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

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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 -lactam via an intramolecular Wolff rearrangement. Photochemistry is promoted with either standard UV irradiation or through the use of a 100W compact fluorescent light (CFL); the latter affords a safe and environmentally friendly alternative to standard photolysis conditions. A continuous-flow photochemical reactor, made from inexpensive laboratory equipment, expedites reaction times and is amenable to scale-up. 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, generally highly crystalline, has been developed. Evidence is presented for C-3 epimerization of Weinreb amide structures via a non-basic, purely thermal route. Subsequent transformations of both the Weinreb amide at C-3 (β -lactam numbering) and amino acid side chain at C-4 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 due to their well-documented impact on small molecule drug discovery. 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 compound 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 absorption³ 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 acids⁶ 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 into the use of EP β -lactams as multifunctional organic motifs for the elaboration of more complex targets¹⁰ and as rigid β -turn scaffolds¹¹ ensures that research into this strained fourmembered ring system will continue unabated for years to come.

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Supporting Information Available. Synthetic procedures, complete spectroscopic data, ¹H and ¹³C 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>.

Given 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 ring system continuously appearing in the literature.^{12,13,14} Indeed, this laboratory recently reported the serendipitous transformation of α -diazo- β -ketoamide **2**, derived from L-serine, to 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,^{17,18,19} affords the product β -lactam. Other key observations from this work were 1) the stability and crystallinity of imidazolides **1**, which translates into handling ease in the sequence; 2) the observation of **3** as the major isolable product from rhodium(II) and 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 on this reaction that document the *versatility* of the route through the facile production of various C-3 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 that 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 that produces high yield of EP *trans*- β -lactams via a facile epimerization reaction, allowing for easy isolation of the major product by crystallization from the reaction mixture.

Synthesis and Related Studies

Our previous work¹⁵ 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 C-3 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* to *cis* (**4**) mixture (Scheme 2). Thus, the trityl group, which has only been explored briefly as a β -lactam ring nitrogen protection group,²³ offers extreme base stability to the normally reactive β -lactam nucleus. Conversely, treatment with TFA results in removal of the trityl group to give **5** in good yield.

The desire for a more malleable functionality at C-3 led initially to the ester group as a replacement for the fully substituted C-3 amide of **3**. The requisite diazo β -ketoester **7** was prepared under mild acylation conditions (Scheme 3).²⁴ Adapting a modified procedure,²⁵ potassium methyl malonate was treated with NEt³ and MgCl² to form the corresponding magnesium salt, which was subsequently added to a solution of imidazolidine *ent*-**1**, derived from D-serine. The resulting β -ketoester **6** was obtained in 82% yield. Subsequent treatment with 4-acetamidobenzene sulfonyl azide and DBU gave compound **7** in an overall 80% yield for the two steps. Under standard photochemical conditions compound **7** afforded 63% of a separable mixture of 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 C-3 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 amides²⁷ 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 imidazolidine **1** was acylated with the lithium enolate (LHMDS) of *N*-methoxy-*N*-methyl acetamide to give the desired β -ketoamide **10** in 86% yield on a 9 g scale. Treatment with diazo transfer reagent gave the desired diazo β -ketoamide **11** in 89% yield.

Using standard photolysis conditions, diazo **11** was irradiated with a medium pressure mercury vapor lamp (MVL) and afforded a roughly 2.5:1 easily separable mixture of β -lactams **12** and **13**, respectively, in 90% isolated yield. The identity of both β -lactam isomers was confirmed by X-ray crystallography. To improve upon our processing capabilities, a simple continuous-flow photochemical reactor was devised 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, Supporting Information). External cooling was employed since diazo compounds are, in general, thermally unstable. Accordingly, on a 1 g scale, the reaction was complete in 3.5 h (versus 0.6 g, 7 h for the batch process) to afford an 81% isolated yield and 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

Nonetheless, the use of the MVL is 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 compact fluorescent light (CFL, Figure S2), which promised far greater safety and distinctly lower cost as compared to 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 as compared to the MVL use, product yield increased and distribution were comparable in both the batch and continuous flow mode (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 compared to the use of metal catalysts, and point to a very facile rearrangement reaction. Recent studies on the Wolff rearrangement³² suggest 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 amino acid chiral center, respectively), and it is this geometry that is found in the single crystal X-ray study of diazoketone **14** (Figure 2 and SI), derived from aspartic acid (*vide infra*). 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 $N_2-C-C=O-C_\alpha$ (all marked with *) 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 of compound **14** were employed. The calculations were performed with no explicit solvent incorporation since the dielectric constant of toluene is very low ($D = 2.38$). Using the crystal structure coordinates of compound **14** as the starting point, four conformations were generated by setting the dihedrals related to the β -dicarbonyl system to either 180° 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 (conformation of **14**), *s*- Z_K ,*s*- Z_W , *s*- E_K ,*s*- E_W , *s*- E_K ,*s*- Z_W , with *K* referring to the conformation around the ketone-

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diazo carbon bond shown in blue and *W* refers to the Weinreb amide-diazo carbon bond, shown in red (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 (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 C-3 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 mono-bactam 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 of 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 C-3 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-bromoanisole³⁴ and 2-bromopropene,³⁵ respectively. Not unexpectedly, the β -lactam carbonyl is 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 C-3 carboxylic acid **19** in 83% isolated yield. For comparison, standard ester hydrolysis of *trans*-isomer **8** afforded *ent*-**19** in 90% yield after purification. Spectral data of the two enantiomeric carboxylic acids were identical and optical rotations were equal in magnitude and opposite in direction. Continuing on the theme of versatility, treatment of C-3 carboxylic acid **19** with diphenylphosphoryl azide³⁷ in the presence of benzyl alcohol afforded the benzyl carbamate **20**, the product of the expected Curtius rearrangement (Scheme 5).³⁸

The remaining protection groups, those on the C-4 amino acid side chain and the ring nitrogen, were also easily manipulated in an orthogonal manner to the Weinreb amide. Deprotection of the serine side chain is accomplished by standard hydrogenolysis conditions, affording alcohol **21** in quantitative yield from **12**. Deprotection of the ring nitrogen was initially investigated employing the only literature procedure available for a β -lactam *N*-Tr functionality.²³ However, this methodology (neat TFA, cat. KClO₄) proved capricious in our hands and was abandoned in favor of the reagents employed for the deprotection of **3** (Scheme 1). Under these conditions [TFA/H₂O/(CH₂SH)₂], a reproducible 85% yield of **22** was obtained (Scheme 5).

Structural Studies

Having obtained X-ray diffraction data for several of the *N*-trityl β -lactams prepared in this study, the details of the solid-state structures of these compounds were examined. A β -lactam differs from a normal amide due to the intrinsically strained four-membered ring, which confers decreased amide resonance.³⁹ For this reason, a monocyclic β -lactam structure exhibits a longer C-2/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).

Data from our structural studies of the *N*-trityl β -lactams are summarized in Figure 3 together with β -lactams, including both monocyclic β -lactams (CEJROZ, ALASAH, CPIPLA) and carbapenems (CEKQUE, BALSOW), from the Cambridge Structural Database (CSD, identified by CSD Refcode).⁴⁰ Select atomic distances ($\text{\AA}$) of interest are highlighted in red; pyramidalization at the carbonyl carbon (Δ , $\text{\AA}$) is given in blue. Compounds **12a** and **12b** are two different molecules found in the asymmetric unit cell of the X-ray diffraction data.

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 C-2/N(amide) and C-2/C-3 bond length (1.52–1.55 $\text{\AA}$). The N/C-4 bond lengths were found to be consistent within the structures defined by this study (1.49–1.51 $\text{\AA}$). However, these values, on average, were longer than the corresponding N/C-4 values of the CSD β -lactams (1.45–1.49 $\text{\AA}$), and likely arise from the steric interaction of the trityl group with the C-4 substituent. Finally, a consistent close contact between the C-3 proton and the oxygen atom of the Weinreb –OMe group was noted in the structures of **12** and **13**.

Pyramidalization (Δ) at the carbonyl carbon of the β -lactam is the perpendicular distance ($\text{\AA}$) from the plane defined by the three substituents (Figure 3, inset).^{39,41} A striking feature from these data is that the majority of the *N*-trityl β -lactams had substantial pyramidalization at the carbonyl carbon ($\Delta = 0.018$ – 0.024 $\text{\AA}$) 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 non-planarity measurements for the monocyclic β -lactams. For further comparison, a larger subset of CSD β -lactams (Appendix A, Table 1, Supporting Information, listed by CSD Refcode) were examined and a pyramidalization database was compiled. A histogram of the results from these data reveals that a large percentage of the CSD β -lactams had pyramidalizations ~ 0.01 $\text{\AA}$. The smaller set of β -lactam structures that accounted for the larger pyramidalizations ($\Delta \geq 0.02$ $\text{\AA}$) is given in Appendix A, Tables 2 and Table 3.

C-3 Stereochemistry and Epimerization

The overall yield of β -lactam product remained consistently high ($\sim 90\%$) throughout the many instances of α -diazo- β -ketoamide **11** photolysis. However, the diastereomeric ratio (*dr*) of *trans*-**12** to *cis*-**13** 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 of 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 co-contamination 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 was taken for the X-ray structure analysis, 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 shows no signs of included solvent, which could have facilitated epimerization.

Mechanistically, the Wolff rearrangement route to β -lactams provides the strained ring system and a new chiral center (C-3 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 work⁴² indicates 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 C-3. The intramolecular tautomerization, which appears reasonable in the present case given that the photolysis reaction takes place in pure non-protic solvent (toluene) is, nonetheless, likely circumvented by impurities in the system that facilitate the 1,3- proton shift.

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 C-3 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 mixture of **13/12** in toluene at 90 °C for several hours delivers a 90:10 mixture of **12/13** (Figure 4). No base is 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 the diastereomer ratio was recorded in either reaction. However, heating pure *trans*-**12** at 90 °C for 20 hours affords a 97:3 mixture of **12** to **13**. As was seen in other equilibrium experiments on β -lactam systems, the time to equilibrium is 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 yields an approximate 94:6 mixture of *trans*-**15** to and a compound assigned structure *cis*-**23** based on LC-MS data.⁴⁴ Clearly there are more experiments to perform before suggesting a mechanism for the purely thermal epimerization of **13** to **12**. One possibility would be an intramolecular, non-basic 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 to all carbapenem antibiotics⁴⁵ 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 toward the carbapenem ring system has occupied many research groups⁴⁷ 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 for aspartic acid. In addition, there was interest in demonstrating a process directly from the amino acid, so that either *R* or *S* stereochemistry could 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 protocol⁵¹ to provide H-Asp(OMe)-OH in 72% yield without a purification step, identical with the literature (Scheme 8). Installation of the trityl protection group and imidazolidine formation was inspired by the protocols of Hoffman⁵² and performed without purification to provide highly crystalline **24** in 93% yield from H-Asp(OMe)-OH. Thus, the route from aspartic acid to **24** is accomplished without chromatography in 67% overall yield.

Following the methods developed for the production of **11** (Scheme 4), the anion of *N*-methoxy-*N*-methyl acetamide 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*-**26** and *cis*-**27**, which was not isolated. Rather, direct treatment of the reaction mixture with DBU at room temperature afforded exclusively the desired *trans*-**26** in 81–90% yield (depending on the light source; highest yield for CFL continuous flow) as a crystalline solid. Thus, highly functionalized crystalline β -lactam **26** is produced in 43% 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 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 desired ketone **27**, together with unreacted **26**, as a roughly 1:1.4 separable mixture in 87% yield based on recovered starting material.

Reduction of the methyl ketone functionality of **27** under previously described conditions⁵³ 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 conditions⁵³ and afforded the desired material **30** in 24% isolated yield for the final two steps, identical by ^1H NMR and melting point with the enantiomer described in the literature.^{48,49}

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 C-3 position, allowing ready transformation to other key functionalities. In addition, the *N*-trityl group, 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 base. Both CFL and MVL continuous flow reactors were utilized in the production of β -lactams structures. Incorporation of different amino acid functionalities at the C-4 position of the β -lactam nucleus, as well as the 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Representative β -lactam structures

Figure 2.
Solid phase structure of diazo **14**.

FULL PAGE WIDTH GRAPHIC

Figure 3.

Bond lengths and distances (red) and pyramidalization (Δ , blue) of *N*-trityl β -lactams from this study (*left*) and selected β -lactams from CSD (*right*). All distances are given in Angstroms (Å). Definition of pyramidalization is shown in box.

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

Scheme 1.
Wolff rearrangement pathway to β -lactams.

Scheme 2.

Scheme 3.
Synthesis and reaction of α -diazo- β -ketoester **7**.

MVL batch (0.6 g, 7 h)	CFL batch (0.1 g, 18 h)
90% (64% <i>trans</i> 12 , 26% <i>cis</i> 13)	95% (75% <i>trans</i> 12 , 20% <i>cis</i> 13)
MVL flow (1.0 g, 3.5 h)	CFL flow (1.0 g, 48 h)
81% (61% <i>trans</i> 12 , 20% <i>cis</i> 13)	91% (70% <i>trans</i> 12 , 21% <i>cis</i> 13)

Scheme 4.
Synthesis and reaction of α -diazo- β -ketoamide **11**.

Scheme 5.
Hydrolysis and Curtius rearrangement

Scheme 6.

Scheme 7.
Epimerization studies

Scheme 8.

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

entry	RLi or RBr; R'Li	ketone	Yield (%)
1	MeLi	15	81
2	<i>t</i> -BuLi	16	63
3	4-bromoanisole; <i>N</i> -BuLi	17	78
4	2-bromopropene; <i>t</i> -BuLi	18	62 (79 brsm)