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New application of the Julia olefination for the synthesis of Tyr-Gly *E*-alkene and carba isostere pseudopeptides

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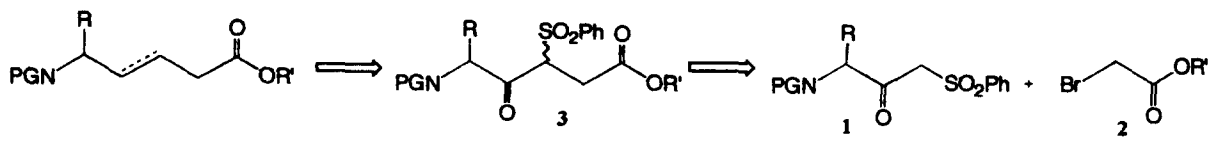
Abstract

A new application of the Julia olefination to the synthesis of TyrΨ[*E*-CH=CH]Gly and TyrΨ[CH_2CH_2]Gly pseudopeptides is described via condensation of tertiobutyl 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[CH_2CH_2]Gly dipeptides according to Scheme 1.



Scheme 1.

Lygo has been the first person 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 **4**[6] was first transformed into the β-ketosulfone **5**[7] by alkylation with two equivalents of the di-lithio anion of methyl phenyl sulfone at −78°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 tertiobutyl bromoacetate onto β-ketosulfone **5** was achieved with potassium carbonate in DMF for 6 h 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

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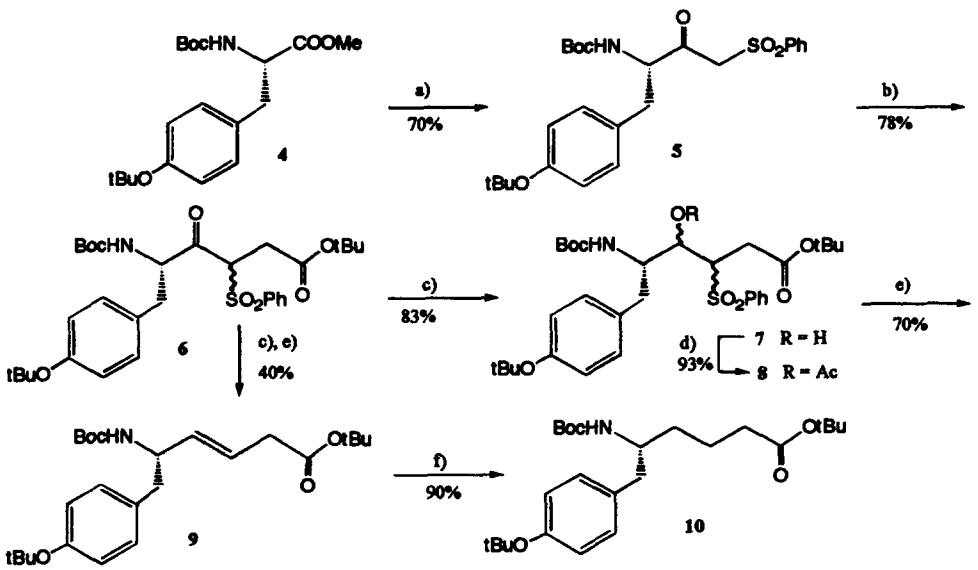
the corresponding Ala-Gly ketosulfone ethyl ester into the *E*-alkene product using sodium borohydride reduction followed by reductive desulfonation with sodium amalgam at −10°C, but instead obtained the fully reduced methyl ester. However, we found that a *t*Bu protecting group for the ester **2** is required for the efficient reductive desulfonation of **3**. In this way, the β-ketosulfone tertiobutyl 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**.



Scheme 2. Reagents: (a) $PhSO_2CHLi_2$, THF, 0°C 30 min then −30°C 3 h; (b) $BrCH_2COOtBu$, 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

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 TyrΨ[*E*-CH=CH]Gly and TyrΨ[CH_2CH_2]Gly pseudopeptide in five (29.5% overall yield) and six steps, respectively, from Boc-protected tyrosine methyl ester. Furthermore, synthesis of XaaΨ[CH=CH]Xbb pseudopeptides would be feasible through condensation of β-ketosulfone **1** with α-substituted bromoester **2**.[9]

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6. Compound **4** was prepared by standard procedures from either the corresponding commercial N^{α}-Boc-protected acid or the free amine methyl ester.
7. All compounds gave satisfactory ^{1}H NMR and FTIR data. Compound **9**: $[\alpha]_D$ +2.6 (*c* 0.57, $CHCl_3$), glassy solid. IR (film, ν cm^{-1}): 3360, 2932, 1713, 1503, 1391, 1237, 1162. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.32 (s, 9H, *t*Bu), 1.39 (s, 9H, *t*Bu), 1.43 (s, 9H, *t*Bu), 2.78 (d, *J*=6.2 Hz, 2H, CH_2), 2.94 (d, *J*=6.6 Hz, 2H, CH_2), 4.37 (m, 1H, CH α or NH), 4.46 (m, 1H, NH or CH α), 5.50 (dd, *J*=15.8 Hz and 5.1 Hz, 1H, =CH), 5.62 (m, 1H, =CH), 6.90 (d, *J*=8.3 Hz, 2H, 2CH ar), 7.05 (d, *J*=8.3 Hz, 2H, 2CH ar).
8. Compound **10** was found enantiomerically pure by C18 RP-HPLC analysis after complete deprotection (TFA/CH_2Cl_2) and derivatization with GITC (see: Nimura, N.; Ogura, H.; Kinoshita, T. *J. Chromatography* **1980**, *202*, 375–379).
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