Ruthenium-Catalyzed Ring Closing Olefin Metathesis of Non-Natural \( \alpha \)-Amino Acids

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Abstract: The use of various enantiopure amino acid-derived diols as substrates for the ring closing olefin metathesis reaction (RCM) has been investigated. This reaction has shown to be an efficient transformation for providing highly functionalized 6- and 7-membered ring amino acids.

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In the past few years, the use of the ring closing metathesis reaction (RCM) for creating cyclic systems from acyclic diolefins has tremendously increased as a result of the ruthenium alkylidene catalysts that have been developed by Grubbs and co-workers. The tolerance towards functional groups and the efficiency of these catalysts have been exemplified by several examples of RCM in the synthesis of complex molecules, in the area of peptide chemistry, and recently also in solid phase strategies. Prompted by a recent report, we wish to disclose a number of preliminary results on cyclizing enantiopure amino acid-derived precursors to give the corresponding unsaturated cyclic amino acids as shown in eq 1. The resulting six- and seven-membered rings are versatile and highly functionalized heterocyclic ring systems that can either be used as building blocks in drug or natural product synthesis, but also for example as conformationally restricted amino acid analogs. In order to obtain the non-natural amino acids we rely on an enzymatic resolution process, consisting of enantioselective hydrolysis of the corresponding amino acid amides with an amidase obtained from *Pseudomonas putida*, which affords both the D- and L-amino acids in enantiomerically pure form.

The synthesis of the precursors is shown in eq 2 and described in detail for enantiopure D-allylglycine (4: \( R = H, n = 1 \)), optically active L-\( \alpha \)-methyl-\( \alpha \)-allylglycine (4: \( R = Me, n = 1 \); 78% ee) and D-3-butenylglycine (4: \( R = H, n = 2 \); >99.6% ee), which was produced on multi-gram scale by enzymatic resolution of the corresponding amino acid amide. The intermediates were prepared via esterification (2.0 equiv of SOCl₂, MeOH, 60 °C, 3 h), followed by mono-alkylation at nitrogen (1.05 equiv of p-methoxybenzyl chloride, 4 equiv of NaHCO₃, LiI (cat), MeCN, reflux). A slightly higher yielding method was also applied, i.e. esterification and subsequent condensation (1.05 equiv of benzaldehyde or ferrocenylaldehyde (ferroceny = Fer), 1.0 equiv of Et₃N, 4 Å MS, CH₂Cl₂, rt, '1 h) provided the corresponding imines, which under carefully controlled conditions could be effectively reduced (1.0 equiv of NaBH₄CN, 1.0 equiv of p-TSA, THF, rt, 4 h)
to afford the amino esters 5 in good to excellent yields. The precursors 6 for the metathesis reaction were either formed via amide formation (1.2 equiv of CH$_2$=CHC(O)Cl, 1.5 equiv of Et$_3$N, CH$_2$Cl$_2$, 0 °C → rt, 15 min) or alkylation with allyl bromide (1.5 equiv, 2.5 equiv of NaHCO$_3$, LiI (cat), MeCN, reflux, 17 h) in good yield (overall yields for these sequences are shown in equations 3-7).

The results with the D-allylglycine-derived substrates 9-11 are summarized in eq 3. The cyclizations were carried out by using the phenyl-substituted ruthenium alkylidene catalyst 7$^{10}$ (5 mol% of Ru-catalyst, 0.05 M in CH$_2$Cl$_2$, reflux) to give in the case of the amine precursors 9 and 10 the corresponding tetrahydropyridine systems in somewhat disappointing yields, even after extended periods of reflux (up to 24 h). However, changing the conformation and the basic character of the nitrogen atom by employing a BOC-protecting group (obtained via the mono-allylated amino ester 8 and subsequent reaction with BOC$_2$Q (3 equiv, 1 equiv of Et$_3$N, 1 equiv of DMAP, CH$_2$Cl$_2$, reflux, 6 h) led to significantly higher reactivity so that 14 was obtained in 93% yield (30 min in refluxing CH$_2$Cl$_2$). Without a protecting group at nitrogen (e.g. in the case of 8), ring-closed products were not observed.

Similarly, cyclization of the acrylic amides 15-17 (eq 4) proved to be dependent on the substituents at the nitrogen atom. While the free amide 15 reacted sluggish (24 h of reflux, additional catalyst added) in a low yield, the corresponding protected amides 16 and 17 cyclized in excellent yields after 3 h of reflux. Deprotection of the ferrocenylmethyl-protected lactam 20 (5 equiv of Et$_3$SiH, 5 equiv of CF$_3$CO$_2$H, CH$_2$Cl$_2$, 0 °C)$^6$ took place in 30 min to give the corresponding $\alpha,\beta$-unsaturated lactam 18 in 95% yield. The enantiomeric purity of 20 was checked by HPLC analysis,$^{13}$ proving that no racemization had occurred during the whole sequence.

Remarkably different behavior was observed upon subjecting the $\alpha$-methyl-substituted allylglycine precursor 21 to identical reaction conditions (eq 5). In contrast with 9 and 10, cyclization of amine 21 took place swiftly, providing the cyclic olefin 23 in good yield. Furthermore, the corresponding amide 22 cyclized...
in nearly quantitative yield to the lactam 24. Most likely, increase of steric bulk adjacent to the nitrogen atom leads to a more favorable transition state for ring closure.

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me} \\
\text{PMB} & \quad \text{PMB} \\
\text{23} & \quad \text{24} \quad (82\%) \quad (95\%)
\end{align*}
\]

Treatment of the homo-allylglycine precursors 25-27 (eq 6) with 7 (5 mol%, 0.1 M in CH\text{}_2\text{Cl}_2, reflux) was expected to give the corresponding azepine systems. Reaction of acrylic amide 25, however, mainly afforded the dimeric product 31 (where only the more electron rich olefin participated in the metathesis process), accompanied by only a small amount of the desired product 28. Opposite to the results with the glycine precursors (eqs 3 and 4), changing the amide into an amine by alkylation with the more electron rich allyl function (26 and 27), led to a clean conversion into the corresponding azepines 29 and 30 in high yields.\(^{14}\)

Moreover, the double bond in the azepine series could be selectively placed at a different position by variation of the substituent at nitrogen. Thus, treatment of 32 with vinylacetic acid under standard peptide coupling conditions (1.05 equiv of HOBT, 1.05 equiv of DCC, CH\text{}_2\text{Cl}_2, rt, 4 h) provided 33 in 55% yield (not optimized), which in turn cyclized in reasonable yield to the enantiopure seven-membered lactam 34. In addition to these results, we also have subjected analogous 4-pentenyl precursors (6: R = H, n = 3; not shown) to similar conditions, but in neither of these cases the desired 8-membered rings could be detected. Instead, intractable mixtures of dimerization and polymerization products were formed.

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me} \\
\text{PMB} & \quad \text{PMB} \\
\text{25} & \quad \text{26} & \quad \text{27} \quad (X = \text{H}_2, R = \text{PMB}, 42\%) \quad (X = \text{H}_2, R = \text{CH}_2\text{Fer}, 49\%) \quad (X = \text{H}_2, R = \text{CH}_2\text{Fer}, 49\%) \\
& \quad \text{28} & \quad \text{29} & \quad \text{30} \quad (X = \text{O}, R = \text{Bn}, 63\%) \quad (X = \text{O}, R = \text{Bn}, 15\%) \quad (X = \text{H}_2, R = \text{CH}_2\text{Fer}, 67\%)
\end{align*}
\]

In conclusion, we have shown that various enantiopure amino acid precursors can be useful starting materials in ring closing metathesis reactions to provide specifically functionalized 6- and 7-membered ring amino acids. At the moment, studies are in progress to extend this methodology to other non-natural enantiopure amino acids (obtained via enzymatic resolution) and application of the resulting cyclic systems in the synthesis of some natural products, as will be reported in a full account in the near future.

Acknowledgment: The authors wish to acknowledge dr B. Kaptein (DSM Research) for generously providing D-allylglycine and L-\(\alpha\)-methyl-\(\alpha\)-allylglycine. Mr. J.M.M. Boesten and dr A.L.L. Duchateau (DSM Research) are kindly acknowledged for carrying out some HPLC analyses.
References and Notes:
8. Both D- and L-allylglycine are commercially available, but can also be obtained in enantiopure form through enzymatic resolution, see: Broxterman, Q.B.; Kaptein, B.; Kamphuis, J.; Schoemaker, H.E. J. Org. Chem. 1992, 57, 6286.
10. Racemic 3-butenylglycine (4: R = H, n = 2) was obtained as described by O’Donnell, esterified (SOCl2, MeOH) and converted into the corresponding amide (25% aqueous ammonia). Subjection of the amide to the enzymatic resolution conditions (Pseudomonas putida, pH 9-10, 37 °C, 60 h) provided D-3-butenylglycine (after hydrolysis of the corresponding amide (2 M HCl, 90 °C, 2 h) and purification on a strongly acidic (Dowex 50W) ion exchange column) in >99.6% ee according to HPLC analysis.
11. All new compounds were appropriately characterized by IR, 1H and 13C NMR spectroscopy, high resolution mass data and rotation values.
12. This result is in agreement with the findings of Grubbs et al. who reported the formation of 14 in racemic form (D-14: [α]D 20° -17.3° (c 1.0, CH2Cl2).
13. Analysis on a Chiralpak AS column (10% i-PrOH in heptane) showed an ee of >99%.
14. A typical cyclization experiment was carried out as follows: to a solution of diolefin 26 (105 mg, 0.335 mmol) in CH2Cl2 (5.5 mL) was added Cl2(PCy3)2Ru=CHPh (7.14 mg, 0.017 mmol) and the solution was refluxed under an argon atmosphere for 3 h. The mixture was evaporated and purified by flash column chromatography (silica, 20—»50% ether in petroleum ether) to give 29 as a light yellow oil (90 mg, 0.315 mmol, 94%). 29: R, 0.31 (50% ether in petroleum ether); [α]D 19° +68.9 (c 1.0, CH2Cl2); IR (CHCl3) ν = 3016, 2984, 2834, 1732, 1511, 1245, 1154, 1036, 759 cm⁻¹; 1H NMR (400 MHz, CDC13) δ 7.24 (d, J = 8.6 Hz, 2 H, ArH), 6.84 (d, J = 8.6 Hz, 2 H, ArH), 5.80-5.75 (m, 1 H, =CH), 5.54-5.49 (m, 1 H, =CH), 3.78 (s, 3 H, CO2CH3), 3.78-3.71 (AB + m, 3 H, CH2Ar + NC6H5), 3.71 (s, 3 H, ArOCH3), 3.58 (dd, J = 6.4, 9.2 Hz, 1 H, NCH), 3.07 (dd, J = 5.7, 17.4 Hz, 1 H, NCH2), 2.33-2.31 (m, 2 H, CH2), 1.08-2.03 (m, 2 H, CH2); 13C NMR (100 MHz, CDC13) δ 173.6, 158.5, 131.4, 130.9, 129.5, 129.3, 113.5, 65.5, 57.9, 55.1, 51.3, 48.0, 29.4, 26.7; HRMS (FAB): calcld for C31H47NO5 (M+H) 276.1600, found 276.1595.

(Received in UK 5 November 1996; accepted 6 December 1996)