Ring Closing Metathesis of Unsaturated Amides as a Route to Short and Medium-Sized Unsaturated Lactams and to Ethylenic Pseudopeptides

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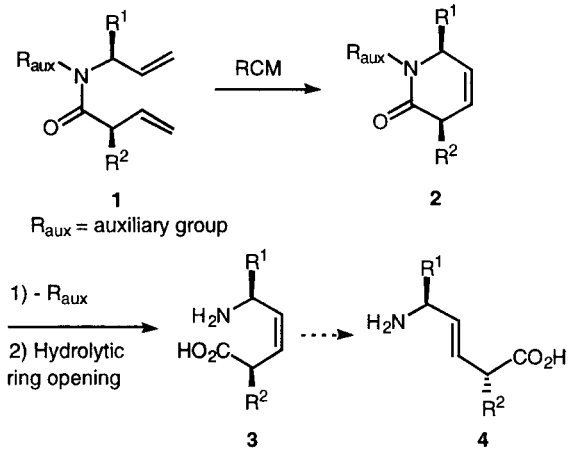
Abstract: Five- to eight-membered unsaturated lactams have been obtained through ring-closing metathesis of unsaturated amides of various chain lengths and substitution patterns. The obtention of nine-membered unsaturated lactams by the same procedure met only with limited success. Also described in this Letter is the obtention of the *Z*-ethylenic pseudopeptidic analog of L-Phe-L-Phe through hydrolytic ring opening of (3*R*, 6*S*)-3,6-dibenzyl-3,6-dihydro-2-pyridone obtained by RCM.

Key words: amides, lactams, metathesis, peptides, ring closure

For some years, we have been involved in the exploration of a new access to ethylenic pseudopeptides **3** and **4** based on ring closing metathesis (RCM)[1] of unsaturated amides **1** to unsaturated lactams **2** in the presence of Grubbs ruthenium catalysts as represented in Scheme 1.[2,3]

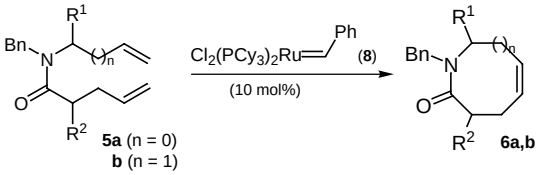


Scheme 1

From a more general point of view, unsaturated amides are, for many of them, easily available according to a modular approach and through well-established synthetic reactions. As to the corresponding unsaturated lactams which would result from RCM of such amides, they constitute interesting molecules, especially due to the presence of the ethylenic bond which allows for further functionalization through various reactions such as epoxidation, dihydroxylation etc. Aside from our work specifically directed towards the obtention of ethylenic pseudopeptides, we have therefore also carried out some investigations of the RCM of various unsaturated amides differing by their substitution patterns or the length of their ethylenic appendages.[4] We report here the results of this study. We also report the conversion of the six-membered enantiomerically pure unsaturated lactam **2** with $R^1 = R^2 = Bn$ to the *Z*-ethylenic pseudopeptidic analogue of *N*-(L-phenylalanyl)-L-phenylalanine.

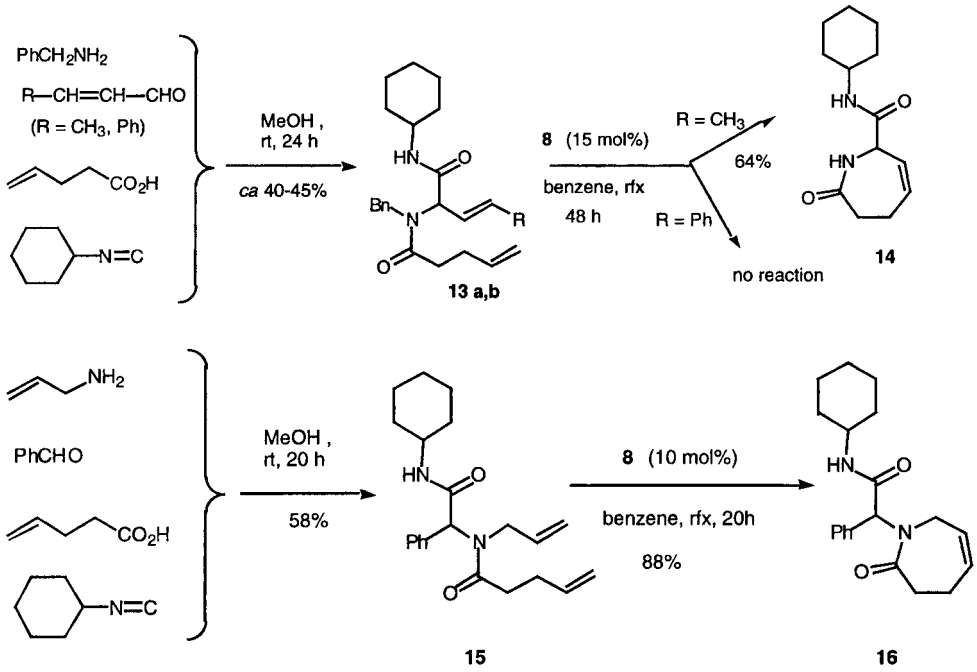
We found that seven (**6a**) and eight-membered (**6b**, **9a**) unsaturated lactams are easily obtained by RCM of unsaturated amides **5a,b** (Table 1) or **7a** (Table 2). All reactions were conducted either in benzene or dichloromethane at reflux using 10 mol% of Grubbs catalyst $Cl_2(PCy_3)_2Ru{=}CHPh$ **8** under moderate dilution (typically 0.035 M in amide).[5] The formation of nine-membered lactams **9b** from amides **7b** proved to be more difficult (Table 2) and loss of activity of the catalyst occurred before completion of the reaction. RCM (on solid support) of diethylenic amides to seven-membered lactams has already been used by Piscopio and co-workers[6] for the obtention of Freidinger lactams. On the other hand, the easy formation of eight-membered unsaturated lactams described here is especially worthy of note as such examples are few.[7,8] The formation of unsaturated eight-membered lactams has already been reported by Beal and Moeller[9] and by Wagner and co-workers[10] starting from amides in

Table 1



n	R^1	R^2	Conditions	Yields [%][a]
0	H	H	CH_2Cl_2, rfx, 4 h	95
0	Ph	H	CH_2Cl_2, rfx, 20 h	80
0	H	Bn	CH_2Cl_2, rfx, 4 h	90
0	Ph	Bn	CH_2Cl_2, rfx, 20 h	74[b]
1	H	H	CH_2Cl_2, rfx, 24 h	60
1	H	H	benzene, rfx, 20 h	74
1	Ph	H	benzene, rfx, 20 h	86
1	H	Bn	benzene, rfx, 20 h	71
1	Ph	Bn	benzene, rfx, 20 h	81[b]

[a] isolated yields; [b] mixture of diastereoisomers



Scheme 2

which the two ethylenic appendages are attached to a five-membered ring system. As already suggested,[4,6,7] such a disposition may preorganize the dienic precursor into a conformation that favors cyclization. The present results which refer to non-cyclic, conformationally more flexible substrates corroborate an early example by Grubbs[6] and show that such a preorganization is not a necessary condition for successful RCM.

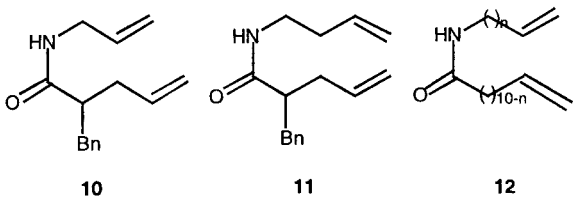
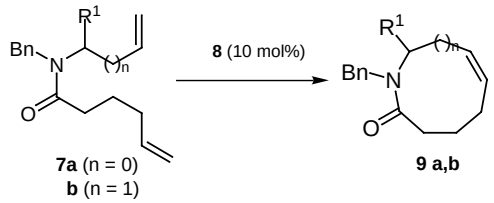


Table 2



n	R^1	Conditions	Yields [%][a]
0	H	CH_2Cl_2, rfx, 24 h	80
0	Ph	benzene, rfx, 20 h	64
1	H	benzene, rfx, 16 h	26[b]
1	H	CH_2Cl_2, rfx, 6 h	59[b]
1	Ph	CH_2Cl_2, rfx, 24 h	56[b]

[a] isolated yieds; [b] ca 25% of starting material was also recuperated

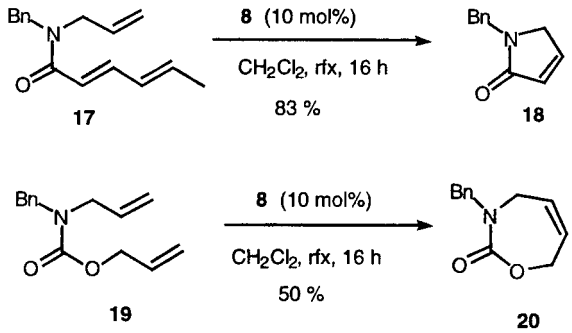
It should be noted that the formation of medium-sized unsaturated lactams by RCM takes place only with tertiary amides. Thus, under the conditions mentioned above, no cyclization is observed with secondary amides such as **10** or **11**. The presence of an auxiliary group on nitrogen probably ensures a sufficient proportion of the rotamer with the two ethylenic appendages *syn* to each other. By contrast, secondary amides of general formula **12** do undergo ring closing metathesis to 14-membered lactams.[11] Most likely, because of the length of the ethylenic appendages, the *anti* rotamer is now also able to cyclize. Some other examples of macrocyclic lactam formation by RCM of secondary amides are described in the literature.[12] Concerning medium-sized unsaturated lactams, it should be noted that unsaturated pyrrolidinones and piperidinones have been obtained by Blechert and co-workers[13] through RCM of some secondary acryloyl amides.

Unsaturated amides **13a**,**b** were readily prepared by Ugi four-component condensation[14] between benzylamine, cyclohexyl isocyanide, 4-pentenoic acid and crotonaldehyde or cinnamaldehyde. Compound **13a** (R = Me) was found to undergo RCM leading to lactam **14**. On the other hand, we failed to cyclize **13b** (R = Ph) under similar conditions (Scheme 2).

Amide **15**, also prepared by Ugi four-component condensation in which, aside from the acidic component, the other ethylenic fragment is now the amine instead of the aldehyde smoothly cyclizes in the presence of Grubbs

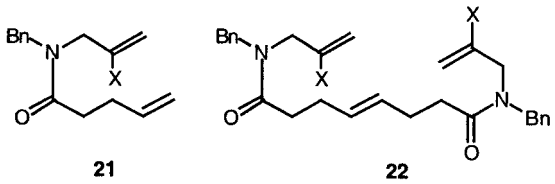
catalyst **8**, leading to the corresponding seven-membered ethylenic lactam **16** in good yield (Scheme 2).

The cyclizations of some other substrates were also briefly examined. Thus amide **17**, derived from condensation of sorbic acid and *N*-allyl benzylamine readily cyclizes, as do acryloyl amides,[13] to the corresponding five-membered conjugated ethylenic lactam **18**, presumably with loss of 1,3-pentadiene (Scheme 3). As demonstrated by Royer and co-workers,[15,16] such five-membered conjugated lactams are important synthons in organic synthesis. Allyl carbamate **19** leads to the expected cyclic product **20** in moderate yield (Scheme 3) while the corresponding vinyl carbamate does not cyclize at all.



Scheme 3

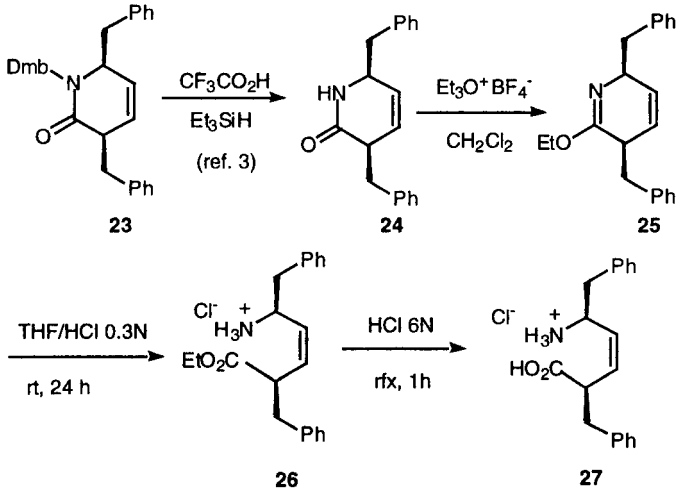
In an attempt to "desymmetrize" the lactam double bond resulting from RCM and thereby increase the diversity of further possible functionalization, metathesis of amides **21** bearing a X group (X = OMe, Cl, Br, CO_2R, CN) at the internal position of the ethylenic bond of the nitrogen moiety was investigated. In no case could the formation of the desired lactam be observed. For X = OMe, Br, Cl and CO_2Et, only dimers **22** resulting from self-metathesis involving the C,C double bond of the carbonyl moiety were obtained in yields ranging from 60% to 80%. For X = CN, no reaction takes place.



Some years ago, we reported[2] the obtention, in enantiomerically enriched form, of the *Z*-ethylenic isostere of L-Phe-Gly by hydrolytic ring-opening of enantiomerically enriched lactam **2** (ee = *ca* 62%) with R^1 = Bn, R^2 = H and R_{aux} = ferrocenyl-methyl. More recently, we described[3] the obtention in enantiomerically pure form (ee > 95%) of lactam **23** in which both carbon substituents are benzyl and the auxiliary group R_{aux} is 2,4-dimethoxybenzyl (Dmb). We now report the conversion of this lactam to the corresponding *Z*-ethylenic pseudopeptide corresponding to the L-Phe-L-Phe sequence (Scheme 4).[17]

As already described,[3] removal of the Dmb group was first achieved in 65-70% yield by treatment[18] with anhydrous trifluoroacetic acid at reflux for 5 min in the presence of triethylsilane (2 equiv.) used as a carbocation scavenger. The expected *N*-deprotected dihydropyridinone was thus obtained as a single enantiopure diastereoisomer **24**. The reaction was repeated on racemic (*R*R**+*R*S**) compound to give a mixture of *R*R** and *R*S** diastereoisomeric dihydropyridones that could easily be separated by column chromatogaphy and fully characterized by NMR spectroscopy.

Compound **24** and its racemic *R*R** diastereoisomer were quantitatively converted to imidate **25** and to the corresponding *R*R** diastereoisomer, respectively, by reaction with triethyloxonium tetrafluoroborate (3.7 equiv.) in dichloromethane at room temperature and under an argon atmosphere. Tetrafluoroboric acid and triethyloxonium tetrafluoroborate in excess were eliminated by addition to the crude reaction mixture of an excess of solid and dried



Scheme 4

$NaHCO_3$ followed by filtration. Imidate **25** was not stored, but directly put in solution in a 1/7 (*v/v*) mixture of THF and 0.3 N aqueous HCl. Stirring for 24 h at room temperature under an argon atmosphere led almost quantitatively to aminoester hydrochloride **26**. This disubstituted aminoester proved much more resistant to acidic hydrolysis than its monosubstituted analogue bearing no substituent next to the carbonyl function.[2] Final conversion to the aminoacid was finally achieved by treatment with 20% aqueous HCl at reflux for 1 h. The crude amino acid hydrochloride thus obtained was purified by ion-exchange chromatography and reprecipitated as its hydrochloride salt **27**. Compound **27** (2*R*, 5*S*) was obtained in > 95% de (NMR analysis) and in 75% yield from dihydropyridone **24**. The racemic *R*R** amino acid hydrochloride was similarly obtained from *N*-deprotected *R*R** dihydropyridone.

Acknowledgement

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References and Notes

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(17) All compounds in this series were fully characterized by spectroscopy (^1H and ^{13}C NMR, IR), and by combustion analysis or HRMS in the case of **23**, **24** and **27**. Selected data: **(*3R,6S*)-*N*-[(2,4-dimethoxyphenyl)methyl]-3,6-dibenzyl-3,6-dihydro-2-pyridone 23:** ^1H NMR (250 MHz, toluene d^8) δ 7.46 (d, *J* = 8.2 Hz, 1H); 7.16-6.87 (m, 10H); 6.31 (m, 2H); 5.64 (d, *J* = 14.8 Hz, 1 H); 5.25 (dd, *J* = 10.3, 3.9 Hz, 1H); 5.18 (dd, *J* = 10.3, 3.9 Hz, 1H); 4.33 (d, *J* = 14.8 Hz, 1 H); 3.91 (m, 1H); 3.37 (s, 3H); 3.32 (s, 3H); 3.14 (m, 1H); 2.92 and 2.33 (two dd, ABX system, J_{AB} = 12.8 Hz, J_{AX} = 3.9 Hz, J_{BX} = 8.7 Hz, (1+1)H); 2.63 and 1.85 (two dd, ABX system, J_{AB} = 13.0 Hz, J_{AX} = 3.3 Hz, J_{BX} = 8.6 Hz, (1+1)H). ^{13}C NMR: δ 170.2; 160.1; 158.4; 138.6; 136.5; 130.7; 129.8; 129.5; 128.1; 128.0; 126.5; 126.2; 125.7; 124.9; 117.5;104.3; 98.2; 57.7; 55.24; 55.2; 43.7; 40.5; 39.8; 39.4. HRMS (EI): calc for $C_{28}H_{29}NO_3$ [M^+]427.2153, found 427.2147.
***(3R*,6R*)*-*N*-[(2,4-dimethoxyphenyl)methyl]-3,6-dibenzyl-3,6-dihydro-2-pyridone**: ^1H NMR (250 MHz, toluene d^8) δ 7.2-6.8 (m, 11 H), 6.34 (d, *J* = 2.3 Hz, 1H), 6.30 (dd, *J* = 8.3, 2.3 Hz, 1H), 5.63 (d, *J* = 14.8 Hz, 1H), 5.38 (dd, *J* = 10.1, 2.1 Hz, 1H), 5.23 (ddd, *J* = 10.0, 4.5, 2.4 Hz, 1H); 4.32 (d, *J* = 14.8 Hz, 1H), 3.88 (m, 1H), 3.38 (s, 3H), 3.30 (s, 3H), 3.18 and 3.08 (two dd, ABX system, J_{AB} = 13.2 Hz, J_{AX} = 4.0 Hz, J_{BX} = 8.0 Hz, (1+1) H), 2.70 and 2.55 (two dd, ABX system, J_{AB} = 13.0 Hz, J_{AX} = 7.1 Hz, J_{BX} = 3.5 Hz, (1+1) H), 2.40 (m, 1H).
(3*R*,6*S*)-3,6-dibenzyl-3,6-dihydro-2-pyridone 24 and its (3R*,6R*) diastereoisomer: see reference 3.
(3*R*,6*S*)-3,6-dibenzyl-2-ethoxy-3,6-dihydropyridine 25: ^1H NMR (250 MHz, CD_2Cl_2): δ 7.4-6.9 (m, 10H); 5.65 (ddd, *J* = 10.2, 1.5, 1.0 Hz, 1H); 5.5 (dd, *J* = 10.2, 3.9 Hz, 1H); 4.2-3.95 (m, 3H); 3.0 (m, 1H); 2.8 (dd, *J* = 13.2 Hz, 3.9 Hz, 1H); 2.9-2.47 (m, 2H); 2.07 (dd, *J* = 12.8, 7.3 Hz); 1.3 (t, *J* = 7.7 Hz, 3H).
***(Z)-(2R,5S)*-2-benzyl-5-amino-6-phenyl-3-hexenoic acid, hydrochloride salt 27**: $[\alpha]^{20}_D$ = - 69.3 (*c* 0.07, D_2O); ^1H NMR (200 MHz, D_2O): δ 7.2-6.9 (m, 10H); 5.55 (t, *J* = 11.5 Hz, 1H); 5.30 (t, *J* = 10.6 Hz, 1H); 4.0 (broad q, 1H); 3.22 (broad q, 1H); 2.55 and 2.15 (two dd, ABX system, J_{AB} = *ca* 13.5 Hz, J_{AX} = *ca* 6.5 Hz, J_{BX} = *ca* 8.5 Hz, (1+1)H); 2.53 and 2.05 (two dd, ABX system, J_{AB} = *ca* 13.5 Hz, J_{AX} = *ca* 7.0 Hz, J_{BX} = *ca* 7.5 Hz, (1+1)H). ^{13}C NMR (D_2O): δ 177.0, 134.9, 133.1, 129.6, 129.1, 128.9, 128.5, 127.4, 126.6, 49.8, 46.4, 37.4, 38.5; Anal. Calcd for $C_{19}H_{22}NO_2Cl \cdot 2.2\ H_2O$: C: 61.47, H: 7.16, N: 3.77. Found: C: 61.47, H: 7.05, N: 3.76.
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