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Z-Selective Olefination of Base-sensitive Chiral β-Hydroxy-α-aminoaldehydes Using a Modified Horner-Wadsworth-Emmons Reaction

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Abstract: The HWE reaction of base-sensitive chiral β-hydroxy-α-aminoaldehydes (serinals) was achieved under mild conditions with complete *Z*-selectivity using bis(trifluoroethyl) phosphonates and LiCl, DBU in THF. The use of the corresponding dimethyl phosphonates resulted in a mixture of *E*- and *Z*-configurated products, the ratio of which was found to depend on the size of the ester group.

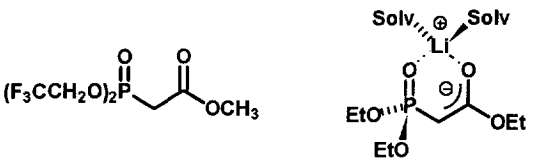
Chiral *N*-protected α-aminoaldehydes are important building blocks widely used in the synthesis of pseudopeptides, modified amino acids, and natural products.[1] However, their chemical and configurational lability prevented their widespread use in organic chemistry. To overcome these problems several protecting groups were developed.[2] We recently reported the efficient synthesis of β-hydroxy-α-aminoaldehydes[3,4], which possess both chemical and configurational stability due to their oligomer or polymer structure. So far, we have shown their potential in the synthesis of vinylogous amino acids[3] and vinylogous peptides[4]; homoallylic alcohols and amino-deoxy-sugars[5]; pseudopeptides containing an aminomethylene moiety, and chiral piperazinones[6] which serve as rigid scaffolds in the synthesis of peptidomimetics[7]. In the course of this research, we recently became interested in Wittig and related reactions leading to α,β-unsaturated esters with high *Z*-selectivity which tolerate base-sensitive substrates, i.e. chiral β-hydroxy-α-aminoaldehydes.

The Horner-Wadsworth-Emmons (HWE) modification of the Wittig reaction[8] is a widely used method for the preparation of α,β-unsaturated esters. Like the related reaction of stabilized ylides with aldehydes, the HWE reaction shows a high preference for the formation of the thermodynamically more stable *E*-olefins. It has been shown that *Z*-selectivity may be obtained under certain conditions using 5-membered cyclic phosphonates[9], 5-membered cyclic phosphonamides[10], and bis(trifluoroethyl) phosphonates like **1** which are known as Still's reagents[11]. Furthermore, the stereochemical outcome is influenced by the presence of α- or β-alkoxy- or hydroxy-groups often resulting in high *Z*-selectivity for the Wittig reaction with stabilized phosphoranes[12], whereas in HWE reactions this effect usually is not observed.[13]

All methods known so far to perform HWE reactions require the use of strong bases as KOtBu, KHMDS, BuLi, LDA, NaH or K_2CO_3 which would lead to racemisation / epimerisation, self-condensation or fragmentation of chiral β-hydroxy-α-aminoaldehydes. On the other hand it was recently reported by *Masamune* and *Roush* et al.[14] and *Rathke* and *Nowak*[15] that in the presence of lithium or magnesium halides much weaker bases as DBU, diisopropylethylamine or triethylamine can be used to achieve *E*-selective olefination of base-sensitive aldehydes in a HWE reaction.

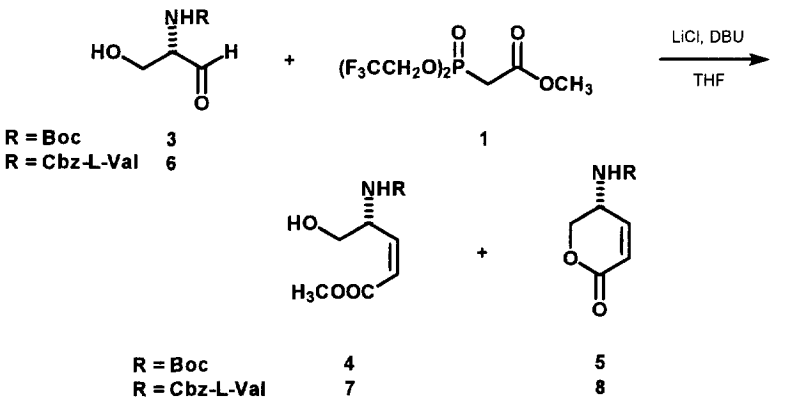
The metal ion forms a stable complex **2** with the carbanion derived from triethylphosphonoacetate **1**, thereby enhancing the acidity so that deprotonation of **1** can be achieved with amines like DBU.

We now report that the combination of the reaction conditons of *Still* (for *Z*-selectivity) and *Masamune* and *Roush* (developed for *E*-selective HWE reactions with base-labile substrates) are well suitable for the mild olefination of β-hydroxy-α-aminoaldehydes leading to high *Z*-selectivity without racemisation.



1 **2**

The *N*-protected α-amino-β-hydroxyaldehyde (*N*-Boc-*L*-serinal[3]) **3** was treated with Still's reagent methyl bis(trifluoroethyl) phosphonoacetate **1** following the protocol of *Masamune* and *Roush* to give the *Z*-configurated product **4** and the resulting lactone **5** in a 70 : 30 ratio with an overall yield of 73 % within only 30 minutes. Formation of the *E*-product was not detected.



Scheme 1

Reaction of more complex α-aminoaldehydes like the dipeptide aldehyde **6**[4] was achieved under the same conditions again resulting in complete *Z*-selectivity. In this case the primarily formed open-chain product underwent complete cyclisation under the reaction conditions to give the lactone **8** as the only product as shown in Scheme 1. Using $LiClO_4$ / Et_3N instead of LiCl / DBU, the reaction of **6** proceeded with improved yield (73 % vs. 36 %) leading to a *Z* / *E*-mixture in a 65 : 35 ratio, from which the *Z*-isomer **7** could easily be separated by column chromatography. Interestingly, under this reaction conditions only the open-chain *Z*-product was obtained. Besides resulting in a better overall yield of the *Z*-olefin, $LiClO_4$ offers advantages in handling, since a commercially available solution can be used. Furthermore, in cases where cyclisation of the *Z*-olefin is undesirable, this protocol may offer an alternative.

The enantiomeric purity of compounds **5** and **12** (Table 1) was assured by shift-experiments using $Eu(hfbc)_3$.[16] The ^1H NMR spectrum unambiguously showed that no racemisation has occurred.

Since all other compounds obtained from dipeptide aldehyde **6** contain a second stereogenic center, epimerisation would have led to diastereomers which were not detected by either tlc or ^1H NMR.

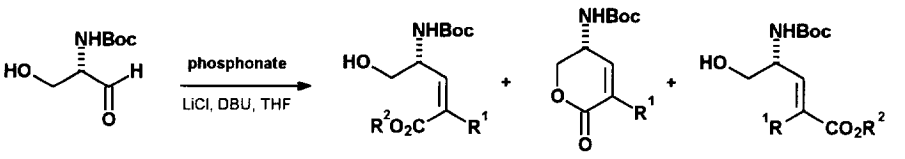
In order to investigate the influence of the phosphonate on the stereochemical outcome of the reaction, *N*-Boc-*L*-serinal **3** was reacted with several other phosphonates (Table 1). Complete *Z*-selectivity could be achieved with Still's reagent **1**, whereas use of the *tert.*-butyl phosphonate **11** led to complete *E*-selectivity. Use of the methyl phosphonate **9** resulted in a mixture of *Z*- and *E*-configurated products.

Similar results were obtained with the α-hexylated phosphonates, which were obtained by alkylation of commercially available phosphonates **9** and **11** with hexyl bromide and KOtBu.[17] The corresponding hexylated bis(fluoroethyl) phosphonate **16** was synthesised from **18** according to the protocol of *Still* and *Gennari*. In case of the *tert.*-butyl phosphonate **20**, the resulting isomers **21** and **22** could not be separated by chromatography. The configuration of **19**, containing a tri-substituted double bond, was determined by NOE experiments, showing a strong NOE between the vinylic proton and the protons of the methylester group, but no effect on the hexyl protons, which is consistent with the *E*-configuration.

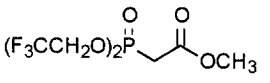
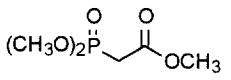
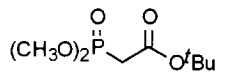
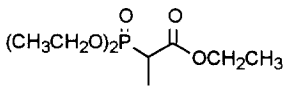
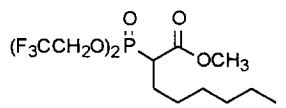
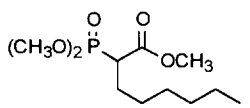
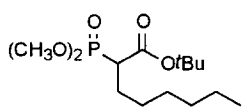
In conclusion, we have shown that combination of two known reaction procedures leads to an efficient protocol for the HWE reaction of base-labile α-aminoaldehydes with bis(fluoroethyl) phosphonates proceeding with high *Z*-selectivity. The procedure therefore should be of interest for the synthesis of natural and other products containing a *Z*-configurated α,β-unsaturated ester moiety and base-sensitive functionalities. However, in case of α-substituted phosphonates the total yields are low, as previously described,[12] whereas in case of unsubstituted phosphonates the products are obtained in good yields.

The open-chain compounds obtained by this method are of interest as vinylogous amino acids and peptides, whereas the lactones represent rigid scaffolds for the synthesis of peptidomimetics. Further investigations are currently underway in our laboratories.

Table 1: HWE reaction of *N*-Boc-*L*-Serinal **3** with Different Phosphonates.



3

Phosphonate	R^1	R^2	Yield [%] *Z*	Yield [%] Lactone	Yield [%] *E*	Total yield [%]
 **1**	H	Me	51 **(4)**	22 **(5)**	-	73
 **9**	H	Me	-	18 **(5)**	49 **(10)**	67
 **11**	H	^{t}Bu	-	-	65 **(12)**	65
 **13**	Me	Et	-	14 **(14)**	31 **(15)**	45
 **16**	hexyl	Me	-	34 **(17)**	-	34
 **18**	hexyl	Me	-	14 **(17)**	18 **(19)**	32
 **20**	hexyl	^{t}Bu	15 **(21)**	-	15 **(22)**	30

EXPERIMENTAL

Solvents were purified in the usual way. Water sensitive reactions were carried out in flame dried glassware under argon. Thin layer chromatography: Merck precoated tlc plates, silica gel 60; column chromatography: silica gel 60 (Merck, 40-63 μm). ^{1}H NMR: Bruker AC-200, Bruker AM-400. Mass spectrometry: A. E. I. MS-30 and MS-50, ion source 180°C, FAB: Kratos Concept 1H, matrix = m-nitrobenzylic alcohol. Elemental analyses were performed at the Institute of Organic Chemistry and Biochemistry, Bonn, microanalytical department.

2-(Dimethylphosphono)-octanoic acid methyl ester (18)
Phosphonate **9** (8.2 g, 45 mmol) was dissolved in absolute DMF (50 ml) and stirred at r.t. under argon atmosphere with KOtBu (5.1 g, 45 mmol) for 1 h. Freshly distilled hexyl bromide (7.5 g, 45 mmol) was added dropwise, upon which a yellowish precipitate was formed. The mixture was stirred for 24 h until the reaction was complete according to tlc. The mixture was quenched with water and extracted with diethyl ether. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude product was purified by distillation. Yield: 8.14 g (68 %); b.p. 111-113 °C (0.5 Torr); R_f = 0.29 (diethyl ether);
^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.86 (t, J = 6 Hz, 3 H, hexyl-CH_3); 1.27 (m, 8 H, hexyl-CH_2); 1.86 (m, 2 H, (P)(COOMe)CHC$\underline{H}_2$-Alkyl); 2.87-3.08 (m, J_{HP} = 11 Hz, J = 4 Hz, 1 H, P-C$\underline{H}$(hexyl)COOMe); 3.74 (m, 6 H, P-OCH_3); 3.82 (m, 3 H, $COOCH_3$).
MS (HR-MS): $C_{11}H_{23}O_5P$ $[M]^+$, calcd.: m/z = 266.1283, found: m/z = 266.1281.

2-(Dimethylphosphono)-octanoic acid *tert.*-butyl ester (20)
Compound **20** was prepared from phosphonate **11** (8.3 g, 35.2 g) and equimolar amounts of KOtBu and hexyl bromide as described above for **18**. Yield: 9.38 g (86 %); b.p. 108-110 °C (0.5 Torr); R_f = 0.43 (diethyl ether);
^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.86 (t, J = 6 Hz, 3 H, hexyl-CH_3); 1.20-1.30 (m, 8 H, hexyl-CH_2); 1.46 (s, 9 H, $C(CH_3)_3$); 1.74 (m, 2 H, (P)(COOtBu)CHC$\underline{H}_2$-Alkyl); 2.73-2.97 (m, J_{HP} = 11 Hz, J = 4 Hz, 1 H, P-C$\underline{H}$(hexyl)COOtBu); 3.74 (m, J_{HP} = 4 Hz, 3 H, P-OCH_3); 3.80 (m, J_{HP} = 4 Hz, 3 H, P-OCH_3).
MS (HR-MS): $C_{14}H_{30}O_5P$ $[M+H]^+$, calcd.: m/z = 309.1831, found: m/z = 309.1830

2-(Bis-(2′,2′,2′-trifluoroethyl)-phosphono)-octanoic acid methyl ester (16)
Phosphonate **18** (7.5 g, 28.2 mmol) was cooled to 0 °C and treated with 2.5 equivalents PCl_5 (14.7 g, 70.4 mmol) under argon atmosphere. The suspension was stirred for 1 h and then for additional 3 h at 70-75 °C until the PCl_5 had completely dissolved. The crude dichlorophosphonate was purified by distillation (93-96 °C, 0.15 Torr) and then directly dissolved in absolute toluene under argon. A mixture of DIPEA (4.03 g, 40.3 mmol) and 2,2,2-trifluoroethanol (5.21 g, 40.3 mmol) was added dropwise at 0 °C. To drive the reaction to completion, it was stirred for additional 12 h at r.t.. After concentration under reduced pressure, the crude product was purified by column chromatography on silica gel using petroleum ether / ethyl acetate (1 : 2) as eluent. Yield: 3.2 g (28 %); R_f = 0.21 (petroleum ether / ethyl acetate = 1 : 2);
^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, J = 6 Hz, 3 H, hexyl-CH_3); 1.22-1.44 (m, 8 H, hexyl-CH_2); 1.92 (m, 2 H, (P)(COOMe)CHC$\underline{H}_2$-Alkyl); 3.00-3.20 (m, J_{HP} = 11 Hz, J = 3 Hz, 1 H, P-C$\underline{H}$(hexyl)COOMe); 3.77 (s, 3 H, $COOCH_3$); 4.30-4.50 (m, J_{HF} = 8 Hz, 4 H, OCH_2CF_3).
MS (HR-MS): $C_{13}H_{21}O_5PF_6$ $[M]^+$, calcd.: m/z = 402.1031, found: m/z = 402.1048.

General experimental procedure for olefination of base-sensitive α-aminoaldehydes.
Anhydrous lithium chloride (3 eq.) was suspended under argon atmosphere in absolute THF and the phosphonate (3 eq.) was added. The mixture was stirred for 15 min at r.t. and then cooled to 0 °C. After addition of DBU (3 eq.), the mixture was stirred for another 30 min before the aldehyde component was added dropwise through a septum. After 0.5-1 h the reaction was complete according to tlc and was quenched with aqueous saturated NH_4Cl and then extracted with diethyl ether (3 x 50 ml). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford the crude products which were purified by column chromatography on silica gel.

4(*R*)-(*N-tert.*-Butoxycarbonylamino)-5-hydroxy-pent-2-(*Z*)-enoic acid methyl ester (4) and 5-(*R*)-(*N-tert.*-Butoxycarbonylamino)-5,6-dihydro-pyran-2-one (5)
Compounds **4** and **5** were obtained from 757 mg (4 mmol) **3**.
Yield (**4**) : 497 mg (51 %) of a colourless oil; R_f = 0.21 (petroleum ether / ethyl acetate = 2 : 1);
^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.43 (s, 9 H, $C(CH_3)_3$); 2.50 (br, 1 H, OH); 3.72 (s, 3 H, CO_2CH_3); 3.67-3.83 (m, 2 H, CH_2OH); 5.08-5.25 (m, 2 H, NH and 4-CH); 5.91 (dd, J = 11.7 Hz, J < 1 Hz, 1 H, 2-CH); 6.22 (dd, J = 11.7 Hz, J = 7.9 Hz, 1 H, 3-CH).
MS (FAB-MS): $C_{11}H_{20}NO_5$ $[M+H]^+$, calcd.: m/z = 246.1341, found m/z = 246.2.
Yield (**5**): 560 mg (22 %); m.p. 122-123 °C; R_f = 0.24 (petroleum ether / ethyl acetate = 2 : 1);
^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.44 (s, 9 H, $C(CH_3)_3$); 4.27-4.53 (m, 3 H, 5-CH and 6-CH_2); 4.82 (br, 1 H, NH); 6.07 (dd, J = 9.8 Hz, J < 1 Hz, 3-CH); 6.86 (dd, J = 9.8 Hz, J = 4.6 Hz, 1 H, 4-CH).
Analysis: $C_{10}H_{15}NO_4$ (213.23) calcd. (%): C 56.33, H 7.09, N 6.57, found (%): C 56.16, H 7.06, N 6.58.
MS (HR-MS): $C_{10}H_{16}NO_4$ $[M+H]^+$, calcd.: m/z = 214.1079, found: m/z = 214.1067.

4-(*R*)-(*N*-Benzyloxycarbonyl-*L*-valinoyl)-amino-5-hydroxy-pent-2-(*Z*)-enoic acid methyl ester (7)
Ester **7** was obtained from 500 mg (1.55 mmol) **6** according to the general procedure using $LiClO_4$ (5 M solution in Et_2O) and Et_3N. Yield: 278 mg Z-7 (47 %) from 428 mg (73 %) Z / E-mixture (ratio = 65 : 35); m.p. 127 °C; R_f = 0.42 (petroleum ether / acetone = 3 : 2);
^{1}H NMR (250 MHz, $CDCl_3$) : δ = 0.74-1.07 (m, 6 H, 2x CH_3); 1.96-2.15 (m, 1 H, C<u>H</u>$(CH_3)_2$); 3.23 (br, 0.8 H, OH); 3.70 (s, 3 H, CO_2CH_3); 3.55-3.85 (m, 1 H); 3.90-4.00 (m, 1 H); 4.95-5.15 (m, 2 H, $PhCH_2$); 5.30-5.46 (m, 1 H); 5.88 (d, J = 12 Hz, 1 H, CH=C<u>H</u>-CO_2CH_3); 6.19 (dd, J = 12 Hz, J = 8.5 Hz, 1 H, CH-C<u>H</u>=CH-CO_2CH_3); 7.08 (d, J = 7 Hz, 0.9 H, NH); 7.20-7.43 (m, 5 H, Ph).
MS (FAB-MS): $C_{19}H_{26}N_2O_6$ $[M]^+$, calcd.: m/z = 378.1791, found: m/z = 378.2.

5-(*S*)-*N*-(*N*-Benzyloxycarbonyl-*L*-valinoyl)-amino-5,6-dihydro-pyran-2-one (8)
Lactone **8** was obtained from 500 mg (1.55 mmol) **6** and 1.47 g (4.65 mmol) **1** according to the general procedure. Yield: 180 mg (37 %), m.p. 184-185 °C, R_f = 0.45 (petroleum ether / acetone = 3 : 2);
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85 (d, J = 6.6 Hz, 3 H, CH_3); 0.90 (d, J = 6.6 Hz, 3 H, CH_3); 2.08 (m, 1 H, $(CH_3)_2$CH-C<u>H</u>); 3.97 (m, 1 H, C<u>H</u>$(CH_3)_2$); 4.26 (dd, J = 10.8 Hz, J = 3.7 Hz, 1 H, O-CH_2); 4.40 (dd, J = 11.8 Hz, J = 3.7 Hz, 1 H, O-CH_2); 4.68 (m, 1 H, 5-CH); 5.02 (s, 2 H, $PhCH_2$); 5.31 (d, J = 7.6 Hz, 1 H, NH); 6.00 (d, J = 9.6 Hz, 1 H, 3-CH); 6.77 (br, 1 H, 4-CH); 6.87 (d, J = 7.9 Hz, 1 H, NH); 7.30 (m, 5 H, Ph).
MS (HR-MS): $C_{18}H_{24}N_2O_5$ $[M+H]^+$, calcd.: m/z = 346.1529, found: m/z = 346.1531.

4(*R*)-(*N-tert.*-Butoxycarbonylamino)-5-hydroxy-pent-2-(*E*)-enoic acid methyl ester (10)
Ester **10** was obtained from 738 mg (3.9 mmol) **3** and phosphonate **9** (together with lactone **5**) according to the general procedure. Yield: 465 mg (49 %) of a colourless oil; R_f = 0.21 (petroleum ether / ethyl acetate = 2 : 1);
^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.43 (s, 9 H, $C(CH_3)_3$); 2.40 (br, 1 H, OH); 3.71 (s, 3 H, CO_2CH_3); 3.61-3.78 (m, 2 H, CH_2OH); 4.39 (br, 1 H, 4-CH); 5.10 (d, J = 8.6 Hz, 1 H, NH); 6.00 (dd, J = 15.8 Hz, J = 2 Hz, 1 H, 2-CH); 6.91 (dd, J = 15.8 Hz, J = 5 Hz, 1 H. 3-CH).
MS (HR-MS): $C_{11}H_{29}NO_5$ $[M]^+$, calcd.: m/z = 245.1263, found m/z = 245.1226.

4-(*R*)-(*N-tert.*-Butoxycarbonylamino)-5-hydroxy-pent-(*E*)-2-enoic acid *tert.*-butyl ester (12)
Ester **12** was obtained from 643 mg (3.4 mmol) **3** and phosphonate **11** according to the general procedure. Yield: 634 mg (65 %); m.p. 90-92 °C; R_f = 0.40 (petroleum ether / ethyl acetate = 2 : 1);
^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.43 (s, 9 H, $C(CH_3)_3$); 1.46 (s, 9 H, $C(CH_3)_3$); 2.48 (t, J = 5.4 Hz, 1 H, OH); 3.61-3.82 (m, 2 H, CH_2OH); 4.38 (br, 1 H, 4-CH); 5.09 (d, J = 8.2 Hz, 1 H, NH); 5.91 (dd, J = 15.7 Hz, J = 2 Hz, 1 H, 2-CH); 6.78 (dd, J = 15.7 Hz, J = 5.6 Hz, 1 H, 3-CH).
Analysis: $C_{14}H_{25}NO_5$ (287.36) calcd. (%): C 58.52, H 8.77, N 4.87, found (%): C 58.29, H 8.87, N 4.88.
MS (HR-MS): $C_{14}H_{26}NO_5$ $[M+H]^+$, calcd.: m/z = 288.1811, found: m/z = 288.1807.

5-(*R*)-(*N-tert.*-Butoxycarbonylamino)-3-methyl-5,6-dihydro-pyran-2-one (14) and
4(*R*)-(*N-tert.*-Butoxycarbonylamino)-5-hydroxy-2-methyl-pent-2-(*E*)-enoic acid ethyl ester (15)
Compounds **14** and **15** were obtained from 3.00 g (15.9 mmol) **3** and the commercially available phosphonate **13** according to the general procedure.
Yield (**14**): 508 mg (14 %); m.p. 83-85 °C; R_f = 0.30 (petroleum ether / ethyl acetate = 2 : 1);
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 9 H, $C(CH_3)_3$); 1.89 (s, 3 H, CH_3); 4.20-4.40 (m, br, 3 H, 6-CH_2 and NH); 4.32 (br, 1 H, 5-CH); 6.50 (d, J = 10.9 Hz, 1 H, 4-CH).
MS (FAB-MS): $C_{11}H_{18}NO_4$ $[M+H]^+$, calcd.: m/z = 228.1236, found: m/z = 228.1.
Yield (**15**): 1.32 g (31 %); m.p. 74-75 °C; R_f = 0.36 (petroleum ether / ethyl acetate = 2 : 1);
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (t, J = 7.2 Hz, 3 H, $OCH_2C\underline{H}_3$); 1.40 (s, 9 H, $C(CH_3)_3$); 1.89 (s, 3 H, CH_3); 2.25 (br, 1 H, OH); 3.60 (m, br, 2 H, 6-CH_2); 4.12 (q, J = 7.2 Hz, 2 H, $OC\underline{H}_2CH_3$); 4.45 (br, 1 H, 5-CH); 5.85 (br, 1 H, NH); 6.50 (d, 1 H, J = 10.5 Hz, 4-CH).
MS (EI-MS): $C_9H_{14}NO_3$ $[M-OtBu]^+$, calcd.: m/z = 200.0923, found: m/z = 200.0.

5-(*R*)-(*N-tert.*-Butoxycarbonylamino)-3-hexyl-5,6-dihydro-2*H*-pyran-2-one (17)
Lactone **17** was obtained from 416 mg (2.2 mmol) **3** and phosphonate **16** according to the general procedure. Yield: 219 mg (34 %); m.p. 83-85 °C; R_f = 0.14 (petroleum ether / ethyl acetate = 10 : 1);
^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, 6.5 Hz, 3 H, hexyl-CH_3); 1.23-1.36 (m, 8 H, hexyl-CH_2); 1.40-1.51 (m, 11 H, $C(CH_3)_3$ and $C=C(CH_2\text{-})CO_2\text{-}$); 4.28-4.36 (m, 1 H, 5-CH); 4.38-4.45 (m, 2 H, 6-CH_2); 4.74 (d, 7.1 Hz, 1 H, NH); 6.54 (d, 5.3 Hz, 4-CH).
MS (HR-MS): $C_{16}H_{28}NO_4$ $[M+H]^+$, calcd.: m/z = 298.2018, found: m/z = 298.2031.

4-(*R*)-(*N-tert.*-Butoxycarbonylamino)-2-hexyl-5-hydroxy-pent-2-(*E*)-enoic acid methyl ester (19)
Ester **19** was obtained from 378 mg (2 mmol) **3** and phosphonate **18** (together with lactone **17**) according to the general procedure. Yield: 117 mg (18 %); m.p. 68-70 °C; R_f = 0.13 (petroleum ether / ethyl acetate = 5 : 1);
^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.87 (t, 2 Hz, 3 H, hexyl-CH_3); 1.15-1.37 (m, 8 H, hexyl-CH_2); 1.39-1.51 (m, 11 H, $C(CH_3)_3$ and $C=C(CH_2\text{-})CO_2\text{-}$); 2.26 (br, 1 H, OH); 3.55-3.79 (m, 2 H, CH_2OH); 3.74 (s, 3 H, CO_2CH_3); 4.53 (br, 1 H, 4-CH); 4.84 (d, 7.7 Hz, 1 H, NH); 6.53 (d, 9.6 Hz, 1 H, 3-CH).
MS (FAB-MS): $C_{17}H_{32}NO_5$ $[M+H]^+$, calcd.: m/z = 330.2280, found: m/z = 330.2.

4-(*R*)-(*N-tert.*-Butoxycarbonylamino)-2-hexyl-5-hydroxy-pent-2-(*Z*)-enoic acid *tert.*-butyl ester (21) and
4-(*R*)-(*N-tert.*-Butoxycarbonylamino)-2-hexyl-5-hydroxy-pent-2-(*E*)-enoic acid *tert.*-butyl ester (22)
Compounds **21/22** were obtained as an inseparable mixture from 205 mg (1.08 mmol) **3** and phosphonate **20** according to the general procedure. Yield: 117 mg (29 %) of a colourless oil; R_f = 0.27 (petroleum ether / ethyl acetate / dichloromethane = 1 : 1 : 1);
^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.86 (m, hexyl-CH_3); 1.18-1.34 (m, hexyl-CH_2); 1.36-1.54 (m, $C(CH_3)_3$ and $C=C(CH_2\text{-})CO_2\text{-}$); 2.32 (br, OH); 3.59-3.82 (m, CH_2OH); 4.42-4.60 (br, 4-CH); 4.68-4.94 (br, NH); 5.64 (d, 8.5 Hz); 6.39 (d, 9.2 Hz) (1 : 1.44 = 0.59 : 0.41).
MS (FAB-MS): $C_{20}H_{38}NO_5$ $[M+H]^+$, calcd.: 372.2750, found: 372.3.

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