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Synthesis of Substituted Cyclohexenyl-Based β-Amino Acids by Ring-Closing Metathesis

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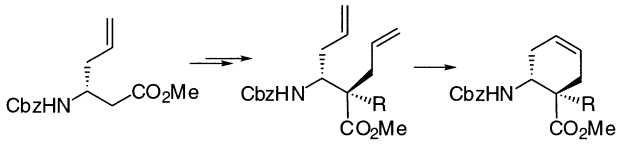
ABSTRACT



A versatile ring-closing metathesis (RCM) approach has been developed for the preparation of cis and trans cyclohexenyl-based β-amino acids that are either unsubstituted (3) or substituted (10 and 12) at the α-position.

The assembly of simple monomeric units into larger more complex structures that display well-defined secondary and tertiary structures is an important means for the identification and study of molecular function. One approach to this endeavor has been to link simple monomeric units that contain a fixed or defined conformation.[1] These simple conformationally constrained monomers impart important physical and chemical properties onto the structures derived from them. For example, proline and hydroxyprolines are responsible for the structure and hence function of collagen, one of nature's most important structural proteins.[2] Another and nonnatural example is provided by cyclic β-amino acids, oligomers of which have recently been shown to adopt helices.[1,3] These structures show discrete and predictable folding patterns that resemble those derived from nature's α-amino acids. A host of cyclic α-amino acids are known; however, there remains a clear need to develop a range of cyclic β-amino acids if one is to control the structure and hence function of β-peptides derived from them in a predictable fashion.[4] New and versatile methods for the preparation of cyclic β-amino acids,[5,6,7] particularly those bearing substituents, are needed to achieve this goal.

In this paper we present a versatile ring-closing metathesis (RCM) approach[8] to cyclic β-amino acids that allows the preparation of examples that are either unsubstituted (**3**) or substituted at the α-position (**10** and **12**). This second class represents a new and important addition to this family of compounds. The constituent olefin of these units is able to be hydrogenated to give the corresponding saturated analogue, simple examples of which have already found wide use in the production of β-peptides or, alternatively, been functionalized[7] to give new and important derivatives.

Our goal was to develop a method whereby both the α-free and α-substituted derivatives were accessible from a common precursor. The basic synthetic strategy involves the stereo-

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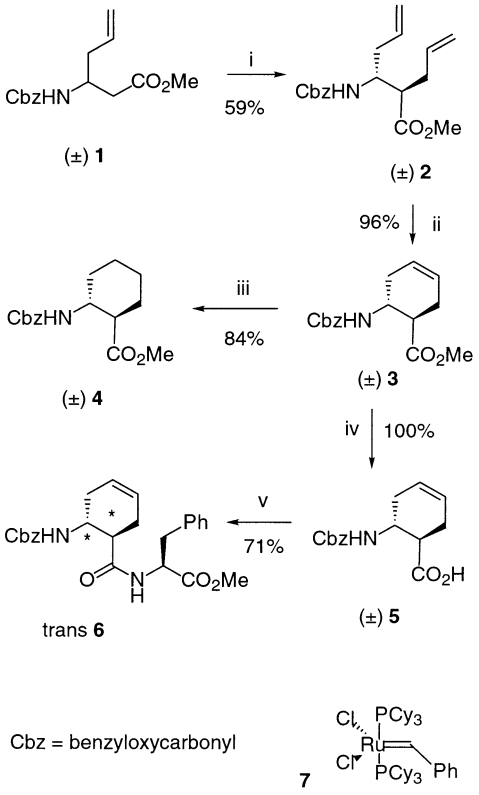
selective allylation of 3-Cbz-aminohex-5-enoate **1**, obtained from Cbz-protected allyl-glycine,[9] to give a diene that is then cyclized by RCM to give the corresponding unsubstituted aminocyclohexanecarboxylic acid (Scheme 1). In addition,

Scheme 1[a]



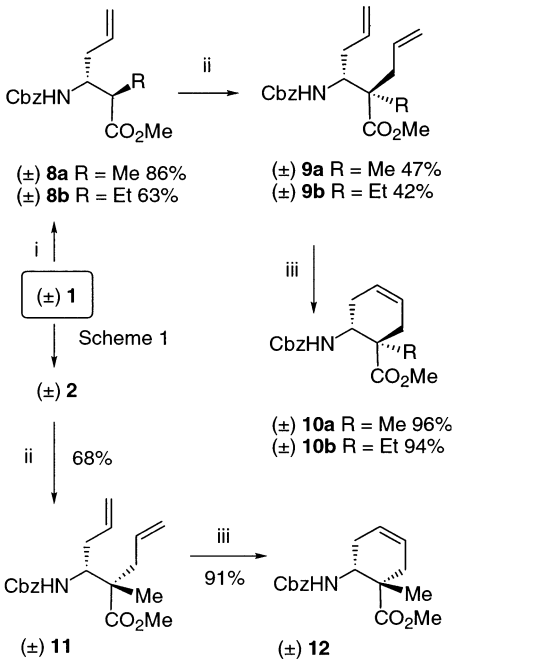
[a] Conditions: (i) LiCl, 2 equiv of LDA, −78 °C, THF, allyl bromide; (ii) **7**, benzene reflux; (iii) H2, Pd/C, MeOH, then DIEA, CbzCl, DMAP, CH_2Cl_2; (iv) NaOH, MeOH; (v) EDCI, HOBt, DIEA, L-PheOMe·HCl, CH_2Cl_2.

the α-substituted cyclohexenyl *β*-amino acids were prepared by an alkylation−allylation sequence, the order of which dictates the stereochemistry of the ring substituents (Scheme 2).

While a number of methods have been developed for the stereoselective preparation of *β*-amino acids, access to α-substituted *β*-amino acids of the type required here remains a challenge. However, the key starting diene **2** was obtained in 59% by allylation of **1** with allyl bromide in the presence of LDA (2 equiv) and LiCl. It is well documented[9,10] that these conditions proceed via a doubly lithiated intermediate to give the relative stereochemistry shown in **2** (see Scheme 2).

We next demonstrated the basic methodology for the preparation of cyclic *β*-amino acids with the conversion of

Scheme 2[a]



[a] Conditions: (i) LiCl, 2 equiv of LDA, THF, −78 °C, MeI or EtI; (ii) LiCl, 2 equiv of LDA, THF, allyl bromide; (iii) **7**, benzene reflux.

2 into a known, but important, aminocyclohexane carboxylic acid (**4**). To this end, treatment of **2** with Grubbs ruthenium catalyst **7**[11] gave the cyclic *β*-amino acid **3** as a single diastereoisomer in excellent yield.[12] The relative stereochemistry of this compound was confirmed after hydrogenation in the presence of 10% Pd-on-C, followed by reprotection with benzyl chloroformate to give the literature compound **4**;[13] this result confirmed the assigned relative configuration of diene **2**. Compound **3** was also hydrolyzed to give **5**, a suitable intermediate for incorporation into peptides. This point was demonstrated by coupling **5** with phenylalanine methyl ester, under standard conditions, to give epimers **6**, which were partially separable by silica-based chromatography.

With the basic methodology for the synthesis of cyclic *β*-amino acids in place, our attention was turned to the synthesis of α-substituted cyclic *β*-amino acids where a second substituent is introduced stereoselectively at the α-position (see Scheme 2). Derivative **1** was again utilized as the key starting material. Alkylation of **1** with either methyl or ethyl iodide, in the presence of LDA (2 equiv) and LiCl, gave the α-methyl and α-ethyl substituted esters **8a** and **8b**, respectively. A second alkylation with allyl bromide gave the diallylated compounds **9a** and **9b** with the

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(11) Grubbs, R. H.; Miller, S. J.; Blackwell, H. E. *J. Am. Chem. Soc.* **1996**, *118*, 9606.

(12) Comparable results were obtained using Grubbs second generation catalyst, tricyclohexylphosphine [1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazole-2-ylidene benzylidene]ruthenium(IV) dichloride.

(13) Appella, D. H.; LePlae, P. R.; Raguse, T. L.; Gellman, S. H. *J. Org. Chem.* **2000**, *65*, 4766.

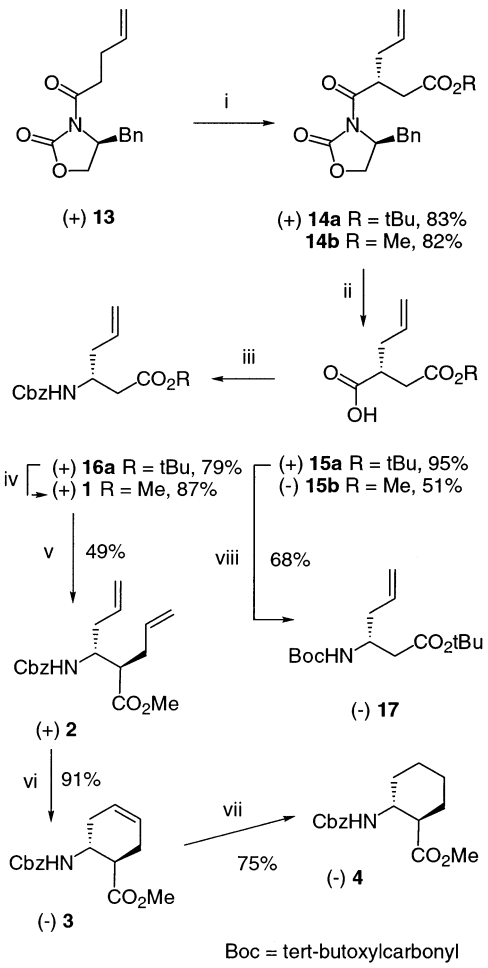
relative stereochemistry shown. RCM of each of these diallylated compound (**9a** and **9b**) gave **10a** and **10b**, respectively,[12] each as a single diastereoisomer as shown; the indicated stereochemistry is based upon the results of the previous sequence (see Scheme 1) and literature precedence.[9,10]

Synthesis of the alternative cis isomer **12** was achieved by reversing the order of the alkylation steps, i.e., alkylation of **1** with allyl bromide followed by alkylation with methyl iodide. This resulted in **11**, an epimer of **9a**, that gave rise to **12** upon RCM (see Scheme 2). Therefore, it is possible to prepare either the cis or trans α-substituted cyclic *β*-amino acids using this methodology. It is interesting to note that while cis isomers of type **12** have not been used to prepare *β*-peptides, they are of interest as inhibitors of matrix metalloproteases.[14]

In the final sequence, we demonstrate that it is possible to prepare a single enantiomer of the cyclic *β*-amino acids using Evans chiral auxiliary chemistry[15,16] to prepare (+)-**1**, which was then subjected to our α-allylation, RCM strategy. The anion of the N-acyl oxazolidinone **13**[17] was alkylated with *tert*-butyl bromoacetate to give the alkylated imide **14a**[18] in 83%. The absolute configuration of **14a** was confirmed as shown by X-ray crystallography.[19] Cleavage of the chiral auxiliary was then carried out using lithium hydroperoxide[15] to give the differentially protected diacid **15a**[18] in 95%. A Curtius rearrangement procedure was then adopted for the conversion of **15a** to give the optically active[18] Cbz-protected *β*-allyl glycine tert butyl ester **16a**. This was achieved by refluxing the acid **15a** in the presence of diphenylphosphoryl azide and triethylamine[15] to give an intermediate isocyanate, which was subsequently trapped with benzyl alcohol. This procedure was also carried out using *tert*-butyl alcohol as the trapping agent to give the known Boc-protected derivative **17**, the optical rotation[18] of which agreed with literature.[16]

Compound **16a** was next converted into (+)-**1** (such that the sequence outlined in Scheme 1 could be repeated with optically active material) by ester hydrolysis and re-esterification with diazomethane. This material gave an optical rotation[18] in close agreement with literature.[20] We also prepared the methyl ester (+)-**1** from **13** by alkylation with methyl bromoacetate, rather than *tert*-butyl bromoacetate, to give **14b**. Hydrolysis of the chiral auxiliary gave (−)-**15b**, which was then subjected to the Curtius rearrangement conditions to give (+)-**1** directly (Scheme 3).

Scheme 3[a]



[a] Conditions: (i) NaHMDS, *tert*-butylbromoacetate or methyl bromoacetate, THF, −78 °C; (ii) LiOH−H_2O_2, THF−H_2O, 0 °C; (iii) DPPA, Et_3N, toluene reflux, BnOH; (iv) TFA/CH_2Cl_2, Me_2S, CH_2N_2; (v) LiCl, 2 equiv LDA, allyl bromide, THF, from −78 °C to room temperature; (vi) **7**, CH_2Cl_2; (vii) H_2, Pd/C, MeOH then DIEA, CbzCl, DMAP, CH_2Cl_2; DPPA, Et_3N, toluene reflux, *t*-BuOH.

The final stage of the synthesis of the optically active cyclic *β*-amino acid (Scheme 3) was carried out as described for the racemic series (see Scheme 1). In particular, (+)-**1**

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(17) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F., Jr. *Tetrahedron* **1998**, *44*, 5525.

(18) Optical rotations $[\alpha]_D$ for: (+)-**1**, +4.2° (*c* 2, $CHCl_3$) (lit.[20] +4.7° (*c* 2, $CHCl_3$)); (+)-**2**, +8.2° (*c* 1, DCM); (−)-**3**, −31.2° (*c* 1.0 $CHCl_3$) (lit.[21] −33.5°); (−)-**4**, −18.4° (*c* 0.9, $CHCl_3$) (lit.[13] −18° (*c* 0.9, $CHCl_3$)); (+)-**14a**, +51.2° (*c* 1, DCM); (+)-**15a**, +3.4° (*c* 1.4 DCM) (lit.[16] +3.4° (*c* 1.4, DCM)); (−)-**15b**, −2.4° (*c* 0.5, DCM); (+) **16a**, +1.8° (*c* 1, DCM); (−)-**17**, −9.8° (1.1 MeOH) (lit.[16] −10.09° (*c* 1.1 MeOH)).

(19) Crystallographic data for **14a**: $C_{21}H_{27}NO_5$, M = 373.44, crystal dimensions 0.55 × 0.38 × 0.33 mm^3, orthorhombic, a = 5.773 (6) Å, b = 10.373 (13) Å, c = 33.36 (4) Å, α = 90 (2)°, β = 90 (2)°, γ = 90 (2)°, V = 1998 (4) Å^3, space group $P2(1)2(1)2(1)$, Z = 4, $F(000)$ = 800, D_{calcd} = 1.242 mg/m^3, absorption coefficient 0.088 mm^{-1}, θ range for data collection = 2.31−26.41, index ranges $-5 \le h \le 2$, $-12 \le k \le 12$, $-41 \le l \le 41$, data/restraints/parameters = 3563/0/244, GOF on F^2 was 0.905, final R indices [$I > 2\sigma(I)$] R_1 = 0.0322, wR_2 = 0.0656, R indices (all data) R_1 = 0.0454, wR_2 = 0.0685, largest difference peak and hole were 0.125 and −0.185 eÅ^{-3}, respectively. A unique data set was measured at 168(2) K. Of the 8924 reflections obtained, 3563 were unique (R_{int} = 0.0221) and used in the full-matrix least-squares refinement. The structure was solved by direct methods. Hydrogen atoms were fixed in idealized positions. All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. Neutral scattering factors and anomalous dispersion corrections for non-hydrogen atoms were taken from Ibers and Hamilton (Ibers, J. A., Hamilton, W. C., Eds.; *International Tables for Crystallography*; Kynoch Press: Birmingham, UK, 1992; Vol. C).

(20) For an alternative synthesis, see: Shono, T.; Kise, N.; Sanda, F.; Ohi, S.; Tsubata, K. *Tetrahedron Lett.* **1988**, *29*, 231.

was allylated with allyl bromide, via the doubly lithiated intermediate, to give the diallylated derivative (+)-**2**,[18] as a single distereoisomer by NMR, which underwent RCM in excellent yield[12] to give (−)-**3**, the optical rotation[18] of which agreed with the literature.[21] The absolute configuration was further confirmed as shown by conversion of (−)-**3** to (−)-**4**,[18] a literature compound.[13]

In summary, we have demonstrated a new and simple procedure for the synthesis of cyclohexenyl β-amino acids based on RCM chemistry. This methodology was used to prepare the unsubstituted trans cyclic β-amino acids **3** and **4** from the simple diene **2** precursor. An α-substituent, as in **10** and **12**, can also be introduced by employing an allylation/alkylation sequence, the order of which defines the absolute configuration of the product. Finally, we have shown that optically active **3** and **4** can be prepared using optically active (+)-**1**.

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Supporting Information Available: General procedures for the alkylation and RCM experimental procedures and spectroscopic data for **2**, **3**, **10**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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