New potential access to ethylenic pseudodipeptides through catalytic alkene metathesis

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Dialkenenic amide 1 (R^1 = CH_2Ph, R^2 = H) is readily converted, through ruthenium-catalysed metathetic ring closure, to ethylenic lactam 2, a close precursor of *Z*-ethylenic pseudodipeptide 3.

Backbone modifications of biologically active peptides constitute an increasingly popular strategy which may be aimed at various goals, such as the improvement of metabolic stability, the obtention of analogues with agonistic or antagonistic properties or the elucidation of structure–activity relationships.[1] Isosteric replacement of the amide bond by an ethylenic linkage is of particular interest since the three-dimensional structures of the *E* and *Z* HC=CH linkages closely resemble those of the *trans* and *cis* amide bonds respectively.[2] Although disfavoured compared to the *trans* one, the *cis* peptide bond geometry is nevertheless not uncommonly encountered in naturally occurring peptides and it has been suggested that it could play an important role in their biological activity.[3] In that respect, replacement of the amide bonds by surrogates in a locked *cis* or *trans* configuration such as the *Z*- and *E*-ethylenic bonds is of obvious interest.

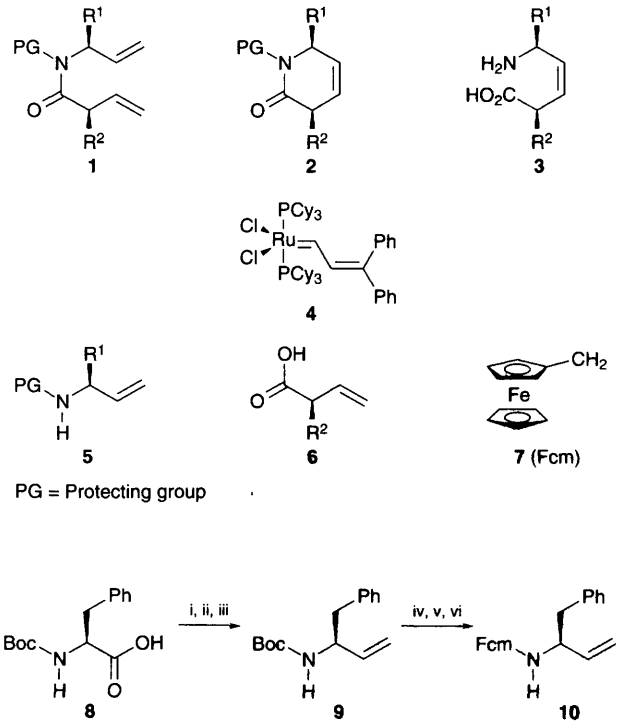
No stereoselective syntheses of dipeptide *Z*-ethylenic isosteres have been reported to date.[4] Recently, Rich and coworkers[5] have prepared the *Z*-ethylenic isostere of (*N*-methylleucyl)leucine as a mixture of (easily separable) diastereoisomers by alkylation with *iso*-butyl iodide of the (*N*-methylleucyl)glycine analogue. Syntheses of dipeptide *E*-ethylenic isosteres which incorporate stereocontrol at the C-2 position of the 5-aminopent-3-enoic unit are relatively few. If we except Hopkins' convergent approach,[6] which is based on Julia's alkene synthesis and in which coupling partners are first synthesized in optically pure form, all other protocols involve simultaneous positioning of the double bond and stereoselective building of the C-2, or more rarely the C-5, chiral centres by way of sigmatropic,[7] *anti* $S_{N2'}$ or $S_{E'}$[8,9] processes. Such strategies require, as a preliminary step, the preparation of optically pure allylic precursors which are not always easily accessible.

We propose a different, convergent approach whose key step is an intramolecular alkene metathesis reaction on diethylenic amides of general structure **1** leading to ethylenic lactams **2**, which are direct precursors of the dipeptide *Z*-ethylenic isosteres **3**. For our purpose, use of the ruthenium metathesis catalyst **4**,[10,11] recently introduced by Grubbs and coworkers, seemed to be particularly well suited, owing to its exceptional resistance to poisoning by polar molecules. As for the precursors of **1**, allylic amines of general structure **5** are readily available from the chiral pool of amino acids, while optically active α-substituted β,γ-ethylenic carboxylic acids **6** may conceivably be obtained by α-regioselective[12,13] and diastereoselective[13] alkylation (or aldolisation) of crotonic or vinylacetic acid derivatives containing chiral auxiliary groups.

Setting aside temporarily the problem of stereoselective introduction of the C^2 substituent, and as a test of the general feasibility of our project, we report herein the results of our preliminary investigations into the synthesis of the Phe-Gly *Z*-ethylenic isostere, **1** with R^1 = CH_2Ph, R^2 = H.

For nitrogen protection of the amide bond in **1**, we selected the ferrocenylmethyl (Fcm) group **7** because: (i) unlike many other *N*-substituted aminoacids, the *N*-Fcm derivatives may be used in conventional peptidic coupling reactions (DCC/DMAP) without apparent difficulties;[14] (ii) the Fcm group is readily removed by trifluoroacetolysis;[14] (iii) the Fcm group could be expected to be bulky enough to induce, at least partially, a *syn* orientation of the two ethylenic appendages in **1** (as effectively represented here). Using well documented chemistry, the *N*-ferrocenylmethylamine **10**† was prepared, as shown in Scheme 1, in six steps and 58% overall yield from *N*-Boc-L-phenylalanine **8**.

Acylation of **10** with vinylacetyl chloride (Et_3N, Et_2O, −15 °C then 0 °C, 1 h) gave **11** in 95% yield which exists (NMR) as a *ca.* 1:1 mixture of its two rotameric forms. Treatment of **11** with 5–10 mol% of catalyst **4** (Scheme 2) produced lactam **12** in 85–90% yield. Removal of the Fcm group from **12** was achieved by trifluoroacetolysis in the presence of triethylsilane as the carbocation scavenger. Attempted hydrolysis of the deprotected lactam **13** under the

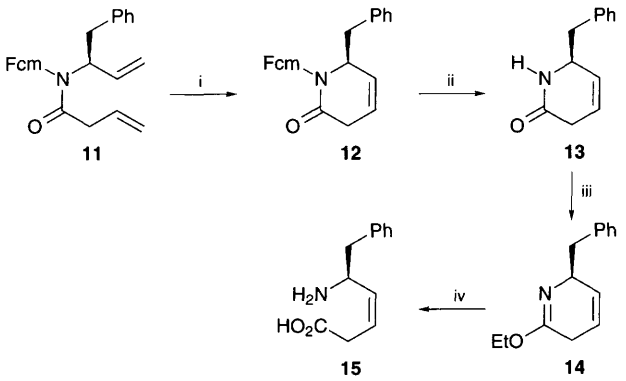


Scheme 1 *Reagents and conditions*: i, Bu^iOCOCl (1 equiv.), *N*-methylmorpholine (1 equiv), thf, −20 °C, 5 min, then HN(OMe)Me·HCl (1 equiv.), NEt_3 (1.1 equiv.), −20 °C to room temp., 95%; ii, $LiAlH_4$ (1.25 mol. equiv.), Et_2O, room temp., 20 min, 83%; iii, $H_2C{=}PPh_3$ (2 equiv.), Me_2SO–thf, −78 °C, 15 min, then 40 °C, 12 h, 85%; iv, CF_3CO_2H–CH_2Cl_2 1:1 (*v*/*v*), room temp., 2 h, 100 °C; v, ferrocenecarbaldehyde (1 equiv.), 4 Å molecular sieves, CH_2Cl_2, room temp., 6 h; vi, $NaBH_4$ (0.5 mol. equiv.), room temp., 40 min, 86% (two steps)

rather harsh standard conditions of hydrolytic cleavage of amide bonds (6 mol dm^{-3} HCl, 100 °C, several h) did not give satisfactory results. Compound **13** was therefore converted (75% yield) by treatment with triethyloxonium tetrafluoroborate to lactim ether **14** which was then quantitatively hydrolysed under mild acidic conditions (0.25 mol dm^{-3} HCl, room temp., 6 days) similar to those used by Schöllkopf for cleavage of cyclic bis-lactim ethers.[15] The desired dipeptide *Z*-ethylenic isostere **15** was thus obtained in 35% overall yield from Boc-L-phenylalanine. Neither during the metathetic nor during the hydrolytic process could any migration of the ethylenic bond be detected. The fact that the hydrolytic cleavage of imidate **14** does not stop at the ethyl ester stage, notwithstanding the mild acidic conditions used, is worthy of note. Such pronounced lability of the ester group is likely to be the result of intramolecular[16] general acid catalysis by the neighbouring NH_3^+ group. Ring cleavage on **14** was also carried out in deuterium oxide, under which conditions no detectable (NMR, GC/MS) deuterium incorporation at the carbon next to the carbonyl group could be detected. Such absence of deuterium incorporation is a strong indication that the hydrolytic ring opening of lactim ethers **14** bearing an R^2 substituent should occur without epimerization.

To check the conservation of enantiomeric purity during our synthesis, the reaction sequence described above was repeated starting from optically pure *N*-Boc-D-phenylalanine and from racemic *N*-Boc-DL-phenylalanine as well. Optical purities of intermediates were determined by HPLC on a chiral column (Chiralcel OD, J. T. Baker Co). Up to the Boc-allylamine stage **9**, virtually complete retention of chiral integrity was observed, resulting in enantiomeric excesses >98.5%. On the other hand, important racemization was found to occur, lowering the enantiomeric excesses to 62%, during the Boc to Fcm transprotection operations. No further racemization was observed during the metathetic process or the final steps leading to **15**.

Work is in progress to modify our protective group strategy in order to avoid the racemization problem mentioned and to generalize the present synthetic approach to homochiral 2,5-disubstituted dipeptide *Z*-ethylenic isosteres. The transformation of ethylenic *Z*-isosteres to the corresponding *E*-isomers by one of the many methods available for alkene inversion[17] is also under study.



Scheme 2 *Reagents and conditions*: i, **4** (5–10 mol%), benzene, Ar atmosphere, room temp., 6–7 h, 85–90%; ii, CF_3CO_2H–CH_2Cl_2 1 : 1 (*v*/*v*), Et_3SiH (2 equiv.), room temp., 9 h, 92%; iii, $Et_3O{\cdot}BF_4$ (1.25 equiv.), CH_2Cl_2, Ar atmosphere, room temp., 30 min, then phosphate buffer; iv, 0.4 mol dm^{-3} HCl (2 equiv.), Ar atmosphere, room temp., 7 days, then Dowex 50-X8, 100%

We thank the Glaxo Company (Les Ulis, France) for a doctoral scholarship (to F. G.-H).

Footnotes

† All compounds were fully characterized by IR, ^1H and ^{13}C NMR spectroscopy, MS and by elemental analysis. When necessary, ^1H NMR attributions were ascertained by irradiation or COSY experiments.

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Received, 1st December 1995; Com. 5/07823G