JOC Article

Enantioselective Synthesis of α-Amino Acids from *N*-Tosyloxy *β*-Lactams Derived from *β*-Keto Esters‡

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A novel synthetic sequence has been developed to convert simple *β*-keto esters into enantiomerically enriched α-amino acids. The key features of this sequence include the addition of azide to the C3 position of *β*-keto ester derived *N*-tosyloxy-*β*-lactams through a concomitant nucleophilic addition/N−O bond reduction reaction, a mild CsF-induced N1 benzylation of α-azido monocyclic *β*-lactams, the preparation of α-keto-*β*-lactams through a novel four-step sequence from the corresponding 3-azido-1-benzyl-*β*-lactams, and TEMPO-mediated ring expansion of these compounds to the corresponding *N*-carboxy anhydrides (NCAs). In addition, the synthesis, isolation, and characterization of unusual 3-imino and 3-chloramino-*β*-lactams is reported.

Introduction

The use of *β*-lactams as chiral building blocks in organic synthesis is now well established and routine.[1,2] Additionally, *β*-lactams have played a key role in the fight against pathogenic bacteria and the subsequent rise in quality of life for the world population as a whole. Given the importance of *β*-lactams, the need to construct highly functionalized *β*-lactams in an asymmetric fashion is of significance. Over 20 years ago, our group developed a biomimetic synthesis of chiral *N*-hydroxy *β*-lactams from the corresponding *β*-hydroxy hydroxamates.[3,4] This technology has been used to prepare scores of biologically and synthetically important molecules.[5−18] Further, in the early 1990s, our group found that under basic conditions *N*-tosyloxy *β*-lactams underwent an unusual nucleophilic addition at the C3 carbon with concomitant N−O bond reduction.[19] This novel reaction allows ready access to highly functionalized monocyclic *β*-lactams in a diastereoselective fashion. While we have provided several initial reports regarding the qualitative features[20−23] and some synthetic applications of this reaction,[24] the full potential of this method and the utility of the chiral synthons available from it have not been fully realized. The goal of this project was to further demonstrate the synthetic utility of these two technologies as ways to prepare highly functionalized heterocycles. We felt that a good target class for such a methodology development would be the preparation of α-keto *β*-lactams[25] **3** (Scheme 1) since these molecules are highly useful synthetic intermediates for the construction of a number of classes of molecules.[26−30] We were especially interested in their

‡ Dedicated to the memory of Professor Henry Rapoport (November 16, 1918−March 6, 2002), University of California−Berkeley; a superb scientist, teacher, mentor, and friend.

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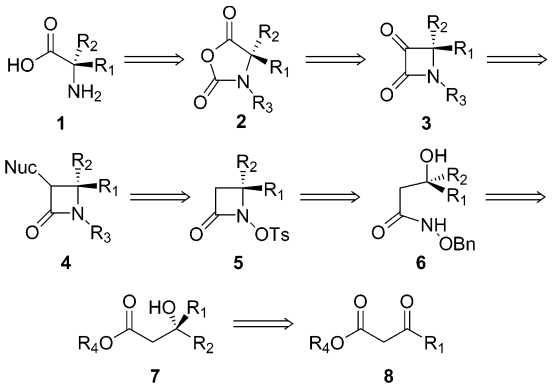
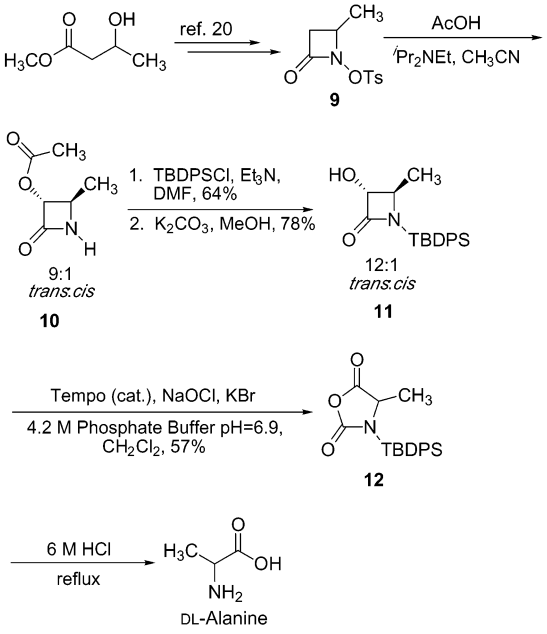
SCHEME 1



conversion to *N*-carboxy anhydrides **2** (NCAs, Scheme 1),[31,32] since this would represent a novel amino acid synthesis in which an umpolung occurs allowing the formal addition of ammonia to the α-position of the corresponding carboxylic acid. This report describes our development of two independent routes to both the targeted α-keto *β*-lactams and the derived NCAs in enantiomerically enriched form as well as the synthesis of novel C3 imino and chloramino monocyclic *β*-lactams.

We envisioned the target NCAs as being prepared as outlined retrosynthetically in Scheme 1. The major synthetic challenges of this proposed strategy include the transformation of nucleophilic addition product **4** to a suitably N1 protected form (R_3 = H → R_3 = protecting group) and subsequent elaboration to the α-keto *β*-lactam **3**. The issue of N1 protection was of paramount importance since previous studies had shown that NCAs in which the nitrogen lacks a sufficiently bulky protecting group were prone to epimerization.[33,34] Since a number of ways to prepare *β*-keto esters from readily available starting materials are known, and catalytic asymmetric reductions of these esters to the corresponding *β*-hydroxy esters is routine and substrate tolerant, this approach should, in theory, allow access to almost any amino acid. However, we recognized early in our synthetic planning that the proposed sequence to the targeted NCAs was relatively lengthy in comparison to other published routes from Palomo and co-workers[31,32] that relied on [2 + 2] ketene−imine cycloaddition strategies. Regardless, we felt that the proposed route was interesting not only for its novel approach but also because it presented a number of synthetic challenges, as mentioned above, and that surmounting these synthetic obstacles would provide the opportunity to develop new *β*-lactam chemistries and, therefore, offered sufficient promise to warrant its investigation.

SCHEME 2



Results and Discussion

The first route to target NCA **2** began with *N*-tosyloxy *β*-lactam **9** (Scheme 2) which is easily converted, using the novel nucleophilic addition/N−O bond reduction protocol, to C3 acetoxy *β*-lactam **10**.[20] Protection of the N1 position followed by unmasking of the hydroxyl functionality gave compound **11**. Treatment of lactam **11** with buffered sodium hypochlorite and a catalytic amount of TEMPO using the conditions developed by Palomo et al.[32] provided the desired NCA in moderate yield by means of in situ oxidation to the α-keto *β*-lactam followed by ring expansion. The labile nature of the TBDPS group was hypothesized to be the agent of inefficiency in this transformation. The identity of compound **12** was further confirmed by hydrolysis and subsequent comparison with commercially available alanine using *o*-phthaldehyde (OPA) derivatization/HPLC analysis.[35]

Encouraged by this initial success, we wanted to test the generality of this synthetic strategy, as well as address the lability of our N1 protecting group by preparing a more amenable model compound. One of the major inconveniences of compound **9** and its progeny was their highly polar nature, which complicated product isolation. To address these concerns, model compound **18a** was prepared from lauric acid in six steps (Scheme 3). However, addition of acetic acid to *N*-tosyloxy *β*-lactam **18a** proceeded in low overall yield. Extensive efforts to improve the efficiency of this reaction by addressing the concentration and molar ratios of the reactants, the source of acetate, use of other carboxylic acids, and modification of the base proved unsuccessful.

Previous studies from our group had shown that carboxylic acids were the only oxygen nucleophiles with reasonable synthetic utility in this transformation.[20,21] Additionally, sulfur nucleophiles had been shown to have low to moderate efficacy.[20] Since the proposed synthetic

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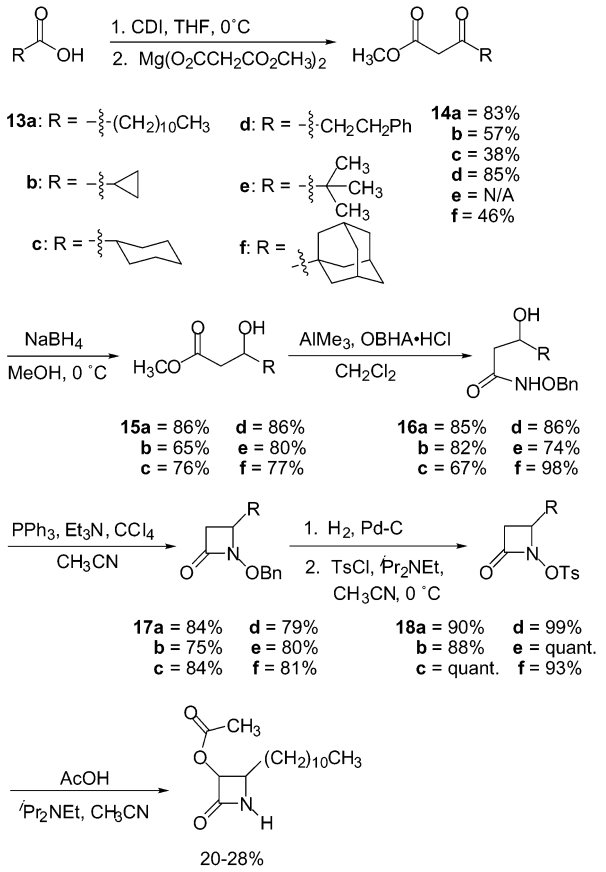
SCHEME 3



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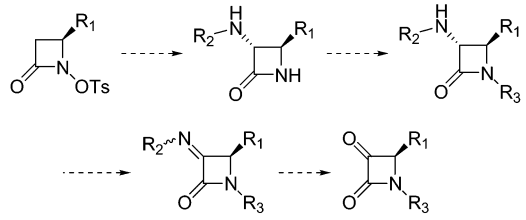
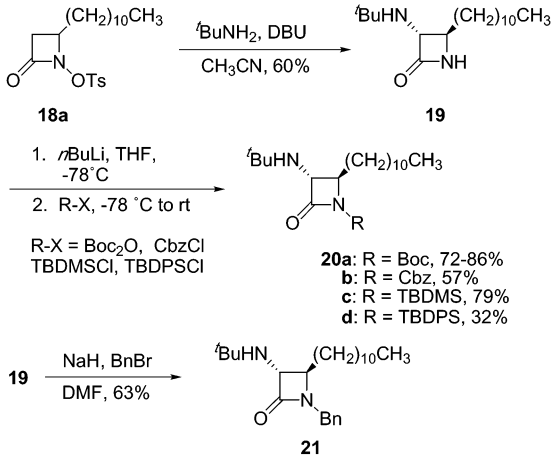


sequence required that the nucleophilic addition product be produced in high yield, other strategies to access the targeted α-keto *β*-lactam demanded consideration. The use of nitrogen nucleophiles in our synthetic plan represented an appealing alternative since both amines[22] and azide[20] had been shown to be highly efficient nucleophiles in this reaction. Although such a strategy would require an eventual heteroatom exchange with oxygen, we felt that other benefits in the robustness and substrate tolerance of this approach could adequately compensate. Further, the opportunity existed using this strategy to prepare some unusual *β*-lactams which might be useful for the preparation of other synthetically and biologically interesting molecules such as novel α,*β*-diamino acids.

Therefore, our newly revised synthetic plan involved introducing a nitrogen substituent at C3 via the nucleophilic addition reaction followed by oxidation to the C3 imino compound and subsequent unmasking of the ketone functionality (Scheme 4). Similar strategies have been employed by other groups to either convert C3

SCHEME 5



primary amino groups to ketones[36] or invert the C3 amino stereochemistry.[37] However, these strategies have relied upon the condensation of the primary amine with a sacrificial aldehyde to first form an initial imine which must then be isomerized to give the desired ketone oxidation state at C3. It was anticipated that such a sequence could be avoided by directly oxidizing the C3 position. Thus, this strategy required the use of an amine nucleophile bearing no other oxidizable carbons to ensure selectivity in the oxidation step.

In keeping with the aforementioned goals, *N*-tosyloxy *β*-lactam **18a** was treated with *tert*-butylamine according to the protocol which this group had originally reported for the functionalization of compound **9** (Scheme 5).[22] Surprisingly, while in the case of *N*-tosyloxy *β*-lactam **9** the product was formed in high yields and conversions, formation of *β*-lactam **19** was sluggish and resulted in a low overall conversion with a significant amount of starting material being recovered. While resubjection of the recovered material to the reaction conditions allowed accumulation of reasonable quantities of the amine over several cycles, we sought to improve this transformation to make it more synthetically useful. Since one current mechanistic hypothesis of the *N*-tosyloxy *β*-lactam nucleophilic addition/N−O bond reduction reaction invokes an S_N2' mechanism in which the rate-limiting step is enolization,[20,38] we hypothesized that a buffering effect by the *tert*-butylamine salt of the tosylate was responsible for the inhibition. Further, we anticipated that addition of a stronger amine base during the course of the reaction should shift the equilibrium allowing higher conversion. Gratifyingly, addition of DBU allowed complete consumption of tosylate **18a**, providing serviceable quantities of compound **19**.

With *β*-lactam **19** in hand, a series of N1 protected compounds was required in order to determine which types of N1 protecting groups could be used in the subsequent steps. In this regard, we were interested in

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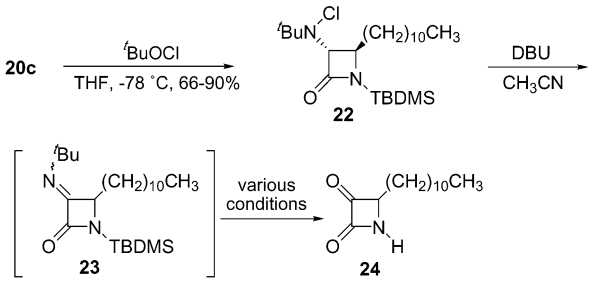
SCHEME 6

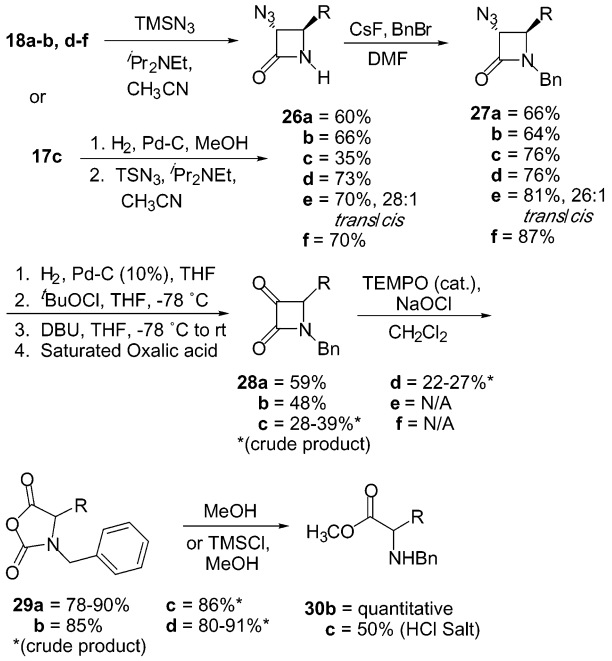


further investigating the possibility of using a silyl protecting group, since we had had some initial success with the TBDPS group (Scheme 2). Additionally, carbamate protecting groups have previously been shown to be useful for the prevention of NCA epimerization.[33] Further, the Palomo group has successfully used the benzyl group for NCA protection and have shown that this group can be removed from the amino acid products via exposure to various hydrogenolysis conditions.[31,32] Therefore, we targeted *β*-lactams **20a**−**d** and **21** for synthesis (Scheme 5). Treatment with *n*-BuLi followed by quenching of the resulting anion allowed differentiation of the amino and amide functionalities providing access to a number of silyl and carbamate protected compounds. Similarly, treatment of compound **19** with NaH followed by BnBr provided the benzyl-protected derivative.[39]

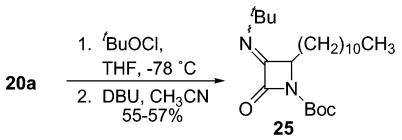
With the preparation of N1-protected *β*-lactams **20a**−**d** and **21** accomplished, conditions were then investigated to allow elaboration to the corresponding α-keto *β*-lactams. As previously stated, we envisioned that the exocyclic amine could be oxidized to the imine and then hydrolyzed to the desired keto compound. To this end, TBDMS protected lactam **20c** was treated with *tert*-butyl hypochlorite to give C3 chloramino *β*-lactam **22** which was isolable by chromatography (Scheme 6). *N*-Acylchloramines have been used as transient intermediates for the introduction of alkoxy substituents at the C3 position of the azetidinone ring[40−42] or to allow direct substitution on the exocyclic nitrogen.[43] However, to the best of the authors' knowledge, this represents the first reported isolation and characterization of such an unusual C3 chloramino *β*-lactam compound. Base-induced elimination provided the desired imine but attempts at hydrolysis provided the desired keto compound *sans* protecting group. Attempts at reinstallation of the protecting group proved futile.

Focus then turned to oxidation of Boc-protected *β*-lactam **20a** (eq 1). Treatment with *t*-BuOCl followed by DBU afforded the desired imine **25** as a mixture of stereoisomers which was stable to chromatography (eq 1). This sequence represents a synthetically useful approach to

SCHEME 7



stable C3 imino *β*-lactams which could be adapted for the preparation of a number of interesting species. Unfortunately, the electron-withdrawing effect of the carbamate



(1)

caused lysis of the ring system under all conditions attempted to effect hydrolysis of the imine to the corresponding ketone. Surprisingly, when benzyl-protected *β*-lactam **21** was oxidized, it was discovered that the resulting imine was too stable to hydrolysis, and all attempts instead resulted in the destruction of the *β*-lactam ring. This stability is most likely due to the steric bulk of the *tert*-butyl moiety. Recognizing the importance of the electronically neutral benzyl moiety as the most suitable protecting group choice, efforts were directed at the preparation of a *N*1-benzyl-C3-imino *β*-lactam which could be readily hydrolyzed. Such a target required the use of an ammonia equivalent in the nucleophilic addition reaction. In this regard, the use of azide seemed appropriate.

Therefore, treatment of lauric acid derived *N*-tosyloxy *β*-lactam **18a** with $TMSN_3$ in the presence of Hunig's base provided the *trans*-azide **26a** in good yield (Scheme 7). Extensive experimentation showed that while a number of other conditions[5,24,44−47] were either unsuccessful or gave inconsistent results, CsF could be used to facilitate the benzylation (eq 2) of this highly sensitive *β*-lactam

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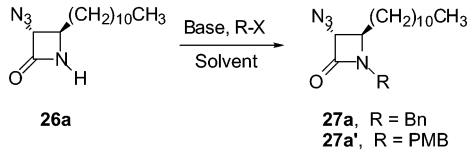
TABLE 1. Benzyl Protection of 3-Azido *β*-Lactam 26a

entry	base (equiv)	solvent	"R-X" (equiv)	yield, %[a]
1[b]	Cs_2CO_3 (1.2)	CH_3CN	BnBr (5.8)	37
			BnBr (3.1)	41
2	Cs_2CO_3 (1.1)	DMF	BnBr (1.1)	55
3[c]	Cs_2CO_3 (1.3)	DMF	BnBr (2.3)	62
4	Cs_2CO_3 (1.3)	DMF/CH_2C_{l2} 1:1	BnBr (2.3)	55
5	Cs_2CO_3 (1.3)	DMF (high dilution)	BnBr (12)	56
6[d]	Ag_2O (1.2)	none	BnBr	N/A
7[d]	Ag_2O (1.2)	DMF	BnBr (2.2)	N/A
8	DEAD/PPh_3	THF	BnOH	NR[i]
9[e]	N/A	CH_2Cl_2	PhCOH, Et_3SiH	N/A
10[f]	CsF (10.8)	DMF	BnBr (2.6)	66
11[g]	KF−Al_2O_3	CH_3CN	PMBCl (3)	27
12[h]	Et_3NBnCl/NaOH	1 M NaOH/CH_2Cl_2 1:2	PMBCl (13)	19
13[d]	Ag_2O (1.2)	CH_3CN	PMBCl (2.3)	22
14	CsF (10.2)	DMF	PMBCl (3.5)	36
15	CsF (10.3)	DMF/3 Å mol sieves	PMBCl (3)	31

[a] Isolated yields. [b] Our Group has previously shown that α-azido *β*-lactams can be alkylated with α-halo esters under these conditions (see ref 24). [c] While the use of Cs_2CO_3 as the base gave comparable results in some cases to the CsF mediated reactions, we found the CsF reaction gave more consistent results. [d] See ref 46 for a related example using these conditions. In the case of entries 6 and 7, subjection of compound **26a** to these conditions resulted in low reactivity and the formation of multiple products. [e] Azide reduction was observed. [f] The use of more than 10 equiv of CsF is necessary to induce complete consumption of *β*-lactam **26a** and maximize the overall yield.[g] See refs 45 and 47 for related examples using these conditions. [h] See ref 5 for a related example using these conditions. [i] NR = no reaction observed.

to provide benzyl derivative **27a** (entry 10, Table 1). *β*-Lactam **27a** was then elaborated to the target α-keto



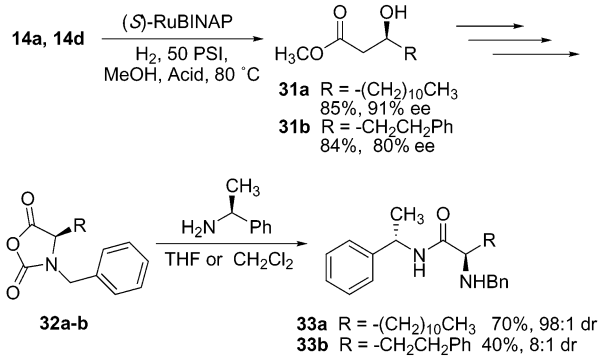
26a **27a**, R = Bn; **27a'**, R = PMB (2)

β-lactam **28a** in a carefully designed four-step procedure which could be carried out in a "single pot" (Scheme 7). TEMPO-mediated ring expansion then provided the desired NCA **29a** (Scheme 7). The overall sequence from *N*-tosyloxy *β*-lactam **18a** consisted of seven steps and an overall yield for this sequence of 20%.

To further examine the scope of this method, C3 azido *β*-lactams **27b**−**f** were prepared from the corresponding starting *β*-keto esters in an analogous manner and subjected to the synthetic sequence just described (Schemes 3 and 7). Gratifyingly, the four-step azide to ketone conversion performed well not only for aryl and cyclohexyl containing *β*-lactams **27c**,**d** but was even more effective with cyclopropane **27b**. The main limitation we have encountered is the preclusion of highly branched substituents at C4 for the azide to ketone conversion to be effective. Based on experimental observations, it appears that in sterically demanding systems such as **27e** and **27f** the intermediate chloramine undergoes alternative reactions to give ring-opened products upon workup.

With an effective sequence in hand, the enantioselectivity of the method was tested by preparing enantiomerically enriched *β*-hydroxy esters **31a**,**b** from *β*-keto esters **14a**,**b** by way of reduction with (*S*)-RuBINAP following Taber's protocol (Scheme 8).[48,24] Elaboration of **31a**,**b** to NCAs **32a**,**b**, and reaction with (*S*)-α-methylbenzylamine provided the corresponding amides showing no noticeable stereochemical degradation as determined by ^{1}H NMR comparison to the 1:1 mixture of diastereomers obtained from coupling with racemic NCAs **29a** and **29d**.[49]

SCHEME 8



Conclusion

The concomitant nucleophilic addition/N−O bond reduction of *N*-tosyloxy *β*-lactams has been used to develop a novel route to enantiomerically enriched α-keto *β*-lactams which were subsequently converted to the corresponding *N*-carboxy anhydrides. The key steps in this process were a mild fluoride-mediated N1 benzylation of

(48) Taber, D. F.; Silverberg, L. J. *Tetrahedron Lett.* **1991**, *32*, 4227−4230.

(49) It is interesting to note that Palomo and co-workers have reported that the condensation of *ent*-NCA **32b** with 2 equiv of (*S*)-leucine benzyl ester under several sets of conditions produced varying mixtures of the corresponding diastereomers due to some epimerization of the NCA during the reaction. The *apparent* difference in outcomes for the results of the Palomo laboratories and our own in the condensation of the two epimers of NCA **32b** with branched amines is not completely clear. However, it is possible that these differences could be due to any of the following causes: (1) our use of 1.1 equiv of amine as opposed to 2.0 equiv as in the report from the Palomo group, (2) subtle differences in reactivity of (*S*)-α-methylbenzylamine and (*S*)-leucine benzyl ester, (3) given that opposite enantiomers of **32b** were used, a matched vs a mismathced effect for the NCA and amine nucleophile/base could have been the causative factor. These results further reinforce the observations previously reported suggesting the importance of the reaction conditions in the condensation NCAs with amine nucleophiles (see refs 33 and 34 for more discussion and examples). For the original report from the Palomo laboratories using *ent*-NCA **32b**, please see Palomo, C.; Oiarbide, M.; Landa, A.; Esnal, A.; Linden, A. *J. Org. Chem.* **2001**, *66*, 4180−4186.

C3 azido β-lactams and a novel four-step conversion of α-azido β-lactams to α-keto β-lactams. This method shows compatibility with reactive functionality like cyclopropanes at C4 but has low affinity for sterically crowding tertiary carbon groups such as adamantyl or *tert*-butyl. Additionally, the preparation and isolation of unusual C3 imino and chloramino β-lactams has been realized.

The technologies described in this paper should allow access to a plethora of highly functionalized β-lactams and other heterocycles of synthetic and biological interest. The *N*-tosyloxy β-lactams generated during these studies have been submitted for assay against β-lactamases, and these studies should provide additional SAR information for this unusual class of β-lactamase inhibitors.[15−18] Further, studies are underway to examine the use of C3-azido-β-lactams as direct precursors to differentially protected *erythro* α,β-diamino acids. The results of these and other related studies will be reported in due course.

Experimental Section

General. *tert*-Butyl hypochlorite,[50] tosyl azide,[51] and monomethyl malonate[52] were prepared according to the reported procedures. All solvents were distilled prior to use. Acetonitrile, triethylamine, and *tert*-butylamine were distilled from calcium hydride under argon. Carbon tetrachloride was stored over molecular sieves. All other reagents were used as received from either Aldrich or Acros chemical companies. Compound **14e** was obtained from commercial sources. Reactions involving *tert*-butyl hypochlorite were conducted in foil-covered round-bottom flasks in the absence of incidental light. During the course of this work, gram scale quantities of 3-azido β-lactams were prepared. Although the authors have noted no explosive tendencies from any of the compounds reported, *caution* in handling is advised. The 3-azido β-lactams showed little to no decomposition after storage for several months at −4 °C. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were measured at 300 and 75 MHz, respectively. All chemical shifts (δ) are relative to either tetramethylsilane or residual solvent. Silica gel flash chromatography was carried out using silica gel 60 (0.040−0.063 mm irregular particles).

(±)-*cis* and *trans*-3-Hydroxy-4-methyl-1-(*tert*-butyl-(diphenyl)silyl)-2-azetidinone (11). Compound **10**[20] (128 mg, 0.895 mmol) was dissolved in dry DMF (0.5 mL) under a nitrogen atmosphere, and TBDPSCl (0.700 mL, 2.692 mmol) was added by syringe. To the resulting solution was then added triethylamine (0.40 mL, 0.287 mmol). The reaction was stirred for 10 h and then diluted with EtOAc (10 mL). The resulting solution was washed with water (3 × 10 mL) and then with brine (10 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated, and the residue was chromatographed (7:1 hexanes/EtOAc) to give an inseparable 1:10 mixture of *cis* and *trans* stereoisomers of the silyl-protected compound (219 mg, 64%) as a light yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.69 (m, 4H), 7.44 (m, 6H), 5.80 (d, J = 5.70 Hz, 0.1H) 5.14 (d, J = 2.10 Hz, 1H), 3.76 (p, J = 6.15 Hz, 0.1H), 3.52 (dq, J = 6.35 Hz, J = 2.02 Hz, 1H), 2.15 (s, 3H), 1.22 (s, 9H), 0.84 (d, J = 6.30 Hz, 3H), 0.77 (d, J = 6.00 Hz, 0.3H); ^{13}C NMR ($CDCl_3$) δ 170.13, 135.92, 135.82, 131.45, 131.39, 130.43, 128.20, 81.41, 75.73, 56.45, 53.201, 27.69, 20.69, 19.34, 19.10, 15.47; IR (neat): 2934, 1752 cm^{-1}; FAB−HRMS: calculated for $C_{22}H_{28}NO_3Si$ ($M - H^+$) 382.1838, found 382.1838.

The TBDPS-protected lactam (194 mg, 0.507 mmol) was dissolved in MeOH (5 mL) and cooled to 0 °C with an ice bath. To the cooled solution was added solid K_2CO_3 (10 mg). Upon consumption of the starting material, the reaction mixture was immediately filtered through a plug of silica and the solvent evaporated. The residue was chromatographed (gradient of 4:1 to 3:1 hexanes/EtOAc), and compound **11** was isolated as a white solid (134 mg, 78%). An analytical sample was obtained by recrystallization from diethyl ether/hexanes as a ∼12:1 mixture of *trans* and *cis* isomers; mp = 184.5−185.0 °C; ^{1}H NMR ($CDCl_3$) δ 7.69 (m, 4H), 7.43 (m, 6H), 5.36 (d, J = 5.40 Hz, 1H), 5.31 (d, J = 6.60 Hz, 0.1H), 5.04 (dd, J = 6.60 Hz, J = 5.40 Hz, 0.1H), 4.52 (dd, J = 5.10 Hz, J = 2.10 Hz, 1H), 3.67 (dd, J = 6.45 Hz, J = 5.55 Hz, 0.1H), 3.59 (dq, J = 6.30 Hz, J = 2.10 Hz, 1H), 1.208 (s, 9H), 0.920 (d, J = 6.60 Hz, 0.1H), 0.77 (d, J = 6.30 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 176.82, 135.97, 135.88, 131.72, 131.51, 130.40, 130.38,128.22, 128.19, 81.62, 75.68, 58.14, 54.71, 27.78, 19.36, 19.12, 15.52; IR (KBr): 3310, 2934, 2857, 1715 cm^{-1}; FAB−HRMS: calculated for $C_{20}H_{26}NO_2Si(M-H^+)$ 340.1733, found 340.1768.

(±)-Alanine *N*-Carboxy Anhydride (12). To compound **11** (99 mg, 0.292 mmol), dissolved in dichloromethane (4 mL), was added a 0.1 M aqueous solution of KBr (20 μL, 0.002 mmol), and the resulting mixture was cooled to 0 °C with an ice bath. In a test tube, a 0.7 M solution of NaOCl (commercial bleach, 415 μL, 0.291 mmol) was saturated with sodium bicarbonate and then diluted with a 4.2 M pH = 6.9 phosphate buffer solution (1 mL). To the previously cooled mixture was then added TEMPO (1 mg) followed by the buffered sodium hypochlorite solution. The heterogeneous solution was stirred vigorously. When the color of the solution changed, the reaction was judged to be over and quenched with a 10% thiosulfate solution and diluted with dichloromethane (20 mL). The aqueous layer was discarded, the organic layer washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator, and the residue was chromatographed (4:1 hexanes/EtOAc) to give the title compound as a white solid (35 mg, 57% based on recovered **11**). ^{1}H NMR ($CDCl_3$) δ 7.70 (m, 4H), 7.48 (m, 6H), 4.09 (q, J = 6.60 Hz, 1H), 1.26 (s, 9H), 0.84 (d, J = 6.60 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 199.69, 168.54, 135.85, 130.88, 130.84, 128.50, 128.46, 68.96, 27.81, 19.59, 16.27; IR (KBr): 2958, 2936, 2862, 2820, 1791, 1751 cm^{-1}; FAB−HRMS: calculated for $C_{20}H_{24}NO_3Si$ ($M - H^+$) 354.1525, found 354.1554.

(±)-*trans*-3-(*N*-(1,1-Dimethylethyl)amino)-1-(*tert*-butoxycarbonyl)-4-undecyl-2-azetidinone (20a). To compound **19** (85 mg, 0.287 mmol) in dry THF (3 mL) at −78 °C under nitrogen was added *n*-BuLi (130 μL, 2.36 M in hexanes, 0.316 mmol). After 15 min, the anion was quenched by syringe addition of a Boc_2O/THF solution (0.620 mL, 0.514 M, 0.319 mmol). After 30 min, 10% aqueous citric acid solution (0.1 mL) was added, and the reaction was then allowed to slowly warm to room temperature. The solvent was evaporated with a rotary evaporator and the resulting residue purified by chromatography (7:1 hexanes/EtOAc) to give the title compound (98 mg, 86%) as a clear oil. ^{1}H NMR ($CDCl_3$) δ 3.77 (d, J = 3.00 Hz, 1H), 3.61 (m, 1H), 2.01 (m, 1H), 1.70 (m, 1H), 1.51 (s, 9H), 1.26 (m, 18H), 1.13 (s, 9H), 0.88 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 169.13, 148.67, 83.17, 65.80, 62.95, 51.01, 32.11, 31.73, 30.09, 29.82, 29.70, 29.64, 29.54, 28.26, 24.92, 22.87, 14.32; IR (neat): 1802 cm^{-1}, 1722 cm^{-1}; FAB−HRMS: calculated for $C_{23}H_{45}N_2O_3$ ($M-H^+$) 397.3430, found 397.3434.

(±)-*trans*-3-(*N*-(1,1-Dimethylethyl)amino)-1-(dimethyl-(1,1-dimethylethyl)silyl)-4-undecyl-2-azetidinone (20c). Compound **19** (131 mg, 0.443 mmol) was placed in a round-bottom flask under a nitrogen atmosphere and dissolved in dry THF (4.6 mL). The resulting solution was cooled to −78 °C, and 2.3 M *n*-BuLi in hexanes (0.200 mL, 0.460 mmol) was added. After stirring for 15 min, the reaction was quenched with a solution of TBDMSCl (460 mL, 1.0M, 0.460 mmol) in THF. The resulting solution was stirred at −78 °C for 20 min and then allowed to warm to room temperature over 45 min.

(50) Mintz, M. J.; Walling, C. *Organic Syntheses*; Wiley: New York, 1973; Coll. Vol. V, pp 184−187.
(51) Regitz, M.; Hocker, J.; Liedhegener, A. *Organic Syntheses*; Wiley: New York, 1973; Coll. Vol. V, pp 179−184.
(52) Hutchinson, C. R.; Nakane, M.; Gollman, H.; Knutson, P. L. *Organic Syntheses*; Wiley: New York, 1990; Coll. Vol. VII, pp 323−325.

The solvent was removed by rotary evaporator and the residue chromatographed (gradient 4:1 hexanes/EtOAc to 100% EtOAc) to give the title compound as a yellow oil (144 mg, 79% overall, 95% based on recovered **19**) plus recovered **19** (22 mg). ^{1}H NMR ($CDCl_3$) δ 3.72 (d, J = 2.40 Hz, 1H), 3.25 (dt, J = 8.70 Hz, J = 3.00 Hz, 1H), 1.81 (m, 1H), 1.27 (bs, 19H), 1.13 (s, 9H), 0.953 (s, 9H), 0.88 (t, J = 6.75 Hz, 3H), 0.22 (d, J = 2.70 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 176.85, 67.32, 61.85, 50.95, 35.16, 32.10, 30.19, 29.92, 29.80, 29.68, 29.51, 26.47, 25.35, 22.87, 18.52, 14.30, −4.98, −5.49; IR (neat): 1743 cm^{-1}; FAB−HRMS: calculated for $C_{24}H_{51}N_2OSi$ (M − H$^+$) 411.3771, found 411.3778.

(±)-*trans*-3-(*N*,*N*-(1,1-Dimethylethyl)chloroamino)-1-(dimethyl(1,1-dimethylethyl)silyl)-4-undecyl-2-azetidinone (22). To a solution of compound **20c** (32 mg, 0.078 mmol) in dry THF (1 mL) at −78 °C was added *tert*-butyl hypochlorite (10.5 μL, 0.093 mmol), and the resulting solution was stirred for 30 min. The solvent was then removed with a rotary evaporator and the resulting residue filtered through a plug of silica (7:1 hexanes/EtOAc) to give the title compound as a clear oil (23 mg, 66%). ^{1}H NMR ($CDCl_3$) δ 4.25 (d, J = 2.70 Hz, 1H), 3.70 (dt, J = 9.20 Hz, J = 3.07 Hz, 1H), 1.85 (m, 1H) 1.49 (m, 3H), 1.32 (s, 9H), 1.27 (bs, 16H) 0.98 (s, 9H), 0.89 (m, 3H), 0.28 (s, 3H), 0.22 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.82, 62.87, 56.33, 34.61, 32.12, 29.99, 29.81, 29.72, 29.68, 29.55, 28.12, 26.42, 25.45, 22.89, 18.78, 14.33, −5.02, −5.47; IR (neat): 1750 cm^{-1}; FAB−HRMS: calculated for $C_{24}H_{49}ClN_2OSi$ (M − H$^+$) 445.3384, found 445.3415.

(±)-1-(*tert*-Butoxycarbonyl)-3-(*tert*-Butylimino)-4-undecyl-2-azetidinone (25). Compound **20a** (106 mg, 0.267 mmol) was dissolved in dry THF (2.5 mL) under nitrogen and cooled to −78 °C. To the cooled solution was then added *tert*-butyl hypochlorite (45 μL, 0.398 mmol), and the resulting solution was stirred for 20 min at −78 °C and then warmed to room temperature. The solvent was removed with a rotary evaporator and the residue redissolved in dry acetonitrile under nitrogen. The resulting solution was cooled to 0 °C. To the cooled solution was then added DBU (44 *m*L, 0.294 mmol), and the solution was stirred for 1 h. The solvent was then removed with a rotary evaporator and the residual material filtered through a plug of silica (10:1 hexanes/EtOAc) to give the title compound (60 mg, 57%) as a clear oil. ^{1}H NMR ($CDCl_3$) δ 4.35 (m, 1H), 1.88 (m, 2H), 1.57 (s, 9H), 1.40 (s, 9H), 1.29 (bs, 18H) 0.88 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 161.06, 155.95, 149.01, 83.92, 64.43, 58.96, 32.11, 30.32, 30.10, 29.81, 29.69, 29.65, 29.54, 29.51, 18.24; IR (neat): 1805, 1793 cm^{-1}; FAB−HRMS: calculated for $C_{23}H_{43}N_2O_3$ (M−H$^+$) 395.3274, found 395.3284.

General Procedure for the Preparation of *trans*-3-Azido-*β*-Lactams. To the *N*-tosyloxy β-lactam dissolved in dry acetonitrile under an inert atmosphere was added $TMSN_3$ (2 equiv) followed by diisopropylethylamine (3 equiv). The resulting mixture was stirred at room temperature until all of the starting material was consumed as determined by TLC analysis (2−5 days). The solution was then concentrated with a rotary evaporator and the residue purified by flash chromatography to yield the desired title compounds.

(±)-*trans*-3-Azido-4-undecyl-2-azetidinone (26a). Flash chromatography (gradient 10:1 to 4:1 hexanes/EtOAc) yielded the title compound as a yellow oil (178 mg, 65%). ^{1}H NMR ($CDCl_3$) δ 6.60 (s, 1H), 4.16 (s, 1H), 3.52 (dt, J = 9.70 Hz, J = 3.37 Hz, 1H), 1.67 (m, 2H), 1.30 (m, 18H), 0.88 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 164.89, 69.87, 57.31, 33.67, 32.08, 29.7629.65, 29.58, 29.50, 29.39, 26.17, 22.85, 14.28; IR (neat) 3256, 2108, 1770 cm^{-1}; FAB−HRMS: calculated for $C_{14}H_{27}N_4O$ (M − H$^+$) 267.2185, found 267.2174.

(±)-*trans*-3-Azido-4-cyclopropyl-2-azetidinone (26b). Flash chromatography (4:1 hexanes/EtOAc) yielded the title compound as a crystalline solid (206 mg, 66%). Analytically pure material was obtained by recrystallization from Et_2O/hexanes: mp = 50.5−51.0 °C; ^{1}H NMR ($CDCl_3$) δ 6.58 (s, 1H), 4.34 (m, 1H), 3.11 (dd, J = 7.95 Hz, J = 1.95 Hz, 1H), 1.02 (m, 1H), 0.65 (m, 2H), 0.33 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 164.91, 69.80, 60.81, 12.92, 3.16, 2.47; IR (KBr): 3219, 2102, 1755 cm^{-1}; FAB−HRMS calculated for $C_6H_9N_4O$ (M − H$^+$) 153.0776 found 153.0785.

General Procedure for the Preparation of 3-Azido-1-benzyl-2-azetidinones. CsF (10−12 equiv) was suspended in dry DMF (1 mL) under Ar, and to this suspension was added BnBr (2.5 equiv). To this flask was then added a solution of the 3-azido β-lactam in dry DMF (total substrate concentrations were kept at 0.1 M) by syringe pump over several hours. During this addition, and for several hours after it was completed, the reaction was stirred vigorously. When TLC analysis indicated complete consumption of the starting lactam, the reaction was diluted with EtOAc and washed with water (4×) followed by brine. The resulting organic phase was dried over sodium sulfate, filtered, and concentrated. The residue was then purified by flash chromatography as described to give the title compounds.

(±)-3-Azido-1-benzyl-4-undecyl-2-azetidinone (27a). Flash chromatography (gradient 10:1 to 7:1 hexanes/EtOAc) provided the title compound (76 mg, 66%) as a light yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 3H), 7.25 (m, 2H), 4.68 (d, J = 15.00 Hz), 4.182 (m, 1H), 4.09 (d, J = 15.30 Hz), 3.33 (m, 1H), 1.69 (m, 1H), 1.33 (m, 19H), 0.88 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 164.02, 135.25, 129.16, 128.36, 128.22, 68.95, 60.10, 44.82, 32.11, 31.20, 29.77, 29.63, 29.57, 29.53, 29.50, 25.52, 22.87, 14.32; IR (neat): 2106, 1767 cm^{-1}; FAB−HRMS: calculated for $C_{21}H_{33}N_4O$ (M − H$^+$) 357.2654, found 357.2672.

(±)-*trans*-3-Azido-1-(*p*-methoxybenzyl)-4-undecyl-2-azetidinone (27a′). Flash chromatography (7:1 hexanes/EtOAc) gave the title compound as a yellow oil (49 mg, 36%). ^{1}H NMR ($CDCl_3$) δ 7.17 (m, 2H), 6.88 (m, 2H), 4.62 (d, J = 15.00 Hz, 1H), 4.15 (d, J = 1.50 Hz, 1H), 4.02 (d, J = 15.00 Hz, 1H), 3.81 (s, 3H), 3.31 (m, 1H), 1.69 (m, 2H), 1.33 (m, 18H), 0.88 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 163.92, 159.56, 128.69, 127.22, 114.52, 68.83, 59.88, 55.50, 44.31, 32.10, 31.22, 29.78, 29.65, 29.59, 29.52, 25.52, 22.88, 14.31; IR (neat): 2105, 1764 cm^{-1}; FAB−HRMS: calculated for $C_{22}H_{35}N_4O_2S$ (M − H$^+$) 387.2760 found 387.2755.

(±)-*trans*-3-Azido-1-benzyl-4-cyclopropyl-2-azetidinone (27b). Flash chromatography (gradient 2:1 to 1:1 hexanes/EtOAc) provided the title compound as a yellow oil (42 mg, 64%). ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 5H), 4.71 (d, J = 15.00 Hz, 1H), 4.36 (d, J = 1.5 Hz, 1H), 4.18 (d, J = 15.00 Hz, 1H), 2.64 (dd, J = 9.45 Hz, J = 1.95 Hz), 0.76 (m, 1H), 0.58 (m, 2H), 0.19 (m, 1H), 0.07 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 163.89, 135.40, 129.02, 128.42, 128.09, 69.15, 65.01, 44.76, 11.14, 4.60, 1.56; IR (neat): 2106 cm^{-1}, 1770 cm^{-1}; FAB−HRMS calculated for $C_{13}H_{15}N_4O$ (M − H$^+$) 243.1246 found 243.1255.

(±)-1-Benzyl-3-oxo-4-undecyl-2-azetidinone (28a). A 10 mL round-bottom flask was charged with nitrogen, compound **27a** (50 mg, 0.140 mmol), dry, deoxygenated THF (1.4 mL), and 10% Pd/C (12 mg) in that order. The flask was then placed under a hydrogen atmosphere (1 atm) and stirred vigorously. Monitoring by TLC showed complete consumption of compound **27a** after 20 min. The flask was then purged with nitrogen for several minutes, and the catalyst was removed from the solution by filtering through a disposable pipet containing a cotton plug. (The subsequent reactions could also be carried out without first removing the catalyst. However, later stage purification was more convenient if the catalyst was removed earlier.) The cotton plug was washed with CH_2Cl_2 (4 mL), and all of the organic solvents were combined and removed with a rotary evaporator. The residue was then redissolved in dry THF (1.4 mL) under a nitrogen atmosphere and cooled to −78 °C. To the cooled solution was then added *tert*-butyl hypochlorite (18 μL, 0.159 mmol), and the resulting solution was stirred for 20 min. To the flask was then added DBU (25 μL, 0.167 mmol), and the flask was allowed to slowly warm to room temperature. After 1.5 h, a saturated aqueous oxalic acid solution (0.7 mL) was added and the reaction stirred for an additional 10 min. The reaction was then diluted with EtOAc

(20 mL) and washed with water (20 mL), 1.2 M HCl (20 mL), saturated $NaHCO_3$ (20 mL), and brine (20 mL). The EtOAC solution was then dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography (4:1 hexanes/EtOAc) to give the title compound as a yellow oil (27 mg, 59%). Prolonged drying of the material under vacuum in some instances produced a crystalline solid. ^{1}H NMR ($CDCl_3$) δ 7.33 (m, 5 H), 5.02 (d, J = 15.00 Hz, 1H), 4.42 (d, J = 14.70 Hz, 1H), 4.02 (dd, J = 6.90 Hz, J = 4.80 Hz, 1H), 1.68 (m, 1H), 1.54 (m, 1H), 1.24 (m, 18H), 0.88 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 197.38, 163.44, 134.19, 129.37, 128.72, 128.66, 71.09, 46.06, 32.11, 29.77, 29.62, 29.56, 29.53, 29.43, 28.69, 24.92, 22.90, 14.33; IR (neat): 1823, 1762 cm^{-1} FAB−HRMS: calculated for $C_{21}H_{32}NO_2$ (M − H$^+$) 330.2433, found 330.2447.

(±)-1-Benzyl-3-oxo-4-(cyclopropyl)-2-azetidinone (28b). The procedure was the same as that used for compound **28a**. Flash chromatography (4:1 hexanes/EtOAc) gave the title compound as a yellow oil (48 mg, 48%). ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 5H), 5.06 (d, J = 15.00 Hz, 1H), 4.54 (d, J = 14.70 Hz, 1H), 3.49 (d, J = 8.40 Hz, 1H), 0.81 (m, 1H), 0.60 (m, 2H), 0.32 (m, 1H), 0.22 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 196.24, 163.48, 134.26, 129.23, 129.04, 128.65, 128.58, 75.33, 45.87, 9.10, 3.47, 1.86; IR (neat): 1825, 1738 cm^{-1}; FAB−HRMS: calculated for $C_{13}H_{13}NO_2$ (M − H$^+$) 216.1025 found 216.1028.

General Procedure for the Preparation of the NCAs. To the 3-oxo-2-azetidinones dissolved in dichloromethane cooled to 0 °C with an ice bath were added 0.1 M KBr (50 μL, 0.005 mmol), TEMPO (1 mg), and a 1:9 mixture of commercial Chlorox bleach (≈ 0.7 M in NaOCl) and 4.2 M pH = 6.9 phosphate buffer solution, in that order. The reaction was stirred vigorously at 0 °C for 1 h. Upon complete consumption of starting material as determined by TLC, the reaction was quenched with 10% sodium thiosulfate solution (4 mL) and diluted with dichloromethane (10 mL). The aqueous layer was separated and discarded. The organic phase was washed with brine (5 mL), dried over Na_2SO_4, filtered, and evaporated to give the title compounds.

3-Benzyl-4-undecyl-oxazolidine-2,5-dione (29a). The title compound was obtained as a yellow oil (14 mg, 78%). ^{1}H NMR ($CDCl_3$) δ 7.37 (m, 3H), 7.28 (m, 2H), 4.95 (d, J = 15.30 Hz, 1H), 4.12 (d, J = 15.30 Hz, 1H), 4.05 (dd, J = 5.85 Hz, J = 3.45 Hz, 1H), 1.88 (m, 1H), 1.76 (m, 1H), 1.25 (m, 18 H), 0.87 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 168.90, 152.41, 134.31, 129.45, 128.96, 128.52, 58.89, 45.97, 32.11, 29.77, 29.75, 29.60, 29.53, 29.41, 29.24, 28.56, 23.35, 22.89, 14.32; IR (neat): 1847, 1778 cm^{-1}; FAB−HRMS: calculated for $C_{21}H_{32}NO_3$ (M − H$^+$) 346.2382, found 346.2394.

3-Benzyl-4-cyclopropyl-oxazolidine-2,5-dione (29b). The title compound was obtained as a yellow oil (44 mg, 85%). ^{1}H NMR ($CDCl_3$) δ 7.33 (m, 5H), 5.02 (d, J = 15.06 Hz, 1H), 4.36 (d, J = 15.3 Hz, 1H), 3.26 (d, J = 9.30 Hz, 1H), 0.98 (m, 1H), 0.74 (m, 2H), 0.55 (m, 1H), 0.30 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 167.86, 151.93, 134.67, 129.29, 128.68, 128.14, 63.13, 45.70, 11.22, 4.47, 1.26; IR (neat): 1848 cm^{-1}, 1775 cm^{-1}; FAB−HRMS: calculated for $C_{13}H_{13}NO_3$ (M − H$^+$) 232.0974 found 232.0959.

Methyl 2-(*N*-Benzylamino)-2-cyclopropyl-ethanoate (30b). Compound **29b** (21 mg, 0.091 mmol) was dissolved in absolute MeOH under nitrogen, and the resulting solution was stirred at room temperature for 4d. The solvent was removed with a rotary evaporator to give the title compound as a brown oil (21 mg, quantitative). ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5H), 3.85 (d, J = 12.90 Hz, 1H), 3.71 (m, 4H), 2.72 (d, J = 8.40 Hz, 1H), 2.66 (bs, 1H), 1.05 (m, 1H), 0.51 (m, 3H), 0.28 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 174.76, 139.34, 128.63, 128.58, 127.41, 64.47, 52.13, 52.01, 14.35, 4.25, 2.59; IR (neat): 3336, 1732 cm^{-1}; FAB−HRMS: calculated for $C_{13}H_{18}NO_2$ (M − H$^+$) 220.1338 found 220.1332.

Methyl 2-(*N*-Benzylamino)-2-cyclohexyl-ethanoate Hydrochloride (30c). Compound **29c** (7 mg, 0.0275 mmol) was dissolved in absolute MeOH (0.7 mL), and TMSCl (0.1 mL) was added. After 15 min, the solvent was removed with a rotary evaporator, and the white residue was triturated with diethyl ether to provide the title compound as a white solid (4 mg, 50%); mp = 188−198 °C (decomposed); ^{1}H NMR (CD_3OD) δ 7.48 (m, 5H), 4.25 (s, 2H), 3.89 (d, J = 3.00 Hz, 1H), 3.80 (s, 3H), 1.96 (m, 2H), 1.79 (m, 4H), 1.25 (m, 4H), 1.01 (m, 1H); ^{13}C NMR (CD_3OD) δ 169.50, 131.81,131.66, 131.19, 130.46, 65.94, 53.71, 52.56, 40.59, 30.94, 28.88, 27.35, 26.94, 26.84; IR (KBr): 3448, 1742 cm^{-1}.

General Procedure for Formation of Amides 33. The NCA was dissolved in dry THF or CH_2Cl_2 under an argon atmosphere. To the resulting solution was added (*S*)-(−)-α-methylbenzylamine (1.1 equiv, 98% optical purity, Aldrich Chemical Co.), and the reaction was stirred at room temperature until all of the starting material was consumed. The solution was then concentrated on the rotary evaporator and the residue purified by flash chromatography to provide the title compounds. The reactions were repeated with the racemic NCAs to give comparable yields of 1:1 mixtures of diastereomers by ^{1}H NMR which were used to determine the enantiomeric excesses.

(*R*)-2-(*N*-Benzylamino)-*N*-((*S*)-1-phenylethyl)tridecanamide (33a). Flash chromatography (4:1 hexanes/EtOAc) gave the title compound as a white solid (16 mg, 70%). ^{1}H NMR ($CDCl_3$) δ 7.52 (d, J = 8.70 Hz, 1H), 7.30 (m, 10H), 5.13 (m, 1H), 3.77 (d, J = 13.20 Hz, 1H), 3.69 (d, J = 12.90 Hz, 1H), 1.71 (m, 1H), 1.55 (m, 2H), 1.47 (d, J = 6.90 Hz), 1.26 (m, 18H), 0.879 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 173.54, 143.75, 139.86, 128.85, 128.81, 128.34, 127.56, 127.39, 126.25, 62.99, 53.25, 48.16, 34.01, 32.12, 29.91, 29.82, 29.72, 29.64, 29.55, 26.09, 22.89, 22.31, 14.33; FAB−HRMS calculated for $C_{28}H_{43}N_2O$ (M − H$^+$) 423.3375 found 423.3351.

(*R*)-2-(*N*-Benzylamino)-*N*-((*S*)-1-phenyl-ethyl)-4-phenylpentamide (33b). Flash chromatography (gradient 4:1 to 2:1 hexanes/EtOAc) gave the title compound as a yellow solid (10 mg, 40%). ^{1}H NMR ($CDCl_3$) δ 7.48 (d, J = 8.10 Hz, 1H), 7.23 (m, 9H), 5.14 (p, J = 7.20 Hz, 1H), 3.73 (d, J = 12.90 Hz, 1H), 3.64 (d, J = 12.90 Hz, 1H), 3.19 (dd, J = 7.50 Hz, J = 3.19 Hz, 1H), 2.64 (t, J = 7.95 Hz, 1H), 2.07 (m, 1H), 1.86 (m, 1H), 1.68 (s, 1H), 1.47 (d, J = 6.90 Hz, 1H).

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Supporting Information Available: Experimental procedures for OPA-HPLC analysis of NCA **12** and the preparation of compounds **14a**−**d**,**f**, **15**−**18**, **19**, **20b**, **20d**, **21**, **26c**−**f**, **27c**−**f**, **28c**,**d**, **29c**,**d**, and **31a**,**b** as well as ^{1}H NMR and ^{13}C NMR spectra for compounds **11**−**14d**, **14f**−**29b**, **30b**, **30c**, **33a** and the ^{1}H NMR spectrum for compound **33b** can be found in the Supporting Information for this article. This material is available free of charge via the Internet at http://pubs.acs.org.

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