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Diastereoselective synthesis of highly functionalized $\beta^{2,2,3}$-substituted amino acids from 4-substituted-1,3-oxazinan-6-ones

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ABSTRACT

1,3-Oxazinan-6-ones were used to generate substituted $\beta^{2,2,3}$-substituted amino acid derivatives. The enolates of 1,3-oxazinan-6-ones were trans-selectively intercepted with electrophiles. This alkylation was subsequently optimized for a one-pot dialkylation to form 5,5-disubstituted oxazinanones. The initial 5-monomethylated compounds could be enolized and then diastereoselectively intercepted with different electrophiles to form differentially 5,5-disubstituted products. The 5,5-dialkylated oxazinanones were then transformed to *N*-methyl $\beta^{2,2,3}$-substituted amino acids by reductive cleavage. Hydrolysis or solvolysis of the oxazinanones afforded $\beta^{2,2,3}$-substituted amino acids or esters, respectively. The chemistry thus provides access to a range of symmetrical and stereopure $\beta^{2,2,3}$-substituted amino acids and further establishes 1,3-oxazinan-6-ones as useful intermediates.

1. Introduction

Previously we reported studies concerned with formation and chemistry of 1,3-oxazolidin-5-ones including, importantly, their reductive cleavage to form *N*-methyl α-amino acids.[1–5] Subsequently, an Arndt–Eistert homologation of numerous α-amino acids allowed formation of novel 1,3-oxazinan-6-ones that were similarly reductively cleaved to give *N*-methyl and *N*-alkyl β-amino acids.[5–8]

These oxazinanones are versatile intermediates and they have potential to be manipulated in various ways that could provide efficient access to a structurally diverse group of β-amino acid derivatives for numerous applications. A key structural feature of the oxazinanones is the 5-methylene group, which is a site for enolization. Indeed, we have reported the successful enolization of 1,3-oxazinan-6-ones and the trans-selective formation of 5-methyl and 5-hydroxy derivatives.[7] The trans-selective methylation in that study was conducted using methyl iodide exclusively as the methyl source.

To further demonstrate the utility of the oxazinanone to gain access to highly substituted β-amino acids, the goal of the work described herein is to employ the oxazinanone to gain access to $\beta^{2,2,3}$-substituted amino acid residues. This class of residue has risen to prominence in recent years through the β-peptide conformation work of Seebach and others.[9–11] The $\beta^{2,2,3}$-substituted amino acid residues are of great interest in this work, because these residues have been shown to induce a specific type of helical conformation in β-peptides, that less substituted β-residues cannot.[9–11] It has been shown by Seebach and others that these β-peptides have immense potential to be of therapeutic relevance.[10–17]

However, gaining access to stereopure $\beta^{2,2,3}$-substituted residues has been synthetically challenging.[18] Herein we describe new conditions for the enolization and alkylation and dialkylation of oxazinanones,[7] that leads to the successful stereoselective generation of this important class of the $\beta^{2,2,3}$-substituted amino acid. And finally, access to β-amino acids is achieved through reductive and hydrolytic cleavages.

To gain access to the $\beta^{2,2,3}$-substituted amino acids, improvements in yields on our previous work[7] were required. This would allow for a more facile transition to the work leading into the stereoselective alkylations to gain access to the $\beta^{2,2,3}$-substituted amino acids.

To improve alkylation yields of the 1,3-oxazinan-6-one it was proposed to replace the iodide electrophile, used in previous studies, with the more reactive methyl triflate. In earlier studies (Scheme 1),[7] it was demonstrated that the methylation product

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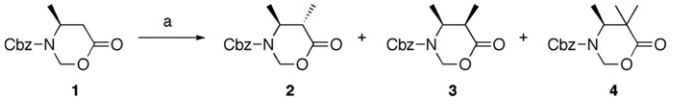
mixture consisted primarily of the monomethyl **2** (and **3** (minor)) and also small amounts of the dimethyl **4** adducts. It was postulated that the reaction (Scheme 1) could be optimized for exclusive formation of the dimethyl adduct **4**, preferably in a one-pot reaction. This methodology could then be extended to other disubstituted adducts, such as those derived from allylation and benzylation.

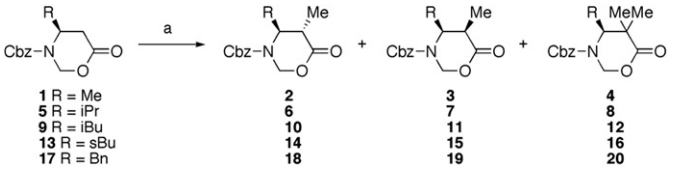


Scheme 1. 5-Alkylation of the 1,3-oxazinan-6-one. Reagents and conditions: (a) 1. Base, THF, −78 °C, 40 min; 2. MeI, 3 h at −78 °C, then warmed to −15 °C, satd aq NH_4Cl quench.

In a further extension of the work it was suggested adducts like **2** could be enolized a second time and then diastereoselectively intercepted with different electrophiles to form optically pure 5,5-disubstituted oxazinanones. And lastly, to demonstrate the utility of these oxazinanone intermediates, reductive cleavages, hydrolysis and solvolysis would be performed to give novel *N*-methyl $\beta^{2,2,3}$-substituted amino acids, $\beta^{2,2,3}$-substituted amino acids and $\beta^{2,2,3}$-substituted amino esters, respectively. Successful conduct of this group of transformations would significantly increase the range of β-amino acid compounds available for peptide and peptidomimetic synthesis.

2. Results and discussion

Previously, oxazinanones **1** were enolized with KHMDS (and other amide bases) and then methylated with methyl iodide (Scheme 1) in a mixture of THF and HMPA (or DMPU).[7] We sought to improve these yields by utilizing methyl triflate. Thus the first series of reactions in the current work employed the oxazinanones **1**, **5**, **9**, **13** and **17** to form the corresponding enolates with KHMDS (Scheme 2). Under the new conditions, the enolates were stirred at −78 °C for 40 min before addition of 1.5 equiv of methyl triflate. It is noteworthy that the solvent used in these studies was toluene, not THF as used in previous studies. Toluene was used to abrogate the reactivity of the triflate with THF.[20] The results of these experiments, aimed at forming the trans-monomethyl adducts **2**, **6**, **10**, **14**, **18**, are summarized in Table 1.



Scheme 2. 5-Methylation of 1,3-oxazinan-6-ones. Reagents and conditions: (a) 1. KHMDS, toluene or toluene/DMPU, −78 °C, 40 min; 2. MeOTf, 3 h at −78 °C, then warmed to −40 °C, satd aq NH_4Cl quench.

In most examples (Table 1) the mixed toluene/DMPU solvent gave better selectivity than toluene only for the trans-monomethyl adducts **2**, **6**, **10**, **14**, **18**. The exception is substrate **17** (entry 8), which gave the trans-monomethyl adduct **18** exclusively (47% yield) when toluene was the solvent. In comparison with the earlier methyl iodide reactions, the methyl triflate reactions are better according to several measures. Recovered starting material (6–15%) is generally less than that recovered from reactions with methyl iodide (18%).[7] Overall conversions with methyl triflate are generally higher, particularly when recovered starting material is taken into account. Further, the amounts of dimethyl adducts **4**, **8**, **12**, **16**, **20** (av 5%) are less than the yields of those adducts using methyl iodide (av 16%). However, the stereoselectivity of the methyl triflate reactions is no better than the earlier iodide reactions.

The results from this study prompted the use of alternate electrophiles, in particular the use of allyl bromide, benzyl bromide and ethyl triflate. The behavior of these electrophiles in oxazinanone alkylations would give valuable insight for the penultimate goal of this work, a study on the sequential stereoselective dialkylation of oxazinanones.

Ethylation of the oxazinanone **5** using ethyl triflate proceeded in a similar manner to the methylation reactions. A 49% yield of the 5-ethyl oxazinanone **25** was obtained (Table 2, entry 3) in comparison to methylation on the same substrate **5** where a 61% yield of **6**/**7** was obtained (Table 1, entry 3).

Table 2
5-Allylation, 5-benzylation and 5-ethylation of 1,3-oxazinan-6-ones

Entry	Substrate	Recovered substrate (%)	*trans* mono adduct (%)	5,5-Disubstituted adduct (%)
1	**1** R=Me	19	**21** 14	**22** 32
2	**1** R=Me	22	**23** t[a]	**24** 33
3	**5** R=^{i}Pr	20	**25** 49	**26** t[a]
4	**5** R=^{i}Pr	14	**27** 42	**28** 13
5	**5** R=^{i}Pr	15	**29** 29	**30** 14
6	**17** R=Bn	30	**31** 10	**32** 20
7	**13** R=^{s}Bu	28	**33** 23	**34** 27

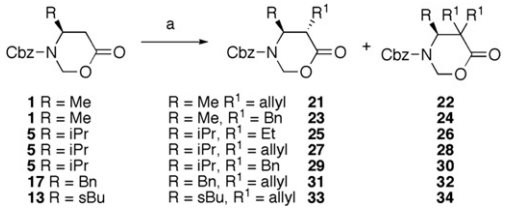
[a] t=trace.

The allylation and benzylation reactions were conducted in a similar manner as the monoethylation. Scheme 3 and Table 2 show that the allylation and benzylation reactions are not well controlled. There were three significant products in each reaction. These products were recovered starting material, the desired trans-mono adduct and the 5,5-diallyl or 5,5-dibenzyl adducts. The poor alkylation control is attributed to the increased acidity of the alpha H-5 proton of the mono benzylated or allyl adducts. This often led to more of the dialkylated product rather than the desired trans-mono adduct (Table 2).

Table 1
5-Methylation of 1,3-oxazinanones using methyl triflate

Entry	Substrate	Solvent	Substrate recovered (%)	Monomethyl yield (%) (*trans*/*cis*)	*trans*/*cis* Monomethyl ratio[a]	Dimethyl adduct (%)
1	**1** R=Me	PhMe	6	**2**/**3** (74)	1.7:1	**4** (-)
2	**1** R=Me	PhMe /DMPU 2:1	14	**2**/**3** (60)	4.7:1	**4** (5)
3	**5** R=^{i}Pr	PhMe	8	**6**/**7** (61)	4.8:1	**8** (5)
4	**5** R=^{i}Pr	PhMe /DMPU 2:1	6	**6**/**7** (53)	>19:1	**8** (7)
5	**9** R=^{i}Bu	PhMe	11	**10**/**11** (44)	12.5:1	**12** (5)
6	**9** R=^{i}Bu	PhMe /DMPU 2:1	9	**10**/**11** (37)	>19:1	**12** (7)
7	**13** R=^{s}Bu	PhMe /DMPU 2:1	15	**14**/**15** (42)	>19:1	**16** (10)
8	**17** R=Bn	PhMe	8	**18**/**19** (47)	>19:1	**20** (–)

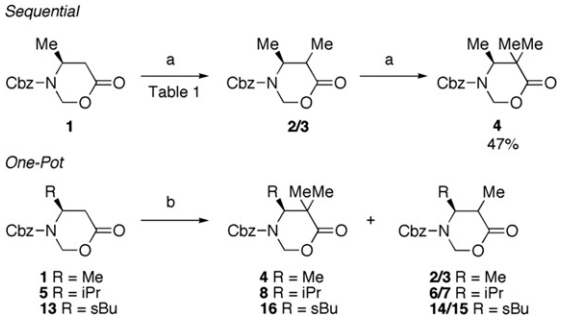
[a] *trans*/*cis* ratio was determined by examination of ^{1}H NMR signal integrations.



Scheme 3. 5-Allylation, 5-benzylation and 5-ethylation of 1,3-oxazinan-6-ones. Reagents and conditions: a) 1. KHMDS (1.1 equiv), toluene, −78 °C, 40 min; 2. Allyl bromide or BnBr or EtOTf (5 equiv), 3 h at −78 °C, then warmed to −40 °C, satd aq NH_4Cl quench.

The results of the monoalkylation study demonstrated that dialkylation products were observed in nearly all cases (Tables 1and 2). This observation suggests that oxazinanones are indeed good candidates for the penultimate goal of this work, a study on the sequential stereoselective dialkylation of the oxazinanone. However, before commencing the stereoselective dialkylations, it was proposed to perform several symmetrical dialkylations to give an indication of what yields might be expected.

The symmetrical dialkylation was planned in two ways. The 5-monoalkylated oxazinanone **1** could be enolized, followed by addition of the alkylating electrophile. Or alternatively, a one-pot dialkylation method could be done, starting from the non-substituted 5-oxazinanones **1**, **5** or **13** (Scheme 4).



Scheme 4. Sequential and one-pot 5,5-dimethylation of 1,3-oxazinan-6-ones. Reagent and conditions: (a) 1. KHMDS (1.1 equiv), toluene, −78 °C, 40 min; 2. MeOTf (1.5 equiv), 3 h at −78 °C, then warmed to −40 °C, satd aq NH_4Cl quench; (b) 1. KHMDS (1.1 equiv), toluene, −78 °C, 40 min; 2. MeOTf (1.5 equiv) at −78 °C, then warmed to −15 °C, 3. KHMDS (2.1 equiv), −78 °C, 40 min; 4. MeOTf (3.0 equiv), then warmed to −15 °C, satd aq NH_4Cl quench.

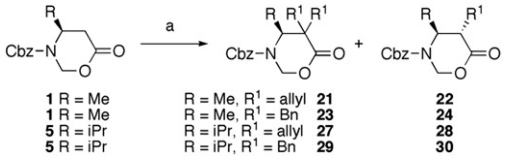
Firstly, the 5-monomethyl adducts **2**/**3** were enolized, by addition of base, and then quenched with methyl triflate, affording the dimethyl adduct **4** in 47% yield (Scheme 4). The overall yield from substrate **1** to adduct **4** was 27%.

The one-pot version of the dimethylation was attempted next. This reaction was conducted in the first part in the same way as for the 5-monomethylation. Then, instead of quenching the reaction (−15 °C) for work-up, the reaction was cooled to −78 °C and a further 2.1 equiv of KHMDS and 3.0 equiv of methyl triflate were added. Subsequent work-up in the usual manner, afforded the dimethyl adducts **8**, **12**, **16** (45–60% yield) (Table 3) from the starting materials **1**, **5** and **13**. It can be seen that the one-pot dimethylation still generated significant amounts of the trans- and cis-monomethyl adducts, but the efficiency of conversion to the dimethyl adducts **1**, **5** and **13** was higher than the sequential reaction scheme.

Table 3
One-pot dimethylation of 1,3-oxazinanones

Entry	Substrate	Dimethyl adduct (%)	*cis*/*trans* Monomethyl (%)
1	**1** R=Me	**8** (49)	**2**/**3** (25)
2	**5** R=^{i}Pr	**12** (45)	**6**/**7** (22)
3	**13** R=^{s}Bu	**16** (60)	**14**/**15** (8)

The ability of the oxazinanones to form enolates in one-pot dimethylation reactions invited the use of other electrophiles. Accordingly, Scheme 5 and Table 4 show use of allyl and benzyl reaction partners in diallylation and dibenzylation reactions.



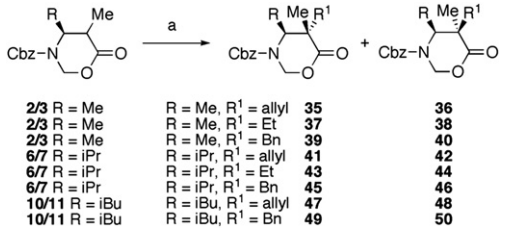
Scheme 5. One-pot diallylation and dibenzylation of 1,3-oxazinan-6-ones. Reagents and conditions: (a) 1. KHMDS (1.1 equiv), toluene, −78 °C, 40 min; 2. BnBr or allyl bromide (1.5 equiv) at −78 °C, then warmed to −15 °C, 3. KHMDS (2.1 equiv), −78 °C, 40 min; 4. BnBr or allyl bromide (3.0 equiv), then warmed to −15 °C, satd aq NH_4Cl quench.

Table 4
One-pot diallylation and dibenzylation of 1,3-oxazinan-6-ones

Entry	Substrate	Dialkylated adduct	*trans*-Mono adduct (%)
1	**1** R=Me	**22** (65)	**21** (3)
2	**5** R=^{i}Pr	**24** (51)	**23** (0)
3	**1** R=Me	**28** (53)	**27** (9)
4	**5** R=^{i}Pr	**30** (48)	**29** (7)

The one-pot diallylation and dibenzylation reactions proceeded smoothly, using both the alanine and valine derived oxazinanones, **1** and **5**, as the starting substrates. Even given the hindered nature of the second alkylation, in the one-pot process, very little mono adduct formation was observed (Table 4), presumably due to the increased acidity of the α-hydrogen once the mono-allylation and benzylation has occurred. This hypothesis is reinforced by the quantity of diallylated or dibenzylated product obtained in the monoalkylation reactions described in Table 2. Further to this theory was the observation that monoethylation of the oxazinanone **5** only resulted in a trace amount of the diethyl adduct **26** (Table 2). The successful dibenzylation and diallylation of the oxazinanones **1** and **5** was reassuring, and confirmed that the hindered sequential stereoselective dialkylation of the oxazinanone was feasible.

All the previous alkylation reactions laid the foundation for the last group of reactions in this study. In the last group, the formation of a chiral center at the 5-position of the oxazinanones was attempted using the monomethyl adducts **2**/**3**, **6**/**7** and **10**/**11**. Enolates were formed from these substrates under the established conditions and then they were quenched with a variety of electrophiles (allyl bromide, benzyl bromide and ethyl iodide or triflate). Scheme 6 and Table 5 show the results of these reactions.



Scheme 6. Stereoselective alkylations 5-methyl-1,3-oxazinan-6-ones. Reagents and conditions: (a) 1. KHMDS (1.1 equiv), toluene, −78 °Cfor 40 min; 2. electrophile (5 equiv), −78 °Cfor 3 h, then −15 °C, satd aq NH_4Cl quench.

Table 5
Stereoselective alkylations of 5-methyl-1,3-oxazinanones

Entry	Substrate	Electrophile	% Recovered substrate	Adduct ratio *trans*/*cis*[a]	% Yield *trans*+*cis*
1	**2**/**3** R=Me	Allyl-Br	12	**35**/**36** 13:1	56
2	**2**/**3** R=Me	EtOTf	9	**37**/**38** 13:1	56
3	**2**/**3** R=Me	BnBr	14	**39**/**40** 10:1	58
4	**6**/**7** R=^{i}Pr	Allyl-Br	14	**41**/**42** >19:1	47
5	**6**/**7** R=^{i}Pr	EtOTf	14	**43**/**44** >19:1	45
6	**6**/**7** R=^{i}Pr	BnBr	10	**45**/**46** >19:1	48
7	**10**/**11** R=^{i}Bu	Allyl-Br	15	**47**/**48** >19:1	47
8	**10**/**11** R=^{i}Bu	BnBr	8	**49**/**50** >19:1	50

[a] *trans*/*cis* ratio was determined by examination of ^{1}H NMR signal integrations.

The data for the preparation of the trans adducts was pleasing in that the reactions were highly stereoselective. The yields of these reactions were similar to those in previous reactions in the study. In Table 5 entries 1–3 where the 4-R group controlling the facial selectivity of the alkylations was a methyl group, the diastereoselectivity was the lowest (10:1–13:1). Presumably the steric bulk of the methyl is the least of all the examples trialled and so the facial bias is not high leading to a few percent of the cis adducts **36**, **38** and **40**. The remaining entries 4–8 all showed >19:1 selectivity for the trans adducts **41**, **43**, **45**, **47** and **49** as assessed by NMR signal integration.

In order to unambiguously assign the diastereoselectivity of the alkylation reactions depicted in Scheme 6, an X-ray crystal structure was acquired on compound **49** (Fig. 1). The X-ray crystallography study confirmed that the amino acid derived R group does control facial selectivity and the trans product is therefore obtained exclusively.

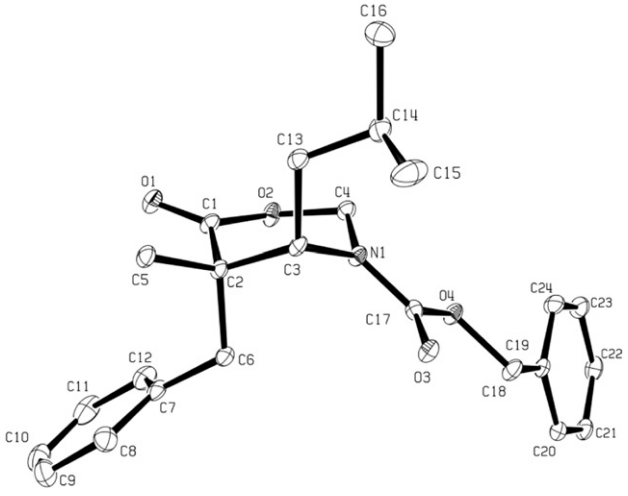


Fig. 1. Thermal ellipsoid plot for **49**. Ellipsoids are at the 20% probability level.

The selectivity obtained can be explained mechanistically, as depicted by Fig. 2. The Houk trajectory suggests the electrophile approaches the molecule at an angle of 106°, near perpendicular to the enolate plane.[19] This is due to the interaction of the highest occupied molecular orbital (HOMO) of the enolate with the lowest unoccupied molecular orbital (LUMO) of the electrophile. Furthermore, the electrophile is tilted at a right angle to the enolate plane, due to the repulsive interaction between the electrophile LUMO and the oxygen atom of the enolate. This also signifies the electrophile starts its approach from the opposite side of the oxazinanone ring to the carbonyl group. Essentially, the electrophile

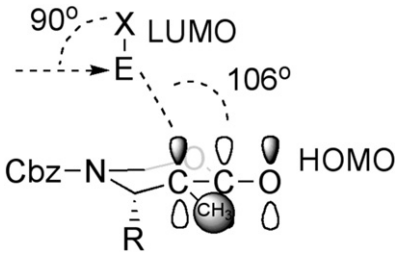
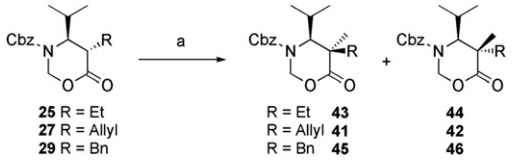


Fig. 2. Illustration of the angle of approach of the electrophile to the oxazinanone enolate.[19]

sweeps across the face of the oxazinanone ring. As one face of the ring is hindered by the substituent at C-4, preferential approach occurs from the opposite face giving excellent *anti* selection as shown in Fig. 2. The 5-methyl substituent is perpendicular to the plane of the oxazinanone ring, and takes no part in the determination of facial approach of the electrophile. When the 4-R group is larger than a methyl, such as compounds **41**, **43**, **45**, **47** and **49** exclusive facial selectivity is observed.

Given the exclusive trans selectivity at the 5-position, when the 4-R group is larger than a methyl, in the next set of reactions it was decided to ascertain the effect on stereoselectivity, if the starting substrates were the 5-mono-allyl **27**, benzyl **29** and ethyl **25** oxazinanones. In these instances the electrophile being used was methyl triflate (Scheme 7). However, when these reactions were conducted, in all instances poor selectivity was observed (Table 6). trans Selectivity was preferred, as determined by a comparison of the ^{1}H NMR spectrum from previously formed compounds **41**, **43** and **45**. The lack of selectivity with this set of reactions was in direct contrast to results obtained from the study shown in Scheme 6 and Table 5.



Scheme 7. Reverse alkylation sequence using methyl triflate. Reagents and conditions: (a) 1. KHMDS (1.1 equiv), toluene, −78 °Cfor 40 min; 2. Methyl triflate (5 equiv), −78 °Cfor 3 h, then −15 °C, satd aq NH_4Cl quench.

Table 6
Reverse alkylation sequence of 5-mono substituted oxazinanones using methyl triflate

Entry	Substrate	% Recovered substrate	Adduct ratio *trans*/*cis*	% Yield *trans*+*cis*
1	**25** R=Et	8	**43**/**44** 1.8:1	61
2	**27** R=allyl	11	**41**/**42** 1.3:1	60
3	**29** R=Bn	10	**45**/**46** 1.1:1	57

It is proposed that little selectivity is observed in these alkylations with methyl triflate (Scheme 7), due to the interplay of the 5-substituent being forced onto the opposite face to the 4-R group by steric repulsion. Hindrance is now observed at the trans face as well as the cis face. This results in repulsion of the electrophile at the trans and cis faces. The slight trans selectivity that was observed was a result of the hindrance of the 4-R substituent (Fig. 3).

From the reactions performed on 5-mono-allyl **27**, benzyl **29** and ethyl **25** oxazinanones and using methyl triflate as an electrophile (Scheme 7), it is now clear that in order to obtain the 5,5-substituted oxazinanones in high stereoselectivity the route depicted in Scheme 6 is preferred.

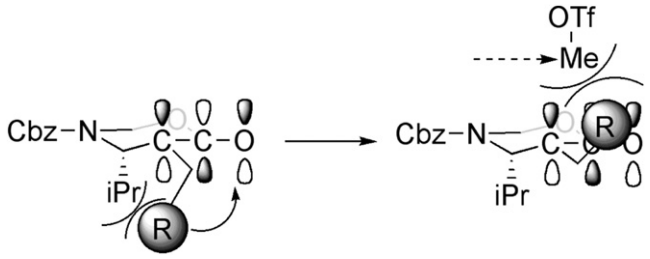
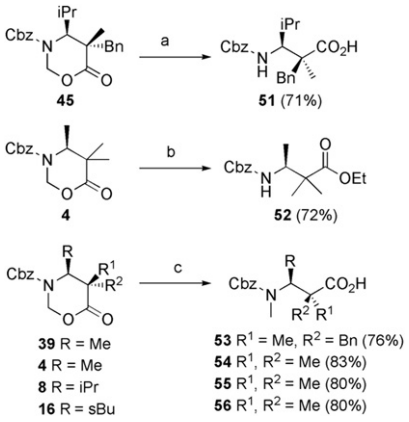


Fig. 3. Mechanistic rationale for the poor selectivity of alkylation, using methyl triflate.[19]

The oxazinanone has previously been shown to be a useful synthon for producing a variety of β-amino acid residues.[1,5–8] To further demonstrate these transformations can also be applied to the highly substituted oxazinanones produced in this study, a small variety of ring opening transformations were performed to demonstrate access to $\beta^{2,2,3}$-substituted amino acid derivatives.

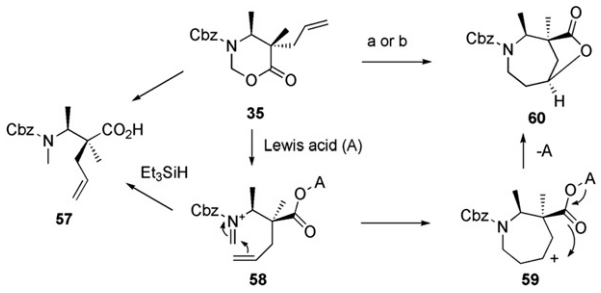
Hydrolysis of the oxazinanone **45** smoothly formed the desired $\beta^{2,2,3}$-substituted amino acid **51** in good yield (71%). The $\beta^{2,2,3}$-substituted amino ethyl ester **52** was also obtained in good yield (72%) by solvolysis of the oxazinanone **4** using sodium hydrogen carbonate in ethanol at reflux (Scheme 8).



Scheme 8. Transformations of the oxazinanone to generate the corresponding $\beta^{2,2,3}$-substituted amino acid derivatives. Reagents and conditions: (a) 4 N LiOH, H_2O/THF, 20 °C, 6 h; (b) $NaHCO_3$, EtOH, reflux, 20 h; (c) $BF_3{\cdot}Et_2O$, Et_3SiH, CH_2Cl_2, 25 °C, 6–20 h.

Previous experience has shown that reductive cleavage of the α-amino acid derived oxazolidinones can also be applied to the homologous oxazinanones.[1,5–8] However, in unpublished work, studies have found that the reductive cleavage of an α,α-disubstituted oxazolidinone does not proceed smoothly and negligible yields of *N*-methyl α,α-disubstituted α-amino acid are obtained. A mechanistic study is currently being undertaken to determine why low yields occur in this circumstance. These results will be reported elsewhere. Based upon this finding it was proposed that the reductive cleavage of the α,α-disubstituted oxazinanone would also be troublesome. However, this was not the case, the reductive cleavage of the α,α-disubstituted compounds **39**, **4**, **8**, and **16**, proceeded smoothly, giving high yields of the *N*-methyl $\beta^{2,2,3}$-residues **53**–**56** (76–83%) (Scheme 8).

However, when the α-substitution was an allyl group (**35**) the reductive cleavage to the expected *N*-methyl residue **57** was not observed. The major product isolated was an intriguing bicyclic adduct **60**. The unexpected formation of this bicyclic lactone **60** can be explained mechanistically as shown in Scheme 9. The addition of the Lewis acid boron trifluoride etherate commits the oxazinanone **35** to ring open and form the iminium ion **58**. In usual reductive



Scheme 9. Reductive cleavage product and mechanistic rationale. Reagents and conditions: (a) $BF_3{\cdot}Et_2O$, Et_3SiH, CH_2Cl_2, 25 °C, 20 h, 65%; (b) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 25 °C, 6 h, 77%.

cleavage circumstances the iminium ion **58** is intercepted by a nucleophilic hydride source, such as triethylsilane, to form the *N*-methyl residue **57**. However, in this instance the more nucleophilic alkene attacks the iminium ion to form a cationic aza nonyl species **59**. The cation **59** is then intercepted by the carboxylic moiety to form the oxa-3-azabicyclo[4.2.1]nonan-8-one **60**. The facial preference of the cation exclusively affords the 1*R*,2*S*,6*R*-isomer **60** in a 65% yield (Scheme 9). Only a trace amount of the *N*-methyl product **57** was obtained. The mechanism leading to the bicycle **60** does not require triethylsilane. The reaction was repeated in the absence of triethylsilane and afforded the bicycle **60** in 77% yield. A study is now being undertaken to ascertain the full synthetic potential of this cyclization and also the application of the lactone adduct products.

3. Conclusions

In conclusion, elaboration of previous oxazinanone enolization work has allowed the synthesis of highly substituted β-amino acids. The symmetrical 5,5-substituted analogues could be obtained via either alkylation of the 5-methyl oxazinanone or the higher yielding one-pot dialkylation of 5,5-unsubstituted oxazinanones. Differential alkylation of the 5-methyl oxazinanone has allowed exclusive formation of the trans diastereoisomer. The trans stereochemistry was unambiguously confirmed by obtaining an X-ray crystal structure. The symmetrical and unsymmetrical 5,5-substituted analogues were then transformed into a variety of $\beta^{2,2,3}$-substituted amino acid derivatives. The methodology described here further establishes the 5-oxazinanone as a useful synthon to gain access to functionalized β-amino acids. Furthermore, the $\beta^{2,2,3}$-substituted residues produced from this work, have application in the increasingly important field of therapeutic β-peptides.

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. 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 (D)-chloroform at 300 K unless otherwise stated on a 300 MHz spectrometer. Data for ^{1}H NMR 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 (hertz). Infrared spectra were recorded on a Fourier transform IR spectrometer using a thin film NaCl plate. 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 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.

4.2. Synthesis

4.2.1. Synthesis of 5-alkylated 1,3-oxazinan-6-ones

. 4.2.1.1. General procedure A. The oxazinanone (0.50 mmol) was dissolved in freshly distilled dry toluene (4.0 mL) and the solution was cooled to −78 °C under an argon atmosphere. Then KHMDS (1.1 equiv, 1.10 mL, 0.55 mmol of a 0.50 M solution in toluene) was added dropwise and the solution was left to stir at −78 °C for 40 min. Methyl triflate (0.184 mL, 1.5 equiv, 0.75 mmol) was 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 mL). The solution was diluted with ethyl acetate (20 mL) and washed with water (20 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give a yellow oily residue. The oil was subjected to column chromatography, eluting with 5–20% ethyl acetate/hexane.

*4.2.1.1.1. (4S,5S)-N-Benzyloxycarbonyl-4,5-dimethyl-1,3-oxazinan-6-one **2**, (4S,5R)-N-benzyloxycarbonyl-4,5-dimethyl-1,3-oxazinan-6-one **3** and (4S)-N-benzyloxycarbonyl-4,5,5-trimethyl-1,3-oxazinan-6-one **4**.* General procedure A was followed for the alkylation of oxazinanone **1** (125 mg, 0.50 mmol) to obtain starting material **1** (7.5 mg, 6% recovery) and a mixture of diastereoisomers **2**/**3** as a colorless oil in a 1.7:1 (*trans*/*cis*) ratio (97 mg, 74%), with spectra identical to those of an authentic sample.[7]

General procedure A was followed for the alkylation of oxazinanone **1** (125 mg, 0.50 mmol) with a toluene/DMPU mixture (2:1, 4.0 mL) as the solvent to afford starting material **1** (17.5 mg, 14% recovery), a mixture of diastereoisomers **3**/**4** as a colorless oil in a 16.5:1 (*trans*/*cis*) ratio (8 mg, 62%) and 5,5-disubstituted oxazinanone **4** (6.9 mg, 5%).

*4.2.1.1.2. (4S,5S)-N-Benzyloxycarbonyl-4-isopropyl-5-methyl-1,3-oxazinan-6-one **6**, (4S,5R)-N-benzyloxycarbonyl-4-isopropyl-5-methyl-1,3-oxazinan-6-one **7** and (4S)-N-benzyloxycarbonyl-4-isopropyl-5,5-dimethyl-1,3-oxazinan-6-one **8**.* General procedure A was followed for the alkylation of oxazinanone **5** (139 mg, 0.50 mmol) to afford starting material **5** (11.0 mg, 8% recovery), a mixture of diastereoisomers **6**/**7** as a colorless oil in a 4.7:1 (*trans*/*cis*) ratio (89.0 mg, 61% yield), and disubstituted oxazinanone **8** (7.6 mg, 5%) with spectra identical to those of an authentic sample.[7]

The general procedure A was followed for the alkylation of oxazinanone **5** (139 mg, 0.50 mmol) with a toluene/DMPU mixture (2:1, 4.0 mL) as the solvent to afford starting material **5** (8.30 mg, 6% recovery), the oxazinanone **6**/**7** as a colorless oil in a >19:1 (*trans*/*cis*) ratio (77.0 mg, 53%) and 5,5-disubstituted oxazinanone **8** (10.7 mg, 7%).

*4.2.1.1.3. (4S,5S)-N-Benzyloxycarbonyl-4-isobutyl-5-methyl-1,3-oxazinan-6-one **10**, (4S,5R)-N-benzyloxycarbonyl-4-isobutyl-5-methyl-1,3-oxazinan-6-one **11** and (4S)-N-benzyloxycarbonyl-4-isobutyl-5,5-dimethyl-1,3-oxazinan-6-one **12**.* The general procedure A was followed for the alkylation of oxazinanone **9** (146 mg, 0.50 mmol) to afford starting material **9** (16 mg, 11% recovery), a mixture of diastereoisomers **10**/**11** as a colorless oil in a 12.5:1 (*trans*/*cis*) ratio (67.0 mg, 44%), and 5,5-disubstituted oxazinanone **12** (8.0 mg, 5%), with spectra identical to those of an authentic sample.[7]

The general procedure A was followed for the alkylation of oxazinanone **9** (146 mg, 0.50 mmol) with a toluene/DMPU mixture (2:1, 4.0 mL) as the solvent to afford starting material **9** (13.0 mg, 9% recovery), the oxazinanones **10**/**11** as a colorless oil in a >19:1 (*trans*/*cis*) ratio (56.0 mg, 37%) and 5,5-disubstituted oxazinanone **12** (11.2 mg, 7%).

*4.2.1.1.4. (4S,5S)-N-Benzyloxycarbonyl-4-benzyl-5-methyl-1,3-oxazinan-6-one **18**.* The general procedure A was followed for the alkylation of oxazinanone **17** (163 mg, 0.50 mmol) to afford starting material **17** (13.0 mg, 8% recovery) and the oxazinanones **18**/**19** as a colorless oil in a >19:1 (*trans*/*cis*) ratio (8.0 mg, 47%), with spectra identical to those of an authentic sample.[7]

*4.2.1.1.5. (4S,5S)-N-Benzyloxycarbonyl-(4R)-sec-butyl-5-methyl-1,3-oxazinan-6-one **14** and (4S,5S)-N-benzyloxycarbonyl-(4R)-sec-butyl-5,5-dimethyl-1,3-oxazinan-6-one **16**.* The general procedure A was followed for the alkylation of oxazinanone **13** (146 mg, 0.50 mmol) with a toluene/DMPU mixture (2:1, 4.0 mL) as the solvent to afford starting material **13** (22.0 mg, 15% recovery). The oxazinanones **14**/**15** was isolated as a colorless oil in a >19:1 (*trans*/*cis*) ratio (64.0 mg, 42%). m/z HRMS (EI): found [M^+], 305.1625; $C_{17}H_{23}NO_4$ requires [M^+], 305.1627; R_f (20% EtOAc/hexane) 0.39; $[\alpha]_D^{26}$ +67.5 (*c* 0.7, MeOH); ν_{max} (NaCl)/cm^{-1} 2968, 2939, 1756, 1705, 1697, 1455, 1408, 1253, 1132, 1076, 1001, 920; ^1H NMR (300 MHz, $CDCl_3$) (325 K): δ 7.38 (5H, s), 5.86 (1H, br s), 5.14 (2H, s), 4.96 (1H, d, *J* 10.6 Hz), 3.81 (1H, br s), 2.76 (1H, dd, *J* 6.8, 13.6 Hz), 1.78–1.65 (1H, m), 1.52 (1H, br s), 1.31 (3H, d, *J* 6.7 Hz), 1.15–1.03 (1H, m), 0.99 (3H, d, *J* 6.3 Hz), 0.89 (3H, t, *J* 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) (325 K): δ 172.5, 154.8, 135.1, 128.2, 128.1, 127.8, 72.5, 67.9, 60.3, 38.0, 37.4, 24.1, 15.7, 15.2, 11.3.

The oxazinanone **16** was isolated as a colorless oil (16.0 mg, 10%). m/z HRMS (EI): found [M^+], 319.1782; $C_{18}H_{25}NO_4$ requires [M^+], 319.1784; R_f (20% EtOAc/hexane) 0.49; $[\alpha]_D^{25}$ +13.0 (*c* 1.0, MeOH); ν_{max} (NaCl)/cm^{-1} 2967, 2934, 1748, 1709, 1454, 1418, 1331, 1244, 1099, 1013, 966, 908; ^1H NMR (300 MHz, $CDCl_3$) (325 K): δ 7.34 (5H, s), 5.94 (1H, br s), 5.21–5.18 (3H, m), 4.05 (1H, br s), 1.75 (1H, br s), 1.57–1.45 (1H, m), 1.29 (6H, s), 1.15–1.03 (1H, m), 1.04 (3H, d, *J* 6.3 Hz), 0.89 (3H, t, *J* 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) (325 K): δ 174.2, 154.4, 135.4, 128.2, 128.0, 127.7, 74.7, 67.8, 63.2, 42.5, 36.6, 27.9, 24.7, 21.3, 16.6, 12.3.

4.2.2. 5-Ethyl/benzyl/allylation of 1,3-oxazinan-6-ones.

4.2.2.1. General procedure B. The oxazinanone (0.50 mmol) was dissolved in dry toluene/DMPU mixture (2:1, 4.0 mL) and the solution was cooled to −78 °C under an argon atmosphere. Then KHMDS (1.1 equiv, 1.10 mL, 0.55 mmol, a 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 equiv, 2.50 mmol) was 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 mL). The solution was diluted with ethyl acetate (20 mL) and washed with water (20 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give a yellow oily residue. The oil was subjected to column chromatography, eluting with 5–20% ethyl acetate/hexane.

*4.2.2.1.1. (4S,5S)-N-Benzyloxycarbonyl-4-methyl-5-allyl-1,3-oxazinan-6-one **21**, and (4S)-N-benzyloxycarbonyl-4-methyl-5,5-diallyl-1,3-oxazinan-6-one **22**.* The general procedure B was followed for the alkylation of oxazinanone **1** (125 mg, 0.50 mmol) with allyl bromide (216 μL, 2.50 mmol) as the electrophile to afford starting material **1** (23.7 mg, 19% recovery). The oxazinanone **21** was isolated as a colorless oil (20.2 mg, 14% yield). *m*/*z* HRMS (ESI, MeOH/AcOH): $[M+H]^+$, found 290.1387. $C_{16}H_{19}NO_4$ requires 290.1387; R_f (20% EtOAc/hexane) 0.24; $[\alpha]_D^{25}$ +144.0 (*c* 0.22, MeOH); ν_{max} (NaCl)/cm^{-1} 3077, 3034, 2977, 2917, 1761, 1717, 1699, 1415, 1334, 1253, 1130, 998, 916; ^{1}H NMR (300 MHz, $(CD_3)_2CO$) (300 K): δ 7.41–7.31 (5H, m), 5.95–5.81 (1H, m), 5.75 (1H, d, *J* 10.9 Hz), 5.31 (1H, d, *J* 11.1 Hz), 5.18 (2H, q, J_{AB} 12.6 Hz), 5.06 (2H, dd, *J* 13.2, 10.2 Hz), 3.93 (1H, dt, *J* 6.0, 10.2 Hz), 2.85 (1H, dt, *J* 6.0, 10.2 Hz), 2.45 (2H, dd, *J* 6.0, 13.2 Hz), 1.37 (3H, d, *J* 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) (300 K): δ 170.9, 153.4, 135.2, 133.9, 128.3, 128.1, 127.8, 117.8, 70.4, 67.7, 49.8, 46.0, 31.7, 15.3.

The oxazinanone **22** was isolated as a colorless oil (52.7 mg, 32% yield). *m*/*z* HRMS (ESI, MeOH/AcOH): $[M+H]^+$, found 330.1700. $C_{19}H_{23}NO_4$ requires 330.1700; R_f (20% EtOAc/hexane) 0.39; $[\alpha]_D^{24}$ +63.5 (*c* 0.52, MeOH); ν_{max} (NaCl)/cm^{-1} 3077, 3034, 2979, 2939 (C–H), 1750, 1717 (C=O), 1699, 1695 (C=C), 1417, 1329, 1275, 1250, 1146, 1107, 1057, 1001, 922; ^{1}H NMR (300 MHz, $CDCl_3$) (325 K): δ 7.34 (5H, s), 5.86 (1H, d, *J* 9.6 Hz), 5.79–5.60 (2H, m), 5.25–5.14 (5H, m), 5.06 (2H, dd, *J* 10.8, 18.3 Hz), 4.34 (1H, d, *J* 6.3 Hz), 2.68 (1H, dd, *J* 7.2, 15.0 Hz), 2.46–2.31 (2H, m), 2.23 (1H, dd, *J* 7.2, 15.0 Hz), 1.31 (3H, d, *J* 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) (325 K): δ 171.0, 153.0, 135.4, 131.7, 131.1, 128.2, 128.1, 127.7, 119.5, 118.8, 72.3, 67.7, 51.5, 50.3, 38.7, 35.0, 14.8.

*4.2.2.1.2. (4S)-N-Benzyloxycarbonyl-4-methyl-5,5-dibenzyl-1,3-oxazinan-6-one **24**.* The general procedure B was followed for the alkylation of oxazinanone **1** (125 mg, 0.50 mmol) with benzyl bromide (297 μL, 2/50 mmol) as the electrophile to afford starting material **1** (27.5 mg, 22% recovery) and trace amount of the oxazinanone **23**. The oxazinanone **24** was isolated as a white solid (70.9 mg, 33% yield). *m*/*z* HRMS (ESI, MeOH/AcOH): $[M+H]^+$, found 430.2013. $C_{27}H_{27}NO_4$ requires 430.2013; mp 103–105 °C; requires 430.2013; mp 103–105 °C; R_f (20% EtOAc/hexane) 0.32 R_f (20% EtOAc/hexane) 0.32; $[\alpha]_D^{25}$ +83.5 (*c* 0.48, MeOH); ν_{max} (NaCl)/cm^{-1} 3031, 2961, 2935, 1750, 1713, 1496, 1419, 1346, 1248, 1140, 1080, 1031, 1003, 913; ^{1}H NMR (300 MHz, $CDCl_3$) (300 K): δ 7.33–7.14 (15H, m), 5.65 (1H, br s), 5.28 (1H, d, *J* 10.2 Hz), 5.08 (1H, d, *J* 12.3 Hz), 5.06 (1H, d, *J* 12.3 Hz), 4.52 (1H, d, *J* 6.8 Hz), 3.26 (2H, dd, *J* 13.5, 14.4 Hz), 2.99 (1H, d, *J* 14.6 Hz), 2.78 (1H, d, *J* 14.6 Hz), 1.36 (3H, d, *J* 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) (300 K): δ 171.1, 154.4, 135.8, 135.2, 135.1, 130.1, 129.9, 128.3, 128.2, 127.9, 127.7, 126.9, 126.7, 73.1, 67.6, 52.5, 51.0, 41.3, 38.5, 15.3.

*4.2.2.1.3. (4S,5S)-N-Benzyloxycarbonyl-4-isopropyl-5-ethyl-1,3-oxazinan-6-one **25**.* The general procedure B was followed for the alkylation of oxazinanone **5** (139 mg, 0.50 mmol) with EtOTf (133 mg, 1.5 equiv) as the electrophile to afford starting material **5** (27.8 mg, 20% recovery) and a trace amount of oxazinanone **26**. The oxazinanone **25** was isolated as a colorless oil (74.8 mg, 49% yield). *m*/*z* HRMS (ESI, MeOH/AcOH): $[M+Na]^+$ found 328.1508. $C_{17}H_{23}NO_4$ requires 328.1519; R_f (20% EtOAc/hexane) 0.36; $[\alpha]_D^{25}$ +116.1 (*c* 0.5, MeOH); ν_{max} (NaCl)/cm^{-1} 2965, 2936, 2878, 1755, 1713, 1466, 1408, 1316, 1252, 1163, 1128, 1020, 993; ^{1}H NMR (300 MHz, $CDCl_3$) (300 K): δ 7.39 (5H, s), 5.89 (1H, br s), 5.22–5.12 (2H, m), 4.96 (1H, d, *J* 10.5 Hz), 3.94 (1H, br s), 2.57 (1H, dd, *J* 6.0, 12.0 Hz), 1.96–1.89 (1H, m), 1.77–1.71 (2H, m), 0.94–0.86 (9H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (300 K): δ 171.4, 154.8, 135.3, 128.2, 128.1, 127.7, 72.3, 67.9, 58.2, 44.9, 30.3, 23.5, 19.6, 17.2, 11.3.

*4.2.2.1.4. (4S,5S)-N-Benzyloxycarbonyl-4-isopropyl-5-allyl-1,3-oxazinan-6-one **27**, and (4S)-N-benzyloxycarbonyl-4-isopropyl-5,5-diallyl-1,3-oxazinan-6-one **28**.* The general procedure B was followed for the alkylation of oxazinanone **5** (139 mg, 0.50 mmol) with allyl bromide (216 μL, 2.50 mmol) as the electrophile to afford starting material **5** (19.5 mg, 14% recovery). The oxazinanone **27** was isolated as a colorless oil (64.1 mg, 42% yield). *m*/*z* HRMS (EI): found $[M^+]$, 317.1621; $C_{18}H_{23}NO_4$ requires $[M^+]$, 317.1627; R_f (10% EtOAc/hexane) 0.22; $[\alpha]_D^{25}$ +157.3 (*c* 1.0, MeOH); ν_{max} (NaCl)/cm^{-1} 3068, 3034, 2966, 2934, 2878, 1756, 1717, 1695, 1404, 1316, 1251, 1156, 1124, 1026, 991, 922; ^{1}H NMR (300 MHz, $CDCl_3$) (325 K): δ 7.30 (5H, s), 5.92 (1H, d, *J* 10.2 Hz), 5.85–5.74 (1H, m), 5.17 (2H, s), 5.08 (2H, d, *J* 11.7 Hz), 4.95 (1H, d, *J* 10.2 Hz), 3.96 (1H, br s), 2.71 (1H, dd, *J* 5.7, 11.7 Hz), 2.44 (2H, dd, *J* 6.9, 12.6 Hz), 1.99–1.88 (1H, m), 1.00 (3H, d, *J* 6.6 Hz), 0.91 (3H, d, *J* 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) (325 K): δ 170.5, 154.6, 135.3, 134.1, 128.2, 128.0, 127.7, 117.9, 72.4, 67.9, 57.7, 43.4, 34.3, 30.3, 19.6, 17.2.

The oxazinanone **28** was isolated as a colorless oil (23.2 mg, 13% yield). *m*/*z* HRMS (EI): found $[M^+]$, 357.1924; $C_{21}H_{27}NO_4$ requires $[M^+]$, 357.1940; R_f (10% EtOAc/hexane) 0.40; $[\alpha]_D^{23}$ +36.0 (*c* 0.5, MeOH); ν_{max} (NaCl)/cm^{-1} 3077, 3035, 2966, 1749, 1714, 1695, 1694, 1416, 1315, 1269, 1245, 1153, 1102, 994, 918; ^{1}H NMR (300 MHz, $(CD_3)_2CO$) (320 K): δ 7.39–7.31 (5H, m), 5.90–5.77 (2H, m), 5.73–5.59 (1H, m), 5.40 (1H, d, *J* 9.9 Hz), 5.23–5.14 (4H, m), 5.03 (2H, d, *J* 13.8 Hz), 4.22 (1H, d, *J* 4.5 Hz), 2.69 (1H, dd, *J* 5.7, 15.0 Hz), 2.45 (1H, dd, *J* 7.2, 14.4 Hz), 2.40–2.22 (3H, m), 1.01 (3H, d, *J* 6.8 Hz), 0.97 (3H, d, *J* 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) (320 K): δ 171.3, 154.2, 135.3, 131.4, 131.3, 128.3, 128.1, 127.8, 119.8, 119.3, 75.2, 67.8, 59.8, 48.3, 39.1, 34.6, 28.9, 20.7, 17.9.

*4.2.2.1.5. (4S,5S)-N-Benzyloxycarbonyl-4-isopropyl-5-benzyl-1,3-oxazinan-6-one **29**, and (4S)-N-benzyloxycarbonyl-4-isopropyl-5,5-dibenzyl-1,3-oxazinan-6-one **30**.* The general procedure B was followed for the alkylation of oxazinanone **5** (139 mg, 0.50 mmol) with benzyl bromide (297 μL, 2.50 mmol) as the electrophile to furnish starting material **5** (20.8 mg, 15% recovery). The oxazinanone **29** was isolated as a colorless oil (53.3 mg, 29% yield). *m*/*z* HRMS (EI): found $[M^+]$, 367.1776; $C_{22}H_{25}NO_4$ requires $[M^+]$, 367.1784; R_f (10% EtOAc/hexane) 0.20; $[\alpha]_D^{25}$ +128.0 (*c* 0.25, MeOH); ν_{max} (NaCl)/cm^{-1} 3030, 2964, 2930, 2877, 1749, 1706, 1404, 1311, 1250, 1151, 1123, 1020, 993; ^{1}H NMR (300 MHz, $CDCl_3$) (325 K): δ 7.39–7.08 (10H, m), 5.96 (1H, d, *J* 10.4 Hz), 5.18 (2H, s), 4.99 (1H, d, *J* 10.4 Hz), 3.91 (1H, br s), 3.17 (1H, dd, *J* 4.8, 13.2 Hz), 2.92–2.77 (2H, m), 1.94–1.83 (1H, m), 0.86 (3H, d, *J* 6.6 Hz), 0.81 (3H, d, *J* 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) (325 K): δ 170.6, 154.6, 137.9, 135.2, 128.8, 128.2, 128.1, 128.0, 127.8, 126.3, 72.4, 68.1, 57.7, 45.8, 36.6, 29.7, 19.6, 17.2.

The oxazinanone **30** was isolated as a colorless oil (32.0 mg, 14% yield). *m*/*z* HRMS (EI): found $[M^+]$, 457.2223; $C_{29}H_{31}NO_4$ requires $[M^+]$, 457.2253; R_f (10% EtOAc/hexane) 0.26; $[\alpha]_D^{25}$ +64.7 (*c* 0.7, MeOH); ν_{max} (NaCl)/cm^{-1} 3030, 2967, 2937, 1746, 1706, 1496, 1454, 1419, 1338, 1246, 1159, 1136, 1082, 995, 912; ^{1}H NMR (300 MHz, $CDCl_3$) (325 K): δ 7.31–7.06 (15H, m), 5.58 (1H, br s), 5.21 (1H, d, *J* 9.6 Hz), 5.07–4.98 (2H, m), 4.46 (1H, br s), 3.35 (2H, dd, *J* 6.9, 14.4 Hz), 3.12 (1H, d, *J* 14.4 Hz), 2.70 (1H, d, *J* 14.4 Hz), 2.44–2.38 (1H, m), 1.07 (3H, d, *J* 6.8 Hz), 0.98 (3H, d, *J* 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) (325 K): δ 171.1, 154.0, 136.1, 135.3, 130.2, 130.1, 128.1, 128.0, 127.9, 127.6, 126.8, 126.5, 73.7, 67.6, 59.2, 52.4, 42.3, 38.7, 29.1, 21.4, 18.3.

*4.2.2.1.6. (4S,5S)-N-Benzyloxycarbonyl-4-benzyl-5-allyl-1,3-oxazinan-6-one **31** and (4S)-N-benzyloxycarbonyl-4-benzyl-5,5-diallyl-1,3-oxazinan-6-one **32**.* General procedure B was followed for the alkylation of oxazinanone **17** (289 mg, 0.89 mmol) with allyl bromide (385 μL, 4.45 mmol) as the electrophile to afford starting material **17** (86.9 mg, 30% recovery). The oxazinanone **31** was isolated as a colorless oil (32.5 mg, 10% yield). *m*/*z* HRMS (EI): found $[M^+]$, 365.1627; $C_{22}H_{23}NO_4$ requires $[M^+]$, 365.1627; R_f (20% EtOAc/hexane) 0.43; $[\alpha]_D^{25}$ +140 (*c* 0.8, MeOH); ν_{max} (NaCl)/cm^{-1} 3063, 3030, 2943, 2924, 1745, 1718, 1693, 1454, 1418, 1331, 1254, 1029, 999; ^{1}H NMR (300 MHz, $CDCl_3$) (325 K): δ 7.38–7.07 (10H, m), 5.96–5.82 (1H, m), 5.68 (1H, d, *J* 9.6 Hz), 5.22–5.05 (4H, m), 4.34

(1H, d, *J* 10.8 Hz), 4.27–4.25 (1H, m), 3.19 (1H, dd, *J* 4.2, 14.0 Hz), 2.88 (1H, dd, *J* 4.2, 14.1 Hz), 2.65–2.58 (1H, m), 2.54–2.42 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (325 K): δ 170.8, 153.7, 135.3, 135.1, 133.9, 129.6, 128.3, 128.0, 127.7, 127.5, 126.8, 117.8, 71.6, 67.8, 53.5, 42.2, 36.9, 31.8.

The oxazinanone **32** was isolated as a colorless oil (72.2 mg, 20% yield). *m*/*z* HRMS (EI): found [M^+], 405.1934; $C_{25}H_{27}NO_4$ requires [M^+], 405.1940; R_f (20% EtOAc/hexane) 0.57; $[\alpha]_D^{24}$ +70.0 (*c* 1.0, MeOH); ν_{max} (NaCl)/cm^{-1} 3065, 3030, 2980, 2922, 1746, 1713, 1699, 1496, 1418, 1323, 1248, 1130, 1111, 1030, 988; ^{1}H NMR (300 MHz, $(CD_3)_2CO$) (320 K): δ 7.31–7.13 (10H, m), 6.03–5.92 (1H, m), 5.88 (1H, d, *J* 10.1 Hz), 5.77–5.63 (1H, m), 5.39 (1H, d, *J* 10.1 Hz), 5.26 (2H, dd, *J* 17.1, 11.1 Hz), 5.11–4.85 (4H, m), 4.65 (1H, br s), 3.25 (1H, dd, *J* 3.9, 10.2 Hz), 2.92–2.76 (2H, m), 2.52–2.35 (3H, m); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) (320 K): δ 170.5, 153.4, 137.0, 136.1, 132.3, 131.8, 128.5, 128.1, 127.9, 127.5, 127.3, 126.1, 118.9, 118.2, 72.3, 66.8, 57.4, 50.1, 39.2, 34.7, 33.1.

4.2.2.1.7. (4S,5S)-N-Benzyloxycarbonyl-(4R)-sec-butyl-5-allyl-1,3-oxazinan-6-one ***33****, and (4S)-N-benzyloxycarbonyl-(4R)-sec-butyl-5,5-diallyl-1,3-oxazinan-6-one* ***34****.* General procedure B was followed for the alkylation of oxazinanone **13** (239 mg, 0.85 mmol) with allyl bromide (368 μL, 4.25 mmol) as the electrophile to afford starting material **13** (66.9 mg, 28% recovery). The oxazinanone **33** was isolated as a colorless oil (64.8 mg, 23% yield). *m*/*z* HRMS (ESI, MeOH/AcOH): $[M+H]^+$ found 332.1853. $C_{19}H_{25}NO_4$ requires 332.1856; R_f (20% EtOAc/hexane) 0.46; $[\alpha]_D^{26}$ +121.9 (*c* 1.8, MeOH); ν_{max} (NaCl)/cm^{-1} 3067, 3034, 2968, 2935, 2878, 1749, 1709, 1700, 1456, 1418, 1316, 1251, 1151, 1126, 1026, 993, 920; ^{1}H NMR (300 MHz, $CDCl_3$) (325 K): δ 7.33 (5H, s), 5.92 (1H, d, *J* 10.5 Hz), 5.85–5.72 (1H, m), 5.17 (2H, s), 5.08 (2H, d, *J* 11.4 Hz), 4.98 (1H, d, *J* 10.5 Hz), 4.01 (1H, br s), 2.74 (1H, dd, *J* 5.7, 11.4 Hz), 2.43 (2H, dd, *J* 6.6, 12.9 Hz), 1.73–1.64 (1H, m), 1.53–1.42 (1H, m), 1.14–1.02 (1H, m), 0.97 (3H, d, *J* 6.9 Hz), 0.89 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (325 K): δ 170.5, 154.4, 135.3, 133.9, 128.2, 128.0, 127.8, 117.9, 72.3, 67.9, 56.9, 43.4, 36.7, 34.7, 24.1, 15.5, 10.7.

The oxazinanone **34** was isolated as a colorless oil (85.2 mg, 27% yield). *m*/*z* HRMS (ESI, MeOH/AcOH): $[M+H]^+$ found 372.2166. $C_{22}H_{29}NO_4$ requires 372.2169; R_f (20% EtOAc/hexane) 0.59; $[\alpha]_D^{26}$ +42.7 (*c* 1.7, MeOH); ν_{max} (NaCl)/cm^{-1} 3068, 3035, 2966, 2935, 2878, 1746, 1710, 1700, 1640, 1454, 1419, 1336, 1302, 1251, 1153, 1103, 1002, 920; ^{1}H NMR (300 MHz, $CDCl_3$) (325 K): δ 7.33 (5H, s), 5.93 (1H, d, *J* 6.8 Hz), 5.85–5.71 (1H, m), 5.69–5.57 (1H, m), 5.24–5.14 (5H, m), 5.05 (2H, dd, *J* 10.1, 17.8 Hz), 4.22 (1H, br s), 2.77 (1H, dd, *J* 6.9, 15.2 Hz), 2.45–2.38 (1H, m), 2.32–2.21 (2H, m), 1.92–1.81 (1H, m), 1.59–1.50 and 1.15–1.02 (2H, m), 0.97–0.87 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (325 K): δ 171.4, 154.2, 135.4, 131.5, 128.2, 128.0, 127.7, 119.4, 118.9, 75.1, 67.8, 60.6, 48.4, 39.7, 36.4, 34.6, 24.6, 16.4, 12.5.

4.2.3. Dimethylation of the oxazinanone in a one-pot reaction

. 4.2.3.1. General procedure C. A solution of oxazinanone (0.102 M in freshly distilled dry toluene) was cooled to −78 °C under an argon atmosphere. Then KHMDS (1.1 equiv of a 0.50 M solution in toluene) was added dropwise and the solution was left to stir at −78 °C for 40 min. Methyl triflate (1.5 equiv) was added dropwise, and stirring was continued for 1.5 h at −78 °C. The solution was then allowed to warm to −15 °C, and the reaction was cooled to −78 °C, and a second addition of KHMDS (2.1 equiv) and MeOTf (3.0 equiv) was carried out in the same manner as the first. The solution was allowed to warm to −15 °C and then the reaction mixture was quenched with satd aq NH_4Cl solution (5 mL). The solution was diluted with ethyl acetate (20 mL) and washed with water (20 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give a yellow oily residue. The oil was subjected to column chromatography, eluting with 5–20% ethyl acetate/hexane.

4.2.3.1.1. (4S)-N-Benzyloxycarbonyl-4,5,5-trimethyl-1,3-oxazinan-6-one ***4*** *and (4S,5S/R)-N-benzyloxycarbonyl-4,5-dimethyl-1,3-oxazinan-6-one* ***2****/****3****.* The general procedure C was followed for the dimethylation of oxazinanone **1** (102 mg, 0.41 mmol) to afford a mixture of diastereoisomers of **2**/**3** (27.0 mg, 25% yield), and the dimethylated oxazinanone **4**, isolated as a colorless oil (55.7 mg, 49% yield) with spectra identical to those of an authentic sample.[7]

4.2.3.1.2. (4S)-N-Benzyloxycarbonyl-4-isopropyl-5,5-dimethyl-1,3-oxazinan-6-one ***8*** *and (4S,5S/R)-N-benzyloxycarbonyl-4-isopropyl-5-methyl-1,3-oxazinan-6-one* ***6****/****7****.* The general procedure C was followed for the dimethylation of oxazinanone **5** (76.3 mg, 0.28 mmol) and afforded a mixture of diastereoisomers **6**/**7** (17.2 mg, 22% yield). The dimethylated oxazinanone **8** was isolated as a colorless oil (37.7 mg, 45% yield) with spectra identical to those of an authentic sample.[7]

4.2.3.1.3. (4S)-N-Benzyloxycarbonyl-(4R)-sec-butyl-5,5-dimethyl-1,3-oxazinan-6-one ***16*** *and (4S,5S/R)-N-benzyloxycarbonyl-(4R)-sec-butyl-5-methyl-1,3-oxazinan-6-one* ***14****/****15****.* The general procedure C was followed for the dimethylation of oxazinanone **13** (134 mg, 0.46 mmol) and afforded a mixture of diastereoisomers **14**/**15** (12.2 mg, 8% yield). The dimethylated oxazinanone **16** was isolated as a colorless oil (88.2 mg, 60% yield) with spectra identical to that reported above.

4.2.4. One-pot synthesis of 5,5-dibenzyl and allyl-β-amino acid derivatives.

4.2.4.1. General procedure D. A solution of oxazinanone (0.063 M in freshly distilled dry toluene/DMPU mixture (2:1)) was cooled to −78 °C under an argon atmosphere. Then KHMDS (1.1 equiv of a 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 added dropwise, and stirring was continued for 1.5 h at −78 °C. The solution was then allowed to warm to −15 °C, and the reaction was cooled to −78 °C, and a second addition of KHMDS (2.50 equiv) and alkylating agent (10.0 equiv) was carried out in the same manner as the first. The solution was allowed to warm to −15 °C and then the reaction mixture was quenched with satd aq NH_4Cl solution (5 mL). The solution was diluted with ethyl acetate (20 mL) and washed with water (20 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give an oil. The oil was subjected to column chromatography, eluting with 5–20% ethyl acetate/hexane.

4.2.4.1.1. (4S)-N-Benzyloxycarbonyl-4-methyl-5,5-diallyl-1,3-oxazinan-6-one ***22****.* General procedure D was followed for the alkylation of oxazinanone **1** (53.5 mg, 0.22 mmol) with allyl bromide (first addition 92.9 μL, 1.07 mmol; second addition 184 μL, 2.14 mmol) as the electrophile to afford the diallyl oxazinanone **22** (45.1 mg, 65%) and the mono adduct **21** (2.1 mg, 3%).

4.2.4.1.2. (4S)-N-Benzyloxycarbonyl-4-methyl-5,5-dibenzyl-1,3-oxazinan-6-one ***24****.* General procedure D was followed for the alkylation of oxazinanone **1** (66.8 mg, 0.27 mmol) with benzyl bromide (first addition 161 μL, 1.35 mmol; second addition 321 μL, 2.70 mmol) as the electrophile to afford the dibenzyl oxazinanone **24** (58.6 mg, 51%).

4.2.4.1.3. (4S)-N-Benzyloxycarbonyl-4-isopropyl-5,5-diallyl-1,3-oxazinan-6-one ***28****.* General procedure D was followed for the alkylation of oxazinanone **5** (88.3 mg, 0.32 mmol) with allyl bromide (first addition 136 μL, 1.59 mmol; second addition 276 μL, 3.18 mmol) as the electrophile to afford the diallyl oxazinanone **28** (60.3 mg, 53%) and the mono adduct **27** (9.1 mg, 9%).

4.2.4.1.4. (4S)-N-Benzyloxycarbonyl-4-isopropyl-5,5-dibenzyl-1,3-oxazinan-6-one ***30****.* General procedure D was followed for the alkylation of oxazinanone **5** (53.5 mg, 0.19 mmol) with benzyl bromide (first addition 115 μL, 0.97 mmol; second addition 230 μL,

1.94 mmol) as the electrophile to afford the dibenzyl oxazinanone **30** (41.6 mg, 65%) and the mono adduct **29** (4.8 mg, 7%).

4.2.5. Diastereoselective alkylation of the 5-methyl-1,3-oxazinan-6-one.

4.2.5.1. General procedure E. A solution of 5-methyl oxazinanone (0.125 M in dry freshly distilled toluene) was cooled to −78 °C under an argon atmosphere. Then KHMDS (1.1 equiv of a 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 −15 °C, and the reaction was then quenched with satd aq NH_4Cl solution (5 mL). The solution was diluted with ethyl acetate (20 mL) and washed with water (20 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give an oily residue. The oil was subjected to flash column chromatography, eluting with 5–10% ethyl acetate/hexane.

*4.2.5.1.1. (4S,5S)-N-Benzyloxycarbonyl-4,5-dimethyl-5-allyl-1,3-oxazinan-6-one **35**/**36**.* General procedure E was followed for the alkylation of α-methyl-1,3-oxazinan-6-one **2**/**3** (125 mg, 0.47 mmol) with allyl bromide (205 μL, 2.35 mmol) as the electrophile to afford starting material **2**/**3** (14.7 mg, 12%). The title compound **35**/**36** was isolated as a mixture of diastereoisomers in a 13:1 (*trans*/*cis*) ratio (79.9 mg, 56% yield) as a colorless oil. *m*/*z* HRMS (ESI, MeOH/AcOH): $[M+H]^+$ found 304.1543. $C_{17}H_{21}NO_4$ requires 304.1543; R_f (20% EtOAc/hexane) 0.38; ν_{max} (NaCl)/cm^{-1} 3066, 3033, 2983, 2935, 1756, 1705, 1697, 1422, 1328, 1246, 1111, 1056, 1001, 919; ^1H NMR (300 MHz, $CDCl_3$) (325 K): δ 7.38 (5H, s), 5.87 (1H, d, *J* 9.9 Hz), 5.78–5.64 (1H, m), 5.23 (1H, d, *J* 9.9 Hz), 5.18 (2H, s), 5.10 (2H, dd, *J* 10.2, 17.4 Hz), 4.32–4.30 (1H, m), 2.39–2.25 (2H, m), 1.31 (3H, d, *J* 7.2 Hz), 1.17 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) (325 K): δ 172.7, 153.1, 135.4, 131.7, 128.2, 128.1, 127.8, 119.2, 72.2, 67.7, 51.7, 47.4, 42.4, 18.9, 14.8.

*4.2.5.1.2. (4S,5S)-N-Benzyloxycarbonyl-4,5-dimethyl-5-ethyl-1,3-oxazinan-6-one **37**/**38**.* General procedure E was followed for the alkylation of α-methyl-1,3-oxazinan-6-one **2**/**3** (176 mg, 0.67 mmol) with EtOTf (179 mg, 1.50 equiv) as the electrophile to afford starting material **2**/**3** (15.7 mg, 9% recovery). The title compound **37**/**38** was isolated as a mixture of diastereoisomers in a 13:1 (*trans*/*cis*) ratio (114 mg, 56% yield) as a colorless oil. *m*/*z* HRMS (EI): found $[M^+]$, 291.1472; $C_{16}H_{21}NO_4$ requires $[M^+]$, 291.1471; R_f (20% EtOAc/hexane) 0.46; ν_{max} (NaCl)/cm^{-1} 2978, 2939, 1748, 1712, 1454, 1418, 1327, 1277, 1248, 1005, 916, 860; ^1H NMR (300 MHz, $CDCl_3$) (320 K): δ 7.32 (5H, s), 5.82 (1H, d, *J* 9.6 Hz), 5.21 (1H, s), 5.18 (2H, s), 4.28 (1H, br s), 1.68–1.52 (2H, m), 1.26 (3H, d, *J* 6.9 Hz), 1.12 (3H, s), 0.86 (3H, t, *J* 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) (320 K): δ 173.1, 153.2, 135.4, 128.2, 128.1, 127.8, 72.2, 67.6, 51.8, 47.8, 30.7, 18.3, 15.0, 8.0.

*4.2.5.1.3. (4S,5S)-N-Benzyloxycarbonyl-4,5-dimethyl-5-benzyl-1,3-oxazinan-6-one **39**/**40**.* General procedure E was followed for the alkylation of α-methyl-1,3-oxazinan-6-one **2**/**3** (97.4 mg, 0.37 mmol) with benzyl bromide (220 μL, 1.85 mmol) as the electrophile to afford starting material **2**/**3** (13.2 mg, 14% recovery). The title compound **39**/**40** was isolated as a mixture of diastereoisomers in a 10:1 (*trans*/*cis*) ratio (75.6 mg, 58% yield) as a colorless oil. *m*/*z* HRMS (ESI, MeOH/AcOH): $[M+H]^+$ found 354.1699. $C_{21}H_{23}NO_4$ requires 354.1700; R_f (20% EtOAc/hexane) 0.33; ν_{max} (NaCl)/cm^{-1} 3030, 2986, 2978, 2933, 1748, 1712, 1496, 1454, 1417, 1328, 1277, 1249, 1136, 1090, 1057, 1002, 913; ^1H NMR (300 MHz, $CDCl_3$) (300 K): δ 7.33–7.13 (10H, m), 5.89 (1H, d, *J* 8.9 Hz), 5.31 (1H, d, *J* 8.9 Hz), 5.25 (1H, d, *J* 12.0 Hz), 5.21 (1H, d, *J* 12.0 Hz), 4.37 (1H, br s), 2.97 (2H, d, *J* 13.5 Hz), 2.92 (1H, d, *J* 13.5 Hz), 1.23 (3H, d, *J* 7.2 Hz), 1.11 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) (300 K): δ 173.1, 153.0, 135.2, 135.1, 130.2, 128.3, 128.2, 128.0, 127.9, 126.7, 72.6, 67.8, 51.9, 48.4, 43.7, 19.2, 15.1.

*4.2.5.1.4. (4S,5S)-N-Benzyloxycarbonyl-4-isopropyl-5-methyl-5-allyl-1,3-oxazinan-6-one **41**.* General procedure E was followed for the alkylation of α-methyl-1,3-oxazinan-6-one **6**/**7** (109 mg, 0.37 mmol) with allyl bromide (161 μL, 1.85 mmol) as the electrophile to afford starting material **6**/**7** (14.8 mg, 14% recovery). The title compound **41** was isolated in a >19:1 (*trans*/*cis*) ratio (60.6 mg, 49% yield) as a colorless oil. *m*/*z* HRMS (EI): found: $[M^+]$, 331.1791; $C_{19}H_{25}NO_4$ requires $[M^+]$, 331.1784; R_f (20% EtOAc/hexane) 0.58; $[\alpha]_D^{24}$ +38.0 (*c* 0.5, MeOH); ν_{max} (NaCl)/cm^{-1} 3075, 3034, 2965, 2941, 1746, 1712, 1700, 1695, 1416, 1316, 1244, 1101, 1011, 918; ^1H NMR (300 MHz, $CDCl_3$) (325 K): δ 7.38 (5H, s), 5.91 (1H, d, *J* 9.0 Hz), 5.73–5.65 (1H, m), 5.28 (1H, d, *J* 9.0 Hz), 5.18 (2H, s), 5.11 (2H, dd, *J* 15.3, 17.1 Hz), 4.12 (1H, br s), 2.39–2.23 (2H, m), 2.12–2.00 (1H, m), 1.26 (3H, s), 1.02 (3H, d, *J* 6.5 Hz), 0.97 (3H, d, *J* 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) (325 K): δ 172.7, 153.1, 135.4, 131.5, 128.2, 128.1, 127.8, 119.4, 74.8, 67.7, 60.6, 46.3, 43.4, 29.7, 20.9, 19.1, 18.1.

*4.2.5.1.5. (4S,5S)-N-Benzyloxycarbonyl-4-isopropyl-5-methyl-5-ethyl-1,3-oxazinan-6-one **43**.* General procedure E was followed for the alkylation of α-methyl-1,3-oxazinan-6-one **6**/**7** (96.3 mg, 0.33 mmol) with EtOTf (90.8 mg, 1.50 equiv) as the electrophile to afford starting material **6**/**7** (13.3 mg, 14% recovery). The title compound **43** was isolated in a >19:1 (*trans*/*cis*) ratio (42.6 mg, 45% yield) as a colorless oil. *m*/*z* HRMS (EI): found $[M^+]$, 319.1781; $C_{18}H_{25}NO_4$ requires $[M^+]$, 319.1784; R_f (20% EtOAc/hexane) 0.57; $[\alpha]_D^{25}$ +32.0 (*c* 1.0, MeOH); ν_{max} (NaCl)/cm^{-1} 2968, 1748, 1705, 1456, 1420, 1314, 1267, 1246, 1099, 1010; ^1H NMR (300 MHz, $CDCl_3$) (325 K): δ 7.37 (5H, s), 5.84 (1H, br s), 5.21 (1H, d, *J* 9.6 Hz), 5.13 (2H, s), 4.11 (1H, br s), 2.10–2.00 (1H, m), 1.66–1.55 (2H, m), 1.23 (3H, s), 1.02 (3H, d, *J* 6.3 Hz), 0.96 (3H, d, *J* 6.9 Hz), 0.86 (3H, t, *J* 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) (325 K): δ 173.0, 154.2, 135.5, 128.2, 128.1, 127.8, 74.9, 67.7, 60.8, 46.3, 31.5, 29.3, 20.9, 18.3, 8.0.

*4.2.5.1.6. (4S,5S)-N-Benzyloxycarbonyl-4-isopropyl-5-methyl-5-benzyl-1,3-oxazinan-6-one **45**.* General procedure E was followed for the alkylation of α-methyl-1,3-oxazinan-6-one **6**/**7** (138 mg, 0.48 mmol) with benzyl bromide (154 μL, 2.40 mmol) as the electrophile to afford starting material **6**/**7** (13.6 mg, 10% recovery). The title compound **45** was isolated in a >19:1 (*trans*/*cis*) ratio (85.7 mg, 48% yield) as a white solid; found: C, 72.51; H, 7.19; N, 3.58; $C_{23}H_{27}NO_4$ requires C, 72.42; H, 7.13; N, 3.67; mp 105–107 °C; R_f (20% EtOAc/hexane) 0.53; $[\alpha]_D^{25}$ +11.3 (*c* 0.6, MeOH); ν_{max} (NaCl)/cm^{-1} 3031, 2965, 1750, 1738, 1495, 1409, 1250, 1140, 1090, 1013; ^1H NMR (300 MHz, $CDCl_3$) (325 K): δ 7.31–7.11 (10H, m), 5.86 (1H, br s), 5.35 (1H, d, *J* 9.6 Hz), 5.19 (2H, s), 4.18–4.10 (1H, m), 2.95 (2H, dd, *J* 13.5, 15.3 Hz), 2.05–1.97 (1H, m), 1.22 (3H, s), 0.99 (3H, d, *J* 6.8 Hz), 0.95 (3H, d, *J* 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) (325 K): δ 172.6, 154.0, 135.4, 135.1, 130.2, 128.2, 128.1, 127.8, 127.5, 126.7, 75.2, 67.8, 61.0, 47.3, 44.7, 29.7, 21.1, 19.5, 18.1.

*4.2.5.1.7. (4S,5S)-N-Benzyloxycarbonyl-4-isobutyl-5-methyl-5-allyl-1,3-oxazinan-6-one **47**.* General procedure E was followed for the alkylation of α-methyl-1,3-oxazinan-6-one **10**/**11** (109 mg, 0.36 mmol) with allyl bromide (154 μL, 1.80 mmol) as the electrophile to afford starting material **10**/**11** (16.4 mg, 15% recovery). The title compound **47** was isolated as a colorless oil in a >19:1 (*trans*/*cis*) ratio (58.1 mg, 47% yield). *m*/*z* HRMS (EI): found $[M^+]$, 345.1941; $C_{20}H_{27}NO_4$ requires $[M^+]$, 345.1940; R_f (20% EtOAc/hexane) 0.57; $[\alpha]_D^{27}$ +44.0 (*c* 1.0, MeOH); ν_{max} (NaCl)/cm^{-1} 3074, 3034, 2957, 2871, 1746, 1705, 1699, 1423, 1250, 1101, 1007, 924; ^1H NMR (300 MHz, $CDCl_3$) (325 K): δ 7.33 (5H, s), 5.98 (1H, d, *J* 8.7 Hz), 5.73–5.65 (1H, m), 5.23 (1H, d, *J* 12.3 Hz), 5.20 (1H, d, *J* 12.3 Hz), 5.09–5.00 (3H, m), 4.28 (1H, br s), 2.36 (2H, dd, *J* 7.2, 15.0 Hz), 1.56–1.24 (3H, m), 1.13 (3H, s), 0.92–0.88 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (325 K): δ 172.9, 153.8, 135.2, 131.7, 128.2, 128.1, 127.9, 119.3, 72.3, 67.9, 54.3, 47.9, 42.7, 36.5, 24.1, 23.7, 20.7, 18.8.

*4.2.5.1.8. (4S,5S)-N-Benzyloxycarbonyl-4-isobutyl-5-methyl-5-benzyl-1,3-oxazinan-6-one **49**.* General procedure E was followed for the alkylation of α-methyl-1,3-oxazinan-6-one **10**/**11** (62.5 mg, 0.20 mmol) with benzyl bromide (122 μL, 1.02 mmol) as the electrophile to afford starting material **10**/**11** (5.1 mg, 8% recovery). The

title compound **49** was isolated as a white solid in a >19:1 (*trans*/*cis*) ratio (41.4 mg, 50% yield). *m*/*z* HRMS (ESI, MeOH/AcOH): $[M+H]^+$ found 396.2172. $C_{24}H_{29}NO_4$ requires 396.2169; mp 117–119 °C; R_f (20% EtOAc/hexane) 0.56; $[\alpha]_D^{26}$ +14.0 (*c* 1.0, MeOH); ν_{max} (NaCl)/cm^{-1} 2956, 1750, 1703, 1423, 1250, 1087, 1009; ^{1}H NMR (300 MHz, $CDCl_3$) (325 K): δ 7.37–7.12 (10H, m), 6.02 (1H, br s), 5.22 (1H, d, *J* 12.3 Hz), 5.18 (1H, d, *J* 12.3 Hz), 5.11 (1H, d, *J* 10.2 Hz), 4.38 (1H, br s), 2.96 (2H, dd, *J* 13.5, 7.2 Hz), 1.65–1.32 (3H, m), 1.06 (3H, s), 0.91–0.85 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (325 K): δ 172.8, 153.9, 135.5, 135.2, 130.2, 128.2, 127.9, 127.8, 127.7, 126.6, 72.5, 68.0, 55.1, 49.1, 44.2, 36.7, 24.3, 23.4, 20.8, 18.9.

4.2.6. Reverse alkylation of 5-substituted oxazinanones.

4.2.6.1. General procedure F. A solution of 5-substituted oxazinanone (0.125 M in dry freshly distilled toluene) was cooled to −78 °C under an argon atmosphere. Then KHMDS (1.10 equiv of a 0.50 M solution in toluene) was added dropwise and the solution was left to stir at −78 °C for 40 min. Methyl triflate (1.50 equiv) was then added dropwise and stirring was continued for 3 h at −78 °C. The solution was then allowed to warm to −15 °C, and the reaction was then quenched with satd aq NH_4Cl solution (5 mL). The solution was diluted with ethyl acetate (20 mL) and washed with water (20 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give an oily residue. The oil was subjected to flash column chromatography, eluting with 5–10% ethyl acetate/hexane.

*4.2.6.1.1. (4S,5S)-N-Benzyloxycarbonyl-4,5-dimethyl-5-allyl-1,3-oxazinan-6-one **41** and (4S,5R)-N-benzyloxycarbonyl-4,5-dimethyl-5-allyl-1,3-oxazinan-6-one **42**.* General procedure F was followed for the alkylation of 5-allyl-1,3-oxazinan-6-one **27** (61.1 mg, 0.19 mmol) with MeOTf (31.3 μL, 0.29 mmol) as the electrophile to afford starting material **27** (6.8 mg, 11%). The 5,5-disubstituted-1,3-oxazinan-6-one **41**/**42** was isolated as a mixture of diastereoisomers in a 1.3:1.0 ratio (38.2 mg, 60% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) (325 K): δ 7.38 (5H, s), 5.90–5.76 (2H, m), 5.32 (1H, d, *J* 9.6 Hz, major), 5.24 (1H, d, *J* 9.7 Hz, minor), 5.18–4.99 (5H, m), 4.10 (1H, br s), 2.77 (1H, dd, major), 2.39–2.56 (2H, m, major+minor), 2.23–2.13 (1H, m, major), 2.07–2.03 (1H, minor), 1.26 (3H, s, minor), 1.24 (3H, s, major), 1.01–0.94 (7H, m, minor+major); ^{13}C NMR (75 MHz, $CDCl_3$) (325 K): δ 172.9, 172.7, 154.3, 154.1, 135.5, 131.8, 131.5, 128.2, 128.0, 127.8, 127.7, 127.6, 119.4, 119.2, 74.9, 74.8, 67.7, 61.6, 60.5, 46.3, 44.6, 43.2, 37.5, 29.3, 28.8, 23.3, 20.9, 20.7, 19.1, 18.1, 17.7.

*4.2.6.1.2. (4S,5S)-N-Benzyloxycarbonyl-4,5-dimethyl-5-ethyl-1,3-oxazinan-6-one **43** and (4S,5R)-N-benzyloxycarbonyl-4,5-dimethyl-5-ethyl-1,3-oxazinan-6-one **44**.* General procedure F was followed for the alkylation of 5-ethyl-1,3-oxazinan-6-one **25** (65.6 mg, 0.21 mmol) with MeOTf (35.6 μL, 0.32 mmol) as the electrophile to afford starting material **25** (5.1 mg, 8%). The 5,5-disubstituted-1,3-oxazinan-6-one **42**/**43** was isolated as a mixture of diastereoisomers in a 1.8:1 ratio (41.2 mg, 61% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) (320 K): δ 7.38 (5H, s), 5.85 (1H, br s), 5.30 (1H, d, *J* 9.6 Hz), 5.18 (2H, s), 4.08 (1H, br s), 2.12–1.94 (2H, m, minor+major), 1.71–1.57 (2H, m), 1.23 (3H, s), 1.02 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) (320 K): δ 173.3, 154.4, 135.5, 128.2, 128.1, 127.7, 74.6, 67.7, 61.5, 45.1, 31.5, 29.3, 28.8, 25.4, 22.4, 21.0, 18.1, 7.4.

*4.2.6.1.3. (4S,5S)-N-Benzyloxycarbonyl-4,5-dimethyl-5-benzyl-1,3-oxazinan-6-one **45** and (4S,5R)-N-benzyloxycarbonyl-4,5-dimethyl-5-benzyl-1,3-oxazinan-6-one **46**.* General procedure F was followed for the alkylation of 5-benzyl-1,3-oxazinan-6-one **29** (37.1 mg, 0.10 mmol) with MeOTf (16.1 μL, 0.14 mmol) as the electrophile to afford starting material **29** (3.6 mg, 10%). The 5,5-disubstituted-1,3-oxazinan-6-one **45**/**46** were isolated as a mixture of diastereoisomers in a 1.1:1.0 ratio (21.9 mg, 57% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) (325 K): δ 7.41–7.06 (10H, m), 5.8.2–5.99 (2H, m), 5.19 (2H, s, minor), 5.14 (2H, s, major), 4.26–4.05 (2H, br s, minor+major), 3.34 (1H, d, *J* 14.0 Hz, major), 2.93 (3H, d, *J* 15.0 Hz, minor+major), 2.51–2.40 (1H, m, major), 2.05–1.99 (1H, m, minor), 1.21 (3H, s, minor), 1.16 (3H, s, major), 1.12 (6H, s, major), 1.01 (3H, d, *J* 6.6 Hz, minor), 0.95 (3H, d, *J* 7.2 Hz, minor); ^{13}C NMR (75 MHz, $CDCl_3$) (325 K): δ 172.6, 154.3, 154.0, 135.4, 134.9, 130.2, 130.1, 128.2, 128.1, 128.0, 127.9, 127.8, 127.5, 126.7, 126.6, 75.2, 74.6, 67.8, 67.7, 62.3, 61.0, 47.3, 46.3, 44.7, 38.2, 29.7, 29.1, 23.2, 21.1, 19.5, 18.1, 17.7.

4.2.7. Base hydrolysis of the dialkylated 1,3-oxazinan-6-one

*. 4.2.7.1. (2R,3S)-N-Benzyloxycarbonyl-3-amino-2-methyl-2-benzyl-4-methyl-pentanoic acid **51**.* The oxazinanone **45** (90.1 mg, 0.24 mmol) was dissolved in THF (2.8 mL) at 0 °C, and a 4 N lithium hydroxide solution (1.98 mL) was added. The mixture was stirred for 6 h at 0 °C (monitored by TLC), and the THF was removed under reduced pressure. The aqueous solution was washed with ether (5 mL), the aqueous layer was acidified with 1 M hydrochloric acid solution, and then it was extracted with ethyl acetate (3×5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The yellow residue was subjected to silica chromatography, eluting with 5–30% ethyl actate/hexane. The acid **51** was isolated as a white solid (62.3 mg, 71% yield); found: C, 71.61; H, 7.36; N, 3.80; $C_{22}H_{27}NO_4$ requires C, 71.52; H, 7.37; N, 3.79; mp 151–152 °C; $[\alpha]_D^{25}$ −59.7 (*c* 2.0, MeOH); ν_{max} (NaCl)/cm^{-1} 3431, 3321–2598, 3030, 2963, 2876, 1713, 1514, 1470, 1454, 1350, 1315, 1223, 1146, 1091, 1007, 974, 908; ^{1}H NMR (300 MHz, $CDCl_3$) (325 K): δ 10.01 (1H, br s), 7.41–7.09 (10H, m), 5.93 (1H, d, *J* 11.8 Hz), 5.22 (1H, d, J_{AB} 11.7 Hz), 5.17 (1H, d, J_{AB} 11.7 Hz), 3.81 (1H, d, *J* 10.5 Hz), 3.32 (1H, d, *J* 13.4 Hz), 2.66 (1H, d, *J* 13.4 Hz), 2.18–2.15 (1H, m), 1.13 (3H, s), 1.01 (3H, d, *J* 6.8 Hz), 0.82 (3H, d, *J* 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) (325 K): δ 181.7, 156.8, 136.4, 136.2, 129.9, 128.1, 127.8, 127.6, 126.4, 66.6, 62.1, 49.7, 43.6, 28.6, 22.2, 18.9, 15.5.

4.2.8. Base solvolysis of the dimethylated 1,3-oxazinan-6-one.

*4.2.8.1. (3S)-Ethyl-N-benzyloxycarbonyl-3-amino-2-dimethyl-butanoate **52**.* The oxazinanone **4** (51.0 mg, 0.19 mmol) was dissolved in dry ethanol (4.0 mL), and dry sodium hydrogen carbonate (42.1 mg, 2.5 mmol) was added under an argon atmosphere. The solution was heated at reflux for 22 h. The solvent was removed in vacuo, the residue was taken up in ethyl acetate (10 mL), and it was then washed with water (10 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography, eluting with 5–10% ethyl acetate/hexane. The ester **52** was isolated as a colorless oil (38.8 mg, 72% yield); *m*/*z* HRMS (ESI, MeOH/AcOH): $[M+H]^+$ found 294.1699. $C_{16}H_{23}NO_4$ requires 294.1700; R_f (20% EtOAc/hexane) 0.56; $[\alpha]_D^{25}$ +24.0 (*c* 1.0, MeOH); ν_{max} (NaCl)/cm^{-1} 3431, 3347, 2980, 2940, 1728, 1531, 1504, 1454, 1261, 1238, 1170, 1143, 1101, 1053, 916, 860; ^{1}H NMR (300 MHz, $CDCl_3$) (320 K): δ 7.34–7.24 (5H, m), 5.29 (1H, br s), 5.09 (2H, s), 4.16 (2H, q, *J* 7.1 Hz), 3.86–3.81 (1H, m), 1.25 (3H, t, *J* 7.1 Hz), 1.18 (6H, s), 1.12 (3H, d, *J* 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers): δ 175.9, 155.7, 136.5, 128.0, 127.6, 66.2, 60.2, 53.1, 45.9, 22.6, 22.4, 16.8, 13.7.

4.2.9. Reductive cleavage of the dialkylated oxazinanone.

4.2.9.1. General procedure G. To the 5,5-dialkyl oxazinanone in dry dichloromethane (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% ethyl acetate/hexane.

*4.2.9.1.1. (2R,3S)-N-Benzyloxycarbonyl-3-methylamino-2-methyl-2-benzylbutanoic acid **53**.* The oxazinanone **39** (46.1 mg, 0.13 mmol) was transformed according to General procedure G,

furnishing *N*-methyl acid **53** as a colorless oil (35.3 mg, 76% yield); *m*/*z* HRMS (ESI, MeOH/AcOH): $[M+H]^+$ found 356.1856. $C_{21}H_{25}NO_4$ requires 356.1856; $[\alpha]_D^{24}$ −83.2 (*c* 1.0, MeOH); ν_{max} (NaCl)/cm^{-1} 3157–2583, 3063, 3030, 2984, 1728, 1694, 1495, 1454, 1327, 1169, 1080, 910, 731; ^1H NMR (300 MHz, $CDCl_3$) (320 K): δ 7.35–7.17 (10H, m), 5.16 (1H, d, J_{AB} 12.6 Hz), 5.14 (1H, d, J_{AB} 12.6 Hz), 4.61 (1H, br s), 3.31 (1H, d, *J* 12.8 Hz), 2.93 (3H, s), 2.63 (1H, d, *J* 12.8 Hz), 1.30 (3H, d, *J* 7.2 Hz), 1.11 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) (320 K): δ 180.3, 157.1, 137.1, 136.4, 130.1, 128.1, 127.7, 127.4, 126.2, 67.1, 57.4, 51.9, 41.2, 30.1, 19.1, 13.2.

*4.2.9.1.2. (3S)-N-Benzyloxycarbonyl-3-methylamino-2-dimethylbutanoic acid **54**.* The oxazinanone **4** (208 mg, 0.75 mmol) was transformed according to General procedure G, affording *N*-methyl acid **54** as a white solid (83% yield); found: C, 64.43; H, 7.42; N, 5.11; $C_{15}H_{21}NO_4$ requires C, 64.50; H, 7.58; N, 5.01; mp 68–70 °C; $[\alpha]_D^{27}$ −13.0 (*c* 2.0, MeOH); ν_{max} (NaCl)/cm^{-1} 3165–2559, 3064, 2980, 1728, 1697, 1477, 1456, 1402, 1323, 1161, 1082, 1041, 910, 866, 843; ^1H NMR (300 MHz, $CDCl_3$) (300 K): δ 7.33–7.28 (5H, m), 5.12 (2H, s), 4.61–4.53 (1H, m), 2.81 (3H, s), 1.23–1.18 (9H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers): δ 182.1, 156.9, 156.5, 136.5, 136.2, 128.1, 127.6, 127.3, 67.1, 66.9, 56.5, 55.9, 46.8, 30.1, 29.7, 23.7, 21.3, 20.9, 13.6, 13.2.

*4.2.9.1.3. (3S)-N-Benzyloxycarbonyl-3-methylamino-2,2-dimethyl-4-methyl-pentanoic acid **55**.* The oxazinanone **8** (128 mg, 0.24 mmol) was transformed according to general procedure G, affording *N*-methyl acid **55** as a white solid (103 mg, 80% yield); found: C, 66.52; H, 8.54; N, 4.49. $C_{17}H_{25}NO_4$ requires C, 66.43; H, 8.20; N, 4.56; mp 147–148 °C; $[\alpha]_D^{27}$ +28.0 (*c* 1.0, MeOH); ν_{max} (NaCl)/cm^{-1} 3041–2639, 2969, 2980, 1728, 1694, 1476, 1455, 1339, 1164, 1135, 971, 871; ^1H NMR (300 MHz, $CDCl_3$) (300 K): δ 7.42–7.26 (5H, m), 5.24–5.14 (2H, m), 4.62–4.53 (1H, m), 2.82 (3H, s), 2.03–1.92 (1H, m), 1.26–1.14 (6H, m), 0.94–0.85 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers): δ 183.8, 183.2, 157.0, 136.5, 128.1, 127.9, 127.4, 127.2, 66.9, 64.4, 64.2, 45.7, 29.9, 29.7, 27.6, 25.7, 20.7, 20.6, 19.6, 19.1.

*4.2.9.1.4. (3S)-N-Benzyloxycarbonyl-3-methylamino-2,2-dimethyl-4-methyl-hexanoic acid **56**.* The oxazinanone **16** (75.5 mg, 0.24 mmol) was transformed according to general procedure G, affording *N*-methyl acid **56** as a white solid (61.9 mg, 80% yield); Found: C, 66.98; H, 8.54; N, 4.45. $C_{18}H_{27}NO_4$ requires C, 67.26; H, 8.47 N, 4.36; mp 125–127 °C; $[\alpha]_D^{25}$ +22.0 (*c* 1.0, MeOH); ν_{max} (NaCl)/cm^{-1} 3163–2630, 2968, 2882, 1728, 1693, 1454, 1339, 1167, 1138, 993, 957; ^1H NMR (300 MHz, $CDCl_3$) (300 K): δ 7.42–7.28 (5H, m), 5.25–5.11 (2H, m), 4.72–4.65 (1H, m), 2.82 (3H, s), 1.81–1.74 (1H, m), 1.8–0.99 (8H, m), 0.89–0.78 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers): δ 183.9, 183.7, 157.1, 136.6, 136.4, 128.1, 127.9, 127.5, 127.4, 127.3, 127.2, 67.9, 66.8, 62.2, 62.1, 45.7, 33.3, 30.0, 29.8, 25.9, 25.8, 19.4, 19.0, 14.7, 14.5, 10.1, 9.8.

*4.2.9.1.5. (1R,2S,6R)-N-Benzyloxycarbonyl-1,2-dimethyl-7-oxa-3-azabicyclo[4.2.1]nonan-8-one **60***

Method 1. The oxazinanone **35** (121 mg, 0.40 mmol) was transformed according to general procedure G, affording bicycle **60** as a colorless oil (79.1 mg, 65% yield) and a trace amount of *N*-methyl product. *m*/*z* HRMS (ESI, MeOH/AcOH): $[M+H]^+$ found 304.1543. $C_{17}H_{21}NO_4$ requires 304.1543; $[\alpha]_D^{24}$ +34.2 (*c* 0.82, MeOH); ν_{max} (NaCl)/cm^{-1} 2979, 1767, 1692, 1470, 1456, 1419, 1318, 1252, 1196, 1119, 1052, 1009, 961, 895; ^1H NMR (300 MHz, $CDCl_3$) (325 K): δ 7.32 (5H, s), 5.15 (2H, m), 4.68 (1H, br s), 4.37–4.16 (1H, m), 3.92–3.76 (1H, m), 2.85 (1H, dt, *J* 4.5 Hz, 11.1 Hz), 2.01–2.19 (2H, m) 1.90–1.74 (2H, m), 1.33 (3H, d, *J* 11.4 Hz), 1.23 (3H, d, *J* 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers): δ 179.2, 179.1, 155.5, 154.9, 136.2, 136.1, 128.2, 127.8, 127.5, 127.4, 74.5, 74.3, 67.1, 67.0, 57.0, 56.5, 45.2, 45.1, 39.2, 39.1, 35.6, 35.2, 32.6, 31.9, 23.9, 23.6, 13.4, 13.0.

Method 2.

To the 4,5-dimethyl-5-allyl-1,3-oxazinan-6-one **35** (35.0 mg, 0.12 mmol) in dry dichloromethane (2.0 mL) was added boron trifluoride etherate (29.2 μL, 0.24 mmol, 2.00 equiv) Then, the reaction mixture was stirred at rt for 6 h (monitored by TLC). The mixture was concentrated under reduced pressure, and the residue was taken up in ethyl acetate (15 mL). The organic phase was washed with satd aq $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give an oily residue. The oil was subjected to column chromatography, eluting with 5–20% ethyl acetate/hexane to afford the bicyclic product **60** as a colorless oil (26.8 mg, 77% yield), with spectra identical to that previously obtained.

4.2.10. X-ray crystallography. Crystals of compound **49** were mounted in low temperature oil then flash cooled to 130 K using an Oxford low temperature device. Intensity data were collected at 130 K with an Oxford XCalibur X-ray diffractometer with CCD detector using Cu-Kα radiation (λ=1.54184 Å). Data were reduced and corrected for absorption.[21] The Structures were solved by direct methods and difference fourier synthesis using the SHELX suite of programs[22] as implemented within the WINGX[23] software. Thermal ellipsoid plots were generated using the program ORTEP-3.

Crystallographic data for **49** have been deposited in the Cambridge Crystallographic Data Centre (CCDC) as supplementary publication number CCDC 840584. These data can be freely obtained from the CCDC by sending an application by email to deposit@ccdc.cam.ac.uk.

Crystal data for compound **49**: ($C_{24}H_{29}NO_4$) (0.5 $CHCl_3$), *M*=910.33, *T*=130.0(2) K, λ=1.54180, Monoclinic, space group $P2_1$ *a*=6.1037(3) *b*=20.0226(9), *c*=18.9650(7) Å, *V*=2317.7(2) $Å^3$, *Z*=4, D_{calcd}=1.304 mg M^{-3} μ(Cu-Kα) 2.239 mm^{-1}, *F*(000)=964, crystal size 0.46×0.07×0.07 mm. 16,609 reflections measured, 8751 independent reflections (R_{int}=0.0424), the final *R* was 0.0420 [$I>2\sigma(I)$] and $wR(F^2)$ (all data) was 0.0986.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2012.04.012.

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