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$CrCl_2$ Mediated Addition of Allylic Halides or Phosphates to *N*-Protected α-Amino Aldehydes. Stereocontrolled Synthesis of a New Core for C_2 Symmetric HIV-Protease Inhibitors.

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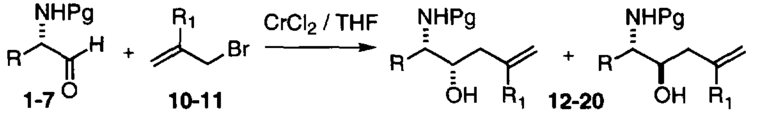
Abstract: *The addition of γ-monosubstituted allylchromium(III) reagents to N-protected α-amino aldehydes proceeds in a stereoconvergent manner in contrast with the case of the unsubstituted reagents, where the stereoselectivity depends on the nature of the group bonded to the nitrogen. The chromium(III) reagent derived from 3-chloromethyl-2-trimethylsilyl-1-propene was used to prepare a* C_2 *symmetric HIV-protease inhibitor.* Copyright © 1996 Elsevier Science Ltd

Allylchromium(III) reagents are useful compounds for the preparation of polyfunctionalized molecules. These reagents prepared starting from the corresponding allylic halides or phosphates and anhydrous $CrCl_2$ react "in situ" with carbonyl compounds or derivatives to give the corresponding homoallylic alcohols.[1] The stereochemistry of the products obtained with γ-substituted allylic halides (crotyl type reagents) is generally anti, regardless of the stereochemistry of the double bond, thus suggesting a six member cyclic transition state where the chromium atom is co-ordinated to the carbonyl oxygen.[2] In contrast with this kind of stereoselection, the influence of a stereogenic centre present in the α position of the aldehyde is often less pronounced. This result has been attributed both to the low Lewis acidity of the Cr(III) atom and the temperature of the reaction.[3]

We recently communicated that allylchromium(III) organometallics react with α-amino aldehydes to give hydroxyethylene dipeptide isosteres.[4] This reaction resulted a not very stereoselective high yielding process. Herein, we report that several differently substituted allylic halides or phosphates add to *N*-protected α-amino aldehydes, or oligopeptido aldehydes, with good stereoselectivity depending on the nature of the nitrogen atom protection and on the relative steric hindrance of the allylic moiety, thus extending the scope of the Hiyama-Nozaki reaction. Moreover we apply this reaction to the preparation of the core of a new family of potential C_2 symmetric HIV-protease inhibitors.

The direction of the diastereoselectivity in the allylation of *N*-protected α-amino aldehydes was examined with respect to optimisation of the factors controlling the diastereoselectivity such as the nature of the protecting group, the solvent, the presence of γ-substituents on the allylic reagent and the presence of different ligands on the metal. For the synthesis of peptidomimetics we decided to use the *tert*-butoxycarbonyl (Boc) and the benzyloxycarbonyl (Cbz) groups for the protection of the nitrogen. The results of the reaction of unsubstituted allylic-Cr(III) reagents with different aldehydes are reported in table I.

Table I. Allylation of *N*-Boc or *N*-Cbz protected α-amino aldehydes



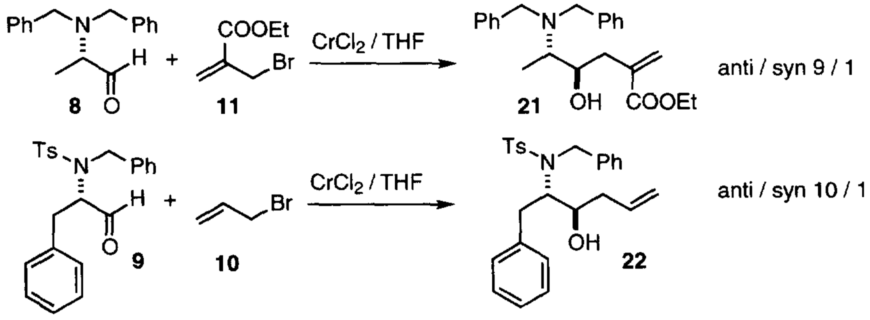
Aldehyde	Reagent	Product	Yield[a] (syn/anti ratio)[b]
1: R = CH_3, Pg = Boc,	**10**: R_1= H,	**12**	72% (60/40)
2: R = $(CH_3)_2CH$, Pg = Boc	**10**. R_1 = H	**13**	65% (65/35)
3: R = $C_6H_5CH_2$, Pg = Boc	**10**: R_1 = H	**14**	77% (60/40)
3: R = $(CH_3)_2CH$, Pg = Boc	**11**: R_1 = COOEt	**15**	75% (55/45)
4: R = $(C_2H_5)(CH_3)CH$ Pg = Boc	**11**: R_1= COOEt	**16**	78% (60/40)
5: R = 3'-Indolyl-CH_2, Pg = Boc	**10**: R_1= H	**17**	61% (60/40)
5: R = 3'-Indolyl-CH_2, Pg = Boc	**11**: R_1= COOEt	**18**	53% (55/45)
6: R = $(NO_2)NHC(NH)NH(CH_2)_3$ Pg = Cbz	**10**: R_1= H	**19**	41% (55/45)
7: R = $CbzNH(CH_2)_3$, Pg = CBz	**10**: R_1= H	**20**	48% (60/40)

a) Yields of isolated and fully characterised products (as diastereomeric mixture).

b) Determined by glc analysis of the crude reaction mixture.

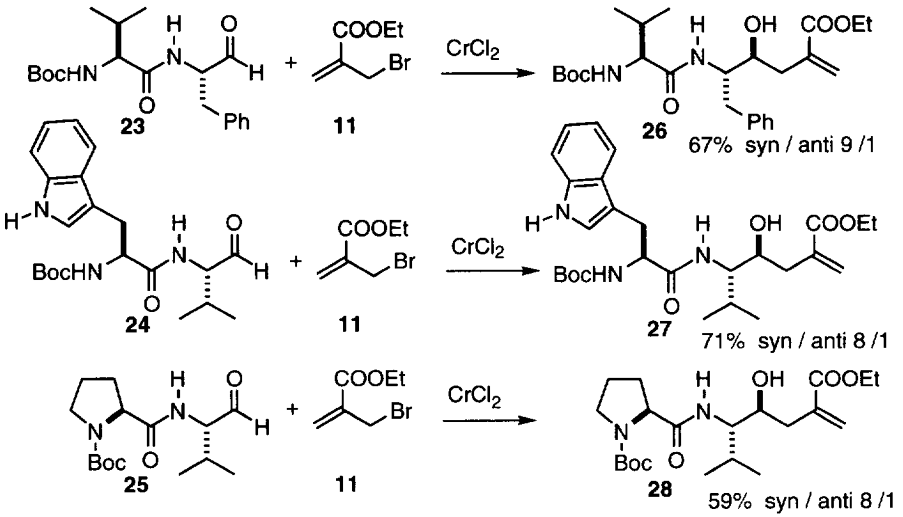
We attempted to improve the stereoselectivity of the reaction using different ligands for the chromium atom such as PPh_3, PBu_3, (+)-DIOP, TMEDA or DMF, unfortunately without appreciable results.

However, the diastereoselectivity was significantly affected by the nature of the protecting group on the nitrogen. Aldehydes **8** and **9**, which carried hindered protecting groups gave anti amino alcohols **21** and **22** in a 9 : 1 and 10 : 1 ratio (see scheme 1).



Scheme 1

On the other hand, oligopeptido aldehydes[4] **23-25** reacted with compound **11** to give the corresponding homoallylic alcohols **26-28** with predominantly syn selectivity (scheme 2).

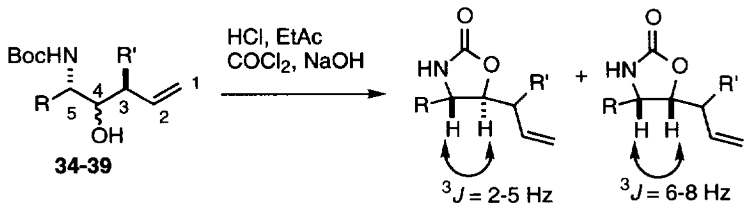


Scheme 2

Analogously, as described in table IIat the next page, crotyl type reagents, prepared either from allylic bromides or phosphates, reacted with α-amino aldehydes to give predominantly the syn isomer *independently from the nature of the group bonded to the N.*

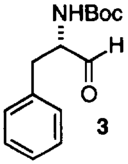
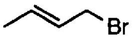
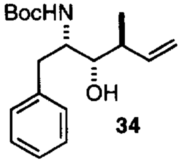
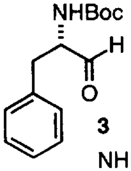
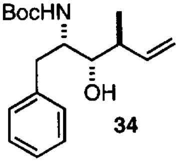
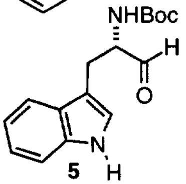
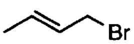
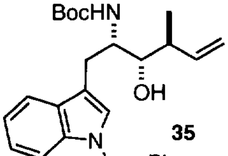
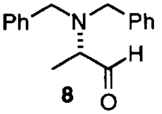
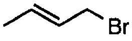
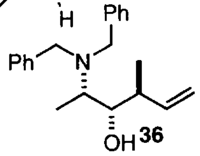
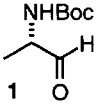
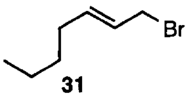
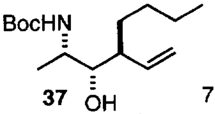
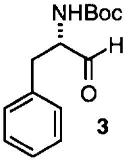
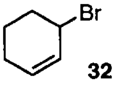
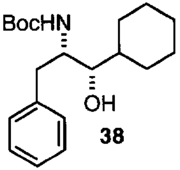
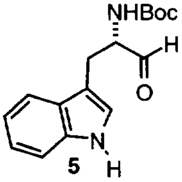
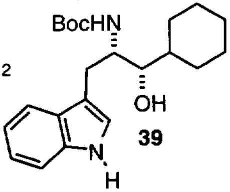
The diastereomeric ratio for compound **34-39** was determined by glc analysis of the crude reaction mixture. Only two peaks were exhibited for the reaction products **34-37**, suggesting that only two of the four possible diastereoisomer were formed. The major isomer was further purified from the crude reaction mixture by column chromatography on silica gel. The stereochemistry of products **21**, **22**, **26-28** and **34-39** was determined by transformation of the alcohol into the corresponding (*R*)- or (*S*)-MTPA ester and examining the differences in chemical shifts of the right and left substituents bonded to the observed stereogenic centre respectively (determination of the absolute configuration).[5] Moreover, after deprotection of the *N*-Boc group, isomerically pure compounds **34**, **35** and **37-39** were transformed into the corresponding oxazolidinone derivatives (scheme 3). The relative stereochemistry at C-4/C-5 was thus determined by estimating the ^3J and comparison with the values reported in the literature.[6] The oxazolidinones were prepared also starting from the crude reaction of products **34** and **35** giving a mixture of oxazolidinones which presented differences in the ^3J (C-4/C-5).

This result suggested that the diastereomeric mixture was due to different configurations of the alcoholic carbon and not related to different configurations of the adjacent alkyl branch. The S absolute configuration of this third centre was assigned by analogy with literature data.[7]



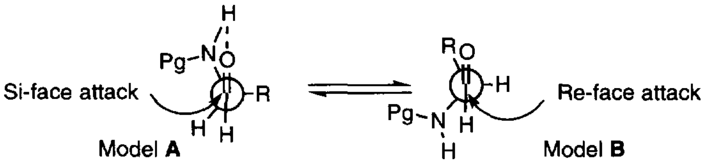
Scheme 3

Table II Reaction of crotyl type allylchromium(III) reagents with *N*-protected α-amino aldehydes

Aldehyde	Reagent	Product	Yield[a] (diastereomeric ratio)[b]
 **3**	 **29**	 **34**	73% (9 / 1)
 **3**	 **30**	 **34**	61% (10 / 1)
 **5**	 **29**	 **35**	71% (8 / 1)
 **8**	 **29**	 **36**	63% (15 / 1)
 **1**	 **31**	 **37**	73% (8 / 1)
 **3**	 **32**	 **38**	71% (8 / 1)
 **5**	 **33**	 **39**	64% (8 / 1)

a) Yields related to isolated and fully characterised single isomers. b) Ratio determined by glc analysis on the crude reaction mixture.

Indeed, differences are observed in the stereochemical trend of the reaction: syn selectivity occurs in NH-containing molecules whereas anti selectivity predominates in molecules without the NH moiety (see table I and scheme 1). This behaviour suggests that a hydrogen bond between the NH and the CO could be reasonably taken in account to explain such selectivity.[8] We postulated that an equilibrium is existing, at room temperature, between the intramolecular hydrogen bonded conformer (**A** in scheme 4) and a not bonded conformer (**B** in scheme 4).



Scheme 4

When the form **A** predominates, we observed syn selectivity whereas the prevalence of the **B**-like conformer gives anti selectivity. It is reasonable that, at room temperature, the population of the two conformers will be influenced by the nature of the protecting group (Pg), the nature of R and, obviously, by the polarity of the reaction medium, thus explaining the apparently randomised variation of the observed selectivity. On the other hand, once a γ-substituted allylchromium(III) reagent was employed, the major hindrance of the nucleophile probably select the less hindered Si-face forming a six member TS where both the hindered groups (the γ-substituent of the crotyl reagent and the chiral residue of the aldehyde) are in pseudo-equatorial position (scheme 5).

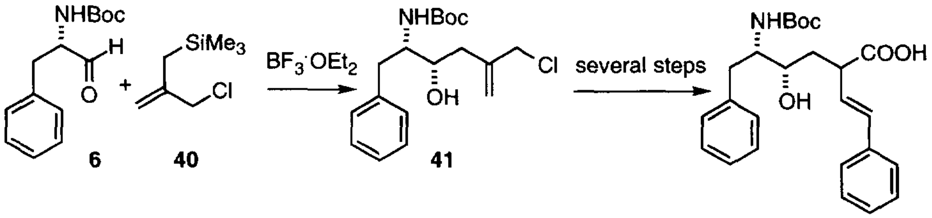
Si-face attack. Favoured

Re-face attack. Disfavoured

Scheme 5

Although not always stereoselective, the $CrCl_2$ mediated addition of allylic halides to α-amino aldehydes is a chemoselective simple one pot reaction which can be employed for the synthesis of polyfunctionalised molecules. We applied it to the preparation of a new family of C_2 symmetric HIV-protease inhibitors.

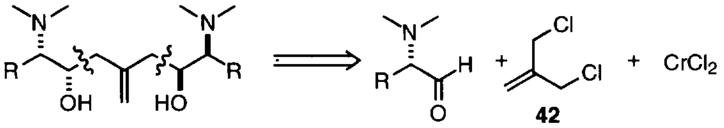
HIV protease is a virus specific enzyme essential for the proliferation of the human immunodeficiency virus. Inhibitors of HIV protease are attractive drug candidates because they provide a different approach (compared to AZT and related drugs) for blocking the viral reproduction. Recently the concept of C_2 symmetric pseudopeptidic inhibitors of HIV protease was developed on the basis of the C_2 axis of the active sites of the enzyme. (The goal was that axes of symmetry of both inhibitor and enzyme could coalign during their interaction).[9] We recently described the preparation of a potent HIV protease inhibitor based on stereoselective allylation of α-amino aldehydes using 3-chloromethyl-2-trimethylsilyl-1-propene (**40**, scheme 6) in the presence of $BF_3{\cdot}OEt_2$.[10]



Scheme 6

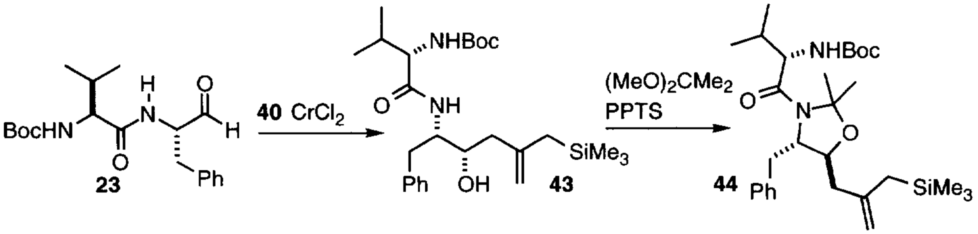
Following the same synthetic approach we decided to prepare a bis-amino alcohol, formally derived from the structure of **41** by substitution of the CH_2Cl group with the same moiety linked to the other side of the double bond, which had a suitable structure to be a C_2 symmetric HIV-protease inhibitor.

The most direct approach to this kind of compound might be the $CrCl_2$ mediated reaction of 2-chloro-2-chloromethyl-1-propene (**42**) with 2 eq of the same α-amino aldehyde (scheme 7).



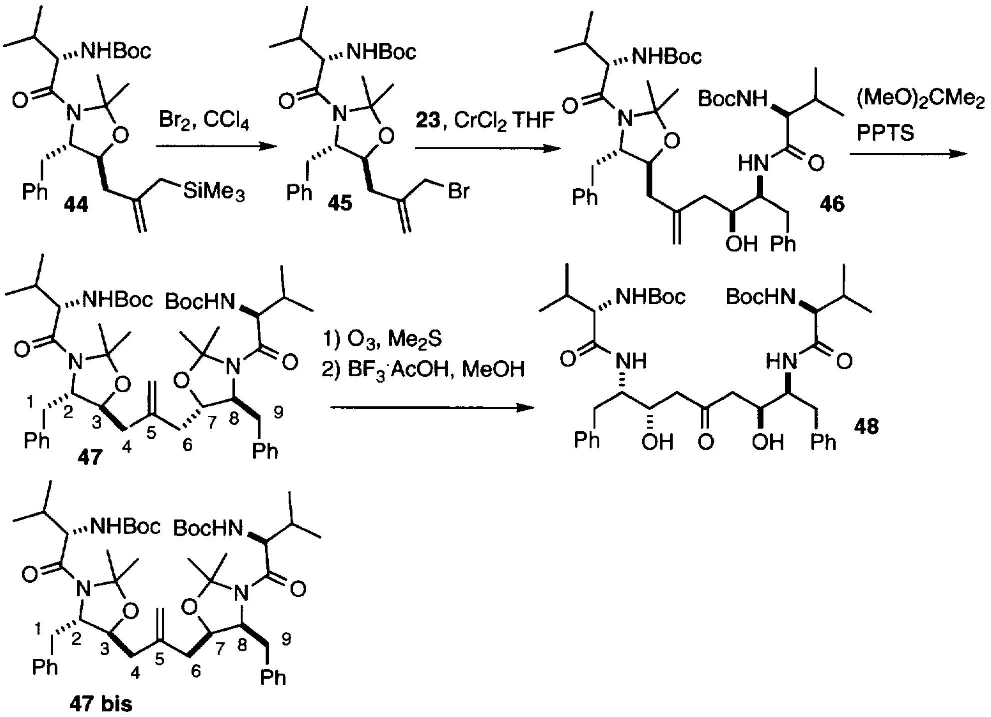
Scheme 7

A common procedure for the design of C_2 symmetric HIV inhibitors is to build the C_2 pseudopeptidic core insight to a lipophilic moiety, generally a Val-Phe sequence.[11] For this reason the aldehyde derived from Boc-Val-Phe (**23**) was prepared and reacted with **42** in the presence of 3 eq of $CrCl_2$, but the expected product was not obtained. Unfortunately large amounts of unreacted aldehyde and decomposition products (probably derived from **42** itself) were observed at the end of the reaction. 3-Chloromethyl-2-trimethylsilyl-1-propene (**40**) still resulted the reagent of choice. It reacted with aldehyde **23** in the presence of dry $CrCl_2$ giving product **43** as a mixture of diastereoisomers in 5 / 1 ratio (scheme 8). Product **43** was isolated as a single diastereoisomer in 55% yield after column chromatography on silica gel. The amino alcohol function was protected as oxazolidine using 2,2-dimethoxypropane and pyridinium *p*-toluenesulfonate (PPTS) to give product **44**.



Scheme 8

Any attempt to react compound **44** as an allylsilane with **23** (or with other simple aldehydes) in the presence of Lewis acids or fluoride ions failed giving mainly the product of protodesilylation of **44**. Consequently allylsilane **44** was treated with Br_2 in CCl_4 to give, in almost quantitative yields, allylic bromide **45** that reacted with aldehyde **23** in the presence of dry $CrCl_2$ to give compound **46** in a diastereomeric ratio of 9 / 1 (scheme 9). Isomerically pure compound **46** was further isolated in 67% yield by column chromatography on silica gel and transformed into the bis-oxazolidine **47**. Also the minor isomer, obtained in the $CrCl_2$ mediated reaction, was transformed into the oxazolidine **47bis**. Comparison of the ^1H NMR spectra of product **47** and **47bis** allowed to assign to the major isomer the desired C_2 symmetric structure. In fact the spectrum of **47** showed a sharp singlet at δ 4.95 for the methylenic protons (integral value 2) and two well separated multiplets at δ 4.1 and 3.8 (integral values: 2 and 2) for H-2, H-8 and H-3, H-7 respectively. On the other hand product **47bis** showed two singlets at δ 5.05 and 4.95 (integral values: 1 and 1) for the two methylenic protons and a large signal from δ 4.6 to δ 3.4 (integral value: 6) due to the different protons in position 2, 3, 7 and 8 and to the α protons of the two valine residues.



Scheme 9

Ozonolysis of the double bond of **47** was subsequently carried out in MeOH in the presence of Me_2S followed by removal of the oxazolidine ring with boron trifluoride-acetic acid complex to give product **48** in 59% yield. The ^{13}C NMR spectrum of **48** showed only seventeen not equivalent carbons thus confirming the proposed C_2 symmetric structure.

Inhibition of HIV protease was carried out in vitro using a purified HIV protease expressed from *E. Coli* and product **48** resulted active at concentration ≥ 60mM.

Experimental Section.

Reaction of allylic halides with amino aldehydes in the presence of $CrCl_2$. General Procedure: (*2S,3S,4S*)-2-(*tert*-Butoxycarbonylamino)-5-Hexen-4-Methyl-1-Phenyl-3-ol (34). Commercially available anhydrous chromium(II) chloride (0.44 g, 3.6 mmol) was placed in a round bottomed flask and heated at 200°C for 25 min under vacuum (0.1 mmHg). After cooling under argon, aldehyde **3** (0.3 g, 1.2 mmol) in dry THF (5 mL) was added at room temperature followed by crotyl bromide **29** (0.32 g, 2.4 mmol). The color of the mixture changed immediately to violet and after 2 h of stirring at room temperature, tlc analysis showed complete conversion of the aldehyde. Ether (15 mL) and a saturated solution of NH_4Cl were added and the ethereal layer separated, washed with water and brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, product **34** was isolated by column chromatography on silica gel (eluent hexane : ethyl acetate 2 : 1) as a colourless oil (0.26 g, 73% yield). ^1H NMR ($CDCl_3$, 200 MHz) δ 7.3 (m, 5H), 5.7-5.5

(m -5 lines- 1H), 5.1 (m, 2H), 5.0 (bd, J=8Hz, 1H), 4.0 (m, 1H), 3.2 (d-like, 1H), 2.9 (m 2H), 2.3 (m, 2H), 1.4 (s, 9H), 0.9 (d, J=7Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 157.2, 140.6, 139.4, 128.3, 128.0, 125.7, 114.4, 71.9, 70.6, 57.5, 36.0, 32.7, 28.7, 17.9. MS-EI (70 eV) 305 (1), 214 (15), 158 (25), 120 (30), 114 (40), 57 (100). Anal Calcd. for $C_{18}H_{27}NO_3$ (305.42079) H, 8.91; C, 70.79; N, 4.59. Found: H, 8.87; C, 70.70; N, 4.67. **(*2S,3RS*)-2-(*tert*-Bu^{t}oxycarbonylamino)-5-Hexen-3-ol (12)**. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.8 (m, 1H), 5.2 (m, 2H), 4.8 (bd, J=8 Hz, 1H), 4.3 (m, 1H), 3.8 (m, 2H), 2.2 (m, 2H), 1.5 (s, 9H), 0.9 (m, J = 7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 158.7, 149.6, 114.9, 74.5, 70.6, 51.9, 35.7, 28.0, 12.3. MS-EI (70 eV) 215 (1), 233 (7), 120 (25), 57 (100). Anal Calcd. for $C_{11}H_{21}NO_3$ (215.29492) H, 9.83; C, 61.37; N; 6.51. Found: H, 9.76; C 61.27; N, 6.50. **(*2S,4RS*)-3-(*tert*-Butoxycarbonylamino)-2-Methyl-6-Hepten-4-ol (13)** ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.9 (m, 1H), 5.2 (m, 2H), 4.8 (bd, J=8Hz, 1H), 3.8 (m, 1H), 3.4 (t-like, 1H), 2.4-2.2 (bm, 3H), 1.8-1.6 (bm, 1H), 1.45 (s, 9H), 0.9 (m, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 158.7, 149.6, 115.0, 70.6, 69.1, 52.2, 36.3, 28.7, 23.1, 17.9, 17.0. MS-EI (70 eV) 243 (0.3), 226 (3), 160 (12), 57 (100). Anal Calcd. for $C_{13}H_{25}NO_3$ (243.3491): H, 10.36; C, 64.16; N, 5.76. Found: H, 10.35; C, 64.10, N 5.86. **(*2S,3RS*) 2-(*tert*-Butoxycarbonylamino)-1-Phenyl-5-Hexen-3-ol (14).** ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.2 (m, 5H), 5.7 (m, 1H), 5.1 (m, 2H), 5.0 (bm, J = 8Hz, 1H), 4.2-4.5 (m, 1H), 3.5-3.8 (m, 1H), 3.1 (d-like, 2H, anti isomer), 2.8 (d-like, 2H, syn isomer), 2. 5 (bs, 1H), 2.2 (m, 2H), 1.40 (s, 9H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 157.2, 140.6, 139.4, 128.3, 128.0, 125.7, 114.4, 71.9, 70.6, 57.5, 36.0, 32.7, 28.7. MS-EI (70 eV) 291(2), 234(12), 108(45), 57(100). Anal Calcd. for $C_{17}H_{25}NO_3$: (291.3937) H, 8.65; C, 70.07; N, 4.81; Found H, 8.35; C, 70.15, N 4.86. **(*4RS,5S*) 5-(*tert*-Butoxycarbonylamino)-4-Hydroxy-6-Methyl-2-Methylen-Heptanoic Acid Ethyl Ester (15).** ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.28 (d, J = 1.5 Hz, 1H syn isomer), 6.25 (d, J = 1.3 Hz, 1H, anti isomer), 5.7 (bs-like, 1H), 4.9 (bd, J = 9 Hz, 1H, syn isomer), 4.5 (bd, J = 9 Hz, 1H, anti isomer), 4.2 (m, 2H), 3.9 (m, 1H, syn isomer), 3.7 (m, 1H, anti isomer), 3.4 (m, 1H, syn isomer), 3.1 (m, 1H), 2.5-2.2 (m, 2H), 1.7 (m, 1H), 1.45 (s, 9H), 1.2 (t-like, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 169.9, 157.2, 145.9, 121.4, 70.6, 66.9, 59.3, 51.8, 36.1, 23.9, 17.7, 13.7. MS-EI (70 eV) 315 (1), 285 (4), 110 (45), 57 (100). Anal Calcd. for $C_{16}H_{29}NO_5$ (315.41323): H, 9.27; C, 60.93; N, 4.44. Found: H, 9.37; C, 60.86, N, 4.49. **(*4RS,5S,6S*) 5-(Benzyloxycarbonylamino)-4-Hydroxy-6-Methyl-2-Methylene-Octanoic Acid Ethyl Ester (16).** ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.4-7.2 (m, 5H), 6.27 (d, J = 1.5 Hz, 1H syn isomer), 6.15 (d, J = 1.3 Hz, 1H, anti isomer), 5.7 (bs-like, 1H), 5.0 (m, 2H), 4.9 (bd, J = 9 Hz, 1H, syn isomer), 4.5 (bd, J = 9 Hz, 1H, anti isomer), 4.2 (m, 2H), 3.9 (m, 1H, syn isomer), 3.6 (m, 1H, anti isomer), 3.4 (m, 1H, syn isomer), 3.1 (m, 1H), 2.5-2.2 (m, 2H), 1.7 (m, 1H), 1.45 (s, 9H), 1.2 (t-like, 6H), 1.1-0.9 (m, 8H). ^{13}C NMR ($CDCl_3$, 50 MHz) d 168.9, 157.0, 145.2, 137.2, 128.6, 127.0, 121.4, 69.6, 67.0, 59.9, 59.7, 36.1, 28.8, 25.4, 15.0, 13.7, 11.5. MS-EI (70 eV) 363(2), 308(5), 190 (34), 57(100). Anal Calcd. for $C_{20}H_{29}NO_5$ (363.45783): H, 8.04; C, 66.09; N, 3.85; Found: H, 8.17; C, 66.06, N, 3.59. **(*2'S,3'RS*) 3-[2'-(*tert*-Butoxycarbonylamino)-3'-Hydroxy-5'-Penten-1-yl]-Indole (17).** ^{1}H NMR ($CDCl_3$, 200 MHz) d 8.15 (bs, 1H), 7.6 (m, 1H), 7.35 (d, J = 8 Hz, 1H), 7.3-7.0 (m, 3H), 6.0-5.5 (bm, 1H), 5.1 (m, 2H), 5.0 (bs, 1H, syn isomer), 4.6 (bs, 1H, anti isomer), 3.9 (m, 1H), 3.7 (m, 1H), 3.0 (m, 2H), 2.4-2.1 (bm, 3H), 1.44 and 1.37 (two s, 9H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 158.0, 149.6, 136.5, 131.6, 122.8, 121.7, 120.5, 119.6, 114.8, 112.1, 111.0, 72.7, 70.7, 53.7, 37.8, 32.1, 28.7. MS-EI (70 eV) 330(1), 257(5), 136(10), 57(100). Anal Calcd. for $C_{19}H_{26}N_2O_3$ (330.43067): H, 7.93; C, 69.06; N, 8.48. Found: H, 8.97; C, 66.06, N, 3.59. ***(2'S,3'S)*** **3-[2'-(*tert*-Butoxycarbonylamino)-5'-(Carboxyethyl)-3'-Hydroxy-5'-Penten-1-yl]-Indole (18).** The mixture of isomers was resolved by semipreparative HPLC on a C-18 column eluting with MeCN containing 35% of hexane. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.15 (bs, 1H), 7.5 (d, J = 8 Hz, 1H), 7.35 (d, J = 8 Hz, 1H), 7.2-7.0 (m, 3H), 6.19 (s-like, 1H), 5.61 (s-like, 1H), 5.05 (bd, J = 9 Hz, 1H), 4.12 (q-like, 2H), 3.8 (m, 2H), 3.2 (bd, 1H), 3.02 (d-like, 2H), 2.4 (m, 2H), 1.40 (s, 9H), 1.2 (m, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.0, 159.8, 145.9, 136.6, 131.1, 123.4, 122.8, 121.7, 120.1, 119.3, 112.0, 111.1, 70.9, 69.0, 59.5, 52.8, 35.9, 32.9, 28.0, 13.6. MS-EI (70 eV) 402.(1), 345(6), 139(10), 57(100). Anal Calcd. for $C_{22}H_{30}N_2O_5$ (402.4948) H, 7.51; C, 65.65; N, 6.96. Found: H, 7.97; C, 65.06, N, 6.59. ***(4S,5RS)*** **4-(Benzyloxycarbonylamino)-1-(Nitroguanidin)-7-Octen-5-ol (19).** ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.5-9.3 (m, 3H), 7.4-7.2 (m, 5H), 6.3 (m, 1H), 5.3 (m, 2H), 5.1 (m, 2H), 4.5 (m, 1H), 3.9 (m, 2H), 3.8 (m, 2H), 2.6-2.2 (m, 3H), 1.7 (m, 4H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 163.8, 157.8, 140.8, 137.3, 128.4, 127.9, 127.6, 114.4, 73.3, 55.1, 69.8, 42.8, 36.0, 24.3, 23.6. MS-EI (70 eV) 379(1), 322(6), 159(18), 57(100). Anal Calcd. for $C_{17}H_{25}N_5O_5$ (379.4193) H, 6.64; C, 53.82; N, 18.46. Found: H, 6.97; C, 53.86, N, 18.49. ***(4S,5RS)*** **1,4-Bis(benzyloxycarbonylamino)-7-Octen-5-ol (20).** ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.4-7.2 (m, 10H), 6.3 (m, 1H), 5.3 (m, 2H), 5.1 and 5.0 (m, 4H), 4.5 (m, 1H), 3.9 (m, 1H), 3.7-3.3 (m, 4H), 2.1 (m, 2H), 1.7 (m, 4H).^{13}C NMR ($CDCl_3$, 50 MHz) δ 159.9, 158.9, 146.6, 137.8, 137.3, 128.6, 127.7, 114.1, 72.3, 69.8, 69.3, 47.1, 55.1, 36.0, 24.3, 23.0. MS-EI (70 eV) 379(1), 322(6), 159(18), 57(100). Anal Calcd. for $C_{24}H_{30}N_2O_5$ (426.5171) H, 7.09; C, 67.59; N, 6.57; Found: H, 7.19; C, 67.76, N, 6.39. ***(4R,5S)*** **5-(Dibenzylamino)-4-Hydroxy-2-Methylene-Hexanoic Acid Ethyl Ester (21).** ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.4-7.2 (m, 10H), 6.2 (s-like, 1H), 5.52 (s-like, 1H), 4.2 (m, 2H), 3.78 (A part of an AB system, J = 7 Hz, 2H), 3.47 (B part of an AB system, J = 8 Hz, 2H), 3.3 (m, 1H), 2.7 (m, 1H), 2.4 (bs, 1H), 2.1 (m, 2H), 1,4-1.0 (m, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.5, 145.9, 136.1, 129.3, 128.2, 127.0, 121.7, 73.1, 59.9, 58.6, 54.8, 36.1, 14.9, 13.9. MS-EI (70 eV) 367(6), 259(18), 77(100). Anal Calcd. for $C_{23}H_{29}NO_3$ (367.49248) H, 7.95; C, 75.17; N, 3.81;. Found: H, 7.99; C, 75.76, N, 3.39. ***(2S,3R)*** **2-(*N*-Benzyl-*N*-Tolyl-Amino)-5-Hexen-1-Phenyl-3-ol (22).** ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.55 (d-like, 2H), 7.4-7.1 (m, 10H), 6.9 (m, 2H), 5.6-5.3 (m, 1H), 4.9 (m, 2H), 4.4-4.2 (AB system, 2H), 3.9 (m, 1H), 3.7 (m, 1H), 3.2-2.8 (eight lines AB part of an ABX system, 2H), 2.42 (s, 3H), 2.3 (bs, 1H), 2.1 (m, 2H).^{13}C NMR ($CDCl_3$, 50 MHz) δ 145.9, 140.9, 139.4, 136.3, 136.0, 129.5, 128.8, 71.7, 55.4, 49.3, 36.6, 32.7, 20.9. MS-EI (70 eV) 420(0.7), 357(10), 77(100). Anal Calcd. for $C_{26}H_{29}NO_3S$ (435.58593) H, 6.71; C, 71.69; N, 3.22; S, 7.36. Found: H, 6.79; C, 71.96, N, 3.30. ***(2'S,4S,5S)*****-5-[2'-(*tert*-Butoxycarbonylamino)-3'-Methyl-*N*-Butanamido]-4-Hydroxy-2-Methylene-6-Phenyl-Hexanoic Acid Ethyl Ester (26).** ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.2 (m, 5H), 6.56 (d, J = 10 Hz, 1H), 6.21 (s-like, 1H), 5.64 (s-like, 1H), 4.1 (m, 3H), 3.9 (m, 2H), 3.7 (m, 1H), 3.4 (m, 1H), 2.92 (d-like, 2H), 2.45 (d-like, 2H), 2.1 (m, 1H), 1.45 (s, 9H), 1.2 (t-like, 3H), 0.9 (m, 6H). Anal Calcd. for $C_{25}H_{38}N_2O_6$ (462.59141) H, 8.28; C, 64.91; N, 6.06. Found: H, 8.27; C, 64.96, N, 6.20. ***(2'S,4S,5S)*****-5-[2'-(*tert*-Butoxycarbonylamino)-3'-Indolyl-N-Propylamido]-5-Hydroxy-6-Methyl-2-Methylene-Heptanoic Acid Ethyl Ester (27).** ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.15 (bs, 1H), 7.5 (d, J = 8 Hz, 1H), 7.35 (d, J = 8 Hz, 1H), 7.2-7.0 (m, 3H), 6.50 (d, J = 10 Hz, 1H), 6.31 (s-like, 1H), 5.54 (s-like, 1H), 4.1 (m, 3H), 3.6 (m, 1H), 3.5 (m, 1H), 3.4 (m, 1H), 2.89 (d-like, 2H), 2.34 (d-like, 2H), 2.1 (m, 1H), 1.45 (s, 9H), 1.2 (t-like, 3H), 0.9 (m, 6H). Anal Calcd. for $C_{27}H_{39}N_3O_6$

(501.62838) H, 7.84; C, 64.65; N, 8.38. Found: H, 7.86; C, 64.49, N, 8.37. ***(4S,5S)*** **5-[(*N-tert*-Butoxycarbonyl)-*S*-Prolinamido]-4-Hydroxy-2-Methylene-6-Methyl-Heptanoic Acid Ethyl Ester (28).** ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.2 (bs, 1H), 6.21 (s-like, 1H), 5.73 (s-like, 1H), 4.6-4.1 (bm, 6H), 3.9 (m, 1H), 3.5 (m, 4H), 3.1 (m, 1H), 2.4-1.9 (overlapped m, 4H), 1.45 (s, 9H), 1.35 (t-like, 3H), 1.0 (m, 6H). Anal Calcd. for $C_{21}H_{36}N_2O_6$ (412.53087) H, 8.80; C, 61.14; N, 6.79. Found: H, 8.87; C, 61.16, N, 6.70. ***(2'S,3'S,4'S)*****-3-[2'-(*tert*-Butoxycarbonylamino)-3'-Hydroxy-4'-Phenyl-5'-Hexen-1-yl]-Indole (35).** ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.10 (bs, 1H), 7.4 (d, J = 8 Hz, 1H), 7.35 (d, J = 8 Hz, 1H), 7.2-7.0 (m, 8H), 6.2 (m, 1H), 5.1 (m, 2H), 4.3 (m, 2H), 3.9 (m, 1H), 3.3-3.0 (dd, Ja = 7 Hz, Jb = 9Hz, 1H), 2.6 (d-like, 2H7, 2.4 (bs, 1H), 1.45 (s, 9H).^{13}C NMR ($CDCl_3$, 50 MHz) δ 167.2, 140.6, 139.4, 1236.2, 131.6, 128.3, 125.7, 122.8, 121.6, 120.5, 119.6, 114.4, 111.0, 77.2, 70.6, 49.9, 42.2, 32.4, 28.7. MS-EI (70 eV) 406(1), 348(10), 57(100). Anal Calcd. for $C_{25}H_{30}N_2O_3$ (406.52945) H, 7.44; C, 73.86; N, 6.89. Found: H, 7.49; C, 73.76, N, 6.39. ***(2S,3S)*** **2-(Dibenzylamino)-4-Methyl-5-Hexen-3-ol (36).** ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.2 (m, 10H), 5.7 (m, 1H), 5.1 (m, 2H), 4.2 (m, 1H), 3.78 (A part of an AB system, J = 7 Hz, 2H), 3.47 (B part of an AB system, J = 8 Hz, 2H), 3.0 (m, 1H), 2.5 (m, 1H), 2.4 (bs, 1H), 1.2 (d, J = 7 Hz, 3H), 1.0 (d, J = 7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.5, 145.9, 136.1, 129.3, 128.2, 127.0, 121.7, 73.1, 59.9, 58.6, 36.1, 14.9, 13.9.MS-EI (70 eV) 309(5), 238(10), 77(100). Anal Calcd. for $C_{21}H_{27}NO$ (309.45544) H, 8.79; C, 81.51; N, 4.53. Found: H, 8.44; C, 81.57, N, 4.43. ***(2S,3S,4S)*** **2-(*tert*-Butoxycarbonylamino)-4-(1'-Ethenyl)-3-Octanol (36).** ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.2 (m, 1H), 5.1 (m, 2H), 4.6 (bd, J = 9 Hz, 1H), 4.5 (m, 1H), 3.9 (m, 1H), 2.7 (bs, 1H), 2.1 (m, 1H), 1.45 (s, 9H), 1.3-0.9 (overlapping m, 12 H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ157.7, 140.7, 114.0, 79.9, 78.6, 49.6, 38.8, 30.7, 28.7, 28.0, 23.6, 15.6, 14.1. MS-EI (70 eV) 271(2), 231(20), 57(100). Anal Calcd. for $C_{15}H_{29}NO_3$ (271.40328) H, 10.77; C, 66.38; N, 5.16. Found: H, 10.74; C, 66.57, N, 5.13. ***(1'S,'S,3'S)*****-1-[2'-(*tert*-Butoxycarbonylamino)-3'-Phenyl-1'-Hydroxy-1'Propenyl]-2-Cyclohexene (38).** ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.2 (m, 5H), 6.3-6.0 (m, 2H), 4.9 (bd, J = 10 Hz, 1H), 4.2-3.7 (overlapped m, 2H), 3.0 (d-like, 2H), 2.1-1.4 (m, 8H), 1.45 (s, 9H).^{13}C NMR ($CDCl_3$, 50 MHz) δ 167.2, 136.2, 131.0, 122.8, 121.7, 120.5, 119.5, 111.9, 78.1, 70.6, 50.1, 36.8, 35.4, 35.1, 33.5, 30.7, 30.4, 28.7. MS-EI (70 eV) 331(1), 313(10), 77(100). Anal Calcd. for $C_{20}H_{29}NO_3$ (331.45903) H, 8.82; C, 72.47; N, 4.23. Found: H, 8.79; C, 72.50, N, 4.19. ***(2'S,3'S,1"S)*** **3-[3'-(2-Cyclohexenyl)-2'-(*tert*-Butoxycarbonylamino)-3'-Hydroxy]-Indole (39).** ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.10 (bs, 1H), 7.4 (d, J = 8 Hz, 1H), 7.35 (d, J = 8 Hz, 1H), 7.2-7.0 (m, 3H), 6.3-6.0 (m, 2H), 4.9 (bd, J = 10 Hz, 1H), 4.2-3.7 (overlapped m, 2H), 2.80 (d-like, 2H), 2.1-1.4 (m, 7H), 1.45 (s, 9H).^{13}C NMR ($CDCl_3$, 50 MHz) δ 167.2, 136.2, 131.6, 131.7, 131.0, 122.8, 121.7, 120.5, 119.5, 111.9, 78.1, 70.6, 50.1, 36.8, 35.4, 35.1, 33.5, 30.7, 30.4, 28.7. MS-EI (70 eV) 370.(2), 352(5), 295 (30), 57(100). Anal Calcd. for $C_{22}H_{30}N_2O_3$ (370.496) H 8.16 C 71.32 N 7.56. Found: H, 8.17; C, 71.50, N, 7.61.

(2S,3S,2'S)**-2-[2'-(*tert*-Butoxycarbonylamino)-3'-Methyl-*N*'-Propanamido]-3-Hydroxy-1-Phenyl-5-(Trimethylsilylmethyl)-5-Hexene (43).** ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.2 (m, 5H), 6.2 (bd, J = 7Hz, 1H), 5.45 (s-like, 1H), 5.35 ((s-like, 1H), 3.8-3.6 (m, 3H), 2.9 (d-like, 2H), 2.4 -2.2 (m, 4H), 2.1 (bs, 1H), 1.7 (m, 1H),1.45 (s, 9H), 1.0 (m 6H), 0.20 (s, 9H).^{13}C NMR ($CDCl_3$, 50 MHz) δ 174.8, 159.7, 150.6, 139.6, 128.3, 125.4, 107.6, 72.6, 70.7, 56.1, 54.6, 49.6, 35.8, 28.9, 27.9, 24.4, 16.2, 0.7. MS-EI (70 eV) 476 (0.5), 403(5), 346 (4), 73 (100).

(*4S,5S,2'S*)-2,2-Dimethyl-3-[2'(-*tert*-Butoxycarbonylamino)-3'-Methyl-*N*'-Propanamido]-4-Phenylmethyl-5-[2'-(Trimethysilylmethyl)-1'-Propenoyl]-1,3-Oxazolidine (44). A solution of **43** (0.35 g, 0.76 mmol) in 2,2-dimethoxypropane (2 mL) and PPTS (25 mg) was stirred at room temperature for 24 h. Ether (35 mL) was added followed by $NaHCO_3$ (10%). The organic layer was separated, dried over anhydrous Na_2SO_4 and the solvent evaporated to give compound **44** sufficiently pure to be used in the next step (0.35 g, 90% yield). ^{1}HNMR ($CDCl_3$, 200 MHz) δ 7.4-7.1 (m, 5H), 6.5 (m, 1H), 5.05 (s-like, 1H), 4.8 (s-like, 1H), 4.1 (m, 1H), 3.8 (m, 1H), 3.3 (m, 1H), 2.5 (m, 2H), 2.4-2.0 (eight lines, AB part of an ABX system, 2H), 1.8-1.1 (series of overlapped m, 15 H), 0.2 (s, 9H).

(*4S,5S,2'S*)-2,2-Dimethyl-3-[2'-(*tert*-Butoxycarbonylamino)-3'-Methyl-*N*'-Propanamido]-4-Phenylmethyl-5-[2'-(Bromomethyl)-1'-Propenoyl]-1,3-Oxazolidine (45). A solution of **44** (0.35 g, 0.64 mmol) in CCl_4 (5 mL) was cooled to 0°C and a solution of bromine (0.1 g, 0.64 mmol) in CCl_4 (1 mL) was added with a syringe under nitrogen. The solution was stirred at room temperature for 3 h and ether was added (15 mL). The organic layer was washed with $NaHCO_3$ (10%) and brine. After drying over anhydrous Na_2SO_4 and evaporation of the solvent, product **45** was obtained by column chromatography on silica gel (eluent hexane : ethyl acetate 1 : 1) as a viscous oil (0.24 g, 73% yield).^{1}HNMR ($CDCl_3$, 200 MHz) δ 7.4-7.1 (m, 5H), 6.5 (m, 1H), 5.05 (s-like, 1H), 4.8 (s-like, 1H), 4.1 (m, 1H), 3.9-3.7 (m, 3H), 3.3 (m, 1H), 2.5 (m, 2H), 2.4-2.0 (eight lines, AB part of an ABX system, 2H), 1.8-1.1 (series of overlapped m, 13 H).

Reaction between allylic bromide 45 and Boc-Val-Phe-CHO (23) in the presence of $CrCl_2$. $CrCl_2$ (0.167 g, 1.3 mmol) was dried as described in the general procedure and dispersed in dry THF (3 mL). A solution containing aldehyde **23** (0.16 g, 0.45 mmol) and bromide **45** (0.24 g, 0.45 mmol) in dry THF (1 mL) was added under argon with a syringe. The mixture was stirred for 4 h at room temperature and than quenched with NH_4Cl and ether. The ethereal layer was separated, washed with water and brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, product **46** was isolated by column chromatography on silica gel (eluent hexane : ethyl acetate 1.5 : 1) as an amorphous solid (0.24 g, 67% yield). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.4-7.1 (m, 10H), 6.5 and 6.3 (bd, 2H), 5.05 (s-like, 1H), 4.8 (s-like, 1H), 4.1 (m, 2H), 3.9-3.6 (m, 2H), 3.5-3.3 (m, 2H), 2.5 (m, 4H), 2.4-2.0 (m, 5H), 1.8-1.1 (series of overlapped m, 26 H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 174.7, 173.9, 158.8, 158.3, 157.3, 139.4, 128.3, 127.9, 125.7, 105.7, 83.9, 78.6, 72.8, 70.8, 69.7, 68.4, 64.2, 56.1, 41.2, 39.9, 35.8, 34.1, 28.3, 27.9, 26.8, 16.3, 16.2.

C_2 Symmetric bis-oxazolidine 47. Product **46** was treated as described for compound **44** to give, after crystallisation with ether, compound **46** as a white solid (0.24 g, 93% yield, m.p. 136°-137°C). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.4-7.2 (m, 10H), 6.2 (bd, J = 9 Hz, 2H), 4.95 (s, 2H), 4.8 (m, 2H) 4.1 (m, 2H), 3.8 (m, 2H), 3.5 (m, 2H), 2.9 (d-like, 4H), 2.2-1.9 (m, 6H), 1.45 (s-like, 30H), 1.0-0.8 (m, 12H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 178.5, 157.3, 150.0, 138.4, 129.8, 126.7, 107.8, 82.2, 78.1, 70.7, 60.1, 49.7, 41.0, 33.9, 28.5, 18.7. Anal Calcd. for $C_{48}H_{72}N_4O_8$ (833.13104) H, 8.71; C, 69.20; N, 6.72. Found: H, 8.77; C, 69.00, N, 6.61.

(*2S,3S,7S,8S*)-2,8-[Bis-(*2S*)-(2'-(*tert*-Butoxycarbonylamino)-3'-Methyl-*N*'-Propanamido]-1,9-Diphenyl-3,7-Dihydroxy-5-Nonanone (48). Compound **47** (0.24 g, 0.28 mmol) was dissolved in methanol (5 mL) containing dimethylsulfide (1 mL) and the mixture cooled to -78°C. This cooled solution was added at -78°C to a solution of methanol (2 mL) containing ozone and ozone was bubbled through for 25 min. Argon was bubbled to take away ozone and the mixture spontaneously reached room temperature. To this solution borontrifluoride-acetic acid complex (0.2 mL) was added and the solution stirred at room temperature for 12 h. The mixture was concentrated to 1 mL under vacuum and ether added to precipitate compound **48** which was separated and purified by crystallization from $CHCl_3$ / acetone. (0.13 g, 61% yield, m.p. 76°-78° C).^1H NMR ($CDCl_3$, 200 MHz) δ 7.4-7.2 (m, 10H), 6.6 (bd, J = 9 Hz, 2H), 4.8 (m, 2H) 4.1 (m, 2H), 3.8 (m, 4H), 3.5 (m, 2H), 2.9 (d-like, 4H), 2.7 (bs, 2H), 2.1 (m, 2H), 1.8 (m, 2H), 1.4 (s, 18 H), 1.0 (d, J = 7 Hz, 12H);. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 208.9, 176.7, 157.5, 139.4, 128.3, 125.7, 82.8, 74.2, 70.8, 69.7, 59.6, 43.9, 37.8, 28.3, 27.6, 27.1, 16.2. Anal Calcd. for $C_{41}H_{62}N_4O_9$ (754.97269) H, 8.28; C, 65.23; N, 7.42. Found: H, 8.27; C, 65.50, N, 7.62.

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