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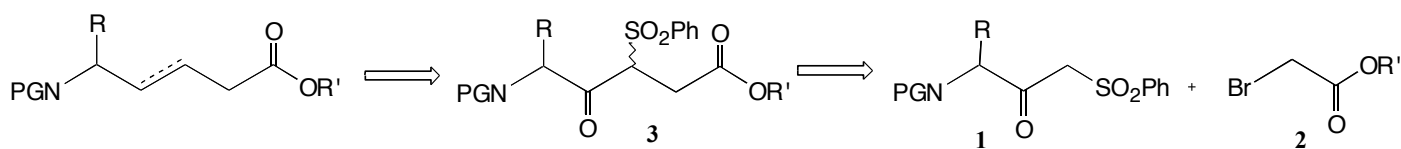
New Application of The Julia Olefination for The Synthesis of Tyr-Ψ *E*-Alkene and Carba Isostere Pseudopeptides

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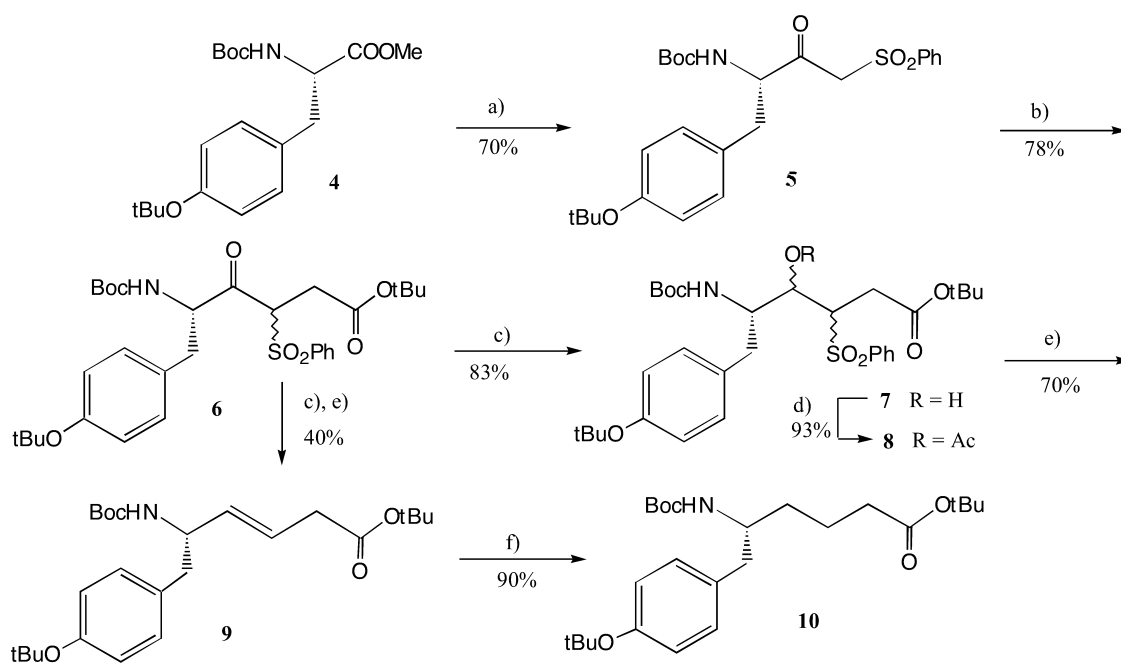
Abstract: A new application of the Julia olefination to the synthesis of TyrΨ[*E*-CH=CH]Gly and TyrΨ[CH₂CH₂]Gly pseudopeptides is described *via* condensation of tertibutyl bromoacetate on tyrosine-derived β-ketosulfone and subsequent reductive desulfonation.

The replacement of the amide bond linkage within peptides is a classical strategy for the study of biologically active peptides and for the preparation of peptide bonds resistant to proteolysis.¹ Among the different described amide bond surrogates, the non-hydrolysable *E*-ethylenic isosteres mimic the three-dimensional structure of the amide bond.² Several synthetic routes of *E*-olefin pseudopeptides are described in the literature.³ Among them, the Julia olefination has been applied in this context.⁴ We would like to disclose herein our results on a new application of the Julia olefination to the synthesis of TyrΨ[*E*-CH=CH]Gly and TyrΨ[CH₂CH₂]Gly dipeptides according to scheme 1.



Scheme 1

Lygo has been the first one to investigate this strategy but has failed to obtain the *E*-olefin isostere of Ala-Gly dipeptide.⁵ *N*α-Boc-Tyr(*t*Bu)-OMe **46** was first transformed into the β-ketosulfone **57** by alkylation with two equivalents of the di-lithio anion of methyl phenyl sulfone at -30°C as described by Lygo (scheme 2). It was necessary to use an excess of the anion to obtain complete conversion of the starting compound **4**. Condensation of tertibutyl bromoacetate onto β-ketosulfone **5** was achieved with potassium carbonate in DMF for 6 hours in 78% yield. Next we turned our attention to the conversion of the β-ketosulfone **6** into the corresponding *E*-alkene isostere **9**. Lygo did not succeed in the transformation of the corresponding Ala-Gly ketosulfone ethyl ester into the *E*-alkene product using sodium borohydride reduction followed by reductive desulfonation with sodium amalgam at -10°C but instead obtained the fully reduced methyl ester. However, we found that a *t*Bu protecting group for the ester **2** is required for the efficient reductive desulfonation of **3**. In this way, the β-ketosulfone tertibutyl ester **6** was transformed in the same conditions into the *E*-alkene isostere **9** in 40% yield. However, we improved the yield by isolating the intermediate alcohols **7** and then reducing the acetylated diastereomers **8** to obtain the dipeptide isostere **9** in 54 % overall yield from **6**.



Reagents: a) $\text{PhSO}_2\text{CHLi}_2$, THF, 0°C 30 mn then -30°C 3 h; b) $\text{BrCH}_2\text{COOtBu}$, K_2CO_3 , DMF, RT, 6 h; c) NaBH_4 , MeOH, -10°C 3 h; d) Ac_2O , DMAP, pyridine, RT, 3 h; e) Na/Hg , MeOH, Na_2HPO_4 , -10°C , 2 h; f) H_2 , Pd/C, EtOH 95° , RT, 20 h.

Scheme 2

Finally, catalytic hydrogenation of *E*-alkene **9** gave the fully protected carbapeptide **10** in 90% yield.⁸

In conclusion, we have shown that a new application of Julia olefination methodology allows for the efficient synthesis of Tyr Ψ [*E*-CH=CH]Gly and Tyr Ψ [CH₂CH₂]Gly pseudopeptide in five (29.5% overall yield) and six steps respectively from Boc-protected tyrosine methyl ester. Furthermore, synthesis of Xaa Ψ [CH=CH]Xbb would be feasible through condensation of β -ketosulfone **1** with α -substituted bromoester **2**.⁹

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- Compound **4** was prepared by standard procedures from either the corresponding commercial *N* $^\alpha$ -Boc-protected acid or the free amine methyl ester.
- All compounds gave satisfactory ¹H NMR and FTIR data. Compound **9**. [α]_D +2.6 (c = 0.57, CHCl₃). Glassy solid. IR (film, ν cm⁻¹): 3360, 2932, 1713, 1503, 1391, 1237, 1162. ¹H NMR (300 MHz, CDCl₃, δ ppm): 1.32 (s, 9 H, tBu), 1.39 (s, 9 H, tBu), 1.43 (s, 9 H, tBu), 2.78 (d, J = 6.2 Hz, 2 H, CH₂), 2.94 (d, J = 6.6 Hz, 2 H, CH₂), 4.37 (m, 1 H, CH α or NH), 4.46 (m, 1 H, NH or CH α), 5.50 (dd, J = 15.8 Hz and 5.1 Hz, 1 H, =CH), 5.62 (m, 1 H, =CH), 6.90 (d, J = 8.3 Hz, 2 H, 2 CH ar), 7.05 (d, J = 8.3 Hz, 2 H, 2 CH ar).
- Compound **10** was found enantiomerically pure by C18 RP-HPLC analysis after complete deprotection (TFA/CH₂Cl₂) and derivatization with GITC (see Nimura, N.; Ogura, H.; Kinoshita, T. *J. Chromatography*, **1980**, *202*, 375-379).
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