The enantiomeric purity of **5** was determined to be >95% by Mosher ester analysis (^{19}F NMR). Moreover **5** was transformed into the (*S*)-MTPA ester and into the (*R*)-MTPA ester and the differences between their d values (^1H NMR spectra) was used to assign the S absolute configuration to C(1').[10] This attribution was confirmed by comparison of the coupling constant of oxazolidinone **8**[7](scheme 4) with literature values.[11] The stereochemistry at C(2') was attributed on the basis of the value of the coupling constants observed in product **10** obtained after oxidation of the double bond to carboxylic acid and subsequent deprotection of the acetonide and the Boc group, followed again by acetalisation and formation of a lactam ring with DCC. The values of the coupling constant for different conformers of **10** (*trans* arrangement between C(4) and C(5) were calculated in

the range of 0-3 Hz, whereas the expected values of the coupling constants for the *cis* isomer were calculated to be in the range of 5-9 Hz.[12]

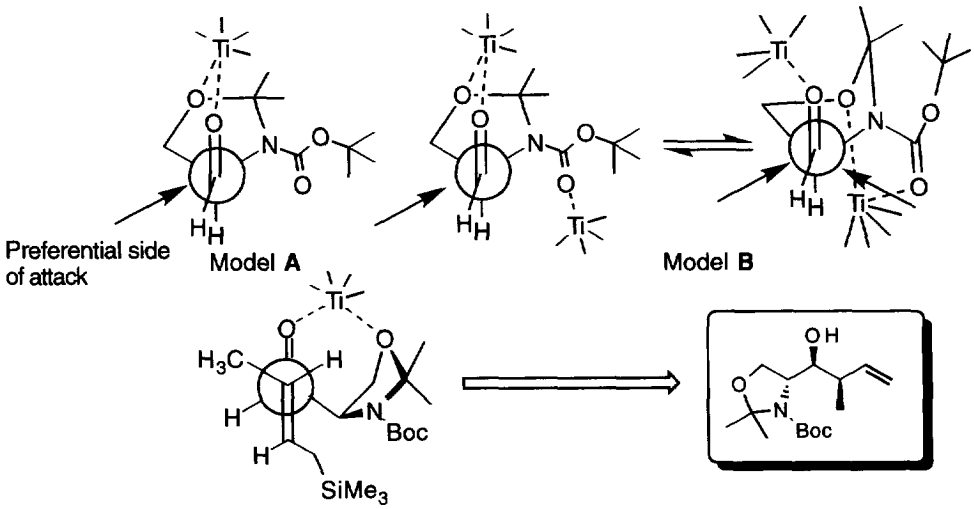


Scheme 4

The data reported in scheme 3 show that independently from the nature of the Lewis acid the anti-Cram product resulted the major diastereoisomer. However the strength of the Lewis acid could induced the opening of the oxazolidine ring and even partial deprotection of the nitrogen. Any attempts to use higher amount of any of the Lewis acid employed in scheme 3, lead to the formation of compounds **6** and **7** in different ratio. However, in these cases, we always isolated compound **6** as a mixture of two diastereoisomers (the anti-Cram and the Cram products) as revealed by ^{1}H NMR analysis. The best reaction conditions for preparing compound **3** are those reported in entry 1 employing a strong chelating Lewis acid in stoichiometric amount, at low temperature and for a short period.

It is noteworthy to observe, as previously described by us[13] and by others,[14] that the level of stereodifferentiation of the reaction is independent by the nature of the Lewis acid but depends by its amount.

The anti-Cram selection can be explained using a model (**A** in scheme 5) where the nucleophile attack the carbonyl from the less hindered *Si* face and the β-chelation of the $TiCl_4$ with the serine oxygen hampers the rotation around the bond between the oxazolidine and the carbonyl group.



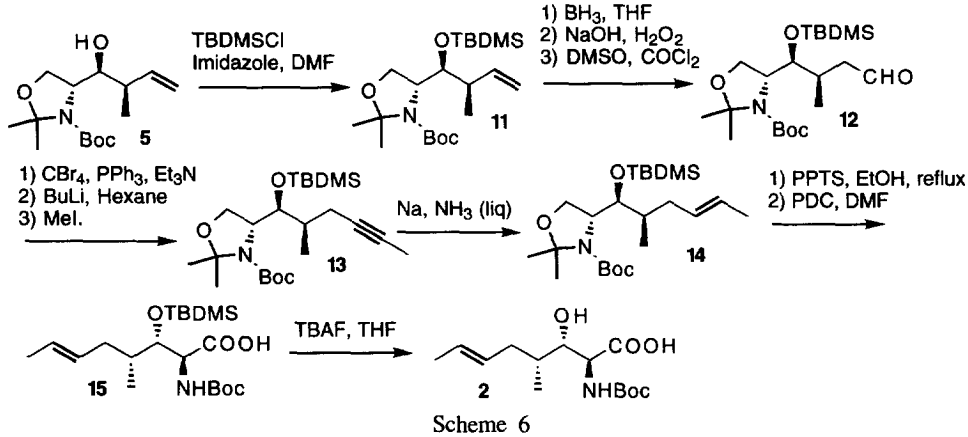
Scheme 5

The drop in the stereoselection using an excess of $TiCl_4$ can be explained with the existence of an equilibrium between different conformers where the possibility of an additional chelation to the urethane group

reduce the difference in steric hindrance around the aldehyde carbonyl (model **B** in scheme 5).The β-chelation of $TiCl_4$ on the Serine oxygen can be also applied to the Kumada anti-periplanar transition state[10] that explains the high stereochemical control observed in the formation of the other stereogenic centre.(scheme 5)

Compound **5** is the common intermediate for the preparation of the stereochemically defined γ-branched amino acids **2** and **3.**

For the synthesis of **2** the hydroxyl group was protected as a *t*-butyldimethylsilyl ether with TBDMSCl in DMF /imidazole. Oxidative hydroboration of **11** followed by Swern oxidation gave aldehyde **12** in good yields (scheme 6). For the transformation of the aldehyde into the E olefin **13** we tried different procedures based on the Wittig reaction but we were not able to have a complete control of the stereochemistry. Only the undesired Z olefin was obtained as a single diastereoisomer reacting aldehyde **12** with ethyltriphenylphosphonium bromide in the presence of $NaN(SiMe_3)_2$ in toluene. We decided to introduce an additional step in the synthesis transforming the aldehyde **12** into the propargylic derivative **13** following a modified procedure of the Corey-Fuchs reaction.[15] Reduction of **13** with Na in liquid ammonia gave the desired product **14** with very good diastereisomeric excess (E /Z > 90%, ^{1}H NMR analysis).

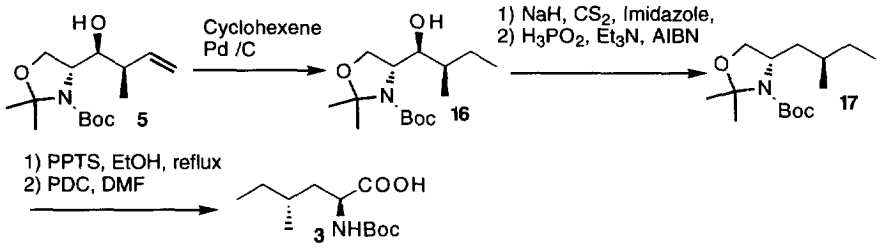


Scheme 6

The final transformation of the oxazolidine ring into the α-amino acid functional group was carried out on **14** (as the enriched mixture of the E isomer) following our well tested protocol:[4c,4g,4h] ring opening with PPTS in refluxing ethanol and oxidation of the crude product with PDC (6 eq) in DMF. Final deprotection was done using TBAF in THF at room temperature to give product **2** (ee > 90% by ^{1}F NMR analysis of the corresponding (S)-MTPA ester) in 21% overall yield starting from **1.**[16]

The "pure" γ-branched amino acid **2** was prepared through deoxygenation of the secondary alcohol **16** obtained after reduction with cyclohexene and Pd/C of the double bond present in compound **3**(scheme 7). Several attempts to use the usual deoxygenation procedure,[17] employing an S-methyl dithiocarbonate as the leaving group and Bu_3SnH as hydrogen donor, gave unsuccessful results in terms of yields due to the difficulties in the purification of product **17** from the stannylated reagent and other by products. Also attempts to use other hydrogen radical donors, as $(Me_3Si)_3SiH$ or t-BuSH gave poor results in terms of yields. However, following a new procedure described by Barton,[18] which employs hypophosphorous acid salts as hydrogen radical donor in the presence of AIBN, the deoxygenated compound **17** was obtained in 91% yields. This product was transformed into the desired amino acid **3** following the same procedure described for the

transformation of **14** into **2.** Compound **3** was obtained in 24% overall yield (ee > 90% by ^{19}F NMR analysis of the corresponding (S)-MTPA anhydride) calculated starting from the Garner aldehyde **1.**



Scheme 7

In summary, we have presented here a practical synthesis of non-natural amino acids present in the structure of immunosuppressive drugs. This synthetic protocol can be also applied to the synthesis of differently substituted γ-branched amino acids, as the stereochemistry of the branch can be controlled simply by the stereochemistry of the aldheyde and the terminal double bond can be elaborated in several ways. This method can be considered complementary to the reaction of crotyltitanium reagents and crotylboranes and boronate for the preparation of γ- (and β-) substituted amino acids with all the possible relative stereochemical arrangements.

Experimental Section.

(*E*)-Crotyltrimethylsilane 4. (*E*)-Crotyl chloride (2.98 g, 33 mmol) was dissolved in dry ether (10 mL) under nitrogen and magnetical stirring. After cooling to 0°C, trichlorosilane (4.47 g, 33 mmol) was added followed by triethylamine (3.33 g, 33 mmol) and copper(I) chloride (0.98 g, 10 mmol). The mixture was stirred at room temperature for 12 h. After addition of dry ether (50 mL) the white precipitate formed was filtered under nitrogen and the ethereal solution, containing trichlorocrotylsilane, was slowly added at 0°C, to a solution of MeMgI (120 mL of a solution containing approximately 140 mmol of the Grignard reagent) under mechanical stirring. The mixture was refluxed for 8 h and, after cooling to 0°C, quenched with a pre-cooled solution of NH_4Cl. The ethereal layer was rapidly separated and dried over anhydrous Na_2SO_4. The ether was evaporated using a Vigreaux column at atmospheric pressure (avoid the use of any vacuum apparatus) and the residual product distilled to give product **4**, b.p. 107-108°C. Obtained 2.75 g, 65% yield ^1H NMR (300 MHz, $CDCl_3$) δ -0.05 (s, 3H), 1.38 (dd, J_1= 7 Hz, J_2 = 0.5 Hz, 2H), 1.65 (dd, J_1 = 7 Hz, J_2 = 0.5 Hz, 3H), 5.2-5.4 (bm, 2H).

(4*R*,1'*S*,2'*R*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyl-4-(1-hydroxy-2-methyl-3-buten-1-yl)-1,3-oxazolidine 5. Aldehyde **1** (1.0 g, 4.36 mmol) was dissolved in dry CH_2Cl_2 (15 mL) under nitrogen, and the solution cooled to -78°C. Titanium tetrachloride (0.83 g, 0.478 mL, 4.36 mmol) was added with a syringe and the resulting yellow solution stirred at -78°C for 10 min. Crotyltrimethylsilane (1.16 g, 8.72 mmol) was added with a syringe and the mixture stirred at -78°C for 2 h. A saturated solution of NH_4Cl (5 mL) was added at -78°C under an efficient stirring followed by ether (50 mL) and the mixture warmed to room temperature. The ethereal layer was separated, washed with $NaHCO_3$ (10%) and brine, dried over anhydrous Na_2SO_4 and the ether evaporated. The composition of the reaction mixture was analyzed by gas-chromatography (capillary column: Carbowax® 20M, 60 m, 0.25μ /0.32 mm, carrier gas: Helium, oven: 50°C hold for 3 min, to

140 at 10°C/m, than to 180°C at 2°C/min. R_t (**5**) = 16.5 min; R_t (diasteroisomer of **5**) = 17.5 min.) Column chromatography on silica gel (eluent hexane ethyl acetate 3 / 1) gave product **5** as an oil. (0.82 g, 66% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (d, J = 7 Hz, 3H), 1.45 (s, 9H), 1.50 (s, 3H), 1.58 (s, 3H), 2.2 (m, 1H), 3.8 (m, 1H), 3.88 (dd, J_1 = 9 Hz, J_2 = 6 Hz, 1H), 4.1 (m, 2H), 5.04 (dd, J_1 = 9 Hz, J_2 = 6 Hz, 1H), 5.06 (dd, J_1 = 13 Hz, J_2 = 3 Hz, 1H), 5.7 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 26.7, 29.6, 32.4, 58.7, 66.9, 74.9, 81.6, 89.8, 114.9, 137.8, 154.3. Anal Calcd. for $C_{15}H_{27}NO_4$: C 63.13, H 9.54, N 4.91. Found C, 62.33, H 9.50, N 4.89.

5-(*tert*-Butoxycarbonylamino)-3-methyl-1-hexen-4,6-diol 6. When the reaction was carried as described above, but using 2 equivalents of $TiCl_4$ or SnCl4 as the Lewis acid, we obtained a mixture of compounds where **6** predominate. This product was isolated, as a mixture of two diastereoisomers, after column chromatography on silica gel (eluent hexane / ethyl acetate 1 / 10). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 and 1.26 (two d, J = 7 Hz, 3H), 1.45 (s, 9H), 2.2 (m, 1H), 3.2 (bm, 2H, OH), 3.8-4.0 (m, 2H), 4.2-4.4 (m, 2H), 5.1 (m, 2H), 5.4-5.8 (m, 1H), 5.9 (bd, 1H).

(4*R*,1'*S*,2'*R*)-3-(*tert*-Butoxycarbonyl)-4-[1-(*tert*-butyldimethylsilyloxy)-2-carboxy-1-propyl]-2,2-dimethyl-1,3-oxazolidine 9. Alcohol **5** (0.2 g, 0.69 mmol) was dissolved in dry DMF (1 mL) in the presence of imidazole (0.1 g, 1.4 mmol) and TBDMSCl (0.15 g, 1 mmol) in a sealed vial and the solution maintained at 65°C for 6 h. Ether (15 mL) was added and after washing several time with water, the organic layer was dried over anhydrous Na_2SO_4, the solvent evaporated and the residue maintained at 0.2 mmHg for 2 h. The residue was dissolved in acetone (10 mL) and a solution of freshly prepared ruthenium tetroxide (50 mg) and sodium periodate (0.8 g) in water (5 ml) was added. The mixture was stirred for 12 h, and twice additional $NaIO_4$ (0.2 g) was added. Propyl alcohol (0.5 mL) was added to destroy the excess of the oxidating agents, the black precipitate was filtered off and washed thoroughly with acetone. After evaporation of the solvent product **9** was isolated after column chromatography on silica gel (eluent $CHCl_3$ / EtOH 10 / 1). 0.18 g, 62% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.21 (s, 3H) 0.27 (s, 3H) 1.23 (d, J = 7 Hz, 3H), 1.40 (s, 9H), 1.48 (s, 9H), 1.50 (s, 3H), 1.58 (s, 3H), 2.7 (dq, J_1 = 7 Hz, J_2 = 2 Hz, 1H), 3.8 (m, 1H), 3.9-4.2 (m, 3H), 10.3 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -2.2, -1.8, 10.7, 15.3, 20.2, 26.4, 26.8, 28.8, 42.7, 54.6, 62.6, 69.8, 79.9, 92.1, 164.3, 179.9.

(3*R*,4*S*,9*R*)-1-Aza-5,7-dioxa-3,6,6-trimethyl-bicylo[4.3.0]-nonan-2-one 10. Compound **9** (0.18 g, 0.43 mmol) was dissolved in CH_2Cl_2 (1 mL) and trifluoroacetic acid (0.63 g, 5.6 mmol) and triethylsilane (0.12 g, 1.07 mmol) added at 0°C and the mixture stirred at room temperature for 12 h. The solvent was evaporated under vacuum and the residue washed several times with ether. To this vitreous solid 2,2-dimethoxyethane (2 mL) and p-TsOH (50 mg) were added and the mixture stirred at room temperature for 24 h. The solvent was evaporated and dry THF (25 mL) was added followed by dry triethylamine (0.1 g, 1 mmol) and dicyclohexylcarbodiimide (0.1 g, 0.49 mmol). After 1 h of stirring we obtained a clear solution and after 3h a precipitate was formed. After filtration the solvent was evaporated, the residue extracted three times with ether and the ethereal solution was washed with a NH4Cl solution followed by water. After drying on anhydrous Na_2SO_4, the solvent was evaporated and product **10** isolated by column chromatography on silica gel (eluent hexane / EtAc 1 /2). 36 mg, 33% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.1 (d, J = 7 Hz, 3H), 1.41 (s, 3H), 1.48 (s, 3H), 3.1 (qd, J_1 = 7 Hz, J_2 = 2 Hz, 1H), 3.7-4.0 (m, 3H), 4.15 (dd, J_1 = 3 Hz, J_2 = 2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.6, 23.1, 24.2, 33.6, 55.8, 59.8, 69.9, 90.4, 179.8.

(4*R*,1'*S*,2'*R*)-3-(*tert*-Butoxycarbonyl)-4-[1-(*tert*-butyldimethylsilyloxy)-2-methyl-3-formyl-1-propyl]-2,2-dimethyl-1,3-oxazolidine 12. Product **11**, obtained as described in the procedure for the preparation of **9**, (1.0 g, 2.5 mmol) was dissolved in dry THF (10 mL) and cooled at 0°C under nitrogen and magnetical stirring. A solution of BH_3 in THF (2.2 mL of a 1 M sol.) was added and the solution stirred at room temperature for 2 h. After cooling again to 0°C, ethanol (1 mL) was added followed by NaOH (2 mL of a 3 M solution) and H_2O_2 (2 mL of a 30% solution) and the mixture stirred at room temperature for 3 h. Ether (40 mL) was added and the organic layer separated, dried over anhydrous Na_2SO_4, and the solvent evaporated. The crude reaction product was dissolved in dry CH_2Cl_2 and added to a solution of dimethylsulfoxyde (0.39 g, 5 mmol) and oxalyl chloride (0.29 g, 2.5 mmol) in CH_2Cl_2 (2 mL) cooled to -60°C. After stirring 30 min, triethyamine (1.0 g, 10 mmol) was added and the solution stirred at room temperature for 3 h. Water is added, the organic layer separated and dried over anhydrous $MgSO_4$. After evaporation of the solvent product **12** was isolated by column chromatography on silica gel (eluent hexane /EtAc 2.5 /1). 0.88 g, 85% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.20 (s, 3H) 0.29 (s, 3H) 1.20 (d, J = 8 Hz, 3H), 1.45 (s, 9H), 1.48 (s, 9H), 1.58 (bs, 6H), 2.5 (m, 1H), 2.6-2.8 (m, 2H) 3.8 (m, 1H), 3.9-4.2 (m, 3H), 9.1 (dd, $J_1 = J_2 =$ 2.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ -3.5, -3.0, 13.9, 16.6, 20.9, 26.7, 26.9, 28.9, 30.2, 45.7, 61.5, 67.9, 73.7, 79.9, 94.3, 160.4, 201.1.

(4*R*,1'*S*,2'*R*)-3-(*tert*-Butoxycarbonyl)-4-[1-(*tert*-butyldimethylsilyloxy)-2-methyl-4-hexyn-1-yl]-2,2-dimethyl-1,3-oxazolidine 13. Triphenylphosphine (1.05 g, 4 mmol) was added to a solution of CBr_4 (1.32g, 4 mmol) in dry dichloromethane (50 mL) cooled to -20°C. After 1 h of stirring, the flask was cooled to -78°C and aldehyde **12** (0.8 g, 1.9 mmol) in dry dichloromethane (5 mL) was slowly added followed by triethylamine (0.2 g, 2 mmol). The mixture was stirred at room temperature for 12 h, than concentrated to 10 mL by evaporation under vacuum and diluted with heptane (70 mL). The precipitated formed was filtered off, the solvent evaporated and the residue extracted three times with dry ether. The solvent was evaporated and the residue dissolved in dry THF, cooled to -78°C and BuLi (2.5 mL of a 1.6 M solution in hexane, 4 mmol) was added. After stirring for 2 h at 0°C, MeI (4.5 g, 32 mmol) was added and the mixture stirred at room temperature for 12 h. Ether (100 mL) was added followed by a NH_4Cl solution. After the usual work-up column chromatography on silica gel gave product **13** (0.6 g, 74% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.21 (s, 3H) 0.27 (s, 3H) 1.10 (s, 3H), 1.25 (d, J = 8 Hz, 3H), 1.40 (s, 9H), 1.48 (s, 9H), 1.51 (s, 3H), 1.53 (s, 3H), 2.05 (A part of an ABX system, 1H), 2.31 (B part of an ABX system, 1H), 2.5 (m, 1H), 3.7 (m, 1H), 3.9-4.2 (m, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ -3.5, -3.0, 5.1, 12.7, 16.9, 18.2, 20.9, 27.7, 28.8, 34.7, 59.9, 68.9, 72.1, 74.5, 79.1, 79.9, 94.3, 156.4.

(4*R*,1'*S*,2'*R*,4'*E*)-3-(*tert*-Butoxycarbonyl)-4-[1-(*tert*-butyldimethylsilyloxy)-2-methyl-4-hexen-1-yl]-2,2-dimethyl-1,3-oxazolidine 14. Ammonia (10 mL) was condensed inside a Shlenk tube containing **12** (0.6 g, 1.41 mmol), cooled to -30°C, and Na (0.2 g, 8.7 mmol) was added in small pieces under vigorous magnetic stirring until appearance of a deep blue colour. After 2 h of stirring the excess of Sodium was eliminated adding solid ammonium nitrate followed by an aqueous solution of ammonia (5%) and ether (50 mL). The ethereal layer was separated, washed with diluted HCl and brine, dried over anhydrous Na_2SO_4 and the solvent evaporated to give product **13** (E / Z 9 /1) sufficiently pure to be used in the next step. (0.58 g, 96% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.22 (s, 3H) 0.27 (s, 3H), 1.25 (d, J = 8 Hz, 3H), 1.40 (s, 9H), 1.48 (s, 9H), 1.52 (s, 6H), 1.72 (d, J = 6 Hz, 3H, E isomer), 1.81 (dd, J_1 = 8 Hz, J_2 = 1 Hz, CH_3 Z isomer), 2.3-2.5 (m, 3H), 3.9 (m, 1H), 4.0-4.2 (m, 3H), 5.9 (m collapsing to a d decoupling at δ 1.72, J =16 Hz, 1H), 6.1

(m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -3.5, -3.0, 13.7, 16.0, 18.8, 20.9, 27.7, 28.8, 31.3, 34.7, 59.9, 68.9, 72.1, 79.9, 94.8, 123.2, 136.9, 156.4.

(2*S*,3*S*,4*R*,6*E*)-2-(*tert*-Butoxycarbonylamino)-3-(*tert*-butyldimethylsilyloxy)-4-methyl-6-octenoic acid 15. Compound **13** (0.58 g, 1.35 mmol) was dissolved in ethanol (20 mL) and pyridinium p-toluensulfonate (0.44 g, 1.75 mmol) was added and the solution refluxed for 3 h. The solvent was evaporated under vacuum and water (10 mL) and dichloromethane (20 mL) added. The organic phase was separated, dried over anhydrous Na_2SO_4, the solvent evaporated and the residue maintained under vacuum (0.1 mmHg) for 3 h. This residue was dissolved in dry DMF (15 ml) and pyridinium dichromate (3.0 g, 8.1 mmol) was added. The mixture was stirred at room temperature for 6 h, after that additional PDC (1g, 2.7 mmol) was added. After stirring for 12 h at room temperature water (10 mL) was added, the acidity adjusted to pH 3 adding HCl 1 M at 0°C and the aqueous phase rapidly extracted three times with ether (20 mL each time). The extracts were mixed, washed with HCl 1% and dried over anhydrous Na_2SO_4. After evaporation of the solvent, column chromatography on silica gel (eluent hexane/ ether/ AcOH 1 /1/ 0.01) gave product **15** as an oil. 0.378 g, 70% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 0.16 (s, 3H), 0.21 (s, 3H), 1.12 (d, J = 7 Hz, 3H), 1.41(s, 9H), 1.48 (s, 9H), 1.67(d ,J = 6 Hz, 3H, E isomer), 1.68 (dd, J_1 = 7 Hz, J_2 = 1 Hz, CH_3 Z isomer), 2.1-2.5 (m, 3H), 3.9 (m, 1H), 4.24 (dd, J_1 = 8 Hz, J_2 = 2 Hz, 1H), 5.9-6.1 (m, 2H), 6.3 (bd, 1H), 10.1, (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.2, -4.7, 13.9, 15.0, 17.0, 21.7, 28.7, 31.9, 34.9, 60.1, 70.2, 78.7, 123.5, 132.8, 157.8, 178.9.

(2*S*,3*S*,4*R*,6*E*)-2-(*tert*-Butoxycarbonylamino)-3-hydroxy-4-methyl-6-octenoic acid 2. Compound **15** (0.35 g, 0.87 mmol) was dissolved in dry THF (5 mL) and TBAF (0.26 g, 1 mmol) was added and the solution stirred at room temperature for 2 h. The solvent was evaporated, the residue dissolved in acetone (30 mL) and passed through a small column filled with florisil eluting with acetone (50 mL). The solvent was evaporated and the residue was crystallised from acetone / hexane to give product **2**, m.p. 109°-111° C, $[\alpha]_D^{25}$ = 12 (c = 1 in DMSO). (186 mg, 81% yield).^1H NMR (300 MHz, d6-DMSO-D_20, 50°C) δ 1.10 (d, J = 7 Hz, 3H), 1.48 (s, 9H), 1.71 (d, J = 8 Hz, 3H), 2.1-2.5 (m, 3H), 3.96 (dd, J_1 = 8 Hz, J_2 = 2 Hz, 1H), 4.31 (d, J = 2 Hz, 1H), 5.9 (m, 2H), 6.1 (m collapsing to a doubled after decoupling at d 1.10, J=16 Hz, 1H).). ^{13}C NMR (75 MHz, d6-DMSO-D_20, 50°C) δ 15.0, 17.0, 28.7, 30.9, 35.4, 59.9, 70.2, 79.9, 122.3, 130.0, 159.7, 178.9. Anal Calcd for $C_{14}H_{25}NO_5$: C 58.52, H 8.77, N 4.87. Found C, 58.02, H 8.86, N, 4.77.

(4*R*,1'*S*,2'*R*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyl-4-(1-hydroxy-2-methyl-1-butyl)-1,3-oxazolidine 16. Product **5** (1.0 g, 3.5 mmol), was dissolved in MeOH (5 mL) and cyclohexene (1 mL) and this solution added to Pd on Carbon 10% (0.8 g) previously activated under an hydrogen atmosphere. The mixture was refluxed under nitrogen for 3 h, than the carbon filtered and the solvent evaporated to give compound **16** sufficiently pure to be used in the next step. (0.95 g, 94% yield).^{13}C NMR (75 MHz, $CDCl_3$) δ 11.5, 13.9, 23.8, 26.7, 27.7, 28.9, 34.8, 59.7, 68.3, 73.7, 79.9, 92.2, 158.8

(4*R*,2'*R*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyl-4-(2-methyl-1-butyl)-1,3-oxazolidine 17. A mixture of product **16** (0.95 g, 3.3 mmol), NaH (158 mg oil free, 6.6 mmol), imidazole (50 mg) and carbon disulphide (0.8 g, 10.5 mmol) in dry THF (15 mL) was refluxed for 3 h under nitrogen. MeI (2 g, 14.2 mmol) was added and the mixture refluxed for additional 3 h. After addition of water and diethyl ether, the ethereal layer was separated, dried over anhydrous Na_2SO_4 and the solvent evaporated and well dried under vacuum (0.1 mmHg). The residue was dissolved in dry dioxane (15 mL), and a solution of dry hypophosphorous acid[18] (2.16 g, 12 mmol) and triethyamine (1.2 g, 12 mmol) in dioxane (5 mL) was added

followed by AIBN (0.1 g, 0.6 mmol) and the mixture refluxed. AIBN (0.1 g, 0.6 mmol) in dioxane (0.5 mL) was added every 30 min. until the starting material disappeared (tlc analysis). The solution was diluted with ethyl ether and washed several times with water. The ethereal layer was dried over anhydrous Na_2SO_4 and the solvent evaporated. Column chromatography on silica gel (eluent hexane / EtAc 1 / 1) gave product **17** as a waxy solid (0.64 g, 72% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 1.1-1.3 (m, 6H), 1.45 (s, 9H), 1.50 (s, 3H), 1.58 (s, 3H), 1.5-1.9 (m, 5H), 3.9 (m, 1H), 4.1-4.2 (m, 2H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.7, 19.8, 26.1, 26.9, 27.8, 29.7, 30.6, 37.4, 54.7, 73.1, 79.9, 91.8, 155.9. Anal Calcd for $C_{15}H_{29}NO_3$: C 66.38, H 10.77, N 5.16; Found C 66.0, H 10.61, N 17.44.

(*2S,4R*)-2-(*tert*-Butoxycarbonylamino)-4-methyl-hexanoic acid 3. This product was prepared following the same procedure described for compound **2**. Starting from 0.60 g of **17** we obtained, after column chromatography on silica gel (eluent hexane /EtAc /AcOH 1 /1 /0.05), product **3** as a solid , m.p. 89°-90° C. (0.39 g, 73% yield). $[\alpha]_D^{25}$ = -31.8 (c = 1 in MeOH) ^1H NMR (300 MHz, d6-DMSO-D_2O 50°C) δ 0.9-1.1 (m, 6H), 1.4-1.9 (m, 5H), 1.45 (s, 9H), 4.32 (X part of an ABX system, 1H). ^{13}C NMR (75 MHz, d6-DMSO-D_2O 50°C) δ 12.0, 19.0, 21.7, 28.5, 29.1, 35.8, 57.7, 78.9, 158.9, 179.6. Anal Calcd for $C_{12}H_{23}NO_4$: C 58.75, H 9.45, N 5.71. Found C, 58.10, H, 9.56, N, 5.66.

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