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Diastereoselective synthesis of cyclic β^{2,3}-amino acids utilizing 4-substituted-1,3-oxazinan-6-ones

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ABSTRACT

The 4-substituted-1,3-oxazinan-6-one scaffold is a versatile synthon enabling access to a diverse array of β-amino acid derivatives. In this study, the synthetic utility of the 1,3-oxazinan-6-one is expanded to include the diastereoselective synthesis of cyclic β^{2,3}-amino acids. Enolate chemistry is used to first alkylate the 4-vinyl, 4-allyl, and 4-butenyl oxazinan-6-ones with various alkenyl electrophiles, in high dr. The resulting 4,5-bis-alkene adducts are then transformed into 4,5-cyclic-1,3-oxazinan-6-ones utilizing the ring closing metathesis reaction. The metathesis products are subsequently converted into a variety of five-, six-, and seven-membered cyclic β^{2,3}-amino acids. The research further highlights the 1,3-oxazinan-6-one as a versatile synthon for producing β-amino acid derivatives.

1. Introduction

The recent rise in applications of β-amino acids has seen a plethora literature reviews summarizing synthetic approaches devised to access these important compounds.[1–31] However, many of these synthetic procedures have limitations, in that they are not stereoselective and they do not produce a large variety of analogues from a common precursor. Recently, we have demonstrated the synthetic utility of the 1,3-oxazinan-6-one to gain access to a variety of known and novel stereopure β-amino acids (Fig. 1).[32–37] Originally, it was demonstrated 1,3-oxazinan-6-ones can allow the production of all 20 homologous proteinogenic *N*-methyl β-amino acids.[32,33] In another study it was shown the enolate chemistry allowed 1,3-oxazinan-6-ones to be 5-alkylated and 5-hydroxylated with high diastereoselectivity.[34] The resulting adducts could then be subjected to a range of transformations to give rise to a variety of stereopure 2-alkyl and 2-hydroxy β^{2,3}-amino acid derivatives.[34] More recently, it was further established the 1,3-oxazinan-6-ones could be utilized to produce an assortment of highly substituted β^{2,2,3}-analogues (Fig. 1).[37] Herein, we investigate the synthetic utility of the 1,3-oxazinan-6-one to enable access to an array of cyclic β^{2,3}-amino acids.

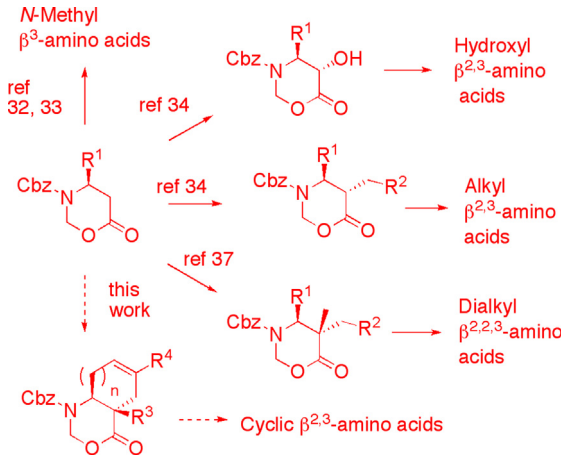

Fig. 1. 1,3-Oxazinan-6-one transformations to produce stereopure β-amino acid derivatives.

Cyclic β-amino acids have risen to prominence in recent times, due to the findings of a number of studies investigating the secondary structures β-peptides form.[38,39] β-Peptides predominately form helical secondary structures. The nature of the β-peptide helix is dependent on the type and make-up of the β-residue used to construct the peptide. It has been demonstrated that cyclic β-amino acids can play an important role in inducing the formation of the

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secondary structure, particularly in β-peptides that possess a small number of residues. It has also been found the type of the cyclic β-residue can dramatically influence the nature of secondary helix formed—that is, a helix that consists of only five-membered cyclic β-residues will be markedly different to a helix that is fabricated from six-membered cyclic β-residues.[39–41]

β-Peptide helices have found use in multiple applications, but most importantly in the design of tool compounds in drug discovery. In particular, β-peptide helices are considered good mimetics for therapeutically important helical α-peptides.[42–46] Several of these β-peptide mimetics, possess a number of cyclic $\beta^{2,3}$-amino residues, to aid in adopting the secondary helical structure desired. These studies have highlighted the importance of cyclic β-residues in this emerging field.

However, given the emerging importance of cyclic β-residues, there are only a limited number of synthetic procedures in the literature.[2,4–6,47] Further, many of these procedures are not stereoselective and do not produce a variety of analogues from a common starting material. Herein, we demonstrate that the 1,3-oxazinan-6-one synthon excels where other synthetic strategies are lacking in the production of cyclic $\beta^{2,3}$-amino acids.

The synthetic strategy proposed to be employed is similar to the research of Abell et al.[48] (Fig. 2). Abell et al. used 4-vinyl, 4-allyl, and 4-butenyl protected β-amino esters as a starting material. In the study by Abell et al. the β-amino esters were enolized, typically using LDA, and trapped with an alkenyl electrophile. The bis-alkene products were obtained in good diastereoselectivity and in poor to good yields. The bis-alkene products were then subjected to ring closing metathesis to obtain the cyclic β-amino ester products. In the study herein, it was proposed to utilize 1,3-oxazinan-6-ones under a similar synthetic strategy to Abell et al., and demonstrate the versatility of this synthon in producing a number of stereopure cyclic $\beta^{2,3}$-amino residues.

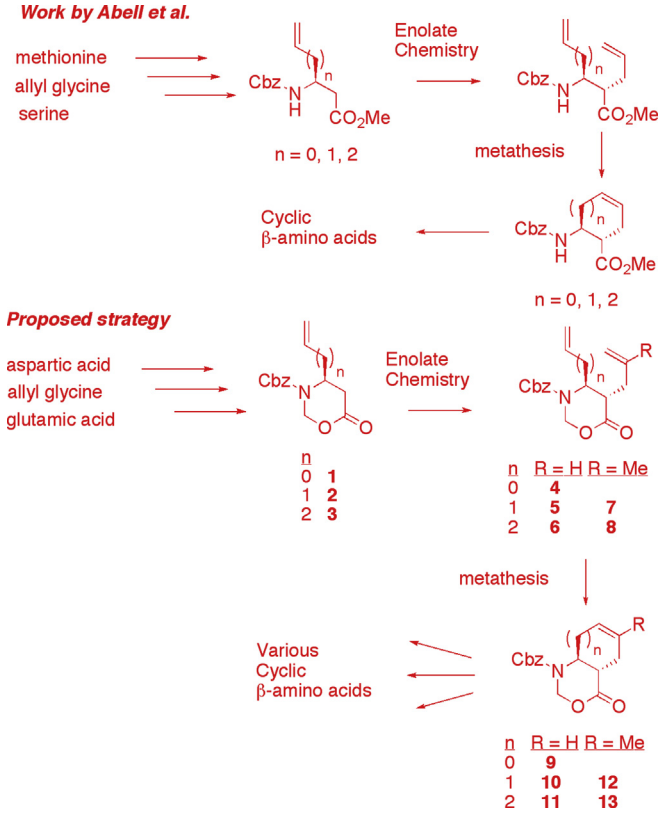


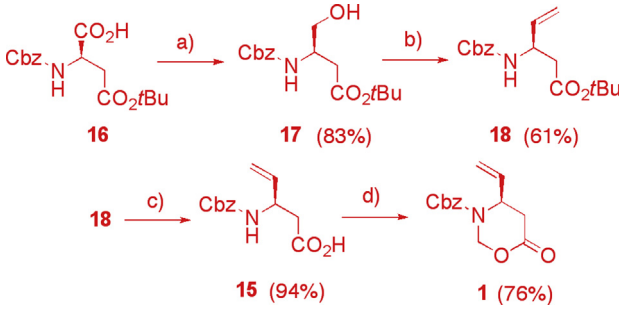
Fig. 2. Comparison of the research by Abell et al.[48] and the proposed strategy for this research.

2. Results and discussion

The starting scaffolds required to perform the metathesis reactions were three 4-alkenyl substituted 1,3-oxazinan-6-ones **1**–**3**. These residues would then be enolized and alkylated with the appropriate alkenyl electrophile. The bis-olefin products **4**–**8** would then be cyclized using a metathesis reaction to afford the cyclic adducts. It was proposed to prepare five-, six-, and seven-membered cyclic adducts **9**–**13**. In order to produce all three sizes of carbocycle, the synthesis of the appropriate starting 1,3-oxazinan-6-ones was required. The 4-vinyl, 4-allyl, and 4-butenyl oxazinan-6-ones **1**–**3** would allow access to the respective five-, six-, and seven-membered cyclic adducts **9**–**13** (Fig. 2).

Previously, 1,3-oxazinan-6-ones have been synthesized in good yields from the corresponding *N*-protected α-amino acid.[32–36] In this study, it was proposed to synthesize the vinyl, allyl, and butenyl β^3-amino acids, from the *N*-Cbz protected α-amino acids, to enable the subsequent cyclization to the corresponding 4-alkenyl substituted oxazinan-6-ones **1**–**3**.

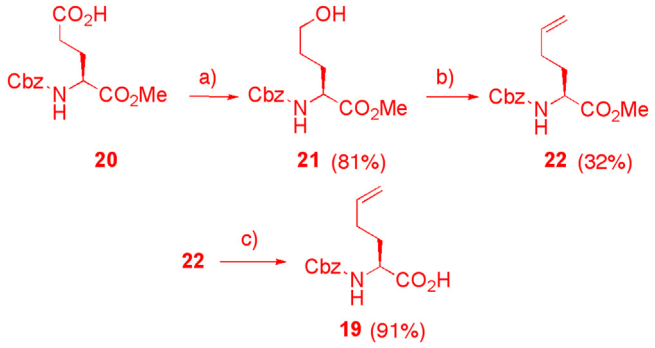
The only commercially available alkenyl α-amino acid was Cbz-L-allyl glycine **14** (L-allyl glycine was Cbz protected). Cbz-L-vinyl β^3-alanine **15** was synthesized from Cbz-L-aspartic acid (*tert*-butyl ester) **16** using a modified procedure by Zappia et al.[49] (Scheme 1). Briefly, the orthogonally protected aspartic acid **16**, was transformed into the alcohol **17**, by firstly activating the acid as a mixed anhydride. Subsequent addition of sodium borohydride gave the alcohol **17** in high yield (83%). A two-step process utilizing a Swern oxidation followed by a Wittig reaction converted the alcohol **17** into the olefin **18** in good yield (61%). Removal of the *tert*-butyl ester gave the Cbz-vinyl β^2-alanine **15** (86% ee) in readiness for the transformation to the 1,3-oxazinan-6-one **1**.



Scheme 1. Synthesis of the Cbz-vinyl β^3-alanine **15** and the 4-vinyl-1,3-oxazinan-6-one **1**.[49] Reagents and conditions: (a) 1. EtOCOCl, *N*-methylmorpholine, THF, −15 °C; 2. $NaBH_4/H_2O$; (b) 1. DMSO, $(COCl)_2$, Et_3N, DCM; 2. THF, KHMDS, CH_3PPh_3Br, −78 °C–25 °C; (c) DCM, TFA; (d) cat. CSA, $(CH_2O)_n$, toluene, 90 °C.

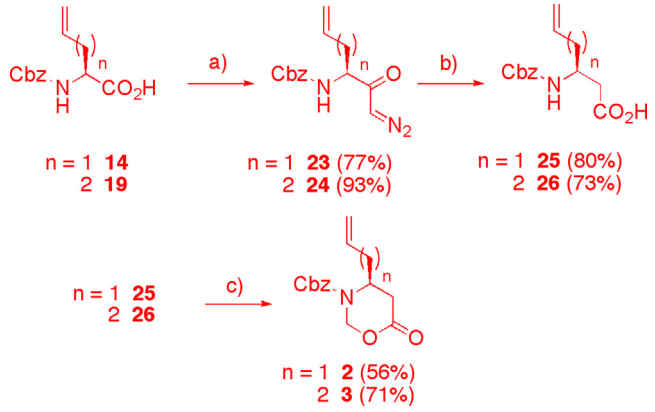
Cbz-L-buten-3-yl β^3-alanine **19** was synthesized from methyl Cbz-L-glutamate **20** using a modified procedure by Zappia et al.[49] (Scheme 2). The unprotected side chain acid of **20** was available to transform into the but-3-enyl group. The acid **20** was reduced via the mixed anhydride using sodium borohydride to afford the alcohol **21** in high yield (81%). Swern and Wittig reactions followed to produce the but-3-enyl methyl ester **22** in a mediocre yield (32%). The low yield was attributed to nucleophilic attack of the methyl ester during the Wittig reaction. Although not undertaken, it was hypothesized a *tert*-butyl ester could be used in future to negate any undesired nucleophilic side reactions. Finally, hydrolysis of the methyl ester **22** under acidic conditions afforded the *N*-Cbz but-3-enyl glycine **19**.

The residues *N*-Cbz-allyl glycine **14** and *N*-Cbz but-3-enyl glycine **19** were then converted into the β^3-amino acids via a procedure used previously, the well-known Arndt–Eistert homologation (Scheme 3).[32–35,50] Both the intermediate diazoketones **23** and **24** and β^3-amino acid products **25** (100% ee) and **26** were obtained in



Scheme 2. Synthesis of *N*-Cbz but-3-enyl glycine **19**. Reagents and conditions: (a) 1. EtOCOCl, NMM, THF, −15 °C; 2. $NaBH_4/H_2O$; (b) 1. DMSO, $(COCl)_2$, Et_3N, DCM; 2. THF, KHMDS, CH_3PPh_3Br, −78 °C–25 °C; (c) AcOH: 1 N aq HCl (1:1), 100 °C.

excellent yields. However, it was noted that the 4-but-3-enyl β-amino acid **26** racemized during the synthetic sequence, as determined by chiral HPLC. Although not determined, it was suspected that racemization occurred during the Wittig transformation (Scheme 2). The racemic 4-but-3-enyl analogue was advanced through the ensuing synthetic sequence as a racemate.

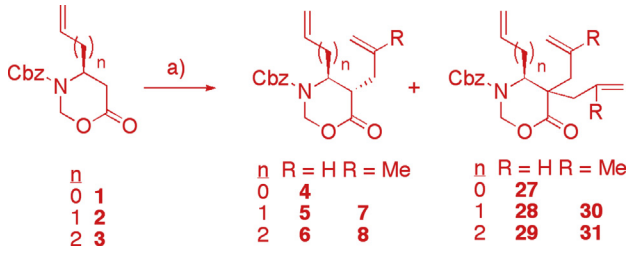


Scheme 3. Synthesis of 1,3-oxazinan-6-ones **2** and **3**. Reagents and conditions: (a) 1. EtOCOCl, *N*-methylmorpholine; 2. CH_2N_2; (b) AgO_2CCF_3, dioxane, H_2O, sonication; (c) cat. CSA, $(CH_2O)_n$, toluene, 90 °C.

The β-residues **15**, **25**, and **26** were then cyclized to the corresponding 1,3-oxazinan-6-ones **1**, **2**, and **3** using a previously described procedure,[32–36] employing paraformaldehyde, a catalytic amount of camphorsulfonic acid (CSA) in toluene at 90 °C for 4–6 h. The 1,3-oxazinan-6-ones **1**, **2**, and **3** were obtained in good yields (56–76%) (Schemes 1 and 3).

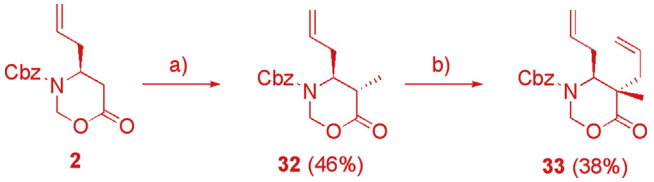
Previously, 5-alkylation and 5-allylation of various 4-substituted oxazinanones were performed in a diastereoselective manner.[37] It was proposed that using the 4-vinyl, 4-allyl, and 4-but-3-enyl oxazinanones **1**, **2**, and **3**, the same high diastereoselectivity would be achieved with allylation reactions. Each oxazinanone **1**, **2**, and **3** was deprotonated with KHMDS at −78 °C. After the enolate had formed the allyl iodide or bromide electrophile was added. The solution was then allowed to slowly warm to −40 °C before the reaction was quenched (Table 1). The yields of the 5-allylation reactions are shown in Table 1. The 5-allylation of the oxazinanones **1**, **2**, and **3** occurred in good yields. In each entry the yields of the desired mono 5-allyl products **4**–**8** were compromised by the formation of diallylated products **27**–**31**. Unreacted starting material was also recovered from the reaction mixture. However, in each transformation the desired mono 5-allyl product **4**–**8** was obtained exclusively in the anti configuration. 2-Methyl allyl iodide was also used as an electrophile to produce the substituted allyl products **7** and **8**, also exclusively in the anti configuration (Table 1).

Table 1
5-Allylation of the 1,3-oxazinan-6-ones **1**–**3**. Reagents and conditions: (a) 1. KHMDS, −78 °C, 45 min; 2. allyl iodide or bromide or 2-methyl allyl iodide, −78 °C to −40 °C; 3. aq NH_4Cl quench



Entry	N	R	Recovered substrate (%)	*trans*-mono adduct (%)		5,5-Disubstituted adduct (%)	
1	0	H	15	**4**	48	**27**	17
2	1	H	16	**5**	38	**28**	20
3	1	Me	17	**7**	42	**30**	9
4	2	H	13	**6**	42	**29**	20
5	2	Me	16	**8**	44	**31**	8

A 5,5-disubstituted oxazinanone **32** was also synthesized. Firstly, the 4-allyl oxazinanone **2** was enolized and the addition of the electrophile methyl triflate exclusively gave the anti diastereoisomer **33** in 46% yield. The oxazinanone **33** was again subjected to enolization, and in this instance allyl bromide was used as the electrophile. The *trans*-5,5-disubstituted oxazinanone **32** was exclusively obtained in a yield of 38% (Scheme 4).

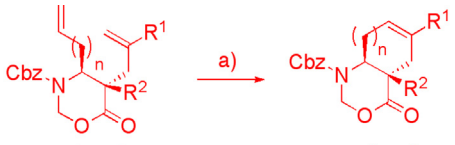


Scheme 4. 5-Allylation of the 5-methyl-1,3-oxazinan-6-one **33**. Reagents and conditions: (a) 1. KHMDS, −78 °C, 45 min; 2. MeOTf, −78 °C to −40 °C; 3. NH_4Cl quench; (b) 1. KHMDS, −78 °C, 45 min; 2. allyl bromide, −78 °C to −40 °C; 3. aq NH_4Cl quench.

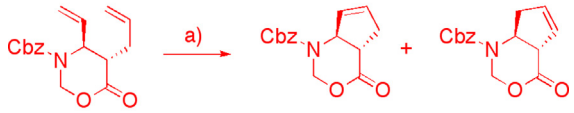
The first analogues to undergo ring-closing metathesis (RCM) were the 4,5-diallyl-oxazinanones **5**, **7**, and **32**. To effect RCM, the Grubbs II catalyst was used in toluene at 25 °C for 20 h (Table 2). The six-membered bicyclic adducts **10**, **12**, and **34** were afforded in excellent yields (80–86%) (Table 2). The same RCM conditions were then applied to the 4-but-3-enyl oxazinanones **6** and **8**. Compared to the six-membered RCM products **10**, **12**, and **34**, the seven-membered RCM products **6** and **8** were obtained in slightly reduced yields of 60% and 69%, respectively. The 4-vinyl oxazinanone **4** was also subjected to the same RCM conditions at 25 °C. However, in this instance only 5% yield of the desired product **9** resulted. When the solution was heated to reflux for 2 days, a mixture of the isomerized five-membered RCM products **9** and **35** were obtained in a 17% yield. No starting material was recovered from the complex reaction mixture, and the side products from the reaction could not be identified. The low yield of the desired product **9** was attributed to the ring strain of the five, six-membered bicyclic ring system. During the RCM transformations all compounds retained their stereochemical integrity as determined by ^1H NMR spectroscopy.

Finally, to highlight the versatility of the 1,3-oxazinanone, the RCM products **10**, **11**, and **13** were subjected to a number of transformations to produce the cyclic $\beta^{2,3}$-amino acids. A particular interest of the authors lies in the production of *N*-methylated amino acid residues.[32–34,50–52] Accordingly, the bicyclic adducts **10** and **13** were subjected to reductive cleavage conditions used previously to produce the novel *N*-methyl cyclic $\beta^{2,3}$-amino acid residues **36** and

Table 2
Synthesis of bicyclic adducts **9**–**13** and **34** by RCM. Reagents and conditions: (a) cat. Grubbs' II, toluene, 25 °C to reflux



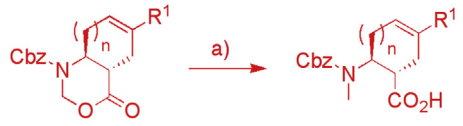
	n	R1	R2		n	R1	R2
5	1	H	H	**10**	1	H	H
7	1	Me	H	**12**	1	Me	H
33	1	H	Me	**34**	1	H	Me
6	2	H	H	**11**	2	H	H
8	2	Me	H	**13**	2	Me	H



4 **9** **35**

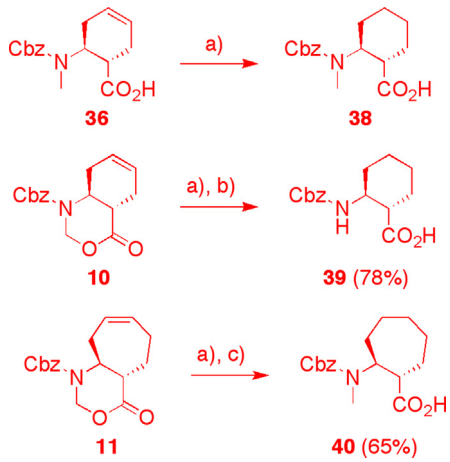
Entry	*n*	R^1	R^2	Cyclic adduct (%)	
1	0	H	H	**9**	5
2	1	H	H	**10**	86
3	1	Me	H	**12**	80
4	1	H	Me	**34**	81
5	2	H	H	**11**	60
6	2	Me	H	**13**	69

37 in 94 and 66%, respectively (Scheme 5). The *N*-methyl product **36** was then subjected to hydrogenation conditions to produce the saturated *N*-methyl cyclic $\beta^{2,3}$-amino acid **38**. Under these conditions the benzyl carbamate remained intact (Scheme 6).



	n	R1		n	R1	
10	1	H	**36**	1	H	(94%)
13	2	Me	**37**	2	Me	(66%)

Scheme 5. Reductive cleavage performed on the bicyclic adducts **10** and **13**. Reagents and conditions: (a) $BF_3{\cdot}Et_2O$, DCM, Et_3SiH, 25 °C.



36 **38**
10 **39** (78%)
11 **40** (65%)

Scheme 6. Hydrogenation of the *N*-methyl cyclic β-amino acid **36** and the bicyclic adducts **10** and **11**. Reagents and conditions: (a) H_2, 10% Pd/C, EtOH, 20 h, 25 °C; (b) LiOH, THF/H_2O; (c) $BF_3{\cdot}Et_2O$, Et_3SiH, DCM.

Hydrogenation of the alkenyl bicyclic adducts **10** and **11**, reduced the alkene, while leaving both the oxazinanone ring and benzyl carbamate intact (Scheme 6). The reduced product was then hydrolyzed with lithium hydroxide to give the N–H cyclic $\beta^{2,3}$-amino acid **39** in high yield (78%). The hydrogenated product of **11** was then converted into the *N*-methyl cyclic $\beta^{2,3}$-amino acid **40** using reductive cleavage conditions in good yield (65%)(Scheme 6).

3. Conclusions

In summary, a route to access stereopure five-, six-, and seven-membered cyclic $\beta^{2,3}$-amino acids utilizing 1,3-oxazinan-6-ones has been described. The precursors required to access such residues were the 4-vinyl-, 4-allyl-, and 4-but-3-enyl-oxazinanones **1**, **2**, and **3**. Modifications of existing procedures were used to smoothly synthesize the oxazinanones **1**, **2**, and **3** from the respective aspartic acid **16**, allylglycine **14**, and glutamic acid **20** starting materials. The 4-alkenyl oxazinanones **1**, **2**, and **3** were then allylated using enolate chemistry. The 4,5-bis-olefinated products **4**–**8** and **32** were obtained in good yields and all exclusively in the anti configuration. These precursors **4**–**8** and **32** were then smoothly converted into the 4,5-cyclic oxazinanones **10**–**13** and **34** using RCM in good to excellent yields. The exception was the five-membered RCM product **9**, which was obtained in a 5% yield. Finally, a number of lactone opening transformations were conducted to produce both the *N*-methylated and NH cyclic $\beta^{2,3}$-amino acids **36**–**40**. The methodology herein again highlights the versatility of the oxazinanone as a useful scaffold to produce a variety of stereopure β-amino acid derivatives.

4. Experimental section

4.1. General methods

Unless otherwise stated, all reactions were carried out under an argon atmosphere in oven-dried glassware. KHMDS was purchased commercially and titrated before use.[53] TLC was performed on kieselgel 60 F_{254} plates and visualized with a UV lamp or staining. Optical rotations were measured at the stated temperatures in the stated solvent using a polarimeter at the sodium d-line (589 nm); $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Elemental analyses were performed by Chemical and Microanalytical Services, Melbourne using a Carlo Erba NA1106 Elemental Analyser. Flash column chromatography was carried out using silica gel 60 particle size 0.040–0.063 μm (230–400 mesh ASTM). NMR spectra were determined in chloroform-*d* at 300 K unless otherwise stated on a 300 MHz spectrometer. Data for ^1H NMR spectroscopy are reported as follows: chemical shift (δ in parts per million), multiplicity (s, singlet; br s, broad singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet). Coupling constant (*J*) are reported in Hertz (Hz). Infrared spectra were recorded on a Fourier transform IR spectrometer using a thin film between NaCl plates. Low-resolution mass spectra were recorded on a mass spectrometer at 300 °C and a scan rate of 5500 *m*/*z*/second using either acetonitrile/formic acid (99:1) or methanol/formic acid (99:1) mixtures as the mobile phase. High-resolution electrospray ionization mass spectra were recorded on a mass spectrometer with an ionization energy of 70 eV using methanol/acetic acid (99:1) mixtures as the mobile phase. High resolution electron ionization mass spectra were recorded on a Kratos Concept ISQ mass spectrometer using an ionization energy of 70 eV and 5.3 kV accelerating voltage with the sample being introduced by direct insertion probe into the ion source and spectra were scanned over the range *m*/*z* 35 to 800, with the ion source held at 200 °C and probe tip heated to 300 °C. Accurate masses were obtained at a resolution of 8000 by 'peak matching' using perfluorokerosene. Parent ion peaks are reported as *m*/*z* values. High performance

liquid chromatography (HPLC) was conducted using a Waters instrument fitted with a Chiralpak AD-H 5 μm, 4.6×250 mm column eluting with an isocratic solvent gradient of 90% petroleum and 10% isopropyl alcohol (IPA) and 0.1% trifluoroacetic acid (TFA) with UV detection of output at 254 nm.

4.2. Synthesis

4.2.1. Synthesis of the alkenyl α-amino acids

4.2.1.1. N-Carbonylbenzyloxy-L-allyl glycine ***14***. To a stirred solution of NaOH (700 mg, 17.4 mmol) in water (40 mL) was added L-allyl (glycine)–OH (2.00 g, 17.4 mmol). *N*-(Benzyloxycarbonyloxy)-succinimide (4.30 g, 17.4 mmol) in acetone (25 mL) was added in one portion with vigorous stirring. After the addition was complete, $NaHCO_3$ (1.50 g, 17.4 mmol) was added and stirring was continued for 20 h. The reaction mixture was extracted once with Et_2O (50 mL) to remove any excess neutral organic compounds and the aqueous layer was acidified to pH 2 with 5 M aq HCl. The aqueous layer was extracted with EtOAc (3×25 mL) and dried ($MgSO_4$) and evaporated in vacuo to give **14** as a brown oil (4.10 g, 95% yield), with spectra identical to those of an authentic sample.[52]

4.2.1.2. tert-Butyl-(3S)-3-([(benzyloxy)carbonyl]amino)-4-hydroxy-butanoate ***17***. To a stirred solution of *N*-(benzyloxycarbonyl-L-aspartic acid) (*tert*-butyl ester) **16** (4.54 g, 14.0 mmol) in THF (70 mL) at −15 °C, *N*-methylmorpholine (1.85 mL, 16.8 mmol) was added followed by ethyl chloroformate (1.61 mL, 16.8 mmol). The reaction mixture was stirred at the same temperature for 15 min, and $NaBH_4$ (1.59 g, 42.4 mmol) in H_2O (20 mL) was added, followed by addition of H_2O (300 mL) at −15 °C immediately afterward. The solution was stirred for 15 min and neutralized with 1 N aq HCl. The reaction mixture was extracted with EtOAc (3×100 mL). The combined organic phases were washed with 1 N aq HCl (70 mL), H_2O (2×70 mL), 5% aq $NaHCO_3$ (2×70 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel chromatography eluting with 30–50% EtOAc/hexane to give the amino alcohol **17** (3.67 g, 83% yield), with spectra identical to those of an authentic sample.[54]

4.2.1.3. Methyl-(3S)-3-([(benzyloxy)carbonyl]amino)-5-hydroxy-pentanoate ***21***. To a stirred solution of *N*-(benzyloxycarbonyl-L-glutamic acid (methyl ester)) **20** (4.16 g, 14.0 mmol) in THF (70 mL) at −15 °C, *N*-methylmorpholine (1.85 mL, 16.8 mmol) was added followed by ethyl chloroformate (1.61 mL, 16.8 mmol). The reaction mixture was stirred at the same temperature for 15 min, and $NaBH_4$ (1.60 g, 42.4 mmol) in H_2O (20 mL) was added, followed by addition of H_2O (300 mL) at −15 °C immediately afterward. The solution was stirred for 15 min and neutralized with 1 N aq HCl. The reaction mixture was extracted with EtOAc (3×100 mL). The combined organic phase was washed with 1 N aq HCl (70 mL), H_2O (2×70 mL), 5% aq $NaHCO_3$ (2×70 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel chromatography eluting with 30–50% EtOAc/hexane to afford the amino alcohol **21** as a colorless oil (3.19 g, 81% yield); R_f (50% EtOAc/hexane) 0.31; *m*/*z* HRMS (ESI, MeOH/AcOH): $[M+H]^+$, found 282.1340. $C_{14}H_{20}NO_5$ requires 282.1336; $[\alpha]_D^{24}$ −18.8 (*c* 5.56, MeOH); ν_{max} (NaCl)/cm^{-1} 3341, 3062, 3036, 2951, 2878, 1748, 1705, 1504, 1498, 1450, 1335, 1215, 1049, 914, 741; δ_H (300 MHz, $CDCl_3$) 7.31 (5H, br s), 5.71 (1H, d, *J* 7.8 Hz), 5.06 (2H, s), 4.38–4.31 (1H, m), 3.68 (3H, s), 3.58 (2H, t, *J* 6.0 Hz), 2.49 (1H, br s), 1.94–1.82 (1H, m), 1.75–1.66 (1H, m), 1.61–1.51 (2H, m); δ_C (75 MHz, $CDCl_3$) 172.7, 155.8, 135.9, 128.1, 127.8, 127.7, 66.6, 61.4, 53.3, 51.9, 28.7, 27.8.

4.2.1.4. 1-Methyl ester-(2S)-2-([(benzyloxy)carbonyl]amino)-5-hexenoate ***22***. Oxalyl chloride (2.20 mL, 25.4 mmol) was dissolved in CH_2Cl_2 (30 mL), the mixture was cooled to −78 °C and a solution of dry DMSO (3.60 mL, 50.7 mmol) in CH_2Cl_2 (10 mL) was added dropwise during 15 min. The *N*-(benzyloxycarbonyl)-L-glutamic amino alcohol (methyl ester) **21** (3.57 g, 12.7 mmol) in CH_2Cl_2 (15 mL) was added dropwise during 10 min, the resulting solution was stirred for 10 min at −78 °C. A solution of triethylamine (10.60 mL, 76.2 mmol) in CH_2Cl_2 (30 mL) was added dropwise during 15 min. After 20 min water (5 mL) was added to the vigorously stirred solution at −78 °C. The resulting slurry was poured into Et_2O (200 mL) and washed with 20% aq $KHSO_4$ (2×70 mL), the layers were separated and the aqueous layer was back-extracted with Et_2O (2×70 mL). The combined organic layers were washed with brine solution (2×50 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure (20 °C) to afford the crude aldehyde, which was immediately used in the next reaction without any further purification.

Methyl triphenylphosphonium bromide (9.08 g, 25.4 mmol) was suspended in dry THF (250 mL) at 25 °C and KHMDS (0.5 M in toluene, 53.20 mL, 26.6 mmol) was added. The resultant yellow solution was stirred at 25 °C for 2.5 h, then cooled to −78 °C and a solution of the crude aldehyde in dry THF (20 mL) was added dropwise. The reaction mixture was slowly warmed to 25 °C over 1 h and then stirred for a further 2 h. The reaction was quenched with MeOH (25 mL) and the resulting mixture was poured into a mixture of satd aq potassium sodium tartrate and H_2O (1:1, 300 mL). Extraction with Et_2O (3×200 mL), drying over $MgSO_4$, and evaporation under reduced pressure gave the crude residue. The residue was purified by silica gel chromatography eluting with 10–20% EtOAc/hexane to give olefin **22** as an oil (1.12 g, 32% yield); R_f (20% EtOAc/hexane) 0.42; *m*/*z* HRMS (ESI, MeOH/AcOH): $[M+H]^+$, found 278.1377. $C_{15}H_{20}NO_4$ requires 278.1387; $[\alpha]_D^{24}$ +6.5 (*c* 1.23, MeOH); ν_{max} (NaCl)/cm^{-1} 3340, 3067, 3032, 2951, 1713, 1694, 1504, 1435, 1346, 1215, 1049, 914, 737; δ_H (300 MHz, $CDCl_3$) (320 K): δ 7.32 (5H, br s), 5.79–5.71 (1H, m), 5.36 (1H, d, *J* 6.9 Hz), 5.09 (2H, s), 5.04 (1H, d, *J* 16.2 Hz), 4.99 (1H, d, *J* 9.3 Hz), 4.39 (1H, d, *J* 4.8 Hz), 3.71 (3H, s), 2.11–2.05 (2H, m), 1.93–1.89 (1H, m), 1.76–1.69 (1H, m); δ_C (75 MHz, $CDCl_3$) (320 K) 172.3, 155.4, 136.4, 136.0, 128.1, 127.7, 127.6, 115.3, 66.6, 53.2, 51.8, 31.6, 28.9.

4.2.1.5. (2S)-2-([(Benzyloxy)carbonyl]amino)-5-hexenoic acid ***19***. A solution of methyl ester **22** (1.80 g, 6.53 mmol) was dissolved in a mixture of AcOH and 1 N aq HCl (1:1, 26.0 mL) and the solution was heated to 100 °C for 3 h. The mixture was concentrated under reduced pressure, and the residue was taken up in Et_2O (50 mL) and washed with H_2O (3×40 mL) and brine. The organic layer was extracted with satd aq $NaHCO_3$ solution (3×30 mL). The combined aq layers were acidified to pH 2 with 5 N aq HCl, and then re-extracted with EtOAc (3×20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by silica gel chromatography eluting with 10–40% EtOAc/hexane to give the acid **19** (1.60 g, 91% yield) as a white solid, with spectra identical to those of authentic sample.[55]

4.2.2. Synthesis of the alkenyl diazoketones

4.2.2.1. General procedure A. Preparation of the diazoketones. The Cbz-L-α-amino acid (1 mmol) was dissolved in anhydrous THF (25 mL) and cooled to −15 °C. To this solution, ethyl chloroformate (100 μL, 1.05 mmol) and *N*-methylmorpholine (115 μL, 1.05 mmol) were added and the mixture was stirred for 15 min. Then, a solution of CH_2N_2 (5 mmol; CAUTION!) in CH_2Cl_2 was added slowly, and the yellow solution was allowed to warm to 25 °C. Stirring was continued until there was no starting material remaining (TLC). Excess CH_2N_2 was destroyed by the addition of AcOH. The mixture was concentrated under reduced pressure, and the residue was taken up in EtOAc (40 mL). The organic phase was washed successively with satd aq $NaHCO_3$ (30 mL), 10% aq citric acid (30 mL), and then

brine (30 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness in vacuo. The product was of sufficient purity to be used directly in the next reaction. The residue was subjected to flash column chromatography for characterization.

*4.2.2.1.1. Phenylmethyl [(1S)-3-diazo-1-allyl-2-oxopropyl] carbamate **23**.* *N*-(Benzyloxycarbonyl-α-allylglycine) **14** (249 mg, 1 mmol) was transformed according to General procedure A to afford the diazoketone **23** as a yellow oil (210 mg, 77% yield); R_f (30% EtOAc/hexane) 0.46; *m*/*z* HRMS (ESI, MeOH/AcOH): $[M+Na]^+$, found 296.1009. $C_{14}H_{16}N_3NaO_3$ requires 296.1006; $[\alpha]_D^{24}$ −37.9 (*c* 3.95, MeOH); ν_{max} (NaCl)/cm^{-1} 3318, 3086, 3034, 2106, 1712, 1643, 1504, 1366, 1250, 1041, 918, 733; δ_H (300 MHz, $CDCl_3$) 7.30 (5H, br s), 5.72–5.63 (1H, m), 5.57 (1H, d, *J* 6.9 Hz), 5.43 (1H, s), 5.12–5.10 (4H, m), 4.28 (1H, br s), 2.54–2.47 (1H, m), 2.39–2.35 (1H, m); δ_C (75 MHz, $CDCl_3$) 192.6, 155.5, 135.8, 131.9, 128.2, 127.8, 127.7, 118.9, 67.7, 56.9, 53.7, 36.2.

*4.2.2.1.2. Phenylmethyl [(1S)-3-diazo-1-butenyl-2-oxopropyl] carbamate **24**.* *N*-Benzyloxycarbonyl-α-butenylglycine **19** (263 mg, 1 mmol) was transformed according to General procedure A to afford the diazoketone **24** as a yellow oil (266 mg, 93% yield); R_f (20% EtOAc/hexane) 0.26; *m*/*z* HRMS (ESI, MeOH/AcOH): $[M+Na]^+$, found 310.1172. $C_{15}H_{17}N_3NaO_3$ requires 310.1162; $[\alpha]_D^{24}$ +23.4 (*c* 0.68, MeOH); ν_{max} (NaCl)/cm^{-1} 3318, 3078, 2947, 2928, 2110, 1713, 1643, 1504, 1369, 1246, 1206, 914, 736; δ_H (300 MHz, $CDCl_3$) (320 K) 7.30 (5H, br s), 5.80–5.69 (1H, m), 5.37 (2H, br s), 5.09–4.97 (4H, m), 4.24 (1H, br s), 2.11 (2H, d, *J* 6.9 Hz), 1.93–1.87 (1H, m), 1.69–1.61 (1H, m); δ_C (75 MHz, $CDCl_3$) 192.9, 155.6, 136.5, 135.8, 128.2, 127.9, 127.7, 115.5, 66.7, 56.8, 53.8, 31.4, 28.9.

4.2.3. Synthesis of the alkenyl β-amino acids

*4.2.3.1. tert-Butyl-(3S)-3-[(benzyloxy)carbonyl]amino-4-pentenoate **18**.* Oxalyl chloride (2.20 mL, 25.4 mmol) was dissolved in CH_2Cl_2 (30 mL), the mixture was cooled to −78 °C and a solution of dry DMSO (3.60 mL, 50.7 mmol) in CH_2Cl_2 (10 mL) was added dropwise during 15 min. The amino alcohol **17** (3.93 g, 12.7 mmol) in CH_2Cl_2 (15 mL) was added dropwise during 10 min, the resulting solution was stirred for 10 min at −78 °C, and a solution of triethylamine (10.63 mL, 76.2 mmol) in CH_2Cl_2 (30 mL) was added dropwise during 15 min. After 20 min, water (5.0 mL) was added to the vigorously stirred solution at −78 °C. The resulting slurry was poured in Et_2O (200 mL) and washed with 20% aq $KHSO_4$ (2×70 mL), the layers were separated and the aqueous layer was back-extracted with Et_2O (2×70 mL). The combined organic layers were washed with brine solution (2×50 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure (20 °C) to afford the crude aldehyde, which was immediately used in the next reaction without any further purification.

Methyl triphenylphosphonium bromide (9.08 g, 25.4 mmol) was suspended in dry THF (250 mL) at 25 °C and KHMDS (0.5 M in toluene, 53.20 mL, 26.6 mmol) was added. The resultant yellow solution was stirred at 25 °C for 2.5 h, then cooled to −78 °C and a solution of the crude aldehyde in dry THF (20 mL) was added dropwise. The reaction mixtures was slowly warmed to 25 °C over 1 h and then stirred for a further 2 h. The reaction was quenched with MeOH (25 mL) and the resulting mixture was poured into a mixture of satd aq potassium sodium tartrate and H_2O (1:1, 300 mL). Extraction with Et_2O (3×200 mL), drying over $MgSO_4$, and evaporation under reduced pressure gave a crude residue. The residue was purified by silica gel chromatography eluting with 10–20% EtOAc/hexane to give olefin **18** as an oil (2.38 g, 61% yield), with spectra identical to those of an authentic sample.[49]

4.2.3.2. General procedure B. Preparation of the N-(benzyloxycarbonyl)-β-amino acids. The diazoketone (1 mmol) was dissolved in 1,4-dioxane/H_2O 9:1 (v/v, 50 mL). On addition of CF_3CO_2Ag (2.21 mg, 0.01 mmol), the mixture was sonicated in an ultrasound bath until no diazoketone remained (TLC). The mixture was then concentrated in vacuo. The residue was dissolved in Et_2O (50 mL) and washed with 10% aq citric acid solution. The organic layer was extracted with satd aq $NaHCO_3$ solution (3×20 mL). The combined aq layers were acidified to pH 2 with 5 N aq HCl, and then re-extracted with EtOAc (3×30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue was subjected to flash column chromatography for characterization.

*4.2.3.2.1. (3S)-3-(([(Phenylmethyl)oxy]carbonyl)amino)hexenoic acid **25**.* Treatment a solution of allylglycine diazoketone **23** (273 mg, 1 mmol) according to General procedure B, furnished the β-amino acid **25** as a white solid (212 mg, 80% yield); *m*/*z* HRMS (ESI, MeOH/AcOH): $[M+H]^+$, found 264.1232. $C_{14}H_{18}NO_4$ requires 264.1230; mp 82–84 °C; $[\alpha]_D^{24}$ +23.8 (*c* 2.93, MeOH); ν_{max} (NaCl)/cm^{-1} 3325, 3071, 2963, 2916, 1697, 1535, 1265, 1130, 918, 733; δ_H (300 MHz, $CDCl_3$) 7.34–7.31 (5H, m), 5.78–5.69 (1H, m), 5.17 (1H, br s), 5.12 (2H, d, *J* 3.3 Hz), 5.08 (2H, s), 4.09–4.05 (1H, m), 2.61 (2H, d, *J* 4.8 Hz), 2.35 (2H, t, *J* 6.9 Hz); δ_C (75 MHz, $CDCl_3$) 176.3, 155.5, 135.9, 133.2, 128.2, 127.8, 127.7, 118.3, 66.5, 47.0, 38.2, 37.6. HPLC (Chiralpak AD-H, 90:10 Pet/IPA, 25 °C 254 nm): t_R (major)=8.7 min, 100% ee.

*4.2.3.2.2. (3S)-3-(([(Phenylmethyl)oxy]carbonyl)amino)heptenoic acid **26**.* Treatment of a solution of the but-3-enyl glycine diazoketone **24** (287 mg, 1 mmol) according to General procedure B, furnished the β-amino acid **26** as a white solid (204 mg, 73% yield); *m*/*z* HRMS (ESI, MeOH/AcOH): $[M+H]^+$, found 278.1388. $C_{15}H_{20}NO_4$ requires 278.1387; mp 81–83 °C; $[\alpha]_D^{24}$ +10.2 (*c* 0.98, MeOH); ν_{max} (NaCl)/cm^{-1} 3323, 3067, 2976, 2916, 1713, 1694, 1520, 1452, 1246, 1056, 910, 733; δ_H (300 MHz, $CDCl_3$) (325 K) 8.88 (1H, br s), 7.32 (5H, br s), 5.81–5.70 (1H, m), 5.19 (1H, br s), 5.09 (2H, s), 5.04 (1H, d, *J* 17.4 Hz), 4.94 (1H, d, *J* 10.2 Hz), 3.99 (1H, br s), 2.58 (2H, s), 2.11 (2H, d, *J* 6.9 Hz), 1.66 (2H, t, *J* 6.9 Hz); δ_C (75 MHz, $CDCl_3$) 176.4, 155.6, 136.9, 136.0, 128.2, 128.1, 127.8, 115.1, 66.5, 47.2, 38.3, 33.1, 29.9. HPLC (Chiralpak AD-H, 90:10 Pet/IPA, 25 °C 254 nm): t_R (major)=8.35 min (52%), t_R (minor)=8.65 min (48%).

4.2.4. Synthesis of the alkenyl 1,3-oxazinan-6-ones

4.2.4.1. General procedure C. Preparation of 1,3-oxazinan-6-ones. To the *N*-benzyloxycarbonyl β-amino acid (1 mmol) in dry toluene (30 mL) were added camphorsulfonic acid (23.2 mg, 0.1 mmol), paraformaldehyde (1.66 g, 6 mmol), and activated 4 Å molecular sieves (150 mg) under an argon atmosphere. The reaction mixture was stirred at 90 °C for 4–6 h. The mixture was allowed to cool and filtered through Celite pad. The filtrate was diluted with EtOAc (30 mL), and the organic layer was washed with satd aq $NaHCO_3$ solution (20 mL) and water (20 mL). The organic layer was dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was subjected to flash column chromatography, eluting with 10–30% EtOAc/hexane.

*4.2.4.1.1. (4S)-N-Benzyloxycarbonyl-4-vinyl-1,3-oxazinan-6-one **1**.* The *N*-Cbz-β-amino acid **15** (249 mg, 1 mmol) was transformed according to General procedure C and afforded the oxazinanone **1** as an oil (149 mg, 76% yield); R_f (30% EtOAc/hexane) 0.29; *m*/*z* HRMS (ESI, MeOH/AcOH): $[M+H]^+$, found 261.1075. $C_{14}H_{16}NO_4$ requires 262.1074; $[\alpha]_D^{24}$ −93.1 (*c* 4.4, MeOH); ν_{max} (NaCl)/cm^{-1} 3088, 3034, 2916, 1757, 1713, 1699, 1414, 1260, 1155, 1001; δ_H (300 MHz, $CDCl_3$) 7.33 (5H, br s), 5.88–5.76 (2H, m), 5.25–5.17 (4H, m), 5.03 (1H, d, *J* 10.5 Hz), 4.71 (1H, br s), 2.93 (1H, dd, *J* 8.4, 16.2 Hz), 2.67 (1H, dd, *J* 8.4, 16.2 Hz); δ_C (75 MHz, $CDCl_3$) (320 K) 168.4, 153.9, 135.1, 131.0, 128.2, 128.1, 127.7, 116.3, 72.1, 67.9, 51.2, 34.5.

*4.2.4.1.2. (4S)-N-Benzyloxycarbonyl-4-allyl-1,3-oxazinan-6-one **2**.* The *N*-Cbz-β-amino acid **25** (263 mg, 1 mmol) was transformed according to General procedure C and afforded the oxazinanone **2** as an oil (155 mg, 56% yield); R_f (30% EtOAc/hexane) 0.43; *m*/*z* HRMS (ESI, MeOH/AcOH): $[M+H]^+$, found 276.1234. $C_{15}H_{18}NO_4$ requires 276.1230; $[\alpha]_D^{24}$ +162.0 (*c* 1.0, MeOH); ν_{max} (NaCl)/cm^{-1}

3067, 2929, 1759, 1713, 1697, 1418, 1261, 1153, 999; δ_H (300 MHz, $CDCl_3$) 7.36–7.28 (5H, m), 5.82 (1H, d, *J* 10.5 Hz), 5.76–5.62 (1H, m), 5.20–5.10 (4H, m), 4.99 (1H, d, *J* 10.5 Hz), 4.27–4.18 (1H, m), 2.75 (1H, dd, *J* 8.6, 16.2 Hz), 2.60 (1H, dd, *J* 8.6, 16.2 Hz), 2.42 (2H, t, *J* 6.6 Hz); δ_C (75 MHz, $CDCl_3$) 169.5, 153.9, 135.1, 131.3, 128.3, 128.2, 127.8, 119.6, 72.2, 67.9, 49.0, 38.4, 33.9.

*4.2.4.1.3. N-Benzyloxycarbonyl-4-butenyl-1,3-oxazinan-6-one **3**.* The *N*-Cbz-β-amino acid **26** (277 mg, 1 mmol) was transformed according to General procedure C and afforded the oxazinanone **3** as an oil (204 mg, 71% yield); R_f (20% EtOAc/hexane) 0.23; *m/z* HRMS (EI): $[M]^+$, found 289.1314. $C_{16}H_{19}NO_4$ requires 289.1314; ν_{max} (NaCl)/cm^{-1} 3067, 2920, 1755, 1713, 1694, 1416, 1261, 1155, 999; δ_H (300 MHz, $CDCl_3$) 7.39–7.30 (5H, m), 5.85–5.73 (2H, m), 5.17 (2H, s), 5.04–4.95 (3H, m), 4.23 (1H, br s), 2.89 (1H, dd, *J* 8.4, 16.2 Hz), 2.52 (1H, dd, *J* 8.4, 16.2 Hz), 2.12–2.02 (2H, m), 1.91–1.79 (1H, m), 1.71–1.63 (1H, m); δ_C (75 MHz, $CDCl_3$) (323 K) 168.8, 154.1, 136.3, 135.2, 128.3, 128.1, 127.9, 115.2, 71.9, 67.9, 49.2, 35.3, 34.2, 29.1.

4.2.5. Alkylation of the 1,3-oxazinan-6-ones

4.2.5.1. General procedure D. 5-Alkylation of oxazinanones. A solution of the oxazinanone (0.125 M in dry freshly distilled THF) was cooled to −78 °C under an argon atmosphere. Then KHMDS (1.1 equiv of 0.50 M solution in toluene) was added dropwise and the solution was left to stir at −78 °C for 40 min. The alkylating agent (5.00 equiv) was then added dropwise and stirring was continued for 3 h at −78 °C. The solution was then allowed to warm to −40 °C, and the reaction was then quenched with satd aq NH_4Cl solution (5.00 mL). The solution was diluted with EtOAc (20 mL) and washed with water (20 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give a residue. The residue was subjected to flash column chromatography, eluting with 5–20% EtOAc/hexane.

*4.2.5.1.1. (4S,5S)-N-Benzyloxycarbonyl-4-vinyl-5-allyl-1,3-oxazinan-6-one **4**, and (4S,5S)-N-benzyloxycarbonyl-4-vinyl-5,5-diallyl-1,3-oxazinan-6-one **27**.* The General procedure D was followed for the alkylation of oxazinanone **3** (119 mg, 0.46 mmol) with allyl iodide (208 μL, 2.3 mmol) as the electrophile to afford starting material **3** (17% recovery). The oxazinanone **4** was isolated as a colorless oil (65.9 mg, 48% yield); R_f (30% EtOAc/hexane) 0.47; *m/z* HRMS (ESI, MeOH/AcOH): $[M+H]^+$, found 302.1385. $C_{17}H_{20}NO_4$ requires 302.1387; $[\alpha]_D^{24}$ −119.5 (*c* 2.9, MeOH); ν_{max} (NaCl)/cm^{-1} 3076, 2980, 2916, 1759, 1713, 1641, 1414, 1252, 1139, 995, 924; δ_H (300 MHz, $CDCl_3$) (325 K) 7.32 (5H, br s), 5.90–5.76 (3H, m), 5.29–5.01 (7H, m), 4.39 (1H, br s), 2.65–2.59 (1H, m), 2.48 (2H, br s); δ_C (75 MHz, $CDCl_3$) (325 K) 170.2, 153.6, 135.2, 133.9, 133.8, 128.2, 128.1, 127.7, 117.9, 117.7, 71.2, 67.8, 55.6, 44.0, 31.3.

The oxazinanone **27** was isolated as a colorless oil (22.8 mg, 15% yield); R_f (30% EtOAc/hexane) 0.62; *m/z* HRMS (EI): $[M]^+$, found 341.1617. $C_{20}H_{23}NO_4$ requires 341.1627. $[\alpha]_D^{24}$ −39.0 (*c* 1.89, MeOH); ν_{max} (NaCl)/cm^{-1} 3078, 2980, 1746, 1713, 1699, 1398, 1246, 1111, 921; δ_H (300 MHz, $CDCl_3$) (310 K) 7.35–7.33 (5H, m), 5.88–5.77 (2H, m) 5.74–5.64 (2H, m), 5.36 (2H, d, *J* 10.2 Hz), 5.30 (1H, d, *J* 10.2 Hz), 5.23–5.04 (6H, m), 4.27 (1H, br s), 2.66 (1H, dd, *J* 7.3, 14.7 Hz), 2.57 (1H, dd, *J* 7.3, 14.4 Hz), 2.33 (1H, dd, *J* 7.3, 14.4 Hz) 2.26 (1H, dd, *J* 7.3, 14.7 Hz); δ_C (75 MHz, $CDCl_3$) (325 K) 170.6, 153.1, 135.3, 131.7, 131.1, 130.9, 128.2, 128.0, 127.7, 119.7 (2), 119.3, 72.7, 67.7, 58.2, 49.1, 38.7, 35.9.

*4.2.5.1.2. (4S,5S)-N-Benzyloxycarbonyl-4,5-diallyl-1,3-oxazinan-6-one **5**, and (4S,5S)-N-benzyloxycarbonyl-4,5,5-triallyl-1,3-oxazinan-6-one **28**.* The General procedure D was followed for the alkylation of oxazinanone **2** (224 mg, 0.81 mmol) with allyl bromide (350 μL, 4.05 mmol) as the electrophile to afford starting material **2** (16% recovery). The oxazinanone **5** was isolated as a colorless oil (98.4 mg, 38% yield); R_f (20% EtOAc/hexane) 0.22; *m/z* HRMS (EI): $[M]^+$, found 315.1456. $C_{18}H_{21}NO_4$ requires 315.1471; $[\alpha]_D^{24}$ +132.8 (*c* 0.47, MeOH); ν_{max} (NaCl)/cm^{-1} 3075, 2916, 2849, 1749, 1713, 1697, 1418, 1254, 1001, 918; δ_H (300 MHz, $CDCl_3$) 7.40–7.31 (5H, m), 5.94–5.80 (3H, m) 5.19–5.09 (6H, m), 4.94 (1H, d, *J* 10.2 Hz), 4.09 (1H, br s), 2.74–2.68 (2H, m), 2.48–2.36 (2H, m), 2.34–2.30 (1H, m); δ_C (75 MHz, $CDCl_3$) 171.2, 153.7, 135.1, 133.8, 131.4, 128.3, 128.1, 127.8, 119.9, 117.9, 71.7, 67.9, 52.5, 42.4, 35.7, 31.5.

The oxazinanone **28** was isolated as a colorless oil (57.3 mg, 20% yield); R_f (20% EtOAc/hexane) 0.41; *m/z* HRMS (ESI, MeOH/AcOH): $[M+H]^+$, found 356.1861. $C_{21}H_{26}NO_4$ requires 356.1856; $[\alpha]_D^{24}$ +94.0 (*c* 1.1, MeOH); ν_{max} (NaCl)/cm^{-1} 3076, 2978, 2916, 1748, 1713, 1639, 1418, 1246, 1107, 921; δ_H (300 MHz, $CDCl_3$) (325 K) 7.34 (5H, br s), 5.89 (1H, br s), 5.84–5.58 (3H, m) 5.21–4.99 (9H, m), 4.37 (1H, br s), 2.75 (1H, dd, *J* 6.9, 15.3 Hz), 2.63 (1H, br s), 2.39 (2H, br s), 2.28–2.17 (2H, m); δ_C (75 MHz, $CDCl_3$) (325 K) 170.9, 153.6, 135.4, 132.5, 131.5, 130.9, 128.3, 128.1, 127.7, 119.6, 118.9, 117.9, 72.6, 67.7, 54.9, 50.2, 39.2, 34.7, 32.2.

*4.2.5.1.3. (4S,5S)-N-Benzyloxycarbonyl-4-allyl-5-(2-methylallyl)-1,3-oxazinan-6-one **7**, and (4S,5S)-N-benzyloxycarbonyl-4-allyl-5,5-di(2-methylallyl)-1,3-oxazinan-6-one **30**.* The General procedure D was followed for the alkylation of oxazinanone **2** (103 mg, 0.37 mmol) with 2-methyl allyl iodide (202 μL, 1.87 mmol) as the electrophile to afford starting material **2** (17% recovery). The oxazinanone **7** was isolated as a colorless oil (50.8 mg, 42% yield); R_f (30% EtOAc/hexane) 0.67; *m/z* HRMS (ESI, MeOH/AcOH): $[M+H]^+$, found 330.1705. $C_{19}H_{24}NO_4$ requires 330.1700; $[\alpha]_D^{24}$ +156.0 (*c* 0.40, MeOH); ν_{max} (NaCl)/cm^{-1} 3076, 2916, 2849, 1749, 1713, 1699, 1418, 1250, 1128, 1003; δ_H (300 MHz, $CDCl_3$) (320 K) 7.38–7.31 (5H, m), 5.87 (1H, d, *J* 10.3 Hz), 5.81–5.67 (1H, m), 5.21–5.08 (4H, m), 5.02 (1H, d, *J* 10.3 Hz), 4.84 (1H, s), 4.76 (1H, s), 4.08 (1H, br s) 2.77 (1H, dd, *J* 6.8, 13.9 Hz), 2.64 (2H, dd, *J* 6.8, 13.9 Hz), 2.39 (1H, dd, *J* 6.4, 14.1 Hz), 2.28 (1H, dd, *J* 6.4, 14.1 Hz), 1.74 (3H, s); δ_C (75 MHz, $CDCl_3$) (323 K) 170.9, 153.8, 141.5, 135.2, 131.7, 128.2, 128.0, 127.7, 119.4, 112.7, 71.7, 67.8, 53.3, 42.0, 36.4 (2), 22.1.

The oxazinanone **30** was isolated as a colorless oil (13.3 mg, 9% yield); R_f (30% EtOAc/hexane) 0.78; *m/z* HRMS (EI): $[M]^+$, found 383.2097. $C_{23}H_{29}NO_4$ requires 383.2097; $[\alpha]_D^{24}$ +69.2 (*c* 0.43, MeOH); ν_{max} (NaCl)/cm^{-1} 3073, 2949, 1749, 1713, 1699, 1418, 1244, 1132, 901; δ_H (300 MHz, $CDCl_3$) (325 K) 7.37–7.33 (5H, m), 5.90 (1H, d, *J* 9.3 Hz), 5.68–5.61 (1H, m), 5.18 (2H, s), 5.14 (1H, d, *J* 16.8 Hz), 5.02–4.97 (3H, m), 4.86 (2H, m), 4.71 (1H, s), 4.65 (1H, d, *J* 11.7 Hz), 2.76 (2H, dd, *J* 4.8, 11.4 Hz), 2.58 (1H, d, *J* 14.7 Hz), 2.33–2.21 (3H, m), 1.78 (3H, s), 1.45 (3H, s); δ_C (75 MHz, $CDCl_3$) (325 K) 171.6, 153.7, 140.5, 140.2, 135.4, 132.9, 128.2, 128.0, 127.7, 117.6, 115.8, 114.3, 72.6, 67.7, 55.1, 52.3, 42.8, 38.3, 32.6, 24.9, 23.1.

*4.2.5.1.4. (4S,5S)-N-Benzyloxycarbonyl-4-butenyl-5-allyl-1,3-oxazinan-6-one **6**, and (4S,5S)-N-benzyloxycarbonyl-4-butenyl-5,5-diallyl-1,3-oxazinan-6-one **29**.* The General procedure D was followed for the alkylation of oxazinanone **3** (153 mg, 0.53 mmol) with allyl iodide (430 μL, 2.65 mmol) as the electrophile to afford starting material **3** (13% recovery). The oxazinanone **6** was isolated as a colorless oil (73.5 mg, 42% yield); R_f (20% EtOAc/hexane) 0.46; *m/z* HRMS (EI): $[M]^+$, found 329.1618. $C_{19}H_{23}NO_4$ requires 329.1627; $[\alpha]_D^{24}$ +53.7 (*c* 0.48, MeOH); ν_{max} (NaCl)/cm^{-1} 3074, 2976, 2922, 1755, 1713, 1682, 1414, 1250, 1126, 989, 916; δ_H (300 MHz, $CDCl_3$) (323 K) 7.36 (5H, br s), 5.89–5.75 (3H, m), 5.17 (2H, s), 5.13–4.94 (5H, m), 4.15–4.09 (1H, m), 2.54–2.43 (3H, m), 2.13 (2H, dd, *J* 7.8, 14.7 Hz), 1.90–1.79 (1H, m), 1.74–1.59 (1H, m); δ_C (75 MHz, $CDCl_3$) 170.8, 154.3, 136.2, 135.1, 133.9, 128.3, 128.1, 127.9, 118.0, 115.1, 71.3, 67.9, 52.7, 44.8, 33.1, 32.6, 28.8.

The oxazinanone **29** was isolated as a colorless oil (38.2 mg, 20% yield); R_f (20% EtOAc/hexane) 0.63; *m/z* HRMS (EI): $[M]^+$, found 369.1940. $C_{22}H_{27}NO_4$ requires 369.1940. $[\alpha]_D^{24}$ +19.8 (*c* 1.41, MeOH); ν_{max} (NaCl)/cm^{-1} 3076, 2978, 2922, 1748, 1713, 1639, 1418, 1248, 1107, 991, 918; δ_H (300 MHz, $CDCl_3$) (325 K) 7.34 (5H, br s), 5.94 (1H, br s) 5.77–5.57 (3H, m), 5.19–4.94 (9H, m), 4.27 (1H, br s), 2.73 (1H, dd, *J* 7.1, 15.3 Hz), 2.37 (2H, br s), 2.29 (1H, dd, *J* 7.1, 15.3 Hz), 1.99–1.81 (3H, m) 1.66–1.53 (1H, m); δ_C (75 MHz, $CDCl_3$) (325 K)

171.1, 153.8, 135.3, 136.2, 131.6, 130.9, 128.2, 128.1, 127.8, 119.5, 118.8, 115.4, 72.3, 67.8, 55.4, 50.4, 39.2, 34.6, 29.1, 26.5.

*4.2.5.1.5. (4S,5S)-N-Benzyloxycarbonyl-4-butenyl-5-(2-methylallyl)-1,3-oxazinan-6-one **8**, and (4S,5S)-N-benzyloxycarbonyl-4-butenyl-5,5-di(2-methylallyl)-1,3-oxazinan-6-one **31**.* The General procedure D was followed for the alkylation of oxazinanone **3** (115 mg, 0.41 mmol) with 2-methyl allyl iodide (215 μL, 1.99 mmol) as the electrophile to afford starting material **3** (16% recovery). The oxazinanone **8** was isolated as a colorless oil (62.4 mg, 44% yield); R_f (20% EtOAc/hexane) 0.41; *m/z* HRMS (EI): $[M]^+$, found 343.1789. $C_{20}H_{25}NO_4$ requires 343.1784; $[\alpha]_D^{24}$ +45.0 (*c* 0.49, MeOH); ν_{max} (NaCl)/cm^{-1} 3076, 2916, 2849, 1749, 1713, 1694, 1418, 1250, 1126, 989; δ_H (300 MHz, $CDCl_3$) (323 K) 7.34 (5H, br s), 5.89 (1H, d, *J* 10.5 Hz), 5.82–5.68 (1H, m), 5.18 (2H, s), 5.04–4.74 (5H, m), 4.12 (1H, br s), 2.62–2.55 (2H, m), 2.28 (1H, dd, *J* 8.1, 16.5 Hz), 2.11 (2H, dd, *J* 7.2, 14.4 Hz), 1.85–1.63 (5H, m); δ_C (75 MHz, $CDCl_3$) (323 K) 170.6, 154.2, 141.4, 135.2, 136.7, 128.2, 128.1, 127.8, 115.0, 112.9, 71.3, 67.9, 53.3, 43.9, 37.3, 32.4, 29.2, 22.3.

The oxazinanone **31** was isolated as a colorless oil (13.4 mg, 8% yield); R_f (20% EtOAc/hexane) 0.51; *m/z* HRMS (EI): $[M]^+$, found 397.2246. $C_{24}H_{31}NO_4$ requires 397.2253; $[\alpha]_D^{24}$ +24.8 (*c* 0.56, MeOH); ν_{max} (NaCl)/cm^{-1} 3074, 2970, 2918, 1746, 1713, 1641, 1418, 1246, 1003, 903; δ_H (300 MHz, $CDCl_3$) (325 K) 7.35 (5H, br s), 5.94 (1H, d, *J* 9.6 Hz) 5.78–5.66 (1H, m), 5.24–5.13 (3H, m), 4.99–4.92 (3H, m), 4.86 (2H, d, *J* 13.5 Hz), 4.69 (1H, s), 4.57 (1H, d, *J* 10.8 Hz), 2.79 (2H, dd, *J* 9.9, 13.5 Hz), 2.31 (1H, d, *J* 4.2 Hz), 2.25 (1H, s), 2.08–1.94 (2H, m), 1.85–1.17 (5H, m), 1.64 (3H, s); δ_C (75 MHz, $CDCl_3$) (325 K) 171.8, 154.0, 140.5, 140.2, 136.5, 135.3, 128.2, 128.1, 127.9, 115.8, 115.1, 114.2, 72.4, 67.8, 55.5, 51.0, 42.7, 38.1, 29.4, 27.0, 24.9, 23.1.

*4.2.5.1.6. (4S,5S)-N-Benzyloxycarbonyl-4-allyl-5-methyl-1,3-oxazinan-6-one **33**.* The General procedure D was followed for the alkylation of oxazinanone **2** (103 mg, 0.37 mmol) with MeOTf (61.5 μL, 0.56 mmol) as the electrophile to afford starting material **2** (26% recovery) and trace amount of the 5,5-disubstituted compound. The oxazinanone **33** was isolated as a colorless oil (50.2 mg, 46% yield); R_f (20% EtOAc/hexane) 0.30; *m/z* HRMS (ESI, MeOH/AcOH): $[M+H]^+$, found 290.1393. $C_{16}H_{20}NO_4$ requires 290.1387; $[\alpha]_D^{24}$ +171.0 (*c* 1.4, MeOH); ν_{max} (NaCl)/cm^{-1} 2978, 2931, 1744, 1713, 1643, 1420, 1250, 1111, 910; δ_H (300 MHz, $CDCl_3$) 7.38–7.29 (5H, m), 5.87–5.71 (2H, m), 5.22–5.09 (4H, m), 4.95 (1H, d, *J* 10.8 Hz), 3.86 (1H, br s), 2.73–2.65 (2H, m), 2.35–2.26 (1H, m), 1.28 (3H, d, *J* 6.6 Hz); δ_C (75 MHz, $CDCl_3$) 172.1, 153.9, 135.2, 131.4, 128.0, 128.2, 127.7, 119.5, 71.8, 67.8, 55.6, 37.5, 36.1, 12.8.

*4.2.5.1.7. (4S,5S)-N-Benzyloxycarbonyl-4-allyl-5-methyl-5-allyl-1,3-oxazinan-6-one **32**.* The General procedure D was followed for the alkylation of 5-methyl-oxazinanone **33** (80.0 mg, 0.28 mmol) with toluene as a solvent and allyl bromide (120 μL, 1.38 mmol) as the electrophile to afford starting material **33** (21% recovery) and 5,5-disubstituted oxazinanone **32** (35.3 mg, 38% yield); R_f (20% EtOAc/hexane) 0.51; *m/z* HRMS (ESI, MeOH/AcOH): $[M+H]^+$, found 330.1703. $C_{19}H_{24}NO_4$ requires 330.1700. $[\alpha]_D^{24}$ +127.1 (*c* 0.39, MeOH); ν_{max} (NaCl)/cm^{-1} 3078, 2982, 2916, 1746, 1713, 1697, 1423, 1248, 1111, 1011, 918, 733; δ_H (300 MHz, $CDCl_3$) (320 K) 7.33 (5H, br s), 5.91 (1H, br s), 5.66 (2H, br s), 5.22–5.01 (7H, m), 4.32 (1H, br s), 2.53 (1H, d, *J* 14.4 Hz), 2.39–2.18 (3H, m), 1.18 (3H, s); δ_C (75 MHz, $CDCl_3$) (325 K) 172.6, 153.6, 135.3, 132.6, 131.4, 128.2, 128.1, 127.8, 119.4, 117.9, 72.5, 67.7, 55.2, 47.5, 42.8, 32.6, 18.8.

4.2.6. Bicyclic adduct formation by way of RCM

4.2.6.1. General procedure E. Ring-closing metathesis. A solution of the diene (0.04–0.11 M solution) in dry degassed toluene was added to a solution of catalyst (Grubb's II) (5 mol %) in dry degassed toluene (0.017 M solution) under argon. The solution was then either stirred at 25 °C or at reflux. The solvent was evaporated under reduced pressure, and the residue was purified by flash column chromatography, eluting with 5–20% EtOAc/hexane.

*4.2.6.1.1. (4S,7S)-N-Benzyloxycarbonyl-4,4a,5,7a-tetrahydro-2H-cyclopenta[d][1,3]-oxazinan-4-one **9**.* The diene oxazinanone **4** (54.0 mg, 0.18 mmol) in toluene (1.70 mL) was transformed at 25 °C for 20 h according to General procedure E, and afforded the oxazinanone **9** as an oil (2.50 mg, 5% yield); R_f (30% EtOAc/hexane) 0.40; *m/z* HRMS (ESI, MeOH/AcOH): $[M+H]^+$, found 274.1075. $C_{15}H_{16}NO_4$ requires 274.1074; ν_{max} (NaCl)/cm^{-1} 3036, 2955, 2916, 2847, 1744, 1713, 1699, 1419, 1250, 1134, 1010, 910; δ_H (300 MHz, $CDCl_3$) (300 K) 7.39–7.33 (5H, m), 6.11–6.08 (1H, m) 5.78 (1H, d, *J* 10.2 Hz), 5.68–5.64 (1H, m), 5.44 (1H, br s), 5.19 (2H, s), 4.85 (1H, d, *J* 10.2 Hz), 3.49–3.41 (1H, m), 3.01 (1H, dd, *J* 10.5, 17.4 Hz), 2.76–2.67 (1H, m); δ_C (75 MHz, $CDCl_3$) 170.7, 153.1, 135.1, 134.5, 128.3, 128.2, 128.0, 127.9, 70.6, 67.9, 59.5, 40.1, 36.7.

*4.2.6.1.2. An isomerized mixture of (4S,7S)-N-benzyloxycarbonyl-4,4a,5,7a-tetrahydro-2H-cyclopenta[d][1,3]-oxazinan-4-one **9** and (7aS)-benzyl 4-oxo-4,4a,7,7a-tetrahydrocyclopenta[d][1,3]oxazine-1(2H)-carboxylate **35**.* The diene oxazinanone **4** (34.3 mg, 0.11 mmol) in toluene (1.00 mL) was transformed at reflux for 2 h according to General procedure E, and afforded the bicyclic-oxazinanone **9** and **35** as an oil (17% yield), in a ratio of 1.8:1. Selected data for **35** (from mixture): δ_H (300 MHz, $CDCl_3$) (325 K) 5.13 (1H, d, *J* 10.2 Hz), 5.09 (1H, br s), 2.47 (1H, br d, *J* 18.0 Hz).

*4.2.6.1.3. (4S,8S)-N-Benzyloxycarbonyl-2,4,4a,5,8,8a-hexahydro-1H-benzo[d][1,3]-oxazinan-4-one **10**.* The diene oxazinanone **5** (52.8 mg, 0.17 mmol) in toluene (2.80 mL) was transformed at reflux for 2 h according to General procedure E, and afforded the cyclic-oxazinanone **10** as an oil (42.2 mg, 86% yield); R_f (20% EtOAc/hexane) 0.24; *m/z* HRMS (ESI, MeOH/AcOH): $[M+Na]^+$, found 310.1050. $C_{16}H_{17}NNaO_4$ requires 310.1050; $[\alpha]_D^{24}$ +174.0 (*c* 2.23, MeOH); ν_{max} (NaCl)/cm^{-1} 3067, 2920, 1755, 1713, 1694, 1416, 1261, 1155, 999; δ_H (300 MHz, $CDCl_3$) (325 K) 7.38–7.32 (5H, m), 5.92 (1H, d, *J* 10.7 Hz), 5.72–5.61 (2H, m), 5.18 (2H, s), 5.10 (1H, d, *J* 10.7 Hz), 3.88–3.83 (1H, m), 2.80–2.71 (2H, m), 2.47–2.38 (2H, m), 2.18–2.12 (1H, m); δ_C (75 MHz, $CDCl_3$) (325 K) 171.1, 154.3, 135.3, 128.2, 128.0, 127.7, 124.9, 124.3, 71.4, 67.8, 52.3, 39.8, 32.1, 26.6.

*4.2.6.1.4. (4S,8S)-N-Benzyloxycarbonyl-6-methyl-2,4,4a,5,8,8a-hexahydro-1H-benzo[d][1,3]-oxazinan-4-one **12**.* The diene oxazinanone **7** (35.3 mg, 0.11 mmol), in toluene (1.80 mL) was transformed at reflux for 2 h according to General procedure E, and afforded the oxazinanone **12** as white solid (25.7 mg, 80% yield); R_f (20% EtOAc/hexane) 0.24; *m/z* HRMS (EI): $[M]^+$, found 301.1303. $C_{17}H_{19}NO_4$ requires 301.1314; mp 113–115 °C; $[\alpha]_D^{24}$ +183.1 (*c* 0.83, MeOH); ν_{max} (NaCl)/cm^{-1} 3032, 2916, 1767, 1713, 1674, 1412, 1265, 1242, 1142, 1011, 972; δ_H (300 MHz, $CDCl_3$) (325 K) 7.38–7.32 (5H, m), 5.93 (1H, d, *J* 10.5 Hz), 5.34 (1H, br s), 5.23 (1H, d, J_{AB} 12.3 Hz), 5.17 (1H, d, J_{AB} 12.3 Hz), 5.10 (1H, d, *J* 10.5 Hz), 3.87–3.78 (1H, m), 2.83–2.66 (2H, m), 2.37 (2H, d, *J* 6.9 Hz), 2.13–2.04 (1H, m), 1.71 (3H, s); δ_C (75 MHz, $CDCl_3$) (325 K) 171.3, 154.3, 135.3, 132.6, 128.2, 128.0, 127.7, 118.4, 71.4, 67.7, 52.3, 39.9, 31.9, 31.1, 22.4.

*4.2.6.1.5. (4S,8S)-N-Benzyloxycarbonyl-4a-methyl-2,4,4a,5,8,8a-hexahydro-1H-benzo[d][1,3]-oxazinan-4-one **34**.* The diene oxazinanone **32** (19.4 mg, 0.06 mmol) in toluene (1 mL) was transformed at reflux for 2 h according to General procedure E, and afforded the oxazinanone **34** as an oil (14.6 mg, 81% yield); R_f (20% EtOAc/hexane) 0.38; *m/z* HRMS (ESI, MeOH/AcOH): $[M+H]^+$, found 302.1387. $C_{17}H_{20}NO_4$ requires 302.1387; $[\alpha]_D^{24}$ +30.9 (*c* 0.52, MeOH); ν_{max} (NaCl)/cm^{-1} 3032, 2974, 2916, 1753, 1713, 1645, 1519, 1454, 1346, 1246, 1045, 1002; δ_H (300 MHz, $CDCl_3$) (325 K) 7.39–7.32 (5H, m), 5.92 (1H, d, *J* 10.7 Hz), 5.68–5.56 (2H, m), 5.36 (1H, d, *J* 10.7 Hz), 5.22 (1H, d, J_{AB} 12.0 Hz), 5.17 (1H, d, J_{AB} 12.0 Hz), 3.89 (1H, dd, *J* 4.8, 11.1 Hz), 2.87 (1H, d, *J* 17.4 Hz), 2.55 (1H, d, *J* 16.2 Hz), 2.32 (1H, dd, *J* 4.8, 16.2 Hz), 2.22–2.18 (1H, m), 1.41 (3H, s); δ_C (75 MHz, $CDCl_3$) (325 K) 171.8, 154.9, 135.3, 128.2, 128.0, 127.8, 125.1, 123.8, 72.4, 67.8, 54.7, 39.3, 37.1, 27.7, 16.5.

*4.2.6.1.6. (4S,9S)-N-Benzyloxocarbonyl-4,4a,5,6,9,9a-hexahydro-2H-cyclohepta[d][1,3]-oxazinan-4-one **11**.* The diene oxazinanone **6**

(80.1 mg, 0.24 mmol) in toluene (5.80 mL) was transformed at 25 °C for 3 h according to General procedure E, and afforded the oxazinanone **11** as an oil (43.6 mg, 60% yield); R_f (20% EtOAc/hexane) 0.33; *m/z* HRMS (EI): $[M]^+$, found 301.1309. $C_{17}H_{19}NO_4$ requires 301.1314; $[\alpha]_D^{24}$ +58.2 (*c* 0.45, MeOH); ν_{max} (NaCl)/cm^{-1} 3028, 2918, 2849, 1755, 1713, 1414, 1248, 1128, 1010, 970; δ_H (300 MHz, $CDCl_3$) (325 K) 7.39–7.30 (5H, m), 5.94–5.79 (3H, m), 5.16 (2H, br s), 5.07 (1H, d, *J* 10.2 Hz), 3.83 (1H, br s), 2.96 (1H, dd, *J* 8.4, 16.2 Hz), 2.44 (1H, t, *J* 10.8 Hz), 2.33–2.03 (4H, m), 1.43–1.39 (1H, m); δ_C (75 MHz, $CDCl_3$) (325 K) 171.3, 153.6, 135.3, 132.2, 128.4, 128.2, 128.0, 127.6, 71.0, 67.7, 59.5, 44.4, 32.8, 26.7, 24.3.

4.2.6.1.7. (4S,9S)-N-Benzyloxycarbonyl-7-methyl-4,4a,5,6,9,9a-hexahydro-2H-cyclohepta[d][1,3]-oxazinan-4-one ***13***. The diene oxazinanone **8** (49.5 mg, 0.14 mmol) in toluene (3.30 mL) was transformed at 25 °C for 3 h according to General procedure E, and afforded the oxazinanone **13** as an oil (31.3 mg, 69% yield); R_f (20% EtOAc/hexane) 0.35; *m/z* HRMS (EI): $[M]^+$, found 315.1466. $C_{18}H_{21}NO_4$ requires 315.1471; $[\alpha]_D^{24}$ +60.6 (*c* 0.67, MeOH); ν_{max} (NaCl)/cm^{-1} 3034, 2960, 2916, 2849, 1759, 1713, 1699, 1409, 1248, 1128, 1014, 962, 912; δ_H (300 MHz, $CDCl_3$) (325 K) 7.37 (5H, br s), 5.87 (1H, d, *J* 10.7 Hz) 5.63 (1H, br s), 5.17 (2H, s), 5.05 (1H, d, *J* 10.7 Hz), 3.84 (1H, t, *J* 10.7 Hz), 2.77 (1H, d, *J* 15.9 Hz), 2.47 (1H, t, *J* 10.7 Hz), 2.27–2.14 (3H, m), 2.08–2.04 (1H, m), 1.77 (3H, s), 1.43–1.33 (1H, m); δ_C (75 MHz, $CDCl_3$) (325 K) 171.6, 153.7, 135.3, 137.2, 128.2, 128.1, 127.6, 125.7, 721.1, 67.7, 59.7, 43.5, 32.9, 31.8, 25.5, 23.9.

4.2.7. Reductive cleavage of the bicyclic adducts

4.2.7.1. General procedure F. Reductive cleavage of the bicyclic oxazinanone. To the bicyclic oxazinanone in dry CH_2Cl_2 (0.06 M solution) were added boron trifluoride etherate (2.00 equiv) and triethylsilane (3.00 equiv). Then, the reaction mixture was stirred for 6–20 h (monitored by TLC). The solvent was evaporated under reduced pressure. The resulting residue was subjected to silica chromatography, eluting with 10–30% EtOAc/hexane.

4.2.7.1.1. (1S,6S)-N-Benzyloxycarbonyl-3-methylamino-cyclohex-3-enecarboxylic acid ***36***. The oxazinanone **10** (40.0 mg, 0.14 mmol) was transformed according to General procedure F, affording *N*-methyl acid **36** as a white solid (38.3 mg, 94% yield); *m/z* HRMS (ESI, MeOH/AcOH): $[M+Na]^+$, found 312.1208. $C_{16}H_{19}NNaO_4$ requires 312.1206; mp 162–164 °C; $[\alpha]_D^{24}$ +7.4 (*c* 0.61, MeOH); ν_{max} (NaCl)/cm^{-1} 3287–2861, 2916, 1703, 1645, 1454, 1408, 1346, 1307, 1147, 912, 733; δ_H (300 MHz, $CDCl_3$) (300 K) 8.15 (1H, br s), 7.33–7.25 (5H, m), 5.63 (2H, s), 5.12 (2H, s), 4.44–4.34 (1H, m), 2.99–2.81 (4H, m), 2.79 (2H, s), 2.43–2.28 (2H, m); δ_C (75 MHz, $CDCl_3$) (320 K) 177.6, 156.1, 136.5, 128.1, 127.4, 127.3, 124.7, 124.1, 66.9, 54.1, 42.7, 29.8, 28.9, 27.5.

4.2.7.1.2. (1S,2S)-N-Benzyloxycarbonyl-3-methylamino-5-methylcyclohept-4-enecarboxylic acid ***37***. The oxazinanone **13** (30.2 mg, 0.096 mmol) was transformed according to General procedure F, affording *N*-methyl acid **37** as an oil (19.9 mg, 66% yield); *m/z* HRMS (ESI, MeOH/AcOH): $[M+H]^+$, found 318.1704. $C_{18}H_{24}NO_4^+$ requires 318.1705; ν_{max} (NaCl)/cm^{-1} 3268–2862, 2932, 2855, 1728, 1697, 1450, 1312, 1211, 1142, 910, 731; δ_H (300 MHz, $CDCl_3$) (300 K) 7.33–7.26 (5H, m), 5.61 (1H, br s), 5.12 (2H, s), 4.29 (1H, d, *J* 11.1 Hz), 2.83 (3H, s), 2.66–2.45 (2H, m), 2.16–1.98 (3H, m), 1.74 (3H, s), 1.59–1.46 (2H, m); δ_C (75 MHz, $CDCl_3$) 177.1, 155.6, 136.9, 136.6, 128.1, 127.5, 127.3, 126.0, 66.7, 61.5, 45.8, 40.9, 30.5, 30.1, 24.8, 24.4.

4.2.8. Hydrogenation to afford β-amino analogues

4.2.8.1. (1S,2S)-N-Benzyloxycarbonyl-3-methylamino-cyclohex-3-ane carboxylic acid ***38***. To a solution of cyclic-β-amino acid **36** (31.9 mg, 0.11 mmol) in ethanol (7 mL) was added 10% palladium-on-charcoal catalyst (20% w/w). The mixture was evacuated and purged with hydrogen (3×), then it was left to stir at 25 °C for 3 h. The mixture was then filtered through a small bed of Celite and washed with ethanol and the solvent was removed under reduced pressure to give an oily residue. The residue was subjected to flash column chromatography, eluting with 10–40% EtOAc/hexane, to afford the desired cyclic *N*-methyl-β-amino acid **38** as an oil (19.5 mg, 61% yield); *m/z* HRMS (ESI, MeOH/AcOH): $[M+H]^+$, found 292.1543. $C_{16}H_{22}NO_4^+$ requires 292.1548; mp 138–140 °C; $[\alpha]_D^{24}$ +10.5 (*c* 0.57, MeOH); ν_{max} (NaCl)/cm^{-1} 3272–2854, 2939, 1697, 1450, 1412, 1319, 1150, 912, 733; δ_H (300 MHz, $CDCl_3$) (300 K) 7.33–7.27 (5H, m), 5.11 (2H, s), 4.11 (1H, br s), 2.84 (3H, s), 2.66–.58 (1H, m), 2.05 (1H, br d, *J* 12.3 Hz), 1.81–1.71 (3H, m), 1.60–1.52 (2H, m), 1.41–1.33 (1H, m), 1.16 (1H, br s); δ_C (75 MHz, $CDCl_3$) (300 K) 178.8, 156.0, 136.5, 128.0, 127.4, 127.3, 66.8, 56.8, 46.4, 46.0, 28.9, 28.5, 24.7, 24.2.

4.2.8.2. (1S,2S)-N-Benzyloxycarbonyl-3-methylamino-cyclohex-3-anecarboxylic acid ***39***. To a solution of oxazinanone **10** (29 mg, 0.10 mmol) in dry ethanol (7 mL) was added 10% palladium-on-charcoal catalyst (20% w/w). The mixture was evacuated and purged with hydrogen (3×), then it was left to stir at 25 °C for 3 h. The mixture was then filtered through a small bed of Celite and washed with ethanol and the solvent was removed under reduced pressure to give an oily residue. The residue was dissolved in THF (5 mL) and 4 M aq LiOH (0.8 mL) was added at 0 °C. The reaction mixture was left to stir at 25 °C for 2 h and THF was removed under reduced pressure. The aqueous solution was washed with ether (5 mL) and the aqueous layer was acidified to pH 2 with 1 M aq HCl and then it was extracted with EtOAc (3×5 mL). The combined organic layers were dried with $MgSO_4$ and evaporated under reduced pressure to give the acid **39** as an oil (27.9 mg, 78% yield) and it was then converted into a *tert*-butylammonium salt for analysis; *m/z* HRMS (ESI, MeOH/AcOH): $[M+H]^+$, found 351.2278. $C_{19}H_{31}N_2O_4^+$ requires 351.2278. Mp 123–125 °C; $[\alpha]_D^{24}$ −13.3 (*c* 0.3, H_2O); ν_{max} (KBr)/cm^{-1} 3341, 2932, 2862, 2739, 2623, 2538, 2199, 1713, 1628, 1543, 1497, 1404, 1219, 1126, 1034, 702; δ_H (300 MHz, D_2O) (323 K) 7.49 (5H, br s), 5.16 (2H, br s), 3.62 (1H, br s), 2.20 (1H, br s), 1.96 (2H, br s), 1.76 (2H, br s), 1.61–1.25 (13H, m); δ_C (75 MHz, D_2O) (320 K) 182.9, 157.2, 136.3, 128.4, 127.9, 127.2, 66.3, 65.2, 52.4, 51.9, 51.6, 31.9, 29.3, 26.2, 24.2.

4.2.8.3. (1S,2S)-N-Benzyloxycarbonyl-3-methylamino-cyclohept-3-anecarboxylic acid ***40***. To a solution of oxazinanone **11** (34.7 mg, 0.12 mmol) in dry ethanol (7.00 mL) was added 10% palladium-on-charcoal catalyst (20% w/w). The mixture was evacuated and purged with hydrogen (3×), then it was left to stir at rt for 3 h. The mixture was then filtered through a small bed of Celite and washed with ethanol and the solvent was removed under reduced pressure to give an oily residue. The residue was dissolved in dry CH_2Cl_2 (5 mL) and boron trifluoride etherate (29.2 μL, 0.23 mmol) and triethylsilane (55.1 μL, 0.35 mmol) were added sequentially. The reaction mixture was left to stir at 25 °C for 3 h. The residue was subjected to flash column chromatography, eluting with 10–40% EtOAc/hexane, to furnish the desired cyclic *N*-methyl-β-amino acid **40** as an oil (18.9 mg, 65% yield); *m/z* HRMS (ESI, MeOH/AcOH): $[M+H]^+$, found 306.1713. $C_{17}H_{24}NO_4^+$ requires 306.1700; $[\alpha]_D^{24}$ +9.5 (*c* 0.6, MeOH); ν_{max} (NaCl)/cm^{-1} 3287–2860, 3032, 2932, 2862, 1697, 1450, 1412, 1319, 1188, 1142, 964, 733; δ_H (300 MHz, $CDCl_3$) (300 K) 7.33–7.28 (5H, m), 5.10 (2H, s), 4.23–4.16 (1H, m), 2.92–2.79 (4H, m), 1.84–1.47 (10H, m); δ_C (75 MHz, $CDCl_3$) 179.8, 155.7, 136.5, 128.0, 127.4, 127.3, 66.9, 60.1, 48.2, 31.9, 30.7, 28.2, 27.5, 24.7 (2).

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Supplementary data

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