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Enantioconservative synthesis and ring closing metathesis of disubstituted dialkenic amides

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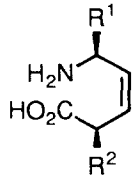
Abstract

Optically pure disubstituted dialkenic amides **2**, which are direct precursors of *Z*-ethylenic pseudopeptides **1**, are readily synthesized and then cyclized to lactams **3** in the presence of Grubbs' ruthenium-based metathesis catalysts with total conservation of enantiomeric purity.

Key words: lactam; metathesis; peptide analogues.

Olefinic pseudopeptides, in which the peptidic bond has been replaced by a *E* or *Z* ethylenic bond are of special interest since they constitute close and, at the same time, configurationally locked mimics of peptides with a *trans* or a *cis* amide bond respectively. However, the syntheses of *E*-ethylenic isosteres including stereocontrol both at the C-5 and (more particularly) at the C-2 center of the 5-aminopent-3-enoic unit are relatively few and require many steps (for leading references, see [1-4]). Furthermore, no stereoselective



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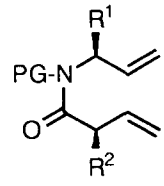
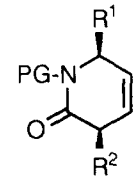


2 (PG: protecting group)



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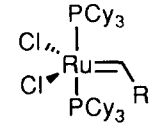

4 **a**: R =

b: R = Ph

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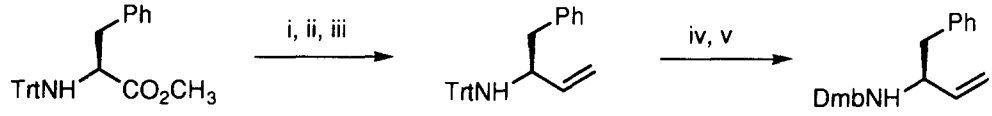
syntheses of dipeptide *Z*-ethylenic isosteres have been reported to date. Some time ago, we reported a new potential access to *Z*-ethylenic pseudodipeptides **1** [5], whose key step was a ring closing metathesis (RCM) of dialkenic amides **2** leading to ethylenic lactams **3** by use of the Grubbs' ruthenium catalyst **4a** [6-9]. By this strategy, we were able to synthesize the *Z*-ethylenic pseudodipeptide corresponding to the Phe-Gly sequence (**1**, R^1= Bn, R^2= H). However, during this synthesis, we found that important racemization (39%) had occured at the C-5 center. We report here further extension of our work, namely the enantioconservative synthesis of the disubstituted lactam **3**, with $R^1 = R^2$ = Bn, which is a direct precursor of the enantiomerically pure *Z*-ethylenic pseudopeptide corresponding to the L-Phe-L-Phe sequence.

Since the racemization process, in our previous synthesis, was found to occur at the stage of the introduction of the ferrocenylmethyl group on the nitrogen atom [5], we decided to change our protecting group strategy. Thus (scheme 1), 1-benzyl-prop-2-enylamine **5**, this time *N*-protected by the 2,4-dimethoxybenzyl (Dmb) group instead of the ferrocenylmethyl group, was synthesized from *N*-trityl-L-phenylalanine methyl ester in five steps and 47% overall yield and in optically pure form (ee > 97%) as determined by chiral HPLC analysis (OD column, hexane/isopropanol 95:5). The Dmb group was chosen on the ground that it is readily cleaved by trifluoroacetolysis and that *ortho*-methoxy substitution of the phenyl ring facilitates the acylation of N-benzylic amines [10]. It was introduced according to the conventional reductive amination procedure (see for instance [11]), by reacting the free amine with 2,4-dimethoxybenzaldehyde in the presence of $NaBH_3CN$ in MeOH/AcOH[2]. As to the trityl group, it was chosen in preference to the *tert*-butoxycarbonyl group used previously [5] because the Wittig olefination reaction exhibits much better reproducibility with *N*-trityl-phenylalaninal than with *N*-Boc-phenylalaninal [12].

Scheme 1



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i) $LiAlH_4$, Et_2O, 93%; ii) $(ClCO)_2$, Et_3N, DMSO, 92%; iii) n-BuLi, $Ph_3P^+CH_3\ Br^-$, THF, 72%; iv) CF_3CO_2H/CH_2Cl_2 1:1, then Na_2CO_3; v) 2,4-dimethoxybenzaldehyde (1 equiv.), $NaBH_3CN$ (1.12 equiv.), MeOH:AcOH, pH 6, rt, overnight, 64% (two steps)

(*R*)-2-benzyl-but-3-enoic acid was prepared according to Oppolzer [13] by regioselective and diastereoselective (de > 99% by HPLC) alkylation of the enolate of the *N*-but-3-enoyl derivative of (-) (*2R*)-bornane-10,2-sultam **6** with benzyl bromide followed by hydroperoxide-assisted saponification. It was then converted ($SOCl_2$) to the corresponding acyl chloride **7**

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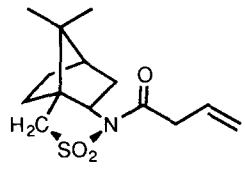
[2] By way of contrast, and for reasons which are not clearly understood, the reductive amination procedure had previously been found [5] to fail for the introduction of the ferrocenylmethyl group. The ferrocenyl imine had therefore to be first prepared and then reduced with sodium borohydride. The basic conditions of the second step could explain the partial racemization observed.

whose optical purity (ee > 98%) was checked after condensation with (-) (2*R*)-bornane-10,2-sultam and NMR and chiral HPLC analysis of the acylation product[3]. The overall yield of **7** from **6** was 30%.

The *N*-Dmb protected allylamine **5** was then acylated with 2-benzyl-but-2-enoyl chloride **7** according to the procedure of Raucher and Jones [14], which involves prior *in situ* silylation of the amino group with BSA. In this reaction, the amine and the acyl chloride were used, on the one hand, in pure *S* and *R* enantiomeric form respectively and as racemates on the other hand. NMR analysis of the resulting amides showed the formation of only one diastereoisomer **8** in the enantiopure series, which indicates that no racemization , especially of the carbon next to the carbonyl group, had occured during the process[4].



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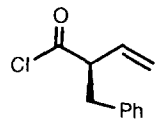

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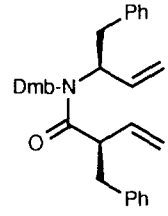

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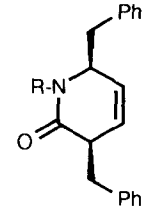

9 a: R = Dmb
b: R = H

Certainly as a result of more severe steric crowding, RCM of the disubstituted amide **8** proved more difficult than that on its monosubstituted analogue **2**(R^1= Bn, R^2= H, PG= ferrocenylmethyl) investigated before [5]. Thus, in the presence of catalyst **4a** and in benzene at room temperature, no ring closure was found to occur, and only very small turnovers (*ca* 2) could be achieved upon heating. Fortunately, much better results were obtained by switching to catalyst **4b**. In the presence of 0.08 molar equivalents of **4b**, more than 50% conversion was obtained after 8h in benzene at 68 °C under argon atmosphere. The reaction mixture was then refed with the same amount of catalyst and heated for 4 additional hours, upon which 100% conversion was attained. Lactam **9a** was thus obtained as a single enantiomerically pure diastereoisomer, in 86% yield after chromatographic purification. Similar treatment of the same diolefinic amide but as a *ca* 1:1 mixture of *R*R** and *R*S** diastereoisomers led to an approximately 1:1 mixture of *R*R** and *R*S** diastereoisomeric lactams which could easily be separated by flash chromatography (silica, heptane/AcOEt 8:2 with 1% triethylamine). The better efficiency of catalyst **4b**, as compared to **4a**,

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[3] In a control experiment, a racemic mixture of (*R*)- and (*S*)-2-benzyl-but-3-enoyl chlorides was condensed on (-) 2R-bornane-sultam (0.5 equiv.). This reaction led to a *ca* 1:1 mixture of the two diastereoisomeric sultam imides, which shows that the acylation process takes place without significant kinetic resolution.

[4] On the other hand, inspection of the ^{1}H and ^{13}C NMR spectra of amide **8** clearly reveals the presence of the two rotameric forms, in a *ca*. 4:1 ratio.

is in keeping with other reports in the litterature [15]. It should be noted that, deprived of the *N*-Dmb group, the diethylenic amide **8** does not undergo RCM. It may be assumed that the presence of the *N*-Dmb group is necessary to ensure a sufficient proportion (see footnote 4) of the rotameric form with a *syn* configuration of the two ethylenic appendages, as effectively represented in **8**. Final removal of the Dmb group from **9a** to give **9b** was achieved in 65% yield by treatment of **9a** with *anhydrous* trifluoroacetic acid at reflux for 5 min. [16], in the presence of triethylsilane (2 equiv.) as the carbocation scavenger[5].

In conclusion, the present study shows that the enantioconservative synthesis of *N*-protected diethylenic amides **2** with substituents both next to carbonyl and next to nitrogen is possible, starting, on the one hand, from the chiral pool of aminoacids and, on the other hand, from optically pure 2-substituted vinylacetic acids that are themselves obtained by diastereoselective alkylation of Oppolzer's camphorsultam derivative **6**. Despite the relatively severe steric crowding, disubstituted *N*-protected diethylenic amides **2** still undergo smooth ring closing metathesis in the presence of the ruthenium catalyst **4b**, leading to substituted ethylenic lactams which are direct precursors of *Z*-ethylenic pseudodipeptides. Further development of the present work will be reported in due course.

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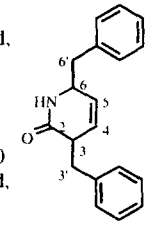
[5] NMR spectra of the cis lactam **9b** and of its trans isomer (^{1}H peak assignments are based on appropriate irradiation experiments):
cis-isomer (9b): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35-7.0 (m, 10 H, C_6H_5), 5.9 (s broad 1H, NH), 5.62 (dd, 2H, C(4), C(5)); 4.05 (m, 1H, C(6)), 3.20 (m, 1H, C(3)), 3.05 (dd, J=13.1, 4.14, 1H, C(3')), 2.85 (dd, J=13.1, 7.5, 1H, C(3')), 2.45 (dd, J=13.31, 4.89, 1H, C(6')), 1.80 (dd, J=13.28, 8.71, 1H, C(6')).
^{13}C NMR (63 MHz, $CDCl_3$), δ 171.3, 137.8, 136.4 , 129.9, 129.44, 129.5, 128.5, 128.1, 126.7, 126.4 , 125.6, 124.8, 55.0, 43.7, 43.45, 38.7.



trans-isomer: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.28-7.05 (m, 10 H, C_6H_5), 6.18 (s, broad, 1H, NH), 5.60 (dd, 2H, C(4), C(5)); 3.90 (m, 1H, C(6)), 3.18 (dd, J=12.9, 3.56, 1H, C(3')), 3.05 (m, 1H, C(3)), 2.90 (dd, J=12.19, 8.03, 1H, C(3')), 2.85 (dd, J=13.76, 5.42, 1H, C(6')), 2.60 (dd, J=13.41, 8.32, 1H, C(6')).
^{13}C NMR (63 MHz, $CDCl_3$), δ 171.6, 137.8, 136.4, 129.5, 129.35, 128.7, 128.14, 126.96, 126.7, 126.32, 125.75, 124.1, 54.56, 42.1, 43.40, 38.5.