Taking control of P1, P1′ and double bond stereochemistry in the synthesis of Phe-Phe (*E*)-alkene amide isostere dipeptidomimetics†

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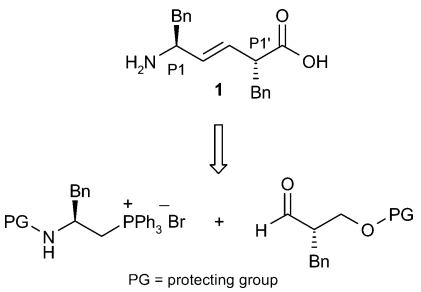
A protocol for the stereocontrolled independent preparation of both C-2 epimers of Phe-Phe *trans*-vinyl amide isostere dipeptidomimetics has been devised based on a Wittig-type reaction, in which two chiral building blocks were joined with excellent *E*-selectivity to give compounds of the type PheΨ[(*E*)-CH=CH]-PheOH.

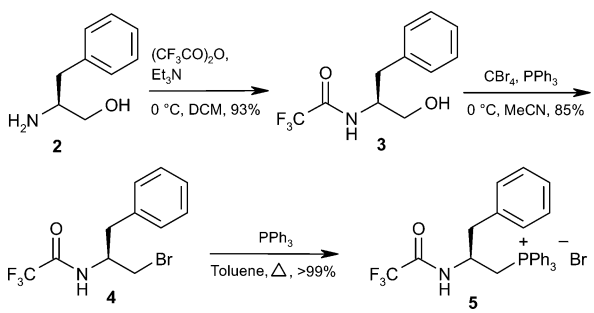
(*E*)-Alkene dipeptidomimetics (*e.g.* **1**, Scheme 1) are of interest as building blocks in artificial pseudopeptides. They can be used to probe the involvement of amide bond geometry and polarity in biomolecular structure, recognition and function,[1,2] since the (*E*)-alkene closely resembles the natural amide with regard to bond lengths, angles and rigidity but is devoid of hydrogen bonding capability.[2] We have for some time been interested in the chemical and pharmacological properties of (*E*)-alkene dipeptidomimetics, mainly Phe-Phe and Phe-Gly derivatives.[3] In spite of their simple structure, the synthesis of these (*E*)-5-aminopent-3-enoic acids can be challenging. Over the years, several interesting routes to (*E*)-alkene dipeptide isosteres have been devised.[1e,3a,4] While many of them display excellent stereoselectivity in double bond formation and/or side chain installation steps, these syntheses are usually quite complex, have not been applied to disubstituted alkene derivatives, or have stereochemical weak spots. We have previously used sulfonium ylide-based chemistry to synthesise derivatives of **1**, where the key Julia olefination step installs the alkene with good *E*/*Z*-selectivity;[3,4c] however, the procedure is laborious and our data indicate loss of the stereochemical integrity at C-2.[3a]

An ideal synthetic route to disubstituted (*E*)-alkene isosteres like **1** would confer stereocontrol of both C-5 and C-2 side chain stereocentres (P1 and P1′ attachment points) as well as of the double bond. We wanted to find conditions to provide good control of all three stereocentres, which could be used also for the synthesis of similar derivatives. For versatility, we desired a convergent approach employing chiral amino acid-like building blocks to install the remote stereogenic centres (Scheme 1).[5] For simplicity, a Wittig-based reaction was chosen for alkene formation and the P1 fragment was chosen to contain the ylide. Full deprotection of the isosteres is rarely reported,[1e] but we also wanted to ensure that mimetics without protective groups could be obtained. With PheΨ[(*E*)-CH=CH]-PheOH dipeptidomimetics as model compounds, we wanted to explore the full utility and stereocontrol of the method by independently synthesising both C-2 epimers of the target compounds. Thus, we set out to prepare chiral phosphonium salt **5** (Scheme 2) and chiral aldehydes **6** (*vide infra*). β-Amino phosphonium salts have been prepared previously,[6] but we were surprised to find that carbamate-protected derivatives were scarce in the literature. For convenient deprotection of the dipeptidomimetic products, we wanted to use Boc-protection; however, the *tert*-butyl carbamate was found to be unstable in the reaction between a Boc-protected amino bromide derivative of phenylalaninol (*i.e.* Boc-analogue of **4**, Scheme 2) with triphenylphosphine using a variety of solvents and temperatures. Similarly, the methylcarbamate- and benzylcarbamate-protected amino bromide analogues afforded only trace amounts of the desired product. In all reactions, the carbamate was cleaved, and a phosphorous-containing adduct was formed according to NMR spectroscopy, probably due to the nucleophilic nature of the carbamate carbonyl oxygen. Instead, trifluoroacetyl protection was tried since its oxygen is less electron-rich. Bromide **4** was found to be perfectly stable in the reaction with triphenylphosphine, giving phosphonium salt **5** in quantitative yield (Scheme 2).

The P1′ building blocks, the chiral aldehydes (*R*)-**6** (82% ee) and (*S*)-**6** (84% ee), were synthesised in five steps from dimethyl



Scheme 1 Retrosynthesis of an (*E*)-alkene dipeptidomimetic (**1**) for a Wittig-based synthetic route.



Scheme 2 Synthesis of the phenylalanine-like P1 synthon; trifluoroacetyl-protected amino phosphonium salt **5**.

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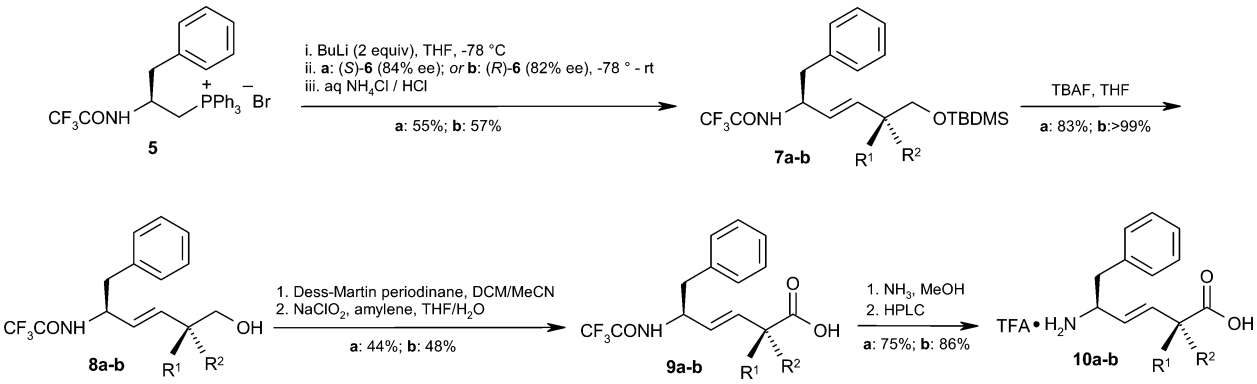
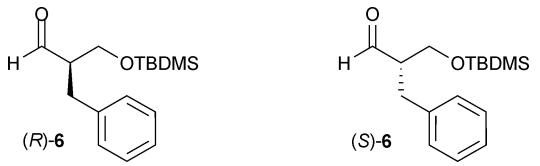


Scheme 3 Independent assembly of Phe-Phe (*E*)-alkene dipeptidomimetics **10a–b** from phosphonium salt **5** and aldehyde (*S*)-**6** or (*R*)-**6**. Key (for compounds **7–10**), **a**: $R^1 = H$, $R^2 = Bn$; **b**: $R^1 = Bn$, $R^2 = H$.

benzyl malonate by a protocol employing lipase-catalysed desymmetrisation or resolution as key steps, respectively. The details of this chemoenzymatic synthesis are described elsewere.[7] With both enantiomers of aldehyde **6** at hand, we hoped to gain control of the C-2 stereochemistry if the following reactions proceeded without epimerisation.



The assembly of dipeptidomimetics **10a–b** commenced with a Wittig reaction involving either enantiomer of aldehyde **6** and the ylide derived from phosphonium salt **5** (Scheme 3). A standard Wittig reaction between an α-branched aliphatic aldehyde and a β-branched non-stabilised ylide can be expected to proceed with *Z*-selectivity;[8,9] however, the presence of the trifluoroacetamide in **5** gives the possibility of double deprotonation, which may influence the outcome of the reaction. Ylides containing anionic groups (*i.e.* lithiated heteroatoms) in proximity to the reacting centre are prone to *E*-selelectivity,[9,10] if suitable reaction conditions are provided. While this has been well established for α-, β- and γ-oxido-, carboxy- and amido-ylides in reactions with aromatic aldehydes,[10] we have found no account of reactions involving lithiated amides and aliphatic aldehydes. Treatment of **5** with 2 equivalents of *n*-butyllithium at −78 °C, followed by addition of **6** and slow warming to room temperature followed by an aqueous quench afforded the alkene products **7a–b** in 55% and 57% yield, respectively. To our delight, no *Z*-isomer could be detected in the ^{1}H-NMR spectra.

Racemisation of the coupling partners or epimerisation of either stereocentre of the product was of concern in this transformation, and for this reason the reactants were thoroughly purified to ensure a precise stoichiometry in the deprotonation. A less than full enantiomeric purity of aldehydes **6** was advantageous in this model study, since this allowed the detection of stereochemical scrambling by NMR more conveniently. No racemisation or epimerisation could be detected at any point in the synthesis of **10a** (Scheme 3), and this was further affirmed by HPLC, since the de of the final product **10a** matched the ee of the starting aldehyde (*S*)-**6**. In the case of **10b**, at most 1% stereochemical scrambling was detected.

In earlier work with compounds like **7–10**,[3c] we have found that the double bond may rearrange under forcing conditions, and this prompted us to complete the synthesis using the mildest reagents possible. The silyl protecting group was removed to yield alcohols **8**, which were converted to carboxylic acids **9** by tandem Dess–Martin/$NaClO_2$ oxidation.

For the mimetics to be useful in the synthesis of pseudopeptides, the *N*-protecting group should be interchangeable, and for this reason we wanted to fully deprotect the acids **9** to give the salts **10**. We were surprised to find that the trifluoroacetamide functions of acids **9** were exceptionally stable toward alkaline hydrolysis; in the case of **9a** the reaction took 30 days to complete with a large excess of K_2CO_3 in H_2O–MeOH. A variety of conditions were investigated on a small scale to obtain a higher reaction rate. While none of the alkali hydroxides or carbonates afforded any appreciable amount of product in methanol or THF with varying amounts water, barium hydroxide was found to cleave the trifluoroacetamide of **9a** efficiently.[11] Ammonia in methanol was somewhat less effective than barium hydroxide, but was the reagent of choice due to the simplified work-up. With suitable conditions for deprotection identified, the corresponding ammonium salts could be isolated. After checking the diastereomeric ratio by HPLC (*vide supra*), compounds **10a–b** were purified by preparative HPLC to full stereochemical purity.

The diastereomeric purity of the alkene derivatives **7–10** (Scheme 3) is of course dependent on the enantiomeric purity of the aldehyde reactant. We and others have reported the preparation of α-chiral aldehydes like **6** in high enantiomeric purity,[7,12] and thus, the current method may be an important addition to stereocontrolled preparation of (*E*)-alkene dipeptidomimetics in high de. Further studies of the generality of this method involving different ylide and aldehyde coupling partners are ongoing. The convergent building block approach presented in this communication can offer versatility in that the peptidomimetic product is assembled from two chiral fragments, which are easily prepared. The key Wittig reaction proceeded with excellent *E*/*Z*-selectivity and with full control of both side-chain stereocentres, and the complexity of the overall sequence is low.

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