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SYNTHESIS OF CONSTRAINED α-AMINO ACID DERIVATIVES *VIA* RING-CLOSING OLEFIN METATHESIS

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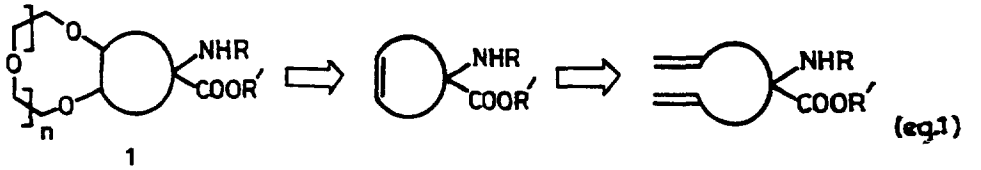
Abstract: Five and seven membered constrained α-amino acid derivatives were synthesized using ring-closing metathesis reaction as a key step.

Unusual amino acids [1] receive increasing attention as starting materials for syntheses of peptidomimetics. They have proven useful for probing the structural requirements for the activity of numerous peptides and for imparting novel properties, such as increasing the binding (or metabolic) stability to receptors, or exhibit enzyme inhibiting properties.[2] Recent efforts have been focused upon gaining direct access to constrained analogues of proteinogenic α-amino acids (AAAs). In the light of demonstrated utility [3] of various non-coded AAAs, we initiated a major project aimed at developing new methodologies for the generation of several AAA derivatives.

Our approach to AAAs is based on the development of new building blocks embodying AAA moiety which are useful in the preparation of diverse non-coded AAAs. In this regard we have shown that 2+2+2 cycloaddition is very useful to prepare various AAAs bearing interesting side chains.[4] Recently, Mazaleyrat and co-workers reported the synthesis of a novel crown-based constrained AAA derivative and suggested interesting crown ether based constrained AAA derivatives (e.g. 1).[5] This report prompted us to disclose our



1 (eq 1)

results [6] related to the synthesis of novel constrained AAA derivatives which are potential precursors for crown-based AAA derivatives. In this regard, we conceived a novel strategy for crown-based constrained AAA derivatives which involve two key steps (eq 1). In the first step, ethyl isocyanoacetate is bis-alkylated to generate various unsaturated AAA derivatives. In the second step, metathesis reaction is used to deliver cyclic AAA derivatives.

Olefin metathesis is a remarkable catalytic reaction in which olefins undergo bond reorganization leading to redistribution of alkylidine moieties. This reaction is fairly common, can be induced by a variety of homogeneous and heterogeneous catalysts and has many varied chemical applications. Recently, Grubbs and co-workers have shown that ruthenium carbene complexes **A** and **B** (Fig. 1) are useful catalysts for ring-closing metathesis reaction.[7] Due to a high degree of functional group tolerance and mild reaction conditions,

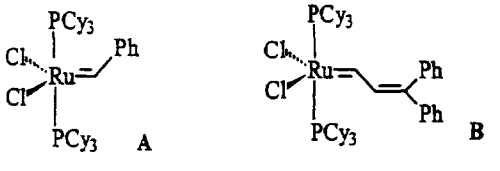


Fig: 1

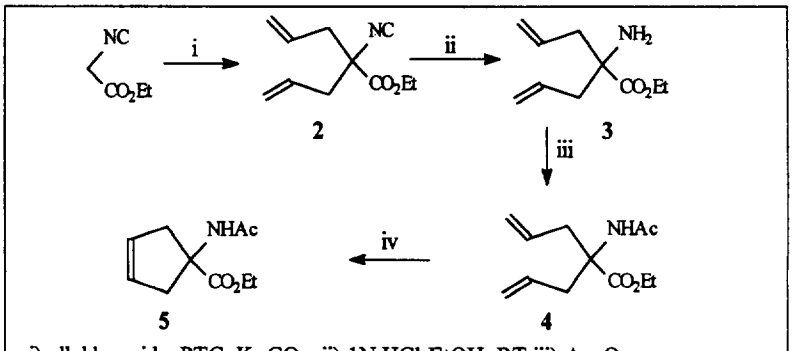
PII: S0960-894X(98)00002-X

a variety of carbocycles and heterocycles were prepared using these catalysts. [8] As mentioned earlier, the necessary synthons for metathesis reaction is generated by alkylation of ethyl isocyanoacetate using the desired electrophiles. Then, appropriately protected bis-alkylated product was subjected to metathesis reaction and there by generating cyclic AAA derivative containing an olefin functionality for further synthetic manipulation. By simply varying the length of electrophile in the alkylation reaction, one can generate various AAA derivatives of varying ring size.

Initially, diallyl compound **4** was prepared to explore the metathesis idea (Scheme 1). In consideration of our favorable experience with ethyl isocyanoacetate [4,9] as glycine equivalent, we attempted bis-allylation reaction under PTC conditions [10] (tetrabutyl ammonium hydrogen sulfate, acetonitrile, potassium carbonate, reflux). Reaction of ethyl isocyanoacetate with two equivalents of allyl bromide gave mono and diallylated product **2**. These two compounds were separated by column chromatography using ethyl acetate/pet ether mixture (1:5) as eluent. The fast moving compound structure was assigned as diallylated product by mass (M^+: 193) and ^1H NMR spectral data. Continued elution of the column with the same solvent gave mono allylated product. Due to volatile nature of mono-allylated product, the exact yield was not determined. Later on, diallylated product **2** was obtained in 88% isolated yield by reacting ethyl isocyanoacetate with excess amount of allyl bromide (3 equivalents) under PTC conditions. Some of these isonitrile compounds tend to decompose even in the refrigerator. It was necessary to hydrolyze immediately and the resulting amino esters were converted to acetylated derivatives which can be stored for longer period of time. Hydrolysis of **2** in presence of 1N HCl/EtOH at RT for 2 h gave the amino ester **3** in 95% yield. Acetylation of **3** using acetic anhydride in dichloromethane in presence of catalytic amount of 4-dimethylaminopyridine gave **4** in 82% yield. The acetylated product was characterized by 9 line ^{13}C NMR data ($CDCl_3$, 75.0 MHz, δ 173.0, 169.3, 132.4, 119.0, 64.3, 62.0, 39.1, 24.1, 14.3).

Then the key metathesis reaction was carried out by refluxing a solution of **4** in toluene in presence of catalytic amount of bis(tricyclohexylphosphine)benzylidine ruthenium dichloride **A** to give cyclopentene derivative **5** (90% yield, mp. 131-132 °C, ^{13}C NMR, $CDCl_3$, 75.0 MHz, δ 173.7, 169.8, 127.8, 64.0, 61.5, 44.4, 23.1, 14.0; Mass, M+1: 198).

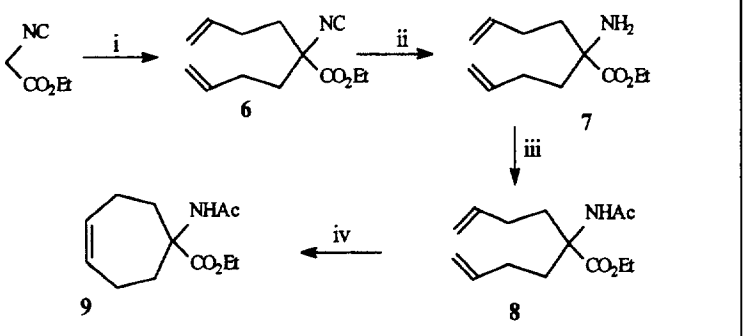
Scheme 1



i) allyl bromide, PTC, K_2CO_3 ii) 1N HCl-EtOH, RT iii) Ac_2O, ultra-sound iv) bis(tricyclohexylphosphine)benzylidine ruthenium dichloride

We next turned our attention to preparation of cycloheptene-based AAA derivative **9** starting from 4-bromo-1-butene and ethyl isocyanoacetate (Scheme 2). After screening several reaction conditions, we found that 4-bromo-1-butene reacts with ethyl isocyanoacetate in presence of sodium hydride/DMSO in ether (at 0°C) to give dialkylated product **6** in 62% yield. Treatment of isonitrile compound **6** with 1 N HCl in ethanol at room temperature gave amino ester **7** (92% yield) which was protected as acetyl derivative **8** using acetic anhydride. Final ring-closing metathesis reaction was effected using ruthenium catalyst **A** to give seven membered AAA derivative **9** (92%, ^{13}C NMR, $CDCl_3$, 75.0 MHz, δ 173.7, 169.6, 130.9, 62.4, 61.2, 34.0, 23.3 (2C?), 14.1; Mass: M^+ 225.

Scheme 2



i) DMSO, NaH, 4-bromo-1-butene, ii) 1N HCl-EtOH, RT iii) Ac_2O, DMAP CH_2Cl_2 iv) bis(tricyclohexylphosphine)benzylidine ruthenium dichloride

In conclusion, we have shown that cyclic AAA derivatives **5** and **9** can be prepared *via* ring-closing olefin metathesis reaction in a simple manner. Given the dearth of cyclic AAAs, access to these derivatives **5**, **9** likely to open new opportunities in the design of peptidomimetic therapeutics. Results from on going studies in these areas will be the subject of future reports from our laboratory.

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