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Diastereoselective Synthesis of α-Methyl and α-Hydroxy-β-Amino Acids via 4-Substituted-1,3-Oxazinan-6-ones

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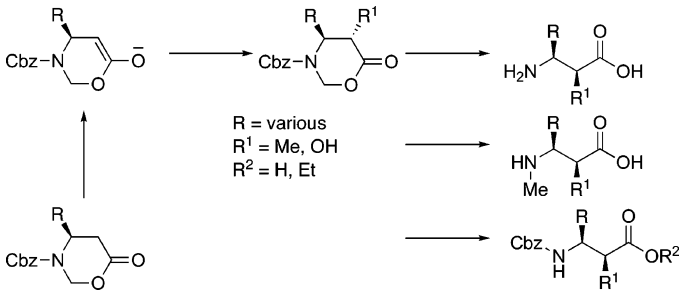

1,3-Oxazinan-6-ones have been utilized in a series of enolate reactions to produce 5-hydroxy and 5-alkyl-4-substituted-1,3-oxazinan-6-ones with excellent *trans* diastereoselectivity. Highlighting the versatility of the oxazinanone, a number of transformations were performed to produce a variety of protected *N*-H and *N*-methyl α-hydroxy- and α-methyl-β-amino acids.

Introduction

β-Amino acids are found uncommonly in natural products;[1,2] however of these, the α,β-disubstituted-β-amino acids are the most abundant. When incorporated in secondary metabolites, α-alkyl-β-amino acids have an important structural and conformational role and *syn* and *anti* stereoisomers of α-hydroxy-β-amino acids are known to be part of the active moiety of secondary metabolites.[1,2] The example most often quoted is the α-hydroxy-β-amino acid residue of Taxol.[3] Such is the utility and importance of these residues as demonstrated in pharmaceutical natural products, they also find application in peptidomimetics[4,5] and as precursors to other synthetic targets.[3] It is for these reasons there has been a plethora of syntheses of β-amino acids in the past 10 years, and these methods have been reviewed.[3,6−16]

A majority of the synthetic methods for β-amino acids are concerned with asymmetric synthesis using non-β-amino acid substrates, and they use expensive chiral catalysts. Furthermore, some methods have been developed to produce a certain type of residue.[14,16] Most importantly, a majority of the syntheses do not produce diastereomerically pure products. Only a handful of methods are capable of producing a range of stereopure β-amino acids.[12]

Manipulating the α-center of a β-amino acid is another attractive method, although stereospecific reactions are scarce.

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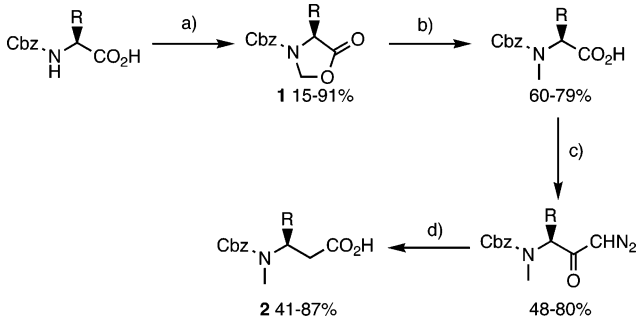
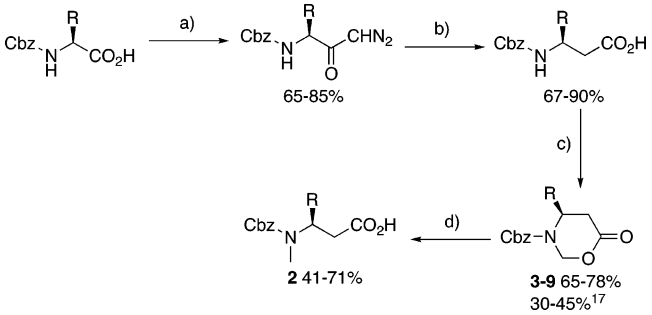
SCHEME 1. Synthesis of *N*-Methyl-*β*-Amino Acids 2 via 1,3-Oxazolidin-5-ones 1[17,18] (R refers to amino acid side chain)[a]



[a] Reagents and conditions: (a) $(CH_2O)_n$, cat. CSA, C_6H_6, reflux; (b) CF_3CO_2H, Et_3SiH, CH_2Cl_2; (c) 1. EtOCOCl, NMM; 2. CH_2N_2; (d) AgO_2CCF_3, H_2O, sonicate.

SCHEME 2. Synthesis of *N*-Methyl-*β*-Amino Acids 2 via 1,3-Oxazinan-6-ones 3−9[17,18] (R refers to alkyl and aryl groups)[a]



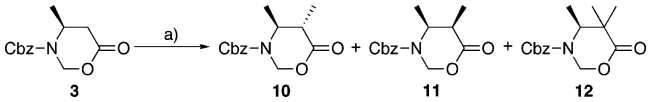
[a] Reagents and conditions: (a) 1. EtOCOCl, NMM; 2. CH_2N_2, $(CH_2O)_n$, cat. CSA, C_6H_6, reflux; (b) AgO_2CCF_3, H_2O, sonicate; (c) $(CH_2O)_n$, cat. CSA, C_6H_6, reflux; (d) CF_3CO_2H, Et_3SiH, CH_2Cl_2.

The only method exhibiting versatility and excellent selectivity uses perhydropyrimidinones.[3] However, these intermediates have the disadvantage of a lengthy preparation reaction sequence, and once the manipulation of the α-center has occurred, a harsh acid hydrolysis is performed to reveal the target *β*-amino acid. This hydrolysis leaves the *β*-amino acid with no protection usually required for subsequent reactions, and it also raises the question as to whether the hydrolysis will be as effective with more highly functionalized side chains. As Liu and Sibi stated in regard to this problem, "*The development of an efficient process suitable for large-scale synthesis, which is easy to operate, practical and inexpensive, remains a significant challenge*".[12] The application of 1,3-oxazinan-6-ones to produce α-substituted-*β*-amino acids, detailed herein, is a significant step toward solving these difficulties and providing access to a diverse range of these compounds.

Results and Discussion

Previously, we have described the use of both 1,3-oxazolidin-5-ones **1** and 1,3-oxazinan-6-ones for the production of *N*-methyl-*β*-amino acid derivatives **2** (Schemes 1 and 2).[17,18] It was found that synthesis of the *N*-methyl-*β*-residues **2** utilizing 1,3-oxazinan-6-ones **3**−**9** proceeded in lower than expected yields (Scheme 2). However, the use of 1,3-oxazolidin-5-ones **1** allowed for smooth conversion of the 20 common α-amino acids to their *N*-methyl homologues **2** using various protective group strategies for specific side chains (Scheme 1).

SCHEME 3. 5-Alkylation of the 1,3-Oxazinan-6-one 3[a]



[a] Reagents and conditions: (a) 1. base, THF, −78 °C, 40 min; 2. MeI, 3 h at −78 °C, then warmed to −15 °C, sat. NH_4Cl quench.

1,3-Oxazinan-6-ones are attractive templates for elaboration of *β*-amino acids in a variety of ways. However, to better utilize 1,3-oxazinan-6-ones in the efficient production of α,*β*-disubstituted-*β*-amino acids, the yields of the oxazinanones **3**−**9** (30−45%) (Scheme 2) we reported[17] using the procedure of Ben-Ishai needed to be improved.[19] Several other methods were attempted without any improvement in yield until the conditions of Burtin et al.[20,21] were applied. It was found that stirring the *N*-protected *β*-amino acids in toluene, with a catalytic amount of acid and activated 4 Å molecular sieves at 90 °C for 3−4 h, resulted in a marked improvement in yields of the oxazinanones **3**−**9** (65−78%).

Recently, Govender et al.[22] reported further improvement to the yields of 1,3-oxazinan-6-ones up to 82−96% using microwave technology. This pleasing development further strengthened our attraction to the oxazinanones as intermediates for the efficient synthesis of *β*-amino acid derivatives.

1,3-Oxazinan-6-one 5-Alkylation. Burtin et al.[20,21] is the only group to have prepared 5-alkyl-1,3-oxazinan-6-ones. The oxazinanones were derived from an *N*-Boc-protected aspartic acid derived residue; thus two acidic protons were present, requiring 2 equiv of base to form enolates. The enolates were then alkylated employing methyl iodide and benzyl bromide. The stereochemistry of the products was predominantly *trans*; however, the diastereoselectivity was poor. These results did not hold great promise for the series of alkylations we intended to perform.

Our initial enolate chemistry involved using the least sterically demanding chiral oxazinanone **3**. This oxazinanone **3** was treated with a variety of common amide bases (LDA, LiHMDS, NaHMDS, and KHMDS), and the resulting enolate was then treated with methyl iodide (Scheme 3).

All alkylations performed provided the *trans*-**10** and *cis*-**11** products (Scheme 3, Table 1). Alkylation using LDA (entry 1) or LiHMDS (entry 2) as base provided selectivity similar to the results observed by Burtin et al.[20,21] However, NaHMDS (entry 3) and KHMDS (entry 4) both afforded significantly better selectivity. This trend in the results suggests the anion is less important than the metal counterion. It appears use of sodium or potassium bases that are less likely to coordinate both the enolate oxygen and carbamate carbonyl, as a lithium counterion could, leads to higher diastereoselectivity (Table 1, entries 3 and 4) than the lithium bases (Table 1, entries 1 and 2).

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TABLE 1. 5-Alkylation of the 1,3-Oxazinan-6-one 3 Using Different Bases

entry	base	recovered **3** (%)	product yield **10** + **11** (%)	ratio **10:11**	product yield **12** (%)
1	LDA	15	33	5:1	11
2	LiHMDS	18	38	5.5:1	18
3	NaHMDS	24	44	9:1	8
4	KHMDS	18	38	11:1	14

TABLE 2. 5-Alkylation of the Oxazinanone 3 Using Different Bases with Cosolvent HMPA or DMPU[a]

entry	base	cosolvent	recovered **3** (%)	product yield **10** + **11** (%)	ratio **10:11**	product yield **12** (%)
1	LDA	HMPA	25	55	4:1	3
2	LiHMDS	HMPA	10	71	4:1	8
3	NaHMDS	HMPA	17	55	14:1	6
4	KHMDS	HMPA	25	38	19:1	20
5	KHMDS	DMPU	26	42	19:1	18

[a] Reagents and conditions: 1. base, THF, HMPA, −78 °C, 40 min; 2. MeI, 3 h at −78 °C, then warmed to −15 °C and sat. NH_4Cl quench.

TABLE 3. 5-Alkylation of the Oxazinanones 4−7 and 8

entry	oxazinanone	recovered oxazinanone (%)	product (%)	ratio *trans*:*cis*	product (%)
1	**4**	21	**13** (49)	>19:1	**17** (17)
2	**5**	28	**14** (30)	>19:1	**18** (20)
3	**6**	17	**15** (55)	>19:1	**19** (10)
4	**7**	35	**16** (35)	>19:1	
5[a]	**8**		**20**/**E**[b]	14:1	
6[c]	**8**	13	**20** (20)	>19:1	

[a] Note the reaction was quenched at −15 °C with sat. NH_4Cl. [b] E = C-5 epimer of compound **20**. [c] Note the reaction was quenched at −40 °C.

The product mixtures from these reactions were purified by column chromatography. Both starting material **3** and dialkylated product **12** were obtained, along with reasonable yields of the desired monoalkylated products **10** and **11**. However, the two diastereoisomers **10** and **11** were inseparable by column chromatography. HPLC separation was attempted on a semi-preparative scale, using a normal phase and both C-8 and C-18 reversed phase columns. The attempted separations all failed.

Fortunately, the *trans* diastereoisomer **10** is crystalline, and pure *trans* isomer **10** was obtained by multiple crystallizations of the mixture using ether and hexane. However, the *cis* isomer **11**, being an oil, could not be purified as some compound **10** persisted. ^{1}H NMR spectroscopy was used to determine the selectivity observed in the α-alkylation reactions by inspection of the integration ratios and *J* couplings. Figure 1 shows the *J* values of H-5 in compounds **10** and **11**.

The addition of hexamethylphosphoramide (HMPA) to enolate reactions had varying effects on reaction yields and stereoselectivity. Burtin et al.[20,21] observed that the addition of HMPA to the α-alkylation of oxazinanones did not affect the stereochemical outcome of the reaction. In their hands, the addition of HMPA resulted only in lower yields of the desired products. The reactions shown in Table 1 were repeated using the solvent THF/HMPA 4:1 (Table 2).

The results of the α-alkylation with lithium amide bases (Table 2) were as expected; a slight decrease in stereoselectivity

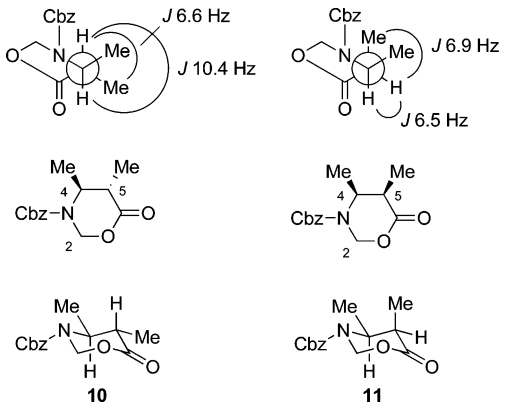
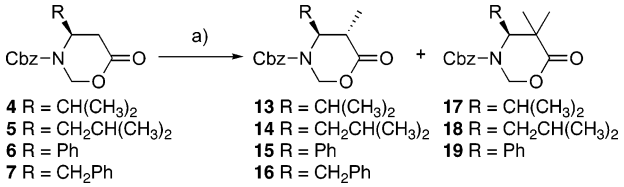


FIGURE 1. Newman and Haworth projections of oxazinanones **10** and **11** showing the H-5 coupling constants.

SCHEME 4. 5-Alkylation of Oxazinanones 4−7[a]



[a] Reagents and conditions: (a) 1. KHMDS, THF, HMPA, 40 min; 2. MeI, 3 h at −78 °C, then warmed to −15 °C and quenched.

was apparent, but there was a significant increase in yield of the desired singly substituted products **10** and **11** (Table 2, entries 1 and 2). Furthermore, pleasing results were found when employing either NaHMDS or KHMDS in association with HMPA (Table 2, entries 3 and 4). The stereoselectivities were increased, and this was attributed to chelation by the HMPA. Although the yield was only increased in the case of NaHMDS, this result was a significant step toward producing diastereoisomerically pure products.

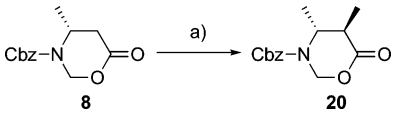
DMPU is less toxic than HMPA and is known as "*the safe alternative to HMPA*."[23] DMPU is reported as a cosolvent to produce similar reaction results as HMPA.[23] Use of DMPU as a cosolvent (DMPU/THF 1:2) was trialed (Table 2, entry 5) to ascertain its effect on the α-alkylation. This reaction confirmed that DMPU was a suitable replacement for HMPA. The reaction yield and selectivity were not compromised. However, due to the availability of DMPU at the time in our laboratory, HMPA was used to complete the remainder of the study.

The conditions determined in Table 2 were then applied to more highly substituted oxazinanones. Alkylation of the residues **4**−**7** employing KHMDS as base in a HMPA/THF solvent system (Scheme 4) proceeded well and with complete diastereoselectivity (as determined by ^{1}H NMR). The yields of the alkylations, however, were slightly lower than desired, ranging between 35 and 55% (Table 3).

It transpired that the temperature at which the alkylation reactions were quenched was of importance for stereoselectivity. When the oxazinanone **8** was alkylated with NaHMDS as base and then quenched at −15 °C, the compound **20** was isolated in 14:1 ratio with its C-5 epimer. When the same reaction was quenched with ammonium chloride solution at −40 °C, the *trans* isomer **20** was obtained exclusively (as determined by ^{1}H NMR)

(23) Seebach, D.; Beck, A. K.; Studer, A. *Mod. Synth. Methods* **1995**, *7*, 1−178.

SCHEME 5. 5-Alkylation of the Oxazinanone 8 Quenched at −40 °C[a]



[a] Reagents and conditions: (a) 1. NaHMDS, 4:1 THF/HMPA, 40 min; 2. MeI, 3 h at −78 °C, then warmed to −40 °C and sat. NH_4Cl quench.

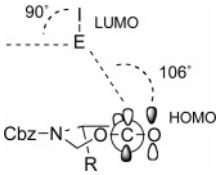


FIGURE 2. Illustration of the angle of approach of the electrophile to the oxazinanone enolate.

albeit in only 20% yield. The yield of the *trans* product **20** was compromised as a result of the lower reaction temperature (Scheme 5 and Table 3, entry 6).

The following rationale may explain the selectivity observed (Figure 2). The Houk trajectory[24] suggests the electrophile approaches the molecule at an angle of 106°, near perpendicular to the enolate plane. 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 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 *trans* selection as observed (Figure 2). Since the R groups in compounds **4**−**7** are larger than the methyl group of oxazinanones **3** and **8**, this facial selectivity is greater and no C-5 epimers of compounds **13**−**16** were isolated.

The series of reactions above shows that the enolates of the 1,3-oxazinan-6-ones can be alkylated at C-5 with exclusive *trans* selectivity if the C-4 substituent is larger than a methyl group. In the case of the R group being methyl, exclusive *trans* selection can be achieved by quenching the reaction at −40 °C albeit at the cost of a low product yield. In the next phase, we aimed to intercept the enolates with hydroxylating reagents that would allow development of 2-hydroxy-*β*-amino acids.

5-Hydroxylation of 1,3-Oxazinan-6-ones. Many methods offer a means of α-hydroxylation of a *β*-amino acid, but the majority do not offer complete selectivity.[3,6−16] Thus, it was postulated that suitably adapted oxazinanone methodology might offer a new avenue to these residues.

In order to 5-hydroxylate oxazinanones via their enolates, an electrophilic source of oxygen was required. Three hydroxylation agents that are commonly used in enolate chemistry were used in the study to determine which reagent would produce the highest yield and diastereoselectivity. The reagents were the camphorsulfonyloxaziridines **21** and **22**,[25] the Davis-type

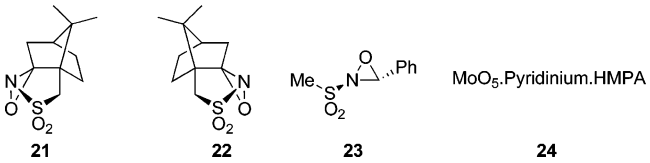
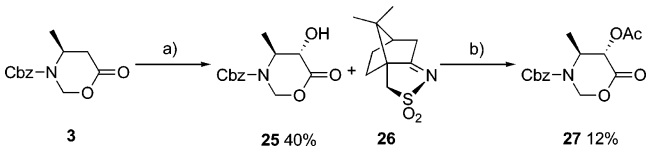


FIGURE 3. Reagents for hydroxylation of oxazinanone enolates.

SCHEME 6. 5-Hydroxylation and Acetylation of the Oxazinanone 3[a]



[a] Reagents and conditions: (a) 1. KHMDs, THF, −78 to −50 °C, 40 min; 2. **21**, −50 to −40 °C, 4 h, then warmed to −20 °C and sat. NH_4Cl quench. (b) acetic anhydride, pyridine, CH_2Cl_2, 0 °C to rt, 20 h.

oxaziridine **23**,[26] and molybdenum oxide pyridinium hexamethylphosphoramide complex (MoOPH) **24**[27] (Figure 3).

The camphorsulfonyloxaziridine was the first electrophile used in conjunction with the oxazinanone **3** (Scheme 6). The first reaction was conducted with KHMDS as a base without HMPA as a cosolvent. The electrophile (+)-(2*R*,8a*S*)-camphorsulfonyloxaziridine **21** was added 40 min after enolate formation. The solution was left to stir for 4 h at −78 °C, and it was then quenched with an ammonium chloride solution. A majority of the imine product **26** was crystallized from the product mixture using ether. Although this measure was taken to remove the imine **26**, separation of the imine and the product was still very difficult using column chromatography. The crude product **25** from the column was obtained in a poor yield (ca.10%). The assumption was that the (+)-(2*R*,8a*S*)-oxaziridine **21** could be the mismatched isomer and so a poor yield resulted.

The reaction was performed again using the protocol above, this time employing the (−)-(2*S*,8a*R*)-oxaziridine **22**. No improvement in yield resulted nor was the product **25** clean after column chromatography. HMPA was then trialed as a cosolvent in a reaction using KHMDS, but again, a poor yield of impure product **25** resulted. Another possibility was that KHMDS was an inappropriate base, and so LDA was tried, but the poor yield persisted.

Although poor yields were obtained throughout this series of reactions, it seemed that the product was one diastereoisomer **25**. Proof of this was obtained when one alcohol was purified by acetylating the hydroxyl group using acetic anhydride and pyridine, enabling the acetate **27** to be easily separated from residual imine **26** (Scheme 6).

The configuration of compound **27** was determined from the coupling constants of the H-4 and H-5 spin system (Figure 4). The observed $J_{4,5} = 9.1$ Hz is consistent with a *trans* configuration.

Since the oxaziridines **21** and **22** did not effect hydroxylation in the desired manner, another electrophilic source of oxygen was required. It was assumed that the oxaziridines **21** and **22** were too hindered, and so the less hindered Davis-type oxaziridine **23** (Figure 3) might enable hydroxylation of the enolate.

(24) Houk, K. N.; Paddon-Row, M. N. *J. Am. Chem. Soc.* **1986**, *108*, 2659−2662.

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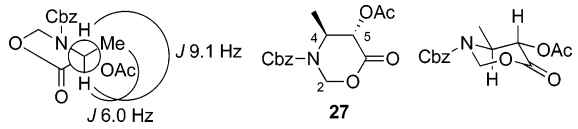
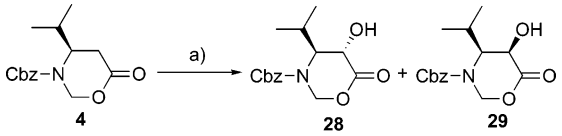


FIGURE 4. Newman and Haworth projections of the acetate **27**.

SCHEME 7. 5-Hydroxylation of the Oxazinanone 4 Employing the Davis-Type Oxaziridine 23 (a 5:3 dr of *trans*:*cis* isomers was obtained)[a]



[a] Reagents and conditions: (a) 1. NaHMDS, THF, −78 to −50 °C, 40 min; 2. **23**, −50 °C, 4 h, then warmed to −20 °C and sat. NH_4Cl quench.

The oxaziridine **23** was exposed to the enolate of compound **4** in similar reaction conditions as the oxaziridines **21** and **22**. Numerous bases were employed to generate the enolate, but no combination of base and oxaziridine **23** gave improved yields in comparison to those obtained with the oxaziridines **21** and **22**. In fact, use of the oxaziridine **23** resulted in lower yields (<10%) (Scheme 7).

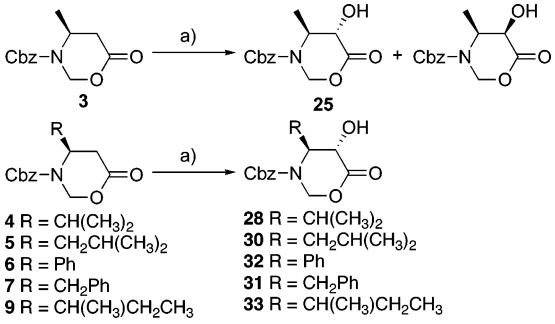
After the workup of the reaction, crystallization of the imine aided its removal from the crude product mixture prior to column chromatography. However, purification of the products **28** or **29** by column chromatography was ineffectual; the product and the remaining imine coeluted. A moderately clean sample of **28** was collected, but a clean sample of **29** was never obtained.

The failure of oxaziridines **21**, **22**, and **23** to hydroxylate effectively was unexpected and disappointing. The findings prompted the use of an inorganic source of electrophilic oxygen. MoOPH **24** (Figure 3) is another reagent commonly used for installing an α-hydroxyl in enolate chemistry.[27−30] MoOPH **24** has been used in the preparation of α-hydroxy-*β*-amino acids.[31−34]

A range of conditions was used in the development of methodology for the application of MoOPH **24** with oxazinanone enolate chemistry. Initial attempts at hydroxylation applying MoOPH **24** as an electrophile failed. The electrophile at −78 °C was allowed 4 h to react, but very little product was observed. Variation in the type of base did not alter the amount of product produced either.

However, when the temperature of the reaction was increased, significantly greater yields of the desired product were obtained. Following formation of the oxazinanone enolate at −78 °C, the reaction temperature was allowed to rise to −50 °C and the MoOPH **24** was then added. The reaction was allowed to warm further to around −40(±5) °C. At this stage, the solution took on a dark green coloration, indicating the reduction of MoOPH **24**, and so the reaction was proceeding. The solution was maintained at this temperature for 3 h and was then quenched at −30 °C with a saturated solution of sodium sulfite. The sodium sulfite destroys excess MoOPH and aids in its removal in the aqueous workup (Scheme 8).

SCHEME 8. 5-Hydroxylation of the Oxazinanones 3−7 and 9 Employing MoOPH 24[a]



[a] Reagents and conditions: (a) 1. NaHMDS, THF, −78 to −50 °C, 40 min; 2. MoOPH **24**, −50 to −40 °C, 4 h, then warmed to −20 °C and sat. NH_4Cl quench.

TABLE 4. 5-Hydroxylation of the Oxazinanones 3−7 and 9 Using MoOPH 24

oxazinanone	recovered oxazinanone (%)	product (%)	ratio *trans*:*cis*
alanine **3**	5	**25** (40)	>6:1
valine **4**	7	**28** (44)	>19:1
leucine **5**	5	**30** (46)	>19:1
phenylglycine **6**	20	**32** (23)	>19:1
phenylalanine **7**	6	**31** (19)	>19:1
isoleucine **9**	7	**33** (39)	>19:1

NaHMDS was used predominantly as the base in these reactions as it complemented the hydroxylation with MoOPH **24** well, allowing good yields and selectivity. The only residue for which this did not occur was the oxazinanone **3**, which was hydroxylated to form compound **25** as a mixture with the C-2 epimer (Scheme 8). Presumably, the lack of steric hindrance conferred by the methyl group meant it was not able to completely control the approach of the electrophile from one face. However, while the larger groups controlled the facial selection very well giving compounds **28** and **30**−**33**, it was observed that the larger the C-4 substituent, the lower were the yields of the desired product (Table 4). Even though complete selectivity in the hydroxylation was pleasing, the lower yields of the larger substituents, such as phenyl or benzyl, were disappointing, as these residues are most sought after (for example, in Taxol[3,35]).

Mitsunobu Inversion of the 5-Hydroxyl Substituent. The 5-hydroxylation of the oxazinanone produced *trans* configured residues. To produce the *cis* isomer, a Mitsunobu inversion of the alcohol might be used. The ester produced from the Mitsunobu reaction would then be hydrolyzed to produce the free inverted alcohol. Numerous syntheses employing a Mitsunobu reaction for inversion of the α-hydroxyl on *β*-amino acids are known.[3,36,37]

(28) Marin, J.; Didierjean, C.; Aubry, A.; Briand, J.-P.; Guichard, G. *J. Org. Chem.* **2002**, *67*, 8440−8449.
(29) Hara, O.; Takizawa, J.; Yamatake, T.; Makino, K.; Hamada, Y. *Tetrahedron Lett.* **1999**, *40*, 7787−7790.
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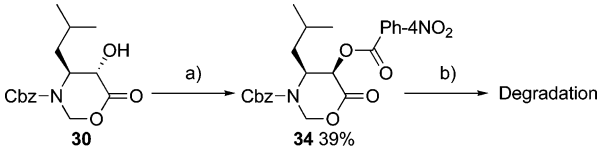
(31) Hanessian, S.; Vanasse, B. *Can. J. Chem.* **1993**, *71*, 1401−1406.
(32) Hanessian, S.; Sanceau, J.-Y. *Can. J. Chem.* **1996**, *74*, 621−624.
(33) May, B. C. H.; Abell, A. D. *Synth. Commun.* **1999**, *29*, 2515−2525.
(34) Sardina, F. J.; Paz, M. M.; Fernandez-Megia, E.; De Boer, R. F.; Alvarez, M. P. *Tetrahedron Lett.* **1992**, *33*, 4637−4640.
(35) Nicolaou, K. C.; Dai, W.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15−44.
(36) Hennings, D. D.; Williams, R. M. *Synthesis* **2000**, 1310−1314.
(37) Cardillo, G.; Tolomelli, A.; Tomasini, C. *Tetrahedron* **1995**, *51*, 11831−11840.

SCHEME 9. Mitsunobu Reaction of the 5-Hydroxyoxazinanone 30 and Resulting Degradation[a]



[a] Reagents and conditions: (a) PPh_3, DEAD, THF, *p*-nitrobenzoic acid, 0 °C to rt, 20 h; (b) silica column chromatography.

The initial attempts at the Mitsunobu inversion of the 5-hydroxyl in the oxazinanones were performed using *p*-nitrobenzoic acid as the nucleophile (Scheme 9). The application of *p*-nitrobenzoic acid affords high reaction yields in comparison to other nucleophiles.[38] Due to the electron-withdrawing nature of *p*-nitrobenzoic acid, saponification of the resulting benzoate is facile.

The Mitsunobu reaction was conducted in the usual manner in THF, and the reaction was complete, as indicated by TLC, in 20 h. An aqueous workup allowed removal of any remaining benzoic acid. The resulting crude could be further purified by crystallization of the triphenylphosphine oxide byproduct, using a mixture of 75% ether/hexane. The crude residue was then purified by column chromatography. The resulting ester **34** was unexpectedly obtained in a low yield (39%). This result was at first puzzling as numerous repetitions of the reaction resulted in yields lower than 39%. On every occasion, the TLC indicated the complete absence of the starting oxazinanone **30** and the crude yield of the product was high. It was assumed that degradation of the product **34** was occurring. When a 2D TLC was performed, it was apparent that the product **34** was degrading on silica (Scheme 9). The use of neutral and basic alumina for chromatography also resulted in no isolation of the desired product.

Due to the electron-withdrawing nature of the *p*-nitrobenzoate, it was postulated that the use of benzoic acid might quell the degradation of the product. However, no improvement was observed using benzoic acid. It was decided not to perform chromatography at this point, but rather attempt purification after the hydrolysis of the benzoate was performed. Chromatography after saponification resulted in incomplete inversion of the hydroxyl stereocenter. This is attributed to incomplete Mitsunobu reaction and remnants of the starting oxazinanone **30**.

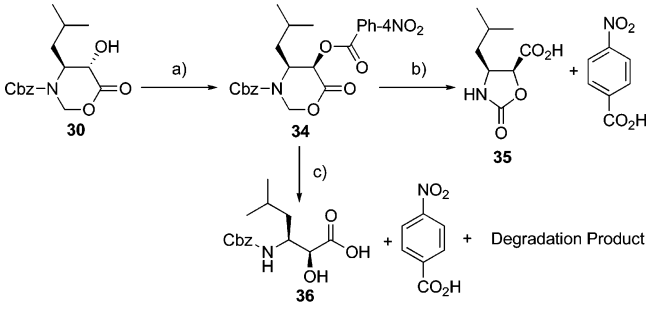
The hydrolysis of the acetate **33** was not very successful, and although saponification of the benzoate **34** occurred using 4 M LiOH at 0 °C in 10 min, hydrolysis of the oxazinanone ring also occurred, resulting in benzoic acid and the lactone **35** (Scheme 10).

When an acidic hydrolysis was performed, employing acetic acid/water 4:1, a mixture of benzoic acid, the product **36**, and an unknown byproduct was obtained. This mixture was diabolical to separate by crystallization and column chromatography. Furthermore, the crude residue was obtained in low yield (Scheme 10).

Further Elaboration of Oxazinanones. 1,3-Oxazinan-6-ones, like many lactones, can undergo useful manipulations contributing to their overall appeal as synthetic intermediates. The following reactions are examples of how the oxazinanone can be manipulated and exploited to deliver various β-amino acid derivatives. The manipulations performed highlight the versatility of oxazinanones (Figure 5), in comparison to other synthetic approaches reviewed elsewhere.[3,6–16]

(38) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017–3020.

SCHEME 10. Mitsunobu Reaction of the Oxazinanone 30 and Resulting Hydrolyses[a]



[a] Reagents and conditions: (a) PPh_3, DEAD, THF, *p*-nitrobenzoic acid, 0 °C to rt, 20 h; (b) 4 M LiOH, MeOH, 0 °C, 10 min; (c) $AcOH/H_2O$, 4:1, 0.01 equiv of HCl, 45 °C, 20 h.

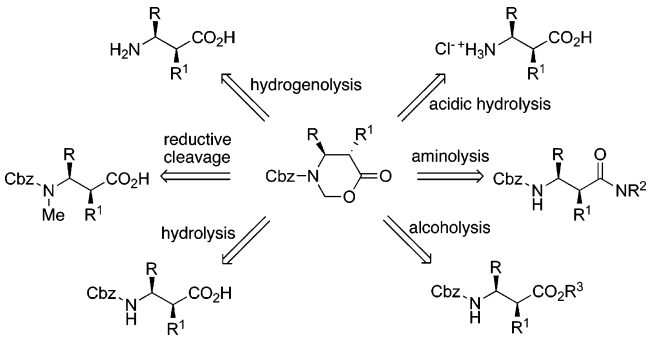
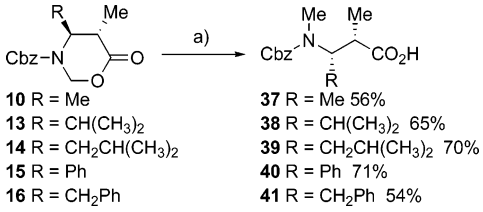


FIGURE 5. Oxazinanone ring openings.

SCHEME 11. Reductive Cleavage of Oxazinanones 10 and 13–16[a]



[a] Reagents and conditions: (a) TFA/CH_2Cl_2, 50:50, Et_3SiH, rt, 3 days.

Reductive Cleavage of 5-Methylated 1,3-Oxazinan-6-ones. *N*-Methyl amino acids are of great interest to us for reasons discussed elsewhere,[17,18,39–41] and so reductive cleavage of the 5-methyl-4-substituted oxazinanones was performed. The reductive cleavage of these oxazinanones occurs in a fashion analogous to the reductive cleavage of 1,3-oxazolidin-5-ones.[40,41] Reductive cleavage of the 5-methyl oxazinanones **10** and **13–16** proceeded smoothly. The yields of the products **37–41** ranged from 54 to 70% (Scheme 11).

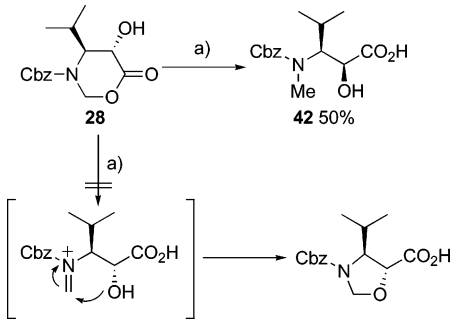
The smooth conversion of the 5-methyl oxazinanones to the *N*-methyl β-amino acids **37–41** prompted examination of the reductive cleavage of the corresponding 5-hydroxy oxazinanones. It was not known whether any hydroxyl protection

(39) Sleebs, B. E. Ph.D. Thesis, La Trobe University, 2006.

(40) Aurelio, L.; Box, J. S.; Brownlee, R. T. C.; Hughes, A. B.; Sleebs, M. M. *J. Org. Chem.* **2003**, *68*, 2652–2667.

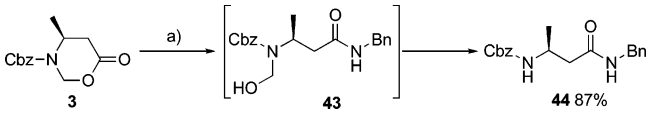
(41) Aurelio, L.; Brownlee, R. T. C.; Hughes, A. B.; Sleebs, B. E. *Aust. J. Chem.* **2000**, *53*, 425–433.

SCHEME 12. Reductive Cleavage of the Oxazinanone 28[a]



[a] Reagents and conditions: (a) Et_3SiH, 50:50 TFA/CH_2Cl_2, rt, 3 days.

SCHEME 13. Opening of the Oxazinanone 3 with Benzyl Amine[a]



[a] Reagents and conditions: (a) 2 equiv of $BnNH_2$, CH_2Cl_2, rt, 24 h.

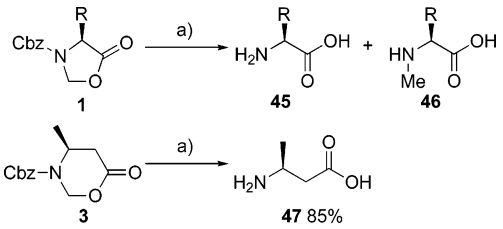
was required for the reductive cleavage of the oxazinanones to the *N*-methyl-α-hydroxy-*β*-amino acid (Scheme 12). In studies conducted by Aurelio et al.,[41] reductive cleavage of an unprotected threonine-derived 1,3-oxazolidin-5-one produced a mixture of products with some resulting from participation of the side chain hydroxyl. This prompted use of side chain protection to give the desired *N*-methyl threonine.[40] In the first instance, the 5-hydroxy oxazinanone **28** was subjected to reductive cleavage using triethylsilane and trifluoroacetic acid over a period of 3 days. Only the *N*-methyl residue **42** was obtained (50% yield) (Scheme 12).

The 5-methyl and 5-hydroxy oxazinanones can thus be converted into the corresponding *N*-methyl 2-methyl and 2-hydroxy-*β*-amino acids. Recently, Govender et al.[22] showed that using microwaves in the presence of a Lewis acid greatly improved the yields in the reductive cleavage of 1,3-oxazinan-6-ones. This is a further enhancement of the effectiveness of oxazinanones as substrates for the synthesis of *β*-amino acid derivatives.

Oxazinanone Aminolysis. Micheel et al.[42] and Ben-Ishai[19] are responsible for initial developments in this area. They used primary amines as nucleophiles to open 1,3-oxazolidin-5-ones, producing amides. In a similar vein, the oxazinanone **3** was exposed to an excess of amine in a minimal volume of methylene chloride. The oxazinanone **3** was consumed in a period of 24 h at room temperature. The transformation most likely proceeded via the *N*-hydroxymethylbenzylamide **43**, affording the benzylamide **44** in excellent yield (87%) (Scheme 13).

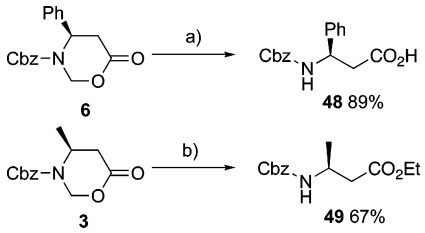
Oxazinanone Hydrogenolysis. Hydrogenolysis of *N*-benzyloxycarbonyl-1,3-oxazolidin-5-ones results in a mixture of *N*-methyl and *N*-H amino acids.[41] Others have described contradictory results for the hydrogenolysis of oxazolidinones,[43] but these results were clarified by Aurelio et al.[41] Aurelio et al.[41] describe the need for an *N*-H to be present for the hydrogenolytic reduction of an oxazolidinone to obtain an

SCHEME 14[a]



[a] Reagents and conditions: (a) H_2, Pd/C, MeOH (R refers to amino acid side chain).

SCHEME 15. Base Hydrolysis of Oxazinanones 3 and 6[a]



[a] Reagents and conditions: (a) 4 M LiOH, H_2O/MeOH, 0 °C, 10 min; (b) $NaHCO_3$, dry EtOH, reflux, 20 h.

N-methyl; that is, the Cbz protection is cleaved to produce an oxazolidinone *N*-H. These findings are in accord with the hydrogenolysis of *N*-*tert*-butyloxycarbonyl-1,3-oxazolidin-5-ones, which produces no *N*-methyl product, and *N*-benzyloxycarbonyl-1,3-oxazolidin-5-one **1** reduction, which produces a mixture of *N*-H **45** and *N*-methyl **46** amino acids.

Hydrogenolysis of the oxazinanone **3** produced the deformylated product **47** (85%) (Scheme 14). Only small amounts (<5%) of the *N*-methyl derivative were observed in the crude ^{1}H NMR spectrum. This result should be compared with that of Burtin et al.,[20] who reported no ring opening when a hydrogenation on a *tert*-butoxycarbonyl-*N*-protected oxazinanone was performed. These results suggest that the oxazinanone is only opened by hydrogenolysis when an *N*-H is present, that is, after the Cbz protection has been hydrogenolytically cleaved, and this is in accord with the results of hydrogenolysis of oxazolidinones described by Itoh[44] and Aurelio et al.[41]

Oxazinanone Basic Hydrolysis. Saponification of the 1,3-oxazolidin-5-one ring affords the *N*-protected α-amino acid. An aqueous methanolic solution of 1 M sodium hydroxide solution at room temperature effects the hydrolysis in 4 h.[44] The same conditions did not cause efficient hydrolysis of the oxazinanone ring. The solution was heated to 50 °C, and only a mixture of the oxazinanone and product was obtained. The difference between the hydrolysis rates of the two lactones is attributable to the oxazinanone ring being more stable than the five-membered analogue. A more concentrated reaction solution was trialed while being cognizant of the possibility of racemization of the residue. To a solution of the oxazinanone **6** in cold methanol was added a 4 M lithium hydroxide solution. The oxazinanone ring **6** hydrolyzed in 10 min at 0 °C, as monitored by TLC. The reaction mixture was acidified to obtain the *N*-benzyloxycarbonyl-*β*-amino acid **48** in 89% yield (Scheme 15).

A more facile solvolysis is cleavage of the oxazolidinone by sodium hydrogen carbonate, as used effectively by Allevi et

(42) Micheel, F.; Meckstroth, W. *Chem. Ber.* **1959**, *92*, 1675−1679.
(43) Reddy, G. V.; Rao, G. V.; Iyengar, D. S. *Tetrahedron Lett.* **1998**, *39*, 1985−1986.
(44) Itoh, M. *Chem. Pharm. Bull.* **1969**, *17*, 1679−1686.

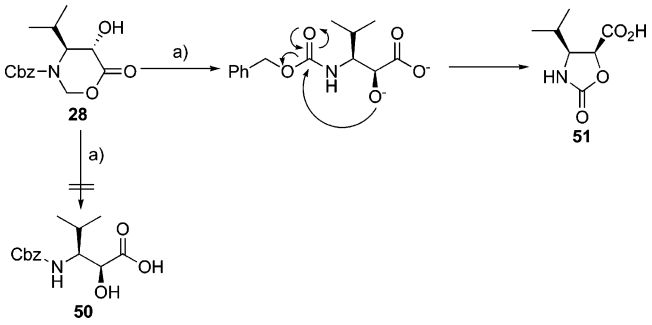
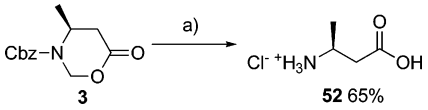


FIGURE 6. Attempted base hydrolysis of 5-hydroxy oxazinanone **28**. (a) Reagents and conditions: 4 M LiOH, MeOH, 0 °C, 10 min.

SCHEME 16. Acidic Hydrolysis of Oxazinanone 3[a]



[a] Reagents and conditions: (a) 6 M HCl, dioxane, reflux, 4 h.

al.[45] This reaction involves refluxing the 1,3-oxazolidin-5-one in dry alcoholic solvent with an excess of dry sodium hydrogen carbonate. Complete reaction occurs in 10 min, and the *N*-benzyloxycarbonyl-α-amino acid ester is obtained in high yields. The same solvolysis performed on oxazinanones was not complete in 10 min as observed by TLC. Complete reaction required 20 h, and again, this was attributed to the stability of the 1,3-oxazinan-6-one over the 1,3-oxazolidin-5-one. The *N*-benzyloxycarbonyl-*β*-amino acid ethyl ester **49** was obtained in 67% yield (Scheme 15).

The LiOH hydrolysis conditions were then applied to the 5-hydroxy-1,3-oxazinan-6-ones. To oxazinanone **28** in methanol was added 4 M lithium hydroxide solution at 0 °C. The hydrolysis of the oxazinanone was complete in 10 min; however, the expected product **50** was not obtained. Although hydrolysis of the oxazinanone did occur, the initial product was able to undergo an intramolecular cyclization. Evidently, the 5-hydroxyl in basic solution was converted to the alkoxide, and the nucleophilic alkoxide attacked the carbamate carbonyl, producing benzyl alcohol and forming a new lactone **51** (Figure 6). There is evidence of this phenomenon occurring elsewhere.[46]

Oxazinanone Acidic Hydrolysis. Acid hydrolysis of any amino acid lactone gives the salt of the amino acid. Acid hydrolysis of the oxazinanone opens the ring, and *N*-carbamoyl protection is also cleaved under these conditions. Refluxing the oxazinanone **3** in 6 M hydrochloric acid/aqueous dioxane solution resulted in a 65% yield of the hydrochloride salt **52** (Scheme 16).

Conclusion

1,3-Oxazinan-6-ones have been utilized in a variety of enolate reactions to produce important α-substituted-*β*-amino acids. The α-position was methylated using methyl iodide. The best conditions for the reaction employed KHMDS with HMPA cosolvent in THF to give the residues with excellent *trans* selectivity.

Similar conditions were used for hydroxylating the 5-position of the 1,3-oxazinan-6-one. A number of electrophilic hydroxylating reagents were tried. It was found that MoOPH was the most successful hydroxylating reagent, also providing the desired residues with excellent *trans* selectivity.

The 5-substituted 1,3-oxazinan-6-ones were then subjected to reductive cleavage conditions to give the *N*-methyl-α-substituted-*β*-amino acids in good yields. A Mitsunobu reaction was attempted on the 5-hydroxy-1,3-oxazinan-6-ones to invert C-5. However, complications occurred, and degradation of the product on silica gel was observed. Subsequent hydrolysis also resulted in poor yields and purification problems. More development is required in this area for the method to find a wider range of applicability.

The 1,3-oxazinan-6-ones are versatile substrates, allowing excellent *trans* selectivity. Subsequent reactions give access to a variety of α-substituted-*β*-amino acids. These residues, many of which are found in nature, are highly biologically active and will find a wide variety of applications in therapeutics or pharmaceutics.

Experimental Section

General experimental details and spectra of key intermediates can be found in the Supporting Information.

General Procedure A. 1,3-Oxazinan-6-ones. To the *N*-benzyloxycarbonyl *β*-amino acid (1 mmol) in dry toluene (30 mL) were added camphorsulfonic acid (0.1 mmol), paraformaldehyde (6 mmol), and activated 4 Å molecular sieves (150 mg) under an inert atmosphere. The reaction mixture was stirred at 90 °C for 4 h. The mixture was allowed to cool and filtered through Celite. The filtrate was diluted with ethyl acetate (30 mL), and the organic layer was washed with saturated sodium bicarbonate (20 mL) and water (20 mL). The organic layer was dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was purified using column chromatography, eluting with 20−45% ethyl acetate/hexane.

(4*S*)-*N*-Benzyloxycarbonyl-4-methyl-1,3-oxazinan-6-one 3. The *N*-Cbz-*β*-amino acid (1 mmol) was transformed according to General Procedure A and afforded the oxazinanone **3** as an oil (65% yield), with spectra identical to those of an authentic sample.[17]

(4*S*)-*N*-Benzyloxycarbonyl-4-(1-methylethyl)-1,3-oxazinan-6-one 4. The *N*-Cbz-*β*-amino acid (1 mmol) was transformed according to General Procedure A and afforded the oxazinanone **4** as an oil (65% yield), with spectra identical to those of an authentic sample.[17]

(4*S*)-*N*-Benzyloxycarbonyl-4-(2-methylpropyl)-1,3-oxazinan-6-one 5. The *N*-Cbz-*β*-amino acid (1 mmol) was transformed according to General Procedure A and afforded the oxazinanone **5** as an oil (68% yield), with spectra identical to those of an authentic sample.[17]

***N*-Benzyloxycarbonyl-4-phenyl-1,3-oxazinan-6-one 6.** The *N*-Cbz-*β*-amino acid (1 mmol) was transformed according to General Procedure A and afforded the oxazinanone **6** as an oil (55% yield), with spectra identical to those of an authentic sample.[17]

(4*S*)-*N*-Benzyloxycarbonyl-4-phenylmethyl-1,3-oxazinan-6-one 7. The *N*-Cbz-*β*-amino acid (1 mmol) was transformed according to General Procedure A and afforded the oxazinanone **7** as an oil (78% yield), with spectra identical to those of an authentic sample.[17]

(4*R*)-*N*-Benzyloxycarbonyl-4-methyl-1,3-oxazinan-6-one 8. The *β*-amino acid (1 mmol) was transformed according to General Procedure A, which afforded the oxazinanone **8** as a clear colorless oil (65% yield). Found: M + H, 250.1079; $C_{13}H_{15}NO_4$ requires M + H, 250.1079. $[\alpha]^{20}_D$ −105.3 (*c* 3.3, CH_2Cl_2). ν_{max}(NaCl)/cm^{-1} 2973, 2932, 1767, 1714, 1455, 1266, 1159, 999, 771, 750, 699. ^{1}H NMR (300 MHz, $CDCl_3$) (rotamers): δ 7.25 (5H, s), 5.67 (1H, d, J = 10.0 Hz), 5.11 (2H, s), 4.95 (1H, d, J = 10.8 Hz), 4.18 (1H,

(45) Allevi, P.; Cighetti, G.; Anastasia, M. *Tetrahedron Lett.* **2001**, *42*, 5319−5321.

(46) Herranz, R.; Castro-Pichel, J.; Vinuesa, S.; Garcia-Lopez, M. T. *J. Org. Chem.* **1990**, *55*, 2232−2234.

br s), 2.65 (1H, dd, J = 6.6 and 16.0 Hz), 2.40 (1H, dd, J = 10.3 and 6.3 Hz), 1.18 (3H, d, J = 6.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers): δ 169.7, 153.7, 135.2, 128.0, 127.9, 127.8, 127.5, 71.2, 67.3, 45.8, 36.3, 20.9.

(2*R*)-*N*-Benzyloxycarbonyl-4-((1*S*)-1-methylpropyl)-1,3-oxazinan-6-one 9. The *N*-Cbz-β-amino acid (1 mmol) was transformed according to General Procedure A and afforded the oxazinanone **9** as an oil (76% yield), with spectra identical to those of an authentic sample.[17]

Synthesis of α,β-Disubstituted-β-Amino Acid Derivatives. 5-Alkylated 1,3-Oxazinan-6-ones. General Procedure B. Alkylation of Oxazinanones. The oxazinanone (0.5 mmol) was dissolved in dry THF (4 mL), and the solution was cooled to −78 °C under an argon atmosphere. The amide base (0.52 mmol) was added dropwise and the solution was left to stir at −78 °C for 40 min. Methyl iodide (5 mmol) was added, and stirring was continued for 4 h at −78 °C. The solution was then allowed to warm to −15 °C, and the reaction was then quenched with saturated ammonium chloride solution (5 mL). The solution was diluted with ethyl acetate (20 mL) and washed with water (20 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give an oily residue. The oil was subjected to column chromatography, eluting with 5−20% ethyl acetate/hexane, to afford starting material, 5,5-disubstituted, and 5-substituted products.

(4*S*,5*S*)-*N*-Benzyloxycarbonyl-4,5-dimethyl-1,3-oxazinan-6-one 10, (4*S*,5*R*)-*N*-Benzyloxycarbonyl-4,5-dimethyl-1,3-oxazinan-6-one 11, and (4*S*)-*N*-Benzyloxycarbonyl-4,5,5-trimethyl-1,3-oxazinan-6-one 12. The oxazinanone **3** (0.5 mmol) was transformed according to General Procedure B using KHMDS (0.5 M in toluene) as the base and a THF/HMPA 4:1 mixture as the solvent to afford starting material **3** (25% recovery) and a mixture of diastereoisomers **10** and **11** in a 18:1 (*trans*:*cis*) ratio. The 5-substituted oxazinanone **10** was crystallized from the mixture using ether and hexane, affording **10** as a white solid (38% yield). Found: C, 63.91; H, 6.62; N, 5.24; $C_{14}H_{17}NO_4$ requires C, 63.97; H, 6.51; N, 5.32. Mp 81−83 °C. $[\alpha]^{20}_D$ +148.1 (*c* 0.77, CH_2Cl_2). ν_{max}(KBr)/cm^{-1} 2981, 1766, 1711, 1413, 1247, 1138, 1010, 752, 698. ^{1}H NMR (300 MHz, $CDCl_3$) (325 K): δ 7.34 (5H, s), 5.84 (1H, d, J = 10.7 Hz), 5.17 (2H, s), 5.02 (1H, d, J =10.6 Hz), 3.80−3.74 (1H, m), 2.47 (1H, dq, J = 10.4 and 6.6 Hz), 1.36 (3H, d, J = 6.2 Hz), 1.28 (3H, d, J = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) (300 K): δ 172.5, 153.9, 135.5, 128.5, 128.3, 128.1, 70.7, 68.0, 52.8, 41.3, 19.2, 13.2.

The *cis* isomer **11** was isolated as a chromatographically inseparable mixture of *cis* and *trans* diastereoisomers (differentiated from the *trans* NMR data). ^{1}H NMR (300 MHz, $CDCl_3$) (325 K): δ 7.32 (5H, s), 5.59 (1H, d, J = 9.5 Hz), 5.41 (1H, d, J = 9.8 Hz), 5.22 (2H, s), 4.28−4.20 (1H, m), 2.98 (1H, dq, J = 6.9 and 6.5 Hz), 1.20 (3H, d, J = 6.6 Hz), 1.19 (3H, d, J = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) (325 K): δ 171.9, 154.0, 135.9, 128.6, 128.4, 128.2, 73.2, 68.1, 50.9, 39.1, 15.9, 11.6.

The 5,5-disubstituted oxazinanone **12** was isolated as a clear colorless oil (20% yield). Found: M + H, 278.1392; $C_{15}H_{19}NO_4$ requires M + H, 278.1392. $[\alpha]^{20}_D$ +44.8 (*c* 0.77, CH_2Cl_2). ν_{max}(NaCl)/cm^{-1} 2980, 2945, 1746, 1712, 1421, 1248, 1109, 1010, 746, 698. ^{1}H NMR (300 MHz, $CDCl_3$) (323 K): δ 7.24 (5H, s), 5.87 (1H, d, J = 9.9 Hz), 5.23−5.18 (3H, m), 4.21−4.15 (1H, m), 1.29−1.22 (9H, m). ^{13}C NMR (75 MHz, $CDCl_3$) (323 K): δ 174.5, 153.7, 135.6, 128.6, 128.5, 128.2, 72.4, 68.1, 54.3, 44.2, 26.8, 19.3, 15.2.

The oxazinanone **3** (0.5 mmol) was transformed according to General Procedure B using a solution of LDA as the base [prepared by adding *n*-butyl lithium (1.53 M solution in hexanes, 0.52 mmol) to a stirred solution of diisopropylamine (0.52 mmol) in dry THF (2 mL)]. The LDA solution was added dropwise at 0 °C under an inert atmosphere to afford starting material **3** (15% recovery), a mixture of the diastereoisomers **10** and **11** in a 5:1 (*trans*:*cis*) ratio (33% yield), and the oxazinanone **12** (11% yield). The spectra were identical to those of the samples prepared above.

The oxazinanone **3** (0.5 mmol) was transformed according to General Procedure B using LiHMDS (1.0 M solution in hexanes) as the base and THF as the solvent to afford the starting material **3** (18% recovery), a mixture of the diastereoisomers **10** and **11** in a 5.5:1 (*trans*:*cis*) ratio (38% yield), and the oxazinanone **12** (18% yield). The spectra were identical to those of the samples prepared above.

The oxazinanone **3** (0.5 mmol) was transformed according to General Procedure B using NaHMDS (1.0 M solution in hexanes) as the base and THF as the solvent to afford starting material **3** (24% recovery), a mixture of the diastereoisomers **10** and **11** in a 9:1 (*trans*:*cis*) ratio (44% yield), and the oxazinanone **12** (8% yield). The spectra were identical to those of the samples prepared above.

The oxazinanone **3** (0.5 mmol) was transformed according to General Procedure B using KHMDS (0.5 M solution in toluene) as the base and THF as the solvent to afford the starting material **3** (18% recovery), a mixture of the diastereoisomers **10** and **11** in a 11:1 (*trans*:*cis*) ratio (38% yield), and the oxazinanone **12** (14% yield). The spectra were identical to those of the samples prepared above.

The oxazinanone **3** (0.5 mmol) was transformed according to General Procedure B using a pre-prepared solution of LDA as the base [prepared by adding *n*-butyl lithium (1.53 M solution in hexanes, 0.52 mmol) to a stirred solution of diisopropylamine (0.52 mmol) in dry THF (2 mL)] in a 4:1 mixture of THF/HMPA as the solvent to afford the starting material **3** (25% recovery), a mixture of the diastereoisomers **10** and **11** in a 4:1 (*trans*:*cis*) ratio (55% yield), and the oxazinanone **12** (3% yield). The spectra were identical to those of the samples prepared above.

The oxazinanone **3** (0.5 mmol) was transformed according to General Procedure B using LiHMDS (1.0 M solution in hexanes) as the base in a 4:1 mixture of THF/HMPA as the solvent to afford the starting material **3** (10% recovery), a mixture of the diastereoisomers **10** and **11** in a 4:1 (*trans*:*cis*) ratio (71% yield), and the oxazinanone **12** (8% yield). The spectra were identical to those of the samples prepared above.

The oxazinanone **3** (0.5 mmol) was transformed according to General Procedure B using NaHMDS (10 M solution in hexanes) as the base and a 4:1 mixture of THF/HMPA as the solvent to afford the starting material **3** (17% recovery), a mixture of the diastereoisomers **10** and **11** in a 14:1 (*trans*:*cis*) ratio (55% yield), and the oxazinanone **12** (6% yield). The spectra were identical to those of the samples prepared above.

The oxazinanone **3** (0.5 mmol) was transformed according to General Procedure B using KHMDS (0.5 M solution in toluene) as the base and a 2:1 mixture of THF/DMPU as the solvent to afford the starting material **3** (26% recovery), a mixture of the diastereoisomers **10** and **11** in a 19:1 (*trans*:*cis*) ratio (42% yield), and the oxazinanone **12** (18% yield). The spectra were identical to those of the samples prepared above.

(4*S*,5*S*)-*N*-Benzyloxycarbonyl-4-isopropyl-5-methyl-1,3-oxazinan-6-one 13 and (4*S*)-*N*-Benzyloxycarbonyl-4-isopropyl-5,5-dimethyl-1,3-oxazinan-6-one 17. The oxazinanone **4** (0.5 mmol) was transformed according General Procedure B using KHMDS (0.5 M in toluene) as the base and a 4:1 mixture of THF/HMPA as the solvent to afford the starting material **4** (21% yield), and the oxazinanone **13** was isolated as a clear colorless oil (49% yield). Found: M + H, 292.1548; $C_{16}H_{21}NO_4$ requires M + H, 292.1549. $[\alpha]^{20}_D$ +119.3 (*c* 0.56, CH_2Cl_2). ν_{max}(NaCl)/cm^{-1} 2968, 1754, 1712, 1408, 1258, 1133, 1000, 698. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (5H, s), 5.89 (1H, br s), 5.16 (2H, s), 4.93 (1H, d, J = 10.7 Hz), 3.80 (1H, br s), 2.71 (1H, dq, J = 6.7 and 8.6 Hz), 2.02−1.94 (1H, m), 1.31 (3H, d, J = 6.7 Hz), 1.01 (3H, d, J = 5.7 Hz), 0.94 (3H, d, J = 6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.8, 155.4, 135.4, 128.6, 128.4, 128.2, 73.0, 68.3, 61.0, 38.1, 31.4, 20.4, 17.0, 15.2.

The oxazinanone **17** was isolated as an oil (17% yield). Found: M + H, 306.1700; $C_{17}H_{23}NO_4$ requires M + H, 306.1705. $[\alpha]^{20}_D$ +17.0 (*c* 0.28, CH_2Cl_2). ν_{max}(KBr)/cm^{-1} 3033, 2967, 1747, 1713, 1392, 1246, 1101, 1011, 747, 698. ^{1}H NMR (300 MHz, $CDCl_3$)

(323 K): δ 7.33 (5H, s), 5.92 (1H, br s), 5.26−5.07 (3H, m), 4.00 (1H, br s), 2.12−2.05 (1H, m), 1.31−1.29 (6H, m), 1.04−0.88 (6H, m). ^{13}C NMR (75 MHz, $CDCl_3$) (323 K): δ 174.3, 154.8, 135.9, 128.6, 128.4, 128.2, 128.1, 128.0, 75.1, 68.2, 63.7, 43.1, 29.6, 27.8, 22.0, 21.4, 18.5.

(4*S*,5*S*)-*N*-Benzyloxycarbonyl-4-isobutyl-5-methyl-1,3-oxazinan-6-one 14 and (4*S*)-*N*-Benzyloxycarbonyl-4-isobutyl-5,5-dimethyl-1,3-oxazinan-6-one 18. The oxazinanone **5** (0.5 mmol) was transformed according to General Procedure B using KHMDS (0.5 M in toluene) as the base and a 4:1 mixture of THF/HMPA as the solvent to afford the starting material **5** (28% recovery), and the oxazinanone **14** was isolated as a clear colorless oil (30% yield). Found: M + H, 306.1705; $C_{17}H_{23}NO_4$ requires M + H, 306.1705. $[\alpha]^{20}_D$ +88.2 (*c* 0.45, CH_2Cl_2). ν_{max}(NaCl)/cm^{-1} 2958, 1757, 1714, 1414, 1251, 1134, 963, 698. ^{1}H NMR (300 MHz, $CDCl_3$) (323 K): δ 7.32 (5H, s), 5.84 (1H, d, *J* = 10.5 Hz), 5.16 (2H, s), 4.96 (1H, d, *J* = 10.6 Hz), 3.94 (1H, br s), 2.40 (1H, dq, *J* = 6.8 and 7.3 Hz), 1.66−1.39 (2H, m), 1.28 (3H, d, *J* = 6.7 Hz), 0.89 (6H, d, *J* = 6.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.22, 155.0, 135.6, 128.6, 128.4, 128.3, 71.5, 68.3, 55.0, 44.2, 41.5, 24.4, 23.7, 21.8, 14.5.

The oxazinanone **18** was isolated as a clear colorless oil (20% yield). Found: M + H, 320.1861; $C_{18}H_{25}NO_4$ requires M + H, 320.1862. $[\alpha]^{20}_D$ +24.7 (*c* 0.36, CH_2Cl_2). ν_{max}(NaCl)/cm^{-1} 2958, 2872, 1746, 1712, 1420, 1249, 1106, 1006, 747, 699. ^{1}H NMR (300 MHz, $CDCl_3$) (rotamers) (323 K): δ 7.33 (5H, s), 5.98 (1H, br s), 5.19 (2H, s), 5.02 (1H, d, *J* = 10.1 Hz), 4.17 (1H, br s), 1.63−1.40 (3H, m), 1.27 (3H, s), 1.19 (3H, s), 0.93−0.88 (6H, m). ^{13}C NMR (75 MHz, $CDCl_3$) (323 K): δ 174.4, 154.5, 135.7, 128.6, 128.5, 128.3, 128.0, 72.7, 68.3, 57.0, 44.9, 36.8, 27.6, 24.5, 23.7, 21.8, 21.0.

(4*R*,5*S*)-*N*-Benzyloxycarbonyl-4-phenyl-5-methyl-1,3-oxazinan-6-one 15 and (4*S*)-*N*-Benzyloxycarbonyl-4-phenyl-5,5-dimethyl-1,3-oxazinan-6-one 19. The oxazinanone **6** (0.5 mmol) was transformed according to General Procedure B using KHMDS (0.5 M in toluene) as the base and a 4:1 mixture of THF/HMPA as the solvent to afford the starting material **6** (17% recovery), and the oxazinanone **15** was isolated as a white solid (55% yield). Found: M + H, 326.1390; $C_{19}H_{19}NO_4$ requires M + H, 326.1392. Mp 127−131 °C. $[\alpha]^{20}_D$ +75.1 (*c* 3.0, CH_2Cl_2). ν_{max}(KBr)/cm^{-1} 3034, 2933, 1761, 1714, 1409, 1256, 1007, 699. ^{1}H NMR (300 MHz, $CDCl_3$) (323 K): δ 7.33−7.07 (10H, m), 6.10 (1H, d, *J* = 9.0 Hz), 5.43 (1H, d, *J* = 10.7 Hz), 5.08 and 5.01 (each 1H, d, J_{AB} = 12.2 Hz), 4.56 (1H, d, *J* = 9.7 Hz), 2.96 (1H, dq, *J* = 11.3 and 6.1 Hz), 1.14 (3H, d, *J* = 6.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9, 154.3, 140.4, 135.5, 128.9, 128.5, 128.4, 128.3, 128.0, 126.8, 72.9, 68.3, 61.1, 41.2, 10.8.

The oxazinanone **19** was isolated as a colorless solid (10% yield). Found: M + H, 340.1552; $C_{20}H_{21}NO_4$ requires M + H, 340.1549. Mp 87−90 °C. $[\alpha]^{20}_D$ 0.0 (*c* 0.1, CH_2Cl_2). ν_{max}(KBr)/cm^{-1} 3033, 2981, 1752, 1713, 1409, 1248, 1102, 1023, 749, 701. ^{1}H NMR (300 MHz, $CDCl_3$) (323 K): δ 7.31−7.21 (10H, m), 5.93 (1H, d, *J* = 9.6 Hz), 5.43 (1H, d, *J* = 9.7 Hz), 5.16−5.04 (3H, m), 1.46 (3H, s), 1.07 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) (323 K): δ 173.9, 153.7, 136.9, 135.6, 128.8, 128.5, 128.4, 128.0, 73.2, 68.2, 63.9, 42.4, 27.0, 22.8.

(4*S*,5*S*)-*N*-Benzyloxycarbonyl-4-benzyl-5-methyl-1,3-oxazinan-6-one 16. The oxazinanone **7** (0.5 mmol) was transformed according to General Procedure B using KHMDS (0.5 M in toluene) as the base and a 4:1 mixture of THF/HPMA as the solvent to afford the starting material **7** (35% recovery), and trace amounts of the 5,5-disubstituted oxazinanone and the oxazinanone **16** were isolated as a clear colorless oil (35% yield). Found: M + H, 340.1546; $C_{20}H_{21}NO_4$ requires M + H 340.1540. $[\alpha]^{20}_D$ +138.4 (*c* 0.96, CH_2Cl_2). ν_{max}(NaCl)/cm^{-1} 3030, 2942, 1760, 1713, 1413, 1249, 1137, 1009, 700. ^{1}H NMR (300 MHz, $CDCl_3$) (323 K): δ 7.39−7.06 (5H, m), 5.66 (1H, br s), 5.17 (2H, s), 4.27 (1H, d, *J* = 10.7 Hz), 4.04 (1H, br s), 3.24−3.20 (1H, m), 2.84 (1H, dd, *J* = 3.2 and 14.0 Hz), 2.60 (1H, dq, *J* = 6.5 and 10.3 Hz), 1.33 (3H, d, *J* = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) (323 K): δ 172.4, 154.1, 135.6, 135.3, 130.0, 128.6, 128.4, 128.1, 127.2, 72.0, 68.2, 56.7, 37.3, 13.2.

(4*R*,5*R*)-*N*-Benzyloxycarbonyl-4,5-dimethyl-1,3-oxazinan-6-one 20. The oxazinanone **8** (0.5 mmol) was dissolved in dry THF (4 mL) and HMPA (1 mL), and the solution was cooled to −78 °C under an argon atmosphere. NaHMDS (0.58 M in hexanes, 0.52 mmol) was added dropwise, and the solution was left to stir at −78 °C for 40 min. Methyl iodide (5 mmol) was added, and stirring was continued for 4 h at −78 °C. The solution was then allowed to warm to −40 °C, and it was then quenched with saturated ammonium chloride solution (5 mL). The solution was diluted with ethyl acetate (20 mL) and washed with water (20 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give an oily residue. The oil was subjected to column chromatography, eluting with 5−20% ethyl acetate/hexane, to afford the starting material **8** (13% recovery), and trace amounts of the 5,5-disubstituted product and the oxazinanone product **20** were isolated as a white solid (20% yield). Mp 97−98 °C. $[\alpha]^{20}_D$ −126.2 (*c* 0.9, CH_2Cl_2). ν_{max}(KBr)/cm^{-1} 2981, 1759, 1713, 1415, 1245, 1136, 1009, 754, 698. ^{1}H NMR (300 MHz, $CDCl_3$) (rotamers) (323 K): δ 7.33 (5H, s), 5.82 (1H, d, *J* = 10.5 Hz), 5.16 (2H, s), 5.02 (1H, d, *J* = 10.6 Hz), 3.80−3.72 (1H, m), 2.47 (1H, dq, *J* = 10.3 and 6.6 Hz), 1.35 (3H, d, *J* = 6.1 Hz), 1.26 (3H, d, *J* = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) (323 K): δ 172.3, 154.0, 135.7, 128.6, 128.4, 128.1, 70.8, 68.0, 53.0, 41.4, 19.4, 13.2.

5-Hydroxylated 1,3-Oxazinan-6-ones. (4*S*,5*S*)-*N*-Benzyloxycarbonyl-5-acetoxy-4-methyl-1,3-oxazinan-6-one 27. The oxazinanone **3** (0.5 mmol) was dissolved in dry THF (4 mL), and the solution was cooled to −78 °C under an argon atmosphere. KHMDS (0.5 M in toluene, 0.525 mmol) was added dropwise with stirring, and then the solution was allowed to warm to −50 °C over 40 min. The (+)-(2*R*,8a*S*)-oxaziridine **21** (0.625 mmol) was added in one portion, and the solution was allowed to warm to −40 °C. The reaction was maintained at this temperature for 4 h or until disappearance of starting material had occurred, as indicated by TLC. The solution was then allowed to warm to −20 °C, and it was then quenched with saturated ammonium chloride solution (5 mL). The solution was diluted with ethyl acetate (20 mL), and the organic phase was washed with water (20 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give in an oily residue. Some of the byproduct imine **26** was removed by crystallization using ether and subsequent filtration. The filtrate was concentrated under reduced pressure, and the residue was dissolved in dichloromethane (3 mL). Acetic anhydride (1.5 mmol) and pyridine (1.5 mmol) were added to the dichloromethane solution at 0 °C. The reaction was allowed to stir for 20 h at room temperature or until the disappearance of starting material had occurred, as indicated by TLC. The mixture was diluted with dichloromethane (5 mL), and the organic phase was washed with water (10 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The oily residue was subjected to column chromatography, eluting with 5−15% ethyl acetate/hexane, to afford starting material **3** (7%) and the acetate **27** as a clear colorless oil (12% yield). $[\alpha]^{20}_D$ +72.0 (*c* 0.15, CH_2Cl_2). ν_{max}(NaCl)/cm^{-1} 2977, 2933, 1784, 1750, 1716, 1416, 1225, 992, 752, 699. ^{1}H NMR (300 MHz, $CDCl_3$) (323 K): δ 7.33 (5H, s), 5.89 (1H, d, *J* = 11.0 Hz), 5.28 (1H, d, *J* = 9.8 Hz), 5.18 (2H, s), 5.07 (1H, d, *J* = 11.0 Hz), 4.18 (1H, dq, *J* = 6.0 and 9.1 Hz), 2.17 (3H, s), 1.35 (3H, d, *J* = 6.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) (323 K): δ 169.4, 166.5, 153.8, 135.4, 128.7, 128.6, 128.2, 71.2, 70.5, 68.6, 51.1, 20.3, 18.4.

General Procedure C. The oxazinanone (0.5 mmol) was dissolved in dry THF (4 mL), and the solution was cooled to −78 °C under an argon atmosphere. NaHMDS (0.4 M in hexanes, 0.52 mmol) was added dropwise with stirring, and then the solution was allowed to warm to −50 °C over 40 min. MoOPH (0.65 mmol) was added in six portions over 30 min, while the solution was allowed to warm to −40 °C. The reaction was maintained at this

temperature for 2 h. The solution was then allowed to warm to −30 °C and was quenched with saturated sodium sulfite solution (5 mL). The solution was diluted with ethyl acetate (20 mL), and it was then washed with water (20 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure give in an oily residue. The residue was subjected to column chromatography, eluting with 10−25% ethyl acetate/hexane, to afford starting material and product.

(4*S*,5*S*)-*N*-Benzyloxycarbonyl-5-hydroxy-4-methyl-1,3-oxazinan-6-one 25. The oxazinanone **3** (0.5 mmol) was transformed according to General Procedure C and gave starting material **3** (5% recovery) and the oxazinanone **25** in a 6:1 (*trans*:*cis*) diastereoisomeric ratio as a clear colorless oil (40% yield). The *trans* isomer **25** was isolated as a chromatographically inseparable mixture of *cis* and *trans* diastereoisomers (differentiated from the *cis* NMR data). Found: M + H, 266.1027; $C_{13}H_{15}NO_5$ requires M + H, 266.1028. ν_{max}(NaCl)/cm^{-1} 3425, 3034, 2977, 1764, 1713, 1415, 1244, 1100, 993, 752, 698. ^{1}H NMR (300 MHz, $CDCl_3$) (325 K): δ 7.34 (5H, s), 5.91 (1H, d, J = 10.8 Hz), 5.17 (2H, s), 5.98 (1H, d, J = 10.8 Hz), 4.13 (1H, d, J = 9.4 Hz), 3.89 (1H, dq, J = 6.1 and 9.3 Hz), 3.30 (1H, br s), 1.46 (3H, d, J = 6.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) (323 K): δ 172.9, 154.0, 135.4, 128.7, 128.6, 128.2, 71.1, 70.8, 68.4, 53.9, 18.8. An insufficient amount of the *cis* isomer was obtained for analysis.

(4*S*,5*S*)-*N*-Benzyloxycarbonyl-5-hydroxy-4-isopropyl-1,3-oxazinan-6-one 28. The oxazinanone **4** (0.5 mmol) was transformed according to General Procedure C and afforded starting material **4** (7% recovery) and the hydroxy product **28** as a clear colorless oil (44% yield). Found: M + H, 294.1341; $C_{15}H_{19}NO_5$ requires M + H, 294.1341. $[\alpha]^{20}_D$ +71.5 (*c* 1.1, CH_2Cl_2). ν_{max}(NaCl)/cm^{-1} 3446, 2965, 1768, 1714, 1410, 1254, 1105, 984, 746, 698. ^{1}H NMR (300 MHz, $CDCl_3$) (323 K): δ 7.34 (5H, s), 5.94 (1H, d, J = 10.8 Hz), 5.17 (2H, s), 4.88 (1H, d, J = 10.8 Hz), 4.33 (1H, d, J = 8.5 Hz), 3.87 (1H, dd, J = 5.6 and 8.0 Hz), 3.42 (1H, br s), 2.16−2.07 (1H, m), 1.05 (1H, d, J = 6.9 Hz), 0.99 (1H, d, J = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) (323 K): δ 173.5, 154.9, 135.3, 128.5, 128.4, 128.1, 72.8, 68.6, 68.0, 62.0, 32.1, 18.6, 18.1.

(4*S*,5*S*)-*N*-Benzyloxycarbonyl-5-hydroxy-4-isobutyl-1,3-oxazinan-6-one 30. The oxazinanone **5** (0.5 mmol) was transformed according to General Procedure C and gave starting material **5** (5% recovery) and the oxazinanone product **30** as a clear colorless oil (46% yield). Found: M + H, 308.1492; $C_{16}H_{21}NO_5$ requires M + H, 308.1498. $[\alpha]^{20}_D$ +44.2 (*c* 0.94, CH_2Cl_2). ν_{max}(NaCl)/cm^{-1} 3437, 2957, 2871, 1765, 1714, 1414, 1249, 1103, 985, 753, 698. ^{1}H NMR (300 MHz, $CDCl_3$) (323 K): δ 7.33 (5H, s), 5.88 (1H, d, J = 10.8 Hz), 5.18 and 5.15 (2H, q, J_{AB} = 12.1 Hz), 4.92 (1H, d, J = 10.8 Hz), 4.12 (1H, d, J = 8.0 Hz), 4.04 (1H, dt, J = 6.4 and 6.9 Hz), 3.53 (1H, br s), 1.82−1.52 (3H, m), 0.90 (6H, d, J = 6.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) (323 K): δ 173.0, 154.5, 135.3, 128.6, 128.5, 128.3, 71.6, 71.2, 68.6, 56.0, 44.1, 24.2, 22.9, 22.6.

(4*S*,5*S*)-*N*-Benzyloxycarbonyl-5-hydroxy-4-phenyl-1,3-oxazinan-6-one 31. The oxazinanone **6** (0.5 mmol) was transformed according to General Procedure C and furnished starting material **6** (20% recovery) and the oxazinanone product **31** as a clear colorless oil (23% yield). Found: M + H, 328.1181; $C_{18}H_{17}NO_5$ requires M + H, 328.1185. $[\alpha]^{20}_D$ 0.0 (*c* 1.0, CH_2Cl_2). ν_{max}(NaCl)/cm^{-1} 2430, 3066, 3034, 1767, 1712, 1413, 1252, 1107, 971, 733, 698. ^{1}H NMR (300 MHz, $CDCl_3$) (323 K): δ 7.35−7.06 (10H, m), 6.16 (1H, d, J = 10.4 Hz), 5.26 (1H, d, J = 10.8 Hz), 5.12 and 5.06 (each 1H, d, J_{AB} = 12.3 Hz), 4.84 (1H, d, J = 9.1 Hz), 4.48 (1H, d, J = 9.5 Hz), 3.44 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) (323 K): δ 172.3, 154.1, 139.1, 135.2, 128.9, 128.5, 128.4, 127.8, 126.1, 72.6, 70.7, 68.5, 60.8.

(4*S*,5*S*)-*N*-Benzyloxycarbonyl-5-hydroxy-4-benzyl-1,3-oxazinan-6-one 32. The oxazinanone **7** (0.5 mmol) was transformed according to General Procedure C and yielded starting material **7** (6% recovery) and the oxazinanone product **32** as a clear colorless oil (19% yield). Found: M + H, 296.1497; $C_{15}H_{21}NO_5$ requires M + H, 296.1498. $[\alpha]^{20}_D$ +77.2 (*c* 0.18, CH_2Cl_2). ν_{max}(NaCl)/cm^{-1} 3440, 3030, 2943, 1768, 1713, 1454, 1250, 1106, 990, 742, 699. ^{1}H NMR (300 MHz, $CDCl_3$) (323 K): δ 7.36−7.10 (10H, m), 5.71 (1H, d, J = 9.9 Hz), 5.21 (2H, s), 4.25 (1H, d, J = 9.9 Hz), 4.14−4.10 (2H, m), 3.30 (1H, dd, J = 12.5 and 2.3 Hz), 3.02 (1H, dd, J = 14.0 and 3.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) (323 K): δ 172.3, 153.8, 135.0, 134.5, 130.0, 128.3, 128.2, 127.9, 126.8, 72.0, 68.6, 65.8, 56.7, 35.7.

(4*S*,5*S*)-*N*-Benzyloxycarbonyl-5-hydroxy-(4*R*)-*sec*-butyl-1,3-oxazinan-6-one 33. The oxazinanone **9** (0.5 mmol) was transformed according to General Procedure C and yielded starting material **9** (7% recovery) and the 5-hydroxy product **33** as a clear colorless oil (39% yield). Found: M + H, 308.1498; $C_{16}H_{21}NO_5$ requires M + H, 308.1489. $[\alpha]^{20}_D$ +95.9 (*c* 1.7, CH_2Cl_2). ν_{max}(NaCl)/cm^{-1} 3450, 2965, 2879, 1769, 1713, 1415, 1246, 1111, 991, 698. ^{1}H NMR (300 MHz, $CDCl_3$) (323 K): δ 7.32 (5H, s), 5.91 (1H, d, J = 10.7 Hz), 5.17 and 5.14 (each 1H, d, J_{AB} = 12.2 Hz), 4.89 (1H, d, J = 10.8 Hz), 4.40 (1H, d, J = 8.6 Hz), 3.93 (1H, dd, J = 5.1 and 7.8 Hz), 2.00−1.17 (3H, m), 1.02 (3H, d, J = 6.9 Hz), 0.88 (3H, t, J = 7.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) (323 K): δ 173.7, 154.7, 135.3, 128.5, 128.3, 128.0, 72.8, 68.5, 67.4, 60.8, 39.0, 25.4, 14.5, 11.7.

(4*S*,5*R*)-*N*-Benzyloxycarbonyl-5-(4-nitrobenzoyloxy)-4-(2-methylpropyl)-1,3-oxazinan-6-one 34. The 5-hydroxy oxazinanone **30** (0.3 mmol), triphenylphosphine (0.6 mmol) and *p*-nitrobenzoic acid (0.6 mmol) were dissolved in dry THF (4 mL) under an argon atmosphere. At 0 °C, diethyl azodicarboxylate (0.57 mmol) was added dropwise while stirring. The solution was allowed to warm to room temperature, and it was stirred at this temperature for 20 h. The mixture was diluted with ethyl acetate (10 mL) and washed with saturated sodium hydrogen bicarbonate solution. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. A majority of the triphenylphosphine oxide byproduct was removed by crystallization, using 75% ether/hexane as the crystallizing solvent, and filtering off the solid. The filtrate was concentrated under vacuum. The residual mixture was applied to a silica column, resulting in degradation of the product. A short chromatography column was performed eluting with 30% ethyl acetate/hexane and afforded the benzoate **34** as a clear colorless oil (39% yield). Found: M + H, 457.1608; $C_{23}H_{24}N_2O_8$ requires M + H, 457.1611. $[\alpha]^{20}_D$ +50.8 (*c* 0.39, CH_2Cl_2). ν_{max}(NaCl)/cm^{-1} 2960, 2870, 1765, 1725, 1529, 1410, 1350, 1244, 1119, 738. ^{1}H NMR (300 MHz, $CDCl_3$) (323 K): δ 8.32−8.20 (4H, m), 7.37 (5H, s), 6.00 (1H, d, J = 9.8 Hz), 5.72 (1H, d, J = 6.3 Hz), 5.26 and 5.23 (each 1H, d, J_{AB} = 12.3 Hz), 5.16 (1H, d, J = 10.4 Hz), 4.87 (1H, br s), 1.72−1.60 (3H, m), 0.96 (3H, d, J = 3.0 Hz), 0.89 (3H, d, J = 2.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) (323 K): δ 165.4, 163.1, 154.0, 151.2, 135.2, 134.2, 131.1, 128.8, 128.3, 123.7, 72.0, 69.2, 69.0, 51.0, 35.3, 24.3, 23.2, 21.4.

General Procedure D. Reductive Cleavage of the Oxazinanones. To the oxazinanone (1 mmol) and triethylsilane (3 mmol) in dichloromethane (min. vol.) was added trifluoroacetic acid (50:50, v/v), and the solution was stirred for 72 h (monitored by TLC). Toluene (15 mL) was added to the solution, and it was then evaporated in vacuo. This process was repeated three times to remove any trace of trifluoroacetic acid. The residue was taken up in ether (30 mL) and extracted with saturated sodium bicarbonate solution (20 mL × 3). The aqueous layer was adjusted to pH 2 with dilute hydrochloric acid solution and extracted with ethyl acetate (25 mL × 3). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The resulting residue was subjected to silica chromatography, eluting with a mixture of ethyl acetate and methanol, to afford the *N*-methyl residue.

***N*-Methyl-α,β-disubstituted-β-amino acids. (2*R*,3*S*)-*N*-Benzyloxycarbonyl-3-methylamino-2-methylbutanoic Acid 37.** The oxazinanone **10** (1 mmol) was transformed according to General

Procedure D, affording the acid **37** as a white solid (56% yield). Found: M + H, 266.1393; $C_{14}H_{19}NO_4$ requires M + H, 366.1392. Mp 86−88 °C. $[\alpha]^{20}_D$ +9.6 (*c* 0.21, CH_2Cl_2). ν_{max}(NaCl)/cm^{-1} 3033, 2980, 1732, 1698, 1682, 1455, 1329, 1139, 698. ^{1}H NMR (300 MHz, $CDCl_3$) (323 K): δ 7.31 (5H, s), 5.11 (2H, s), 4.27 (1H, dq, J = 6.8 and 9.3 Hz), 2.82 (3H, s), 2.75 (1H, br s), 1.19 (3H, d, J = 5.9 Hz), 1.16 (3H, d, J = 6.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers): δ 179.6, 156.2, 136.8, 128.4, 127.8, 127.7, 67.3, 67.0, 54.5, 54.2, 43.6, 43.3, 29.6, 15.6, 15.2, 14.7.

(2*R*,3*S*)-*N*-Benzyloxycarbonyl-3-methylamino-2,4-dimethylpentanoic Acid 38. The oxazinanone **13** (1 mmol) was transformed according to General Procedure D, furnishing the acid **38** as a clear colorless oil (65% yield). Found: M + H, 294.1705; $C_{16}H_{23}NO_4$ requires M + H, 294.1705. $[\alpha]^{20}_D$ −29.0 (*c* 0.15, CH_2Cl_2). ν_{max}(NaCl)/cm^{-1} 3032, 2966, 1733, 1698, 1761, 1456, 1340, 1162, 697. ^{1}H NMR (300 MHz, $CDCl_3$) (323 K): δ 7.31 (5H, s), 5.12 (2H, s), 4.04 (1H, br s), 2.96−2.85 (1H, m), 2.81 (3H, s), 2.17−2.10 (1H, m), 1.21−1.15 (3H, m), 1.05−0.96 (3H, m), 0.88−0.84 (3H, m). ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers): δ 179.3, 157.5, 157.1, 137.1, 136.9, 128.4, 128.0, 127.9, 127.6, 67.4, 67.2, 64.5, 40.4, 31.1, 28.6, 28.4, 20.3, 19.5, 19.2, 14.8, 14.6.

(2*R*,3*S*)-*N*-Benzyloxycarbonyl-3-methylamino-2,5-dimethylhexanoic Acid 39. The oxazinanone **14** (1 mmol) was transformed according to General Procedure D, affording the *N*-methyl amino acid **39** as a clear colorless oil (70% yield). Found: M + H, 308.1862; $C_{17}H_{25}NO_4$ requires M + H, 308.1862. $[\alpha]^{20}_D$ −22.0 (*c* 0.14, CH_2Cl_2). ν_{max}(NaCl)/cm^{-1} 2956, 1706, 1664, 1447, 1326, 1161, 696. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (5H, s), 5.11 (2H, s), 4.29 (1H, br s), 2.77 (3H, s), 2.67 (1H, br s), 1.51−0.91 (6H, m), 0.91−0.77 (6H, m). ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers): δ 178.6, 178.4, 156.7, 137.2, 136.8, 128.4, 128.1, 127.8, 127.6, 67.4, 67.1, 57.5, 43.2, 38.6, 38.4, 30.1, 24.9, 24.6, 23.7, 21.6, 21.4, 14.8.

(2*R*,3*R*)-*N*-Benzyloxycarbonyl-3-methylamino-2-methyl-3-phenylpropanoic Acid 40. The oxazinanone **15** (1 mmol) was transformed according to General Procedure D, yielding the acid **40** as a clear colorless oil (71% yield). Found: M + H, 328.1554; $C_{19}H_{21}NO_4$ requires M + H, 328.1549. $[\alpha]^{20}_D$ +57.9 (*c* 1.7, CH_2Cl_2). ν_{max}(NaCl)/cm^{-1} 3033, 2982, 1713, 1681, 1455, 1329, 1160, 703. ^{1}H NMR (300 MHz, $CDCl_3$) (325 K): δ 10.64 (1H, br s), 7.32 (10H, s), 5.40 (1H, d, J = 11.4 Hz), 5.15 (2H, s), 3.43 (1H, br s), 2.84 (3H, s), 1.12 (3H, d, J = 6.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) (323 K): δ 179.2, 156.3, 136.8, 136.7, 128.6, 128.3, 128.0, 127.7, 67.4, 62.3, 40.6, 29.8, 15.5.

(2*R*,3*R*)-*N*-Benzyloxycarbonyl-3-methylamino-2-methyl-4-phenylbutanoic Acid 41. The oxazinanone **16** (1 mmol) was transformed according to General Procedure D, affording the acid **41** as a clear colorless oil (54% yield). Found: M + H, 342.1712; $C_{20}H_{23}NO_4$ requires M + H, 342.1705. $[\alpha]^{20}_D$ −58.0 (*c* 0.2, CH_2Cl_2). ν_{max}(NaCl)/cm^{-1} 3029, 2977, 1725, 1703, 1677, 1452, 1343, 1146, 737, 698. ^{1}H NMR (300 MHz, $CDCl_3$) (323 K): δ 7.34−7.07 (10H, m), 5.26−4.88 (2H, m), 4.40−4.13 (1H, m), 3.14−2.58 (6H, m), 1.29 (3H, d, J = 6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) (323 K): δ 179.1, 178.9, 156.4, 156.1, 138.2, 138.0, 137.1, 136.7, 129.0, 128.4, 128.4, 127.9, 127.8, 127.6, 126.8, 126.7, 126.5, 67.3, 66.8, 63.1, 61.5, 43.1, 42.6, 35.7, 35.2, 33.6, 15.2.

(2*R*,3*S*)-*N*-Benzyloxycarbonyl-3-methylamino-2-hydroxy-4-methylpentanoic Acid 42. The oxazinanone **28** (1 mmol) was transformed according to General Procedure D and afforded the *N*-methyl amino acid **42** as a clear colorless oil (63% yield). Found: M + H, 296.1497; $C_{15}H_{21}NO_5$ requires M + H, 296.1498. $[\alpha]^{20}_D$ −1.3 (*c* 0.39, CH_2Cl_2). ν_{max}(NaCl)/cm^{-1} 3432, 2965, 2876, 1729, 1673, 1456, 1312, 1138, 975, 736, 697. ^{1}H NMR (300 MHz, $CDCl_3$) (323 K): δ 7.33 (5H, s), 5.15 (2H, s), 4.44−4.36 (1H, m), 3.75 (1H, br s), 2.97−2.90 (3H, m), 2.43−4.30 (1H, m), 0.95 (3H, d, J = 6.5 Hz), 0.90 (3H, d, J = 6.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) (323 K): δ 174.0, 158.3, 136.3, 128.6, 128.2, 127.7, 73.5, 72.5, 68.6, 67.9, 34.9, 26.4, 20.2, 19.5.

(3*S*)-*N*-Benzyloxycarbonyl-3-aminobutan-1-benzylamide 44. The oxazinanone **3** (0.5 mmol) was dissolved in dichloromethane (4 mL), and benzyl amine (1.05 mmol) was added. The solution was allowed to stir at room temperature for 20 h. The reaction mixture was washed successively with 1 M hydrochloric acid (4 mL) and then water (4 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Column chromatography was performed on the resulting oil, eluting with 70% ethyl acetate/hexane, to afford the amide **44** as a clear colorless oil (87% yield). Found: M + H, 327.1710; $C_{19}H_{22}N_2O_3$ requires M + H, 327.1709. $[\alpha]^{20}_D$ +16.7 (*c* 1.5, CH_2Cl_2). ν_{max}(NaCl)/cm^{-1} 3314, 3031, 2973, 2934, 1698, 1650, 1549, 1424, 1341, 1258, 1028, 698. ^{1}H NMR (300 MHz, $CDCl_3$) (325 K): δ 7.29−7.16 (10H, m), 6.55 (1H, br s), 5.09 and 5.04 (each 1H, d, J_{AB} = 12.8 Hz), 4.87−4.33 (2H, m), 4.28 (2H, br s), 2.85−2.32 (2H, m), 1.22−1.11 (3H, m). ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) (325 K): δ 171.2, 155.6, 138.4, 138.1, 136.3, 136.1, 128.45, 128.41, 128.0, 127.9, 127.8, 127.6, 127.5, 127.2, 127.1, 74.8, 70.0, 67.4, 67.1, 50.3, 43.4, 42.3, 19.1.

(3*S*)-3-Aminobutanoic Acid 47. The oxazinanone **3** (0.5 mmol) was dissolved in methanol (5 mL), and 10% palladium-on-carbon catalyst (0.05 mmol) was added. The mixture was stirred at room temperature for 20 h under an atmosphere of hydrogen. The mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The resulting residue was triturated with ethanol to furnish the amino acid **47** as a white solid (85% yield). The data were identical to that previously described.[47]

(3*R*)-*N*-Benzyloxycarbonyl-3-aminophenylpropanoic Acid 48. The oxazinanone **6** (0.3 mmol) was dissolved in methanol (3.5 mL) at 0 °C, and a 4 M lithium hydroxide solution (2.5 mL) was added. The mixture was stirred for 10 min while warming to room temperature, and the methanol was removed under vacuum. 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 in vacuo to afford the acid **48** as a white solid (89% yield). This compound had data identical to that previously described.[48]

(3*S*)-Ethyl-*N*-benzyloxycarbonyl-3-aminobutanoate 49. The oxazinanone **3** (1 mmol) was dissolved in dry ethanol (10 mL), and dry sodium hydrogen carbonate (2.5 mmol) was added under an inert atmosphere. The solution was refluxed for 20 h. The solvent was removed in vacuo, the residue was taken up in ethyl acetate (20 mL), and it was then washed with water (20 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography, eluting with 35% ethyl acetate/hexane. The ester **49** was isolated as a clear colorless oil (67% yield). Found: M + H, 266.1392; $C_{14}H_{19}NO_4$ requires M + H, 266.1392. ν_{max}(NaCl)/cm^{-1} 3344, 2980, 2937, 1731, 1530, 1245, 1058, 738, 697. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (5H, s), 5.26 (1H, br s), 5.06 (2H, s), 4.14−4.07 (3H, m), 2.48 (2H, d, J = 5.38 Hz), 1.24−1.20 (6H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 155.4, 136.5, 128.4, 127.9, 66.4, 60.4, 44.0, 40.5, 20.3, 14.0.

(3*S*)-3-Aminobutanoic Acid Hydrochloride 52. To the oxazinanone **3** (1 mmol) dissolved in dioxane (10 mL) was added 6 M hydrochloric acid solution (10 mL). The solution was refluxed for 4 h, and the solution was cooled to room temperature. The solvent was evaporated to dryness in vacuo, and the resulting residue was dissolved in a minimal volume of isopropanol. Diethyl ether

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was added to the alcoholic solution, and a precipitate formed. The precipitate was filtered off and washed with diethyl ether to give the salt **52** as a white solid (65%). This compound had data identical to that previously described.[49]

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Supporting Information Available: General experimental procedures, including spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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