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Novel Synthesis of a Phe-Gly *E*-Alkene Dipeptide Isostere

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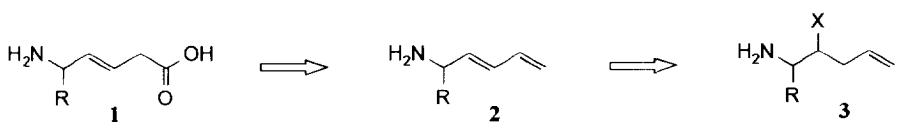
Abstract: A new strategy for the synthesis of Boc-Pheψ(*E*-CH=CH)Gly-OH (**11**) is described. The double bond is generated employing a β elimination of the mesyloxy group of **6**. This elimination proves to be the key step within the synthesis. Different products are obtained dependent on the base as well as on the reaction conditions. Employing KO*t*Bu leads to *E*-(5*S*)-(*t*-Butyloxycarbonylamino)-6-phenyl-1,3-hexadiene **7** whereas NaOMe causes a γ elimination resulting the aziridine **9**. Diene **7** is converted into the corresponding Pheψ(*E*-CH=CH)Gly isostere by subsequent hydroboration and *Jones* oxidation.

The isosteric replacement of amide bonds within peptides is an important tool in the development of bioactive compounds due to their enhanced stability against biodegradation.[1] Cyclic peptides represent ideal lead structures to investigate the influence of peptide mimetics on both, conformation and biological activity. Within various projects we have replaced dipeptide moieties by dipeptide isosteres,[2] sugar amino acids[3] and β turn mimetics.[4] Therefore, we are interested in the developement of new strategies for the synthesis of dipeptide mimetics. The *E*-alkene moiety represents an ideal isosteric replacement of the peptide bond in terms of bond length and bond angles, while electrostatic properties are altered. Since its first introduction by Hann et al.[5] various strategies to generate *E*-alkene dipeptide isosteres have been reported.[6-9]

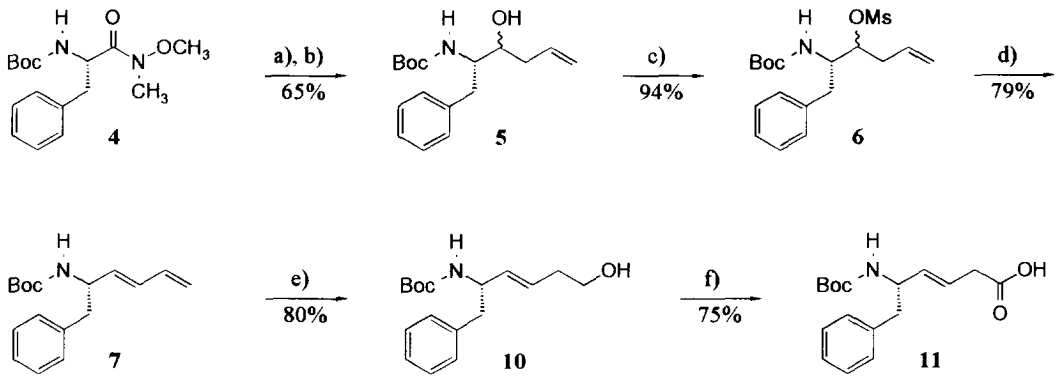
Herein we describe the development of a new approach to *E*-alkene dipeptide isostere **1** (Scheme 1) in which a β elimination is employed to generate the double bond for the first time. The strategy is based on the synthesis of the conjugated diene **2** as the key intermediate which is accessible by eliminating the leaving group X of compound **3**. Regioselective hydroboration of **2** leads to the corresponding primary alcohol which is transferred into the dipeptide isostere by subsequent oxidation.



Scheme 1

Alternatively to the standard procedure of Fehrentz et al.[10] the *N*-methoxy-*N*-methylcarboxamide **4**[11] was prepared in 96% yield starting from Boc-Phe-OH using propylphosphinic anhydride (PPA)[12] for *C*-terminal activation. Addition of 3 eq allyl magnesium bromide (Aldrich®) provided the corresponding unsaturated

homoallylic ketone.[13] Subsequent reduction gave the homoallylic alcohol **5** in 65% yield as a 7:1 mixture of diastereomers (Scheme 2).[14,15] The alcohol was readily converted into the mesylate **6**.[16]



Reagents: a) $BrMg\text{-}CH_2CH{=}CH_2$, Et_2O, -15°C, 3 h; b) $NaBH_4$, MeOH, -20°C → 0°C, 1 h; c) MsCl, Et_3N, CH_2Cl_2, 0°C, 1 h; d) KO*t*Bu, THF, -78°C → -40°C, 5 h; e) 9-BBN, THF, RT, 6 h followed by NaOH, H_2O_2, 60°C, 1 h; f) 2M *Jones* reagent, acetone, 0°C, 1 h.

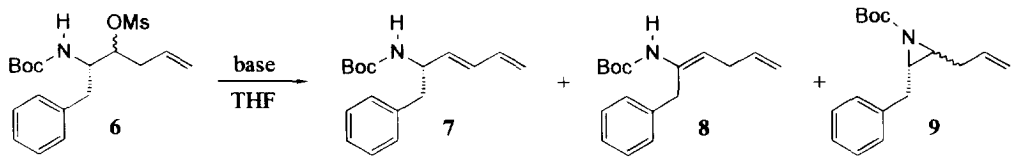
Scheme 2

We expected to generate the thermodynamically favoured conjugated diene **7**[17] by a β elimination of the mesyloxy moiety of **6**.[16,18a] Within the first attempts we employed 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base yielding **7** in 41% after flash chromatography (Table 1; entry 1). No further optimization could be achieved altering *N*-terminal protective group, leaving group, base, solvent and temperature. In general, slow and incomplete turnover rates were detected at low temperature, while elevating temperature led to an increased rate of decomposition products.

Later on potassium *tert*-butoxide (KO*t*Bu) was used since the bulky *t*-butyl group should cause a regioselective deprotonation of the C^3 proton while preserving the C^5 proton. A 4:1 mixture of the isomeric dienes **7** and **8** was obtained at -40°C (entry 2)[18b,19] while reaction at room temperature (RT) and at 67°C gave both isomers in an almost equimolar ratio (entries 3, 4). Encouraged by these results NaOMe (entry 5) as well as KOH were employed in THF to decrease the base strength. Surprisingly, these eliminations gave exclusively the aziridine **9**[18c] in excellent yield due to a γ elimination.[20]

Regioselective hydroboration of **7** was achieved using 9-borabicyclo[3.3.1]nonane (9-BBN) and led to the primary alcohol **10**[16] in 80% yield after flash chromatography (R_f (**10**) 0.25, 1:1 EtOAc/n-hexane).[21] Boc-Pheψ(*E*-CH=CH)Gly-OH (**11**)[16] was obtained by subsequent *Jones* oxidation in 35% overall yield. In addition, the synthesis of Boc-Alaψ(*E*-CH=CH)Gly-OH as well as Z-Pheψ(*E*-CH=CH)Gly-OH[22] proved the feasibility of this method generating various *E*-alkene and *carba* dipeptide isosteres. The dipeptide isosteres were used as building blocks within solid phase peptide synthesis.

Table 1: Base Dependent Regioselectivity of the Elimination Reaction



Entry	Base	Temperature [°C]	Yield [%] 7	8	9
1	DBU	67	41[A]	-	-
2	KO*t*Bu	-40	79[A]	19	-
3	KO*t*Bu	RT	50	45[B]	-
4	KO*t*Bu	67	45	50[B]	-
5	NaOMe	RT	-	-	90[A]

[A] Isolated yield after flash chromatography. [B] The isomeric ratio was determined by integration of the GC spectra.

In conclusion, we have developed an efficient and convenient synthesis of Xaaψ(*E*-CH=CH)Gly dipeptide isosteres employing a β elimination to generate the olefinic peptide bond replacement. The regioselectivity of the elimination step is directed applying different bases and reaction conditions. The desired conjugated diene **7** was obtained in good yield employing KO*t*Bu in THF at low temperature, while increasing the temperature promoted the formation of the diene **8**. In contrast, the use of NaOMe led exclusively to the formation of aziridine **9** due to a γ elimination of the mesyloxy moiety.

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16. Compounds were characterized after flash chromatography by ^{1}H NMR, mass spectra and elemental analysis. The carboxylic acid **11** was converted into the corresponding methyl ester with CH_2N_2.
17. The configuration of the double bond was determined by analysis of the coupling constants of the diene **7**.[18a] Only the formation of the *E* configurated diene **7** was observed.
18. a) *E*-(5*S*)-(*t*-Butyloxycarbonylamino)-6-phenyl-1,3-hexadiene (**7**): R_f 0.59, 1:2 EtOAc/n-hexane; ^{1}H NMR (250 MHz, DMSO-d_6, 300K): δ 7.29-7.14 (m, 5 H, aromat.), 6.98 (d, 1 H, N*H*), 6.31 (dt, 1 H, C^2*H*, $^3J_{2\text{-}1a}$ = 16.9 Hz, $^3J_{2\text{-}1b}$ = $^3J_{2\text{-}3}$ = 10.2 Hz), 6.04 (dd, 1 H, C^3*H*, $^3J_{3\text{-}4}$ = 15.2 Hz, $^3J_{3\text{-}2}$ = 10.2 Hz), 5.70 (dd, 1 H, C^4*H*, $^3J_{4\text{-}3}$ = 15.2 Hz, $^3J_{4\text{-}5}$ = 6.2 Hz), 5.15 (dd, 1 H, C^1*H*^{a}, $^3J_{1a\text{-}2}$ = 16.9 Hz, $^2J_{1a\text{-}1b}$ = 1.5 Hz), 5.03 (dd, 1 H, C^1*H*^{b}, $^3J_{1b\text{-}2}$ = 9.9 Hz, $^2J_{1b\text{-}1a}$ = 1.5 Hz), 4.29-4.08 (m, 1 H, C^5*H*), 2.73 (d, 2 H, C$^6H_2$), 1.30 (s, 9 H, Boc) ppm; ms (EI): *m/z* 273 M^+, 217 $(M - C_4H_8)^+$, 182 $(M - C_7H_7)^+$, 126 $(182 - C_4H_8)^+$; $C_{17}H_{23}NO_2$ (273.38): calcd C 74.69, H 8.48, N 5.12; found C 74.29, H 8.14, N 5.11.

b) 5-(t-Butyloxycarbonylamino)-6-phenyl-1,4-hexadiene (**8**): R_f 0.63, 1:2 EtOAc/n-hexane; ^{1}H NMR (250 MHz, DMSO-d_6, 300K): δ = 7.29-7.14 (m, 5 H, aromat.), 6.98 (d, 1 H, N*H*), 6.48-6.37 (m, 1 H, C^4*H*), 5.92-5.54 (m, 1 H, C^2*H*), 5.22-4.95 (m, 2 H, C$^1H_2$), 3.47-3.06 (m, 2 H, C$^6H_2$), 2.32-2.18 (dd, 2 H, C$^3H_2$), 1.30 (s, 9 H, Boc); ms (EI): *m/z* 232 $(M - C_3H_5)^+$, 176 $(232 - C_4H_8)^+$.

c) *N*-*t*-Butyloxycarbonyl-3-allyl-2-benzylaziridine (**9**): R_f 0.68, 1:1 EtOAc/n-hexane; ^{1}H NMR (250 MHz, DMSO-d_6, 300K): δ = 7.35-7.15 (m, 5 H, aromat.), 5.85-5.65 (m, 1 H, -CH_2CH=CH_2), 5.10 (dd, 1 H, -CH_2CH=CH_2), 5.00 (dd, 1 H, -CH_2CH=CH_2), 2.94 (dd, 1 H, -CH_2-Ph), 2.58-2.25 (m, 4 H, C^2*H*, C^3*H*, -CH_2-Ph and -CH_2CH=CH_2), 2.05-1.90 (m, 1 H, -CH_2CH=CH_2), 1.38 (s, 9 H, Boc); ms (EI): *m/z* 217 $(M - C_4H_8)^+$, 172 $(M - Boc)^+$; $C_{17}H_{23}NO_2$ (273.38): calcd C 74.69, H 8.48, N 5.12; found C 74.77, H 8.56, N 5.02.
19. The isomeric dienes were separated by careful silica gel flash chromatography.
20. Starting from diastereomeric pure mesylate the formation of only one diastereomer of the aziridine **9** was observed. The configuration of the corresponding chiral center was not determined.
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22. Boc-Ala ψ(*E*-CH=CH)Gly-OH and Z-Phe ψ(*E*-CH=CH)Gly-OH were synthesized employing DBU. The syntheses were not optimized. The isosteres were isolated in 15% and 8% overall yield, respectively.

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