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Enantiomerically Pure *trans*-β-Lactams from α-Amino Acids via Compact Fluorescent Light (CFL) Continuous-Flow Photolysis

Yvette S. Mimieux Vaske, Maximillian E. Mahoney, Joseph P. Konopelski,* David L. Rogow, and William J. McDonald

Department of Chemistry and Biochemistry, University of California, Santa Cruz, California 95064

Received June 18, 2010; E-mail: joek@chemistry.ucsc.edu

Abstract: Photolysis of α-diazo-*N*-methoxy-*N*-methyl (Weinreb) β-ketoamides derived from enantiomerically pure (EP) α-amino acids affords the corresponding EP β-lactams via an intramolecular Wolff rearrangement. The photochemistry is promoted with either standard UV irradiation or through the use of a 100 W compact fluorescent light; the latter affords a safe and environmentally friendly alternative to standard photolysis conditions. A continuous-flow photochemical reactor made from inexpensive laboratory equipment reduced reaction times and was amenable to scale-up. The diastereoselectivity (cis or trans) of the product β-lactams has been shown to vary from modest to nearly complete. An extremely facile, atom-economical method for the epimerization of the product mixture to the trans isomer, which is generally highly crystalline, has been developed. Evidence for C3 epimerization of Weinreb amide structures via a nonbasic, purely thermal route is presented. Subsequent transformations of both the Weinreb amide at C3 (β-lactam numbering) and the amino acid side chain at C4 are well-tolerated, allowing for a versatile approach to diverse β-lactam structures. The technology is showcased in the synthesis of a common intermediate used toward several carbapenem-derived structures starting from unfunctionalized aspartic acid.

Introduction

Azetidin-2-ones (β-lactams) are among the most investigated of all heterocyclic ring systems because of their well-documented impact on small-molecule drug discovery. When suitably functionalized, the β-lactam ring in enantiomerically pure (EP) form represents the core of a vast array of antibiotics,[1] including some used to treat drug-resistant bacterial strains.[2] Included in this array are carbapenem structures inspired by the natural product thienamycin and monocyclic β-lactam compounds exemplified by aztreonam, each possessing trans stereochemistry at the two chiral centers of the azetidinone ring (Figure 1). Additional uses for EP β-lactams in medicinal chemistry include inhibition of such diverse targets as intestinal cholesterol absorption[3] and viral proteases.[4] However, the β-lactam ring system is a "privileged structure" in more than the usual medicinal chemistry sense.[5] A ready route to EP β-lactams provides access to β-amino acids[6] by the well-established synthetic dynamic between the two functionalities,[7] and interest in polymers of EP β-amino acids ("β-foldamers"[8,9]) remains high. In addition, studies of the use of EP β-lactams as multifunctional organic motifs for the elaboration of more complex targets[10] and as rigid β-turn scaffolds[11] ensure that research into this strained four-membered ring system will continue unabated for years to come.

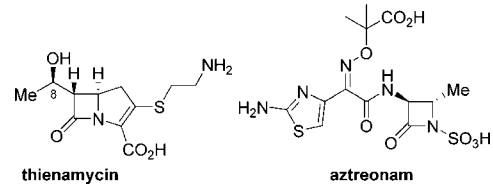

Figure 1. Representative β-lactam structures.

In view of the triple utilization of β-lactams in biomedical, synthetic, and structural chemistry, it is not surprising to find new methods for the preparation of both the racemic and EP

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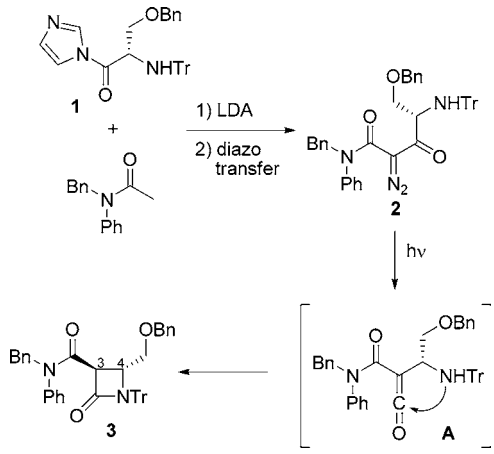
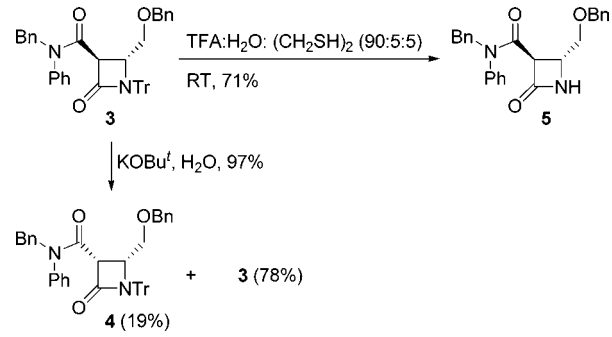
Scheme 1. Wolff Rearrangement Pathway to β-Lactams



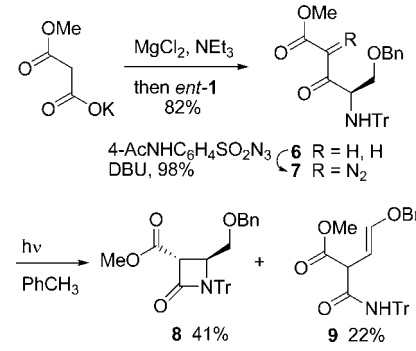
ring systems continuously appearing in the literature.[12−14] Indeed, this laboratory recently reported the serendipitous transformation of α-diazo-β-ketoamide **2** derived from L-serine into β-lactam **3** (Scheme 1).[15] The results are consistent with a mechanism involving a stereospecific intramolecular Wolff rearrangement with full retention of absolute configuration.[16] Intramolecular attack by the trityl-protected amine on the intermediate ketene **A**, formally a disfavored 4-exo-dig process under Baldwin's rules,[17−19] affords the product β-lactam. Other key observations from this work were (1) the stability and crystallinity of imidazolides **1**, which translate into handling ease in the sequence; (2) the observation of **3** as the major isolable product from rhodium(II) catalysis, silver(I) catalysis, and light (somewhat rare,[20] fully expected,[21] and best yields, respectively); and (3) the stereospecificity of the Wolff rearrangement, as gauged by the clean formation of *ent*-**3** when starting with D-serine-derived *ent*-**1**.

Herein are presented further studies of this reaction that document the *versatility* of the route through the facile production of various C3 functionalities and incorporation of different amino acid side chains; the *economy* of the route through the direct incorporation of the native α-amino acid into the reaction scheme; the *safety* of the chemistry, which requires neither metal nor organic catalysis to provide the strained ring system but rather can be performed with a compact fluorescent light (CFL); and the *simplicity* of the route, which produces high yields of EP *trans*-β-lactams via a facile epimerization reaction, allowing

Scheme 2



Scheme 3. Synthesis and Reaction of α-Diazo-β-ketoester **7**



for easy isolation of the major product by crystallization from the reaction mixture.

Results and Discussion

Synthesis and Related Studies. Our previous work[15] led to the isolation of *N*-phenyl-*N*-benzyl amide **3**, which, while attractive for our initial goals, was deemed cumbersome for manipulation into desired C3 β-lactam functionalities. For example, treatment of pure **3** with Gassman's "anhydrous hydroxide[22]" for 24 h resulted in near-quantitative recovery of the starting structure, now as an approximately 4:1 trans/cis (**3**/**4**) mixture (Scheme 2). Thus, the trityl group, which has been explored only briefly as a β-lactam ring nitrogen protection group,[23] offers extreme base stability to the normally reactive β-lactam nucleus. Conversely, treatment with trifluoroacetic acid (TFA) resulted in removal of the trityl group to give **5** in good yield.

The desire for a more malleable functionality at C3 led initially to the ester group as a replacement for the fully substituted C3 amide of **3**. The requisite α-diazo-β-ketoester **7** was prepared under mild acylation conditions (Scheme 3).[24] In an adaptation of a modified procedure,[25] potassium methyl malonate was treated with NEt_3 and $MgCl_2$ to form the corresponding magnesium salt, which was subsequently added to a solution of imidazolide *ent*-**1** derived from D-serine. The resulting β-ketoester **6** was obtained in 82% yield. Subsequent treatment with 4-acetamidobenzenesulfonyl azide and 1,8-

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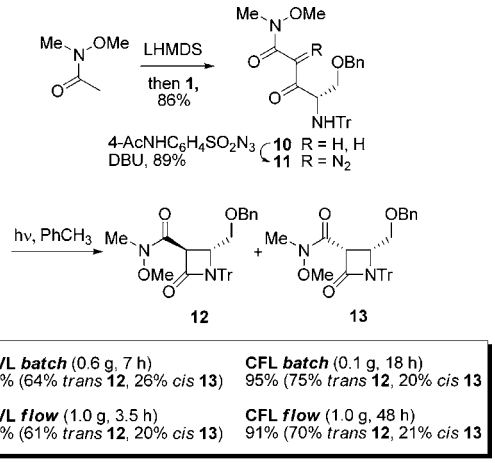
Scheme 4. Synthesis and Reaction of α-Diazo-β-ketoamide **11**



diazabicyclo[5.4.0]undec-7-ene (DBU) gave compound **7** in an overall 80% yield for the two steps. Under standard photochemical conditions, compound **7** afforded a 63% yield of a separable mixture of the desired *trans*-β-lactam **8** and alkene **9**. The structure of β-lactam **8** was confirmed by X-ray crystallography; alkene **9** was assigned by 2D NMR analysis. While the mechanistic pathway for the alkene product is not entirely clear, the new amide functionality clearly suggests that **9** originates from Wolff rearrangement/β-lactam cascade followed by further reaction.[26]

The modest yield of β-lactam **8** prompted the search for a C3 amide functionality that would maintain or exceed the higher product yields encountered in our initial studies while offering facile functional group manipulation. After some consideration, the *N*-methoxy-*N*-methyl (Weinreb) amide was chosen for study, as Weinreb amides[27] hold a reserved place as valuable and versatile synthetic intermediates.[28]

Weinreb β-ketoamide **10** was prepared by a modified literature procedure (Scheme 4).[29] Accordingly, serine imidazolide **1** was acylated with the lithium enolate (LHMDS) of *N*-methoxy-*N*-methylacetamide to give the desired β-ketoamide **10** in 86% yield on a 9 g scale. Treatment with diazo transfer reagent gave the desired α-diazo-β-ketoamide **11** in 89% yield.

Under standard photolysis conditions, diazo **11** was irradiated with a medium-pressure mercury vapor lamp (MVL), which afforded an easily separable, roughly 2.5:1 mixture of β-lactams **12** and **13**, respectively, in 90% isolated yield. The identities of the two β-lactam isomers were confirmed by X-ray crystallography. To improve upon our processing capabilities, a simple continuous-flow photochemical reactor was constructed from common laboratory equipment[30] and consisted of the requisite tubing and a medium-pressure liquid chromatography pump in addition to standard flasks (see Figure S1 in the Supporting Information). External cooling was employed, as diazo compounds are, in general, thermally unstable. Accordingly, on a 1 g scale, the reaction was complete in 3.5 h (vs 0.6 g, 7 h for the batch process) and afforded an 81% isolated yield of a roughly 3:1 separable mixture of **12** and **13**, respectively. The improved reaction time and ease of processing material on a larger scale made the modified continuous-flow photochemical process the preferred method, despite slightly diminished yields.[31]

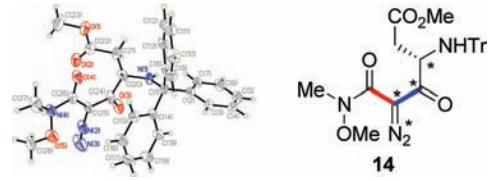


Figure 2. Solid-phase structure of diazoketone **14**.

Nonetheless, the use of the MVL was not without concern regarding heat and UV radiation for the experimentalist, and we were drawn to consider alternative light sources by the photochemist's adage that the wavelength choice should be "as long as possible and as short as necessary". Therefore, a 100 W CFL (Figure S2 in the Supporting Information), which promised far greater safety and distinctly lower cost than the conventional light source, was investigated. To our knowledge, there are no previous reports of CFL use for the photochemical Wolff rearrangement, but we were delighted to find that while the rate of the reaction was diminished relative to that for the MVL, the product yield was increased and the distributions were comparable in both the batch and continuous-flow modes (Scheme 4). In addition, the CFL-promoted reaction required no external cooling.

What is the origin of the facile Wolff rearrangement of α-diazo-β-ketoamide **11**? Optimized yields arise from photochemical decomposition as opposed to the use of metal catalysts and point to a very facile rearrangement reaction. Recent studies of the Wolff rearrangement[32] have suggested that ketene can form from two different reaction pathways: an extremely rapid rearrangement of the diazo excited state concomitant with nitrogen loss and a slower rearrangement from the ketocarbene after nitrogen loss. The rearrangement is facilitated by the antiperiplanar geometry of the leaving and migrating groups (N_2 and the amino acid chiral center, respectively), and it is this geometry that was found in the single-crystal X-ray study of diazoketone **14** (Figure 2 and the Supporting Information), which is derived from aspartic acid (see below). The structure shows the molecule in the *s*-Z_K,*s*-E_W conformation (K for ketone, W for Weinreb amide), with the dihedral angle defined by $N_2-C-C_{C=O}-C_\alpha$ (all marked with *) having a value of 172.6°. Thus, the solid-state structure possesses the exact conformation necessary for efficient Wolff rearrangement.

To more fully understand the preferred solution conformation of the diazo substrates, hybrid density functional theory calculations on compound **14** were employed. The calculations were performed with no explicit solvent incorporation, since the dielectric constant of toluene is very low ($D = 2.38$). The crystal structure coordinates of compound **14** were used as the starting point, and four conformations were generated by setting the dihedral angles related to the β-dicarbonyl system to either 180

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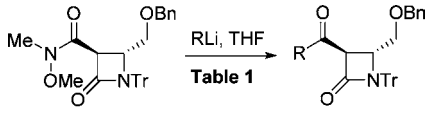
Table 1. Ketones from Weinreb Amide **12**



12 **15-18**

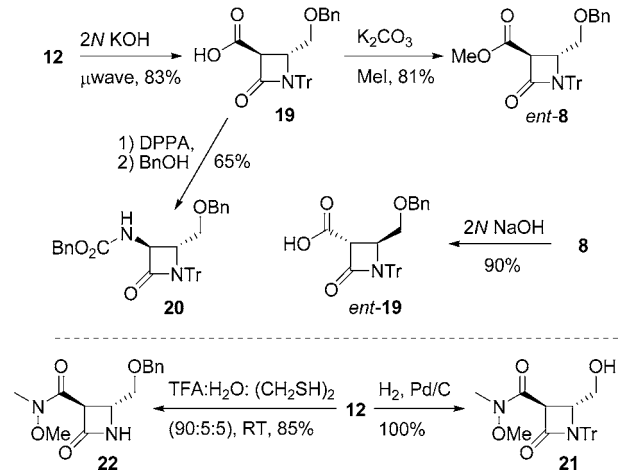
entry	RLi or RBr; R′Li	ketone	yield (%)
1	MeLi	**15**	81
2	*t*-BuLi	**16**	63
3	4-bromoanisole; *n*-BuLi	**17**	78
4	2-bromopropene; *t*-BuLi	**18**	62 (79 brsm)

or 0° in recognition of the partial double bond character of these bonds.[16] These four structures were designated *s*-Z_K,*s*-E_W (the conformation of **14**), *s*-Z_K,*s*-Z_W, *s*-E_K,*s*-E_W, and *s*-E_K,*s*-Z_W, where K refers to the conformation around the ketone−diazo carbon bond (shown in blue in Figure 2) and W refers to the Weinreb amide−diazo carbon bond (shown in red in Figure 2). Each of these four conformers was minimized at the RI-PBE/TZVP(P) level of theory.[33] Four minimized structures, each residing in the structural space of its starting conformation, were obtained and are shown, with relative energies, in Figure S3 in the Supporting Information. The calculated lowest-energy conformer agrees closely with the X-ray conformer, with no other minimized structure within 15 kJ of the *s*-Z_K,*s*-E_W conformation. In addition, each structure has one of the trityl group aromatic rings in close facial contact with the α-diazo-*β*-dicarbonyl functionality. The origin of this close proximity is not understood at the present time and is under investigation, but we are unaware of other examples of this type of close interaction between the π system of an aromatic ring and a diazo functionality.

The Weinreb amide functionality at the C3 position afforded the opportunity to explore various transformations to highlight the versatility of this functional group within the present structure. In particular, the carbapenem and monobactam classes of antibiotics, exemplified by the structures in Figure 1, bear the hydroxyethyl and amino functionalities, respectively, at this position of the ring. The former group, a key element in carbapenems having high biological activity, is usually developed via stereocontrolled reduction of the corresponding methyl ketone. Thus, trans isomer **12** was treated with a series of organolithium reagents, and the corresponding C3 ketones were obtained in good to excellent yields (Table 1). Entries 1 and 2 proceeded directly from the commercially available organolithium reagent. For entries 3 and 4, the organolithium agents were prepared by lithium−halogen exchange using 4-bromoanisole[34] and 2-bromopropene,[35] respectively. Not unexpectedly, the *β*-lactam carbonyl was fully protected by the large trityl group.

Hydrolysis of *trans*-*β*-lactam **12** was examined next (Scheme 5). Under microwave-assisted hydrolysis conditions,[36] **12** cleanly afforded C3 carboxylic acid **19** in 83% isolated yield. For comparison, standard ester hydrolysis of the trans isomer **8** afforded *ent*-**19** in 90% yield after purification. The spectral data for the two enantiomeric carboxylic acids were identical, and

Scheme 5. Hydrolysis and Curtius Rearrangement



their optical rotations were equal in magnitude and opposite in direction. Continuing on the theme of versatility, treatment of C3 carboxylic acid **19** with diphenylphosphoryl azide[37] in the presence of benzyl alcohol afforded benzyl carbamate **20**, the product of the expected Curtius rearrangement (Scheme 5).[38]

The remaining protection groups, those on the C4 amino acid side chain and the ring nitrogen, were also easily manipulated in an orthogonal manner with respect to the Weinreb amide. Deprotection of the serine side chain was accomplished by standard hydrogenolysis conditions, affording alcohol **21** from **12** in quantitative yield. Deprotection of the ring nitrogen was initially investigated by employing the only literature procedure available for a *β*-lactam *N*-Tr functionality.[23] However, this methodology (neat TFA, cat. $KClO_4$) proved to be capricious in our hands and was abandoned in favor of the reagents employed for the deprotection of **3** (Scheme 1). Under these conditions [TFA/H_2O/$(CH_2SH)_2$], a reproducible 85% yield of **22** was obtained (Scheme 5).

Structural Studies. After X-ray diffraction data for several of the *N*-trityl *β*-lactams prepared in this study were obtained, the details of the solid-state structures of these compounds were examined. A *β*-lactam differs from a normal amide because of the intrinsically strained four-membered ring, which confers decreased amide resonance.[39] For this reason, a monocyclic *β*-lactam structure exhibits a longer C2−N(amide) bond length (typically 1.35−1.38 Å vs 1.33 Å for a normal amide) and shorter C═O bond length (1.21−1.23 Å vs 1.24 Å for a standard amide).

The data from our structural studies of the *N*-trityl *β*-lactams are summarized in Figure 3 together with data for *β*-lactams from the Cambridge Structural Database (CSD, identified by CSD refcode), including both monocyclic *β*-lactams (CEJROZ, ALASAH, CPIPLA) and carbapenems (CEKQUE, BALSOW).[40] Selected interatomic distances of interest (Å) are highlighted in red; pyramidalization at the carbonyl carbon (Δ, Å) is given in blue. Compounds **12a** and **12b** are two different molecules found in the asymmetric unit cell of the X-ray diffraction data.

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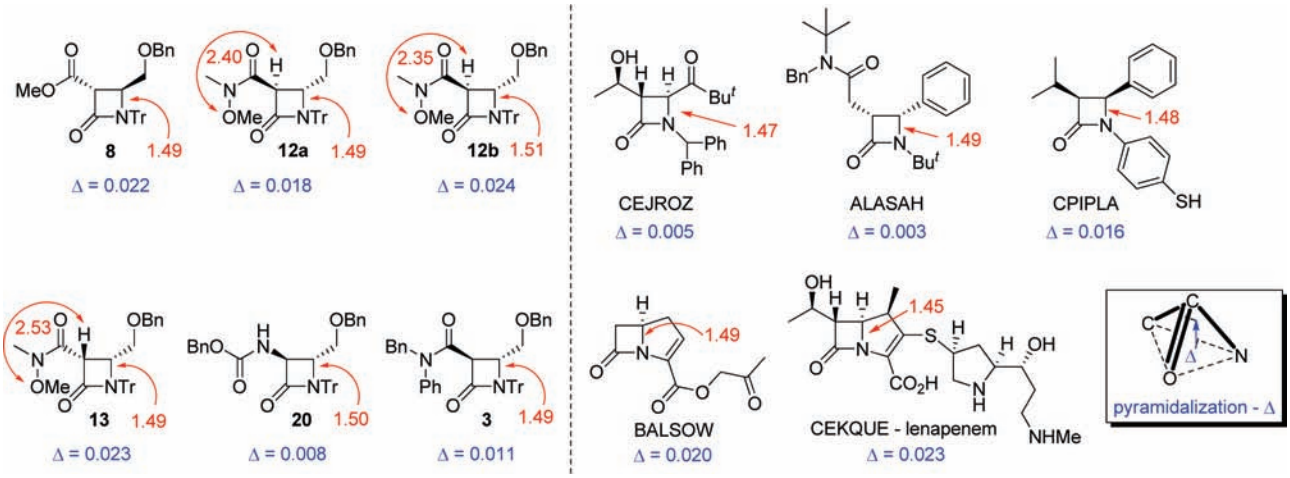


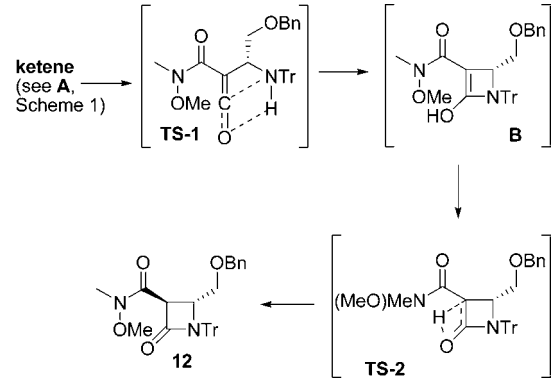
Figure 3. Bond lengths and interatomic distances (red) and pyramidalization (Δ, blue) of *N*-trityl β-lactams from this study (left) and selected β-lactams from the CSD (right). All distances are given in Å, and the definition of Δ is shown in the inset at the right.

Inspection of the structural data revealed that the *N*-trityl β-lactam C═O bonds were within the expected range for a monocyclic β-lactam, as were the C2−N(amide) and C2−C3 bond lengths (1.52−1.55 Å). The N−C4 bond lengths were found to be consistent within the structures defined by this study (1.49−1.51 Å). However, on average, these values were longer than the corresponding N−C4 values of the CSD β-lactams (1.45−1.49 Å), likely as a result of the steric interaction of the trityl group with the C4 substituent. Finally, a consistent close contact between the C3 proton and the oxygen atom of the Weinreb −OMe group was noted in the structures of **12** and **13**.

The pyramidalization (Δ) at the carbonyl carbon of the β-lactam is the perpendicular distance of this atom from the plane defined by the three substituents (Figure 3 inset).[39,41] A striking feature of these data is that the majority of the *N*-trityl β-lactams had substantial pyramidalization at the carbonyl carbon (Δ = 0.018−0.024 Å), in sharp contrast to most monocyclic β-lactams, which are essentially planar at this center. This trend is highlighted by the CSD structures in Figure 3, which display large pyramidalizations for the two carbapenem structures (CEKQUE and BALSOW) and smaller nonplanarity measurements for the monocyclic β-lactams. For further comparison, a larger subset of CSD β-lactams (listed by CSD refcode in Table 1 of Appendix A in the Supporting Information) were examined, and a pyramidalization database was compiled. A histogram of these data revealed that a large percentage of the CSD β-lactams had pyramidalizations of ∼0.01 Å. The smaller set of β-lactam structures that accounted for the larger pyramidalizations (Δ ≥ 0.02 Å) is given in Tables 2 and 3 of Appendix A in the Supporting Information.

C3 Stereochemistry and Epimerization. The overall yield of β-lactam product remained consistently high (∼90%) throughout the many instances of photolysis of α-diazo-β-ketoamide **11**. However, the trans/cis (**12**/**13**) diastereomeric ratio (dr) varied on a case-by-case basis, always favoring a higher yield of the more thermodynamically stable and highly crystalline trans isomer. Thus, **12** could be directly isolated from the concentrated crude reaction mixture (toluene) and recrystallized to purity (ethyl acetate/hexanes), thus avoiding the need for column chromatography. However, the isolated yield of the minor product, *cis*-β-lactam **13**, varied significantly. Furthermore, despite rigorous column chromatography using various eluting systems, cis isomer **13** was often accompanied by cocontamination with trans isomer **12**, making isolation of **13** as a single pure compound a challenge. Moreover, this crystalline sample of **13**, from which the single crystal for the X-ray structure analysis was taken, epimerized on standing at room temperature in a desiccator from 100% cis to 62% cis over the course of 4 months. The X-ray crystal structure showed no signs of included solvent, which could have facilitated the epimerization.

Scheme 6



Mechanistically, the Wolff rearrangement route to β-lactams provides the strained ring system and a new chiral center (C3 of the β-lactam ring) through proton transfer. As first shown in Scheme 1 for the synthesis of **3** and elaborated in Scheme 6 for a synthesis of **12**, Wolff rearrangement affords a ketene such as **A** (Scheme 1). Theoretical work[42] has indicated that addition of amines to ketenes occurs via a cyclic transition state (depicted as **TS-1**) that forms the corresponding enol amide **B** as a high-energy intermediate. Compound **B** undergoes intramolecular tautomerization (possibly through **TS-2**) to afford the final amide product with a new chiral center at C3. The intramolecular tautomerization, which appears reasonable in the present case since the photolysis reaction takes place in pure nonprotic solvent (toluene), is nonetheless likely circumvented by impurities in the system that facilitate the 1,3-proton shift.

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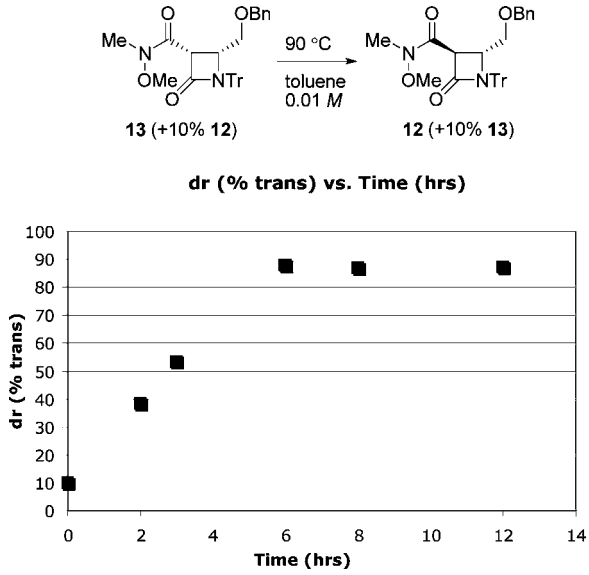
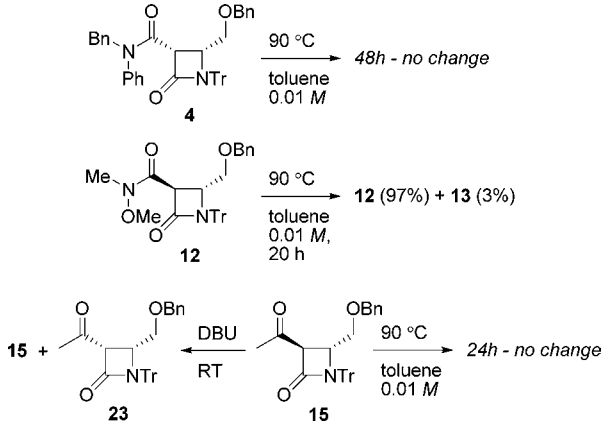


Figure 4. Thermal epimerization of **13** to **12**. Data were obtained by HPLC analysis during the course of the reaction.

Scheme 7. Epimerization Studies



Alternatively, this crucial proton transfer could be mediated by a functionality within the molecule, with the serine side chain −OBn group and the Weinreb amide oxygen atoms key possibilities. The solid-state epimerization data seemed to support this view, and the proximity of the Weinreb −OMe oxygen to the key C3 proton in the X-ray structures of **12** and **13** reinforced this idea. Finally, and most importantly, it was discovered that simply heating a 90:10 **13**/**12** mixture in toluene at 90 °C for several hours delivered a 90:10 **12**/**13** mixture (Figure 4). No base was added for the transformation. These results are in sharp contrast to the harsh conditions needed to effect epimerization of amide **3** (Scheme 2).

To investigate this transformation more thoroughly, cis amide isomer **4** and trans ketone isomer **15** were subjected to toluene at 90 °C (Scheme 7); no change in dr was recorded in either reaction. However, heating pure trans isomer **12** at 90 °C for 20 h afforded a 97:3 mixture of **12** and **13**. As was seen in other equilibrium experiments on β-lactam systems, the time to equilibrium was much longer when starting from the more stable trans isomer than from the cis isomer.[43] Likewise, treatment of ketone **15** with DBU at room temperature for 18 h yielded an approximately 94:6 mixture of trans isomer **15** and the compound assigned as the cis structure **23** on the basis of LC−MS data.[44] Clearly, more experiments must be performed before suggesting a mechanism for the purely thermal epimerization of **13** to **12**. One possibility would be an intramolecular, nonbasic epimerization reaction mediated by the Weinreb amide functionality, a previously unknown reaction. However, regardless of the mechanism of the reaction, a facile route to high yields of EP *trans*-β-lactams and compounds directly related to these systems, such as $\beta^{2,3}$-amino acids, is available.

Application. Thienamycin, shown in Figure 1, is the ancestor of all carbapenem antibiotics[45] and has a storied place in the annals of synthetic organic chemistry through the efforts of the Merck process group.[46] Synthetic work on key intermediates leading toward the carbapenem ring system has occupied many research groups[47] and offered an ideal platform for extending this methodology toward a recognizable target. As envisioned, a concise approach to a carbapenem synthetic intermediate would abandon the serine derivatives that dominated our initial development work in favor of aspartic acid. In addition, there was interest in demonstrating a process directly from the amino acid, which would allow either *R* or *S* stereochemistry to be incorporated into the synthetic target with equal ease and the lowest possible cost.

Our target became β-lactam **30**, the enantiomer of which has been prepared previously[48,49] and employed in the synthesis of thienamycin and other carbapenems.[48,50] Thus, L-aspartic acid was subjected to the Rapoport protocol[51] to provide H-Asp(OMe)-OH in 72% yield without a purification step, identical to the literature (Scheme 8). Installation of the trityl protection group and imidazolide formation was inspired by the protocols of Hoffman[52] and performed without purification, providing highly crystalline **24** in 93% yield from H-Asp(OMe)-OH. Thus, the route from aspartic acid to **24** was accomplished without chromatography in 67% overall yield.

Following the methods developed for the production of **11** (Scheme 4), the anion of *N*-methoxy-*N*-methylacetamide was reacted with **24** to provide β-ketoamide **25** in 72% yield. Diazo transfer to afford **14** was accomplished in 94% yield through the use of MsN_3. Photochemical decomposition of the diazo functionality afforded the expected mixture of trans isomer **26** and cis isomer **27**, which was not isolated. Rather, direct treatment of the reaction mixture with DBU at room temperature afforded exclusively the desired isomer **26** as a crystalline solid in 81−90% yield (depending on the light source; the highest yield was obtained using CFL continuous flow). Thus, highly functionalized crystalline β-lactam **26** was produced in 43% yield from L-Asp with only one chromatographic purification.

Introduction of the methyl ketone functionality to afford **27** was far from trivial, since the inherent reactivity of the methyl

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(44) Only trans isomer **15** was obtained upon attempted isolation of the new compound assigned as structure **23**.

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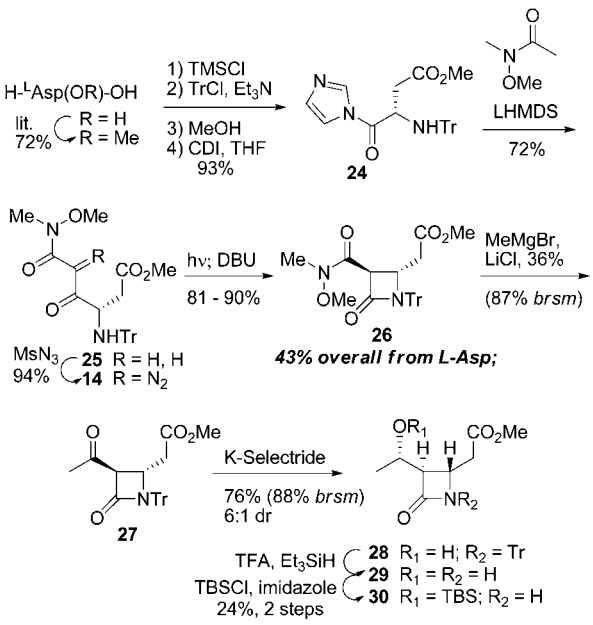
(52) Hoffman, R. V.; Maslouh, N.; Cervantes-Lee, F. *J. Org. Chem.* **2002**, *67*, 1045–1056.

Scheme 8



ester proved greater than that of the Weinreb amide toward standard methyl nucleophiles. We theorized, however, that complexation of lithium ion to the Weinreb amide would activate the functionality toward nucleophilic attack. In the event, addition of MeMgBr to a solution of **26** and anhydrous LiCl in THF at 0 °C, with warming to room temperature, provided the desired ketone **27** together with unreacted **26** as a roughly 1:1.4 separable mixture in 87% yield based on recovered starting material (brsm).

Reduction of the methyl ketone functionally of **27** under previously described conditions[53] led to a 76% yield (88% brsm) of **28** as an inseparable 6:1 mixture of stereoisomers at the newly installed secondary alcohol favoring the stereoisomer shown. The identity of this major isomer was confirmed by the production of known compound **30**. Removal of the trityl protection group through the use of TFA and Et_3SiH was followed by silyl ether formation under the published conditions[53] and afforded the desired material **30** in 24% isolated yield for the final two steps; the product was identical with the enantiomer described in the literature on the basis of ^{1}H NMR and melting point data.[48,49]

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Conclusion

The methodology outlined herein delineates a route to differentially substituted EP β-lactams. The power of the technology arises from the unique one-step formation of an EP *N*-trityl β-lactam via a stereospecific intramolecular Wolff rearrangement directly from the corresponding α-amino acid. The use of a Weinreb amide substituent permits a control element on the C3 position, allowing ready transformation to other key functionalities. In addition, the *N*-trityl group, which is rarely encountered on the β-lactam nucleus, offers superb protection to the strained heterocycle during the course of treatment with reactive nucleophiles such as organolithium reagents and strong bases. Both CFL and MVL continuous-flow reactors were utilized in the production of β-lactam structures. Incorporation of different amino acid functionalities at the C4 position of the β-lactam nucleus and examination of diastereomer control in the formation of the β-lactam ring are ongoing efforts in our laboratory and will be reported in due course.

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Supporting Information Available: Synthetic procedures, complete spectroscopic data, ^{1}H and ^{13}C NMR spectra for all new compounds, and CIF files for all new X-ray structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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