Organic LETTERS

Letter

pubs.acs.org/OrgLett

# *Syn*-Selective Synthesis of β-Branched α-Amino Acids by Alkylation of Glycine-Derived Imines with Secondary Sulfonates

Sha Lou,* Grace M. McKenna,† Steven A. Tymonko,‡ Antonio Ramirez,* Tamas Benkovics, David A. Conlon, and Francisco González-Bobes

Chemical Development, Bristol-Myers Squibb, One Squibb Drive, New Brunswick, New Jersey 08903, United States

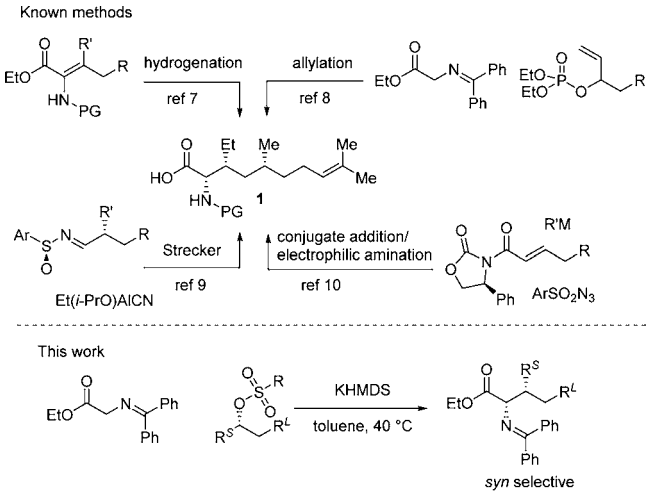
Supporting Information

**ABSTRACT:** A *syn*-selective synthesis of β-branched α-amino acids has been developed based on the alkylation of glycine imine esters with secondary sulfonates. The potassium counterion for the enolate, the solvent, and the leaving group on the electrophile were key levers to maximize the diasteroselectivity of the alkylation. The optimized conditions enabled a straightforward preparation of a number of β-branched α-amino acids that can be challenging to obtain.


The incorporation of nonproteinogenic β-branched α-amino acids into peptide-like structures results in conformational restrictions and increased rigidity which can lead to resistance toward proteolysis and enhanced biological activities.[1] Accordingly, β-branched α-amino acids are found in numerous natural products and pharmaceuticals including halipeptin A and D,[2] hormaomycin,[3] daptomycin[4] and Telaprevir.[5] Several of these compounds exhibit potent anti-inflammatory, antitumor, antibiotic, or antiviral activities. Common methods for the asymmetric synthesis of β-branched α-amino acids[6] include asymmetric hydrogenation of β-substituted dehydro alanines,[7] allylic alkylation with glycine-derived nucleophiles,[8] enantioselective Strecker reaction,[9] diastereoselective Michael addition followed by electrophilic amination,[10] asymmetric Mannich reaction of glyoxylate imines[11] and Ireland-Claisen rearrangement of glycine allylic esters.[12,13] To support the preparation of a pharmaceutical candidate, we required access to β-branched α-amino acid derivative **1**. Evaluation of the above-mentioned approaches either yielded suboptimal results for the preparation of **1** or resulted in undesired functional group manipulation steps downstream (Scheme 1). We thus decided to examine an alternative approach that could potentially offer a more direct synthesis of our target. Herein we report a *syn*-selective synthesis of β-branched α-amino acids via alkylation of unactivated secondary sulfonates with glycine-derived imines.[14]

Initially, we investigated the alkylation of benzophenone imine **3a** with mesylate **2a**. Upon screening both inorganic and organic bases, the potassium enolate generated after deprotonation of **3a** with KHMDS was found to be more reactive. Using THF as the solvent resulted in the formation of product **4a** as a 1:1 mixture of diastereomers as previously reported (entry 1, Table 1).[14] Interestingly, replacement of THF by toluene provided an initial lead, yielding a promising 3:1 *syn*/*anti* ratio (entry 2). Furthermore, monitoring the diastereomeric ratio of **4a** over the course of the reaction revealed that the selectivity was higher at earlier stages (5:1 dr at 2 h) and it decreased as the reaction progressed (3:1 dr at 4 h). We hypothesized that erosion of selectivity caused by unselective reaction pathways would occur more readily at the high reaction temperatures (70 °C) used in the alkylation of mesylate **2a**. To circumvent this issue, the use of electrophiles that were more reactive than **2a**, and could enable performance of the reaction at lower temperatures, were explored (entries 3−5).

**Scheme 1. Selected Methods for Preparation of β-Branched α-Amino Acids**




These experiments led to the identification of 4- bromobenzenesulfonate (brosylate, Bs) as a superior leaving group. Gratifyingly, alkylation of **4a** with brosylate **2c** could be conducted at lower temperatures (40 °C vs 70 °C) to generate **4a** in 8:1 dr (entry 4). Continuing to reduce the reaction temperature showed that the desired alkylation occurred at room temperature to provide superior selectivities at the expense of slower rates (24 h vs 8 h, 10:1 dr, entry 6). We chose 40 °C as the optimal reaction temperature for further investigations of the alkylation as it provided a good balance of reactivity and

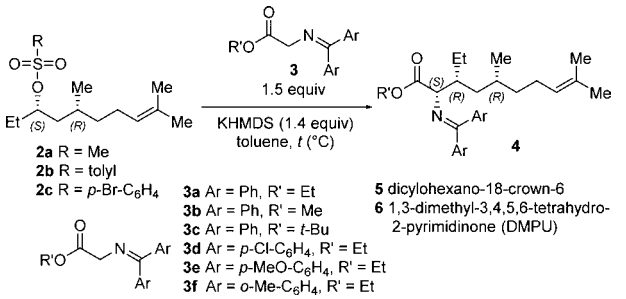
**Received:** August 26, 2015
**Published:** October 7, 2015





DOI: 10.1021/acs.orglett.5b02448
*Org. Lett.* 2015, 17, 5000−5003

**Table 1. Optimization of the Reaction Conditions for Alkylations of Unactivated Secondary Sulfonates with Glycine Imines**[a]



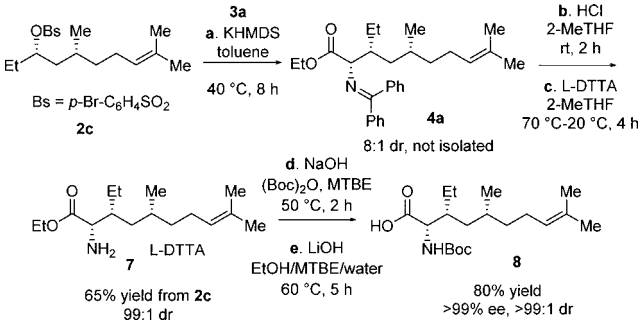

| entry | sulfonate | imine | $t$ (°C) | conv.[b] (%) | dr[b] |
|---|---|---|---|---|---|
| 1 | **2a** | **3a** | 70 | 91 | 1:1 (in THF) |
| 2 | **2a** | **3a** | 70 | 86 | 3.2:1 |
| 3 | **2b** | **3a** | 50 | 88 | 4.1:1 |
| 4 | **2c** | **3a** | 50 | 89 | 4.0:1 |
| 5[c] | **2c** | **3a** | 40 | 79 | 8:1 |
| 6 | **2c** | **3a** | 25 | 72 | 10:1 |
| 7 | **2c** | **3b** | 40 | 83 | 6:1 |
| 8 | **2c** | **3c** | 40 | <5 | NA |
| 9 | **2c** | **3d** | 40 | 79 | 5:1 |
| 10 | **2c** | **3e** | 40 | 81 | 2:1 |
| 11 | **2c** | **3f** | 40 | 80 | 4:1 |
| 12[d] | **2c** | **3a** | 40 | 80 | 1:1.5 (with **5**) |
| 13[e] | **2c** | **3a** | 40 | 76 | 3:1 (with **6**) |

[a]Sulfonate (1.0 mmol), glycine imine (1.70 mmol), and KHMDS in toluene (0.5 M, 1.4 equiv). [b]Conversion was measured by $^1$H NMR after alkylation, and dr was measured by $^1$H NMR after hydrolysis of the benzophenone imine with HCl (1 N). [c]The analogous reaction using LiHMDS or NaHMDS afforded a 7% and 14% yield, respectively, after 8 h. [d]2.0 equiv of **5** were used. [e]2.0 equiv of **6** were used.

selectivity. The effect of modifying the glycine imine derivative was studied first. Alkylations of glycine methyl ester **3b** in the presence of **1c** afforded adduct **4b** with good conversion and 6:1 dr (entry 7). The *tert*-butyl ester **3c**, however, proved to be unreactive (entry 8). We then explored the effect of the electronic nature of the substituents on the benzophenone moiety (entries 9 and 10) as well as the introduction of methyl groups at the ortho position (entry 11). These changes did not improve the *syn*/*anti* selectivity when compared to the unsubstituted imine **3a**. It is noteworthy that the use of lithium or sodium enolates of glycine imine **3a** afforded very low yields and diminished dr in the alkylation with brosylate **2c** (7−14% yield, 2:1 to 3:1 dr).[15] Since the optimal conditions required a nonpolar solvent such as toluene, we hypothesized that aggregation and solvation effects associated with the potassium glycine imine enolate could play a significant role in the stereochemical outcome of the alkylation. Phosphoryl ligands and crown ethers are known to modify structure−reactivity relationships of organometallic species and hence alter mechanisms, relative rates, and selectivities.[16] Consequently, we tested dicylohexano-18-crown-6 (**5**) and 1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone (DMPU, **6**) and observed a significant reduction on the alkylation diastereoselectivities (entries 12−13).

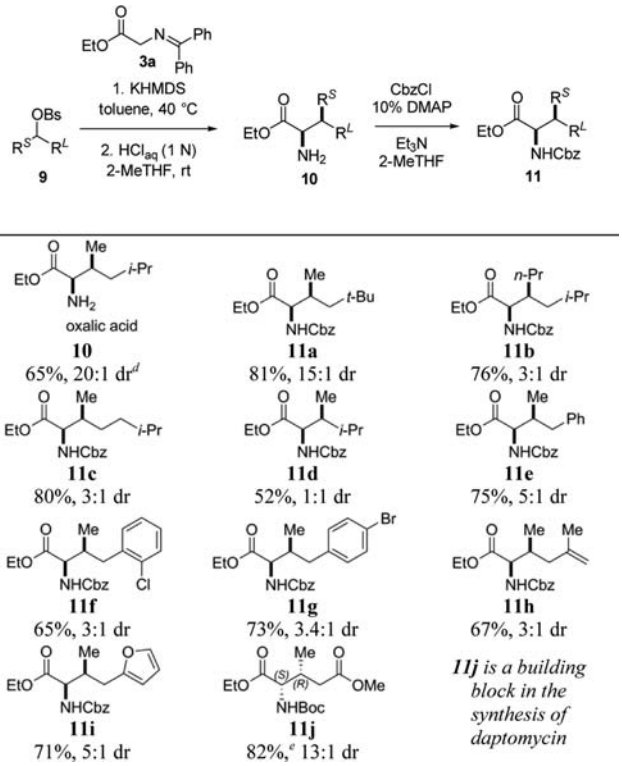
The preparation of **4a** was successfully demonstrated on kilogram scale. Subsequent deprotection of the imine afforded crude $\alpha$-amino ester **7**, which was crystallized as a single diastereomer using L-DTTA. Protection of the free amino group and ester hydrolysis provided amino acid **8** in >99:1 dr and >99% ee (Scheme 2).[17] The absolute stereochemistry of $\alpha$-amino acid **8** was confirmed by single crystal X-ray (see Supporting Information).

**Scheme 2. Stereoselective Synthesis of 8**




We were intrigued by the high *syn*/*anti* selectivity observed in the formation of **4a** and decided to investigate the generality of this reaction to determine if this procedure could be extended to the synthesis of $\beta$-branched $\alpha$-amino-acids with different substitution patterns (Scheme 3). Alkylation of imine **3a** with 4-methylpentan-2-ol sulfonate generated the corresponding $\alpha$-amino ester **10** in excellent yield and 6:1 dr, which was further

**Scheme 3. Alkylation of Secondary Sulfonates with Glycine Imine Derivatives 2a**[a,b,c]




[a]Sulfonate (1.0 mmol), **3a** (1.70 mmol) and KHMDS in toluene (0.5 M, 1.4 equiv). [b]Isolated yield. [c]dr measured by $^1$H NMR spectroscopy after derivatization to the Cbz protected diastereomeric mixture **11**. [d]dr of the crude amine was 6:1 prior to crystallization of **10** as an oxalic acid salt. [e]$Boc_2O$ was used for *in situ* protection of the $\alpha$-amino ester to produce **11j**.



DOI: 10.1021/acs.orglett.5b02448
*Org. Lett.* 2015, 17, 5000−5003

upgraded via crystallization as its oxalate salt (>20:1 dr). To facilitate compound isolation, analysis, and storage, the additional $\alpha$-amino esters listed in Scheme 3 were protected *in situ* as their corresponding Cbz carbamates. Increasing the steric hindrance at the C4 position of the sulfonate resulted in substantial improvement of the diasteroselectivity (15:1 dr, **11a**). Conversely, the presence of a longer side chain (**11b**) or $\gamma$-substitution on the electrophile (**11c**) had a negative impact, and methyl substitution at the C3 position resulted in a complete loss of selectivity (**11d**). Homobenzylic and homoallylic secondary sulfonates underwent successful alkylation and enabled the introduction of aryl halide and alkene functionalities that provide an entry for further product elaboration (**11e**–**h**). The reaction also tolerated the presence of heteroaromatic rings such as the 2-furyl substituent (**11i**).

The preparation of enantiopure (2*S*,3*R*)-3-methyl glutamic acid (**11j**) is particularly relevant. This unnatural amino acid is present in nonribosomal lipopeptide antibiotics such as daptomycin, which has been used in the treatment of systemic, life-threatening infections caused by Gram-positive bacteria.[18] A ten-step asymmetric synthesis of (2*S*,3*R*)-3-methyl glutamic acid has recently been published using L-pyroglutamic acid as the starting material.[19] We decided to evaluate the application of our methodology to complete a simple synthesis of this important building block. To our delight, the alkylation of glycine imine **3a** with the readily available (*S*)-methyl 3-hydroxybutanoate sulfonate gave the desired product in excellent yield and 13:1 dr with inversion of configuration at the electrophilic center. The amino acid derivative was immediately converted into its Boc derivative to prevent lactam formation and undesired oligomerization pathways. This rapid and efficient synthesis of (2*S*,3*R*)-3-methyl glutamic acid in high diastereoselectivity represents a significant advancement compared to previous approaches.[19]

We pursued DFT calculations to develop a stereochemical model that could explain the experimentally observed diastereoselectivities. The alkylation of glycine imine **3a** with 4,4-dimethyl-2-pentanol sulfonate ester was modeled with the monomeric form of the corresponding potassium enolate ligated to toluene.[20] At the onset, examination of the enolate configurations revealed a large preference for the (*Z*)-enolate relative to its *E* counterpart (~13.0 kcal/mol, Figure 1). Both *Z* and *E* enolates exhibit a nonplanar arrangement of the phenyl rings, which adopt a skew angle of ≈35°, and present $\eta^6$-complexes of potassium with the toluene used as implicit solvent.[21] The (*Z*)-enolate displays a cationic center stabilized by N,O-chelation as well as intramolecular $\pi$ interactions with the adjacent phenyl ring. In contrast, the (*E*)-enolate is incompatible with chelation and $\pi$ coordination, and forms an internal potassium $\eta^3$-complex with the enolate carbon and oxygen atoms.

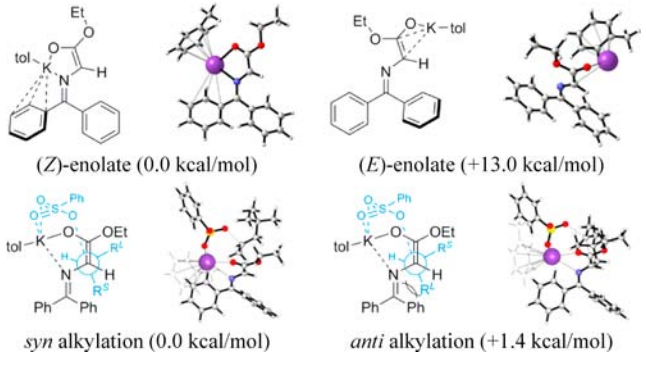



**Figure 1.** Lowest energy structures for the (*Z*)- and (*E*)-enolates of **3a**, and (*Z*)-enolate-based transition structures.[22]

Subsequently, a range of geometries were tested to identify plausible transition structures. We considered all reasonable combinations of enolate stereoisomers (*E* vs *Z*) and relative configurations (*syn* vs *anti*) at the reacting centers. The dominant stability of the (*Z*)-enolates reappeared, and attempts to optimize transition structures containing (*E*)-enolates converged spontaneously to their *Z* isomers.[23] The resulting (*Z*)-enolate-based geometries displayed a series of common features, namely: (a) the occurrence of S═O−K contacts between the sulfonyl leaving group and the potassium ion,[24] (b) $S_N2$ trajectory C−C−O angles that deviate from the ideal 180°,[25] (c) a rigid enolate scaffold that biases the steric accessibility of the electrophile, and (d) an increased skew of the $Ph_2C$═N− phenyl rings (>50°) that aggravates the steric congestion about the substitution center. Most importantly, inspection of the relative configurations and individual conformations at the electrophilic carbon revealed that viable transition structures must place the H atom of the secondary sulfonate ester adjacent to the congested flank of the N,O-chelate. This premise defines two diastereomeric geometries characterized by the orientation of the small ($R^S$) and large ($R^L$) alkyl substituents. A gauche relationship between $Ph_2C$═N− and $R^S$ generates *syn* adducts whereas the analogous arrangement of $Ph_2C$═N− and $R^L$ leads to *anti* products. In agreement with experiment, calculations predict that *syn* alkylation is preferred over *anti* alkylation: the sulfonate ester approach that places the $Ph_2C$═N− substituent proximate to $R^S$ is sterically more manageable than the analogous approach to the $R^L$ group ($\Delta G$ = −1.4 kcal/mol).

In summary, we have identified and further developed a diastereoselective alkylation of nonactivated secondary sulfonates with glycine-derived imines to access synthetically useful $\beta$-branched $\alpha$-amino acid derivatives. The use of a potassium enolate and toluene as solvent were two key factors identified to maximize the *syn* selectivity in the reaction. These conditions have been successfully applied to a range of secondary electrophiles, allowing rapid entry to a class of molecules that can be challenging to obtain with other synthetic methods, such as (2*S*,3*R*)-3-methyl glutamic ester derivatives. We believe these results will be of interest to others considering the preparation of these important synthetic building blocks. On a general note, whereas the results shown herein contend with the perennial difficulty of achieving stereocontrol in alkylations with secondary electrophiles, they also draw attention to the merits of routinely screening nonpolar solvents to optimize reactions classically run in polar media.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02448.

Experimental procedures, spectroscopic and analytical data for all new compounds, and computation information (PDF)

## ■ AUTHOR INFORMATION

### Corresponding Authors

*E-mail: sha.lou@bms.com.
*E-mail: antonio.ramirez1@bms.com.



DOI: 10.1021/acs.orglett.5b02448
*Org. Lett.* 2015, 17, 5000−5003

## Present Addresses

†Department of Chemistry, Stanford University, 333 Campus Dr., Stanford, CA 94305.
‡Cambridge Major Laboratories, W130N0497 Washington Dr., Germantown, WI 53022.

## Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We acknowledge Bristol-Myers Squibb (BMS) colleagues, Drs. Jason Stevens, Chris Sfouggatakis, Steve Silverman, Annie Tam, Gregory Beutner, Matthew Haley, Amarjit Singh, Ronald Hanson, Jaan Pesti, and Akin Davulcu, for investigating alternative methods and Dr. Ian Young (BMS) for helpful suggestions. We thank Mr. Jun Qiu (BMS) for high-throughput screening support, Mrs. Merrill Davies (BMS) for HPLC analytical assistance, Dr. Qi Gao (BMS) for X-ray characterization of a single-crystal, and Mr. Jonathan Marshall (BMS) for providing HRMS data. The Chemical Development senior management at BMS is acknowledged for support during the preparation of this manuscript.

## ■ REFERENCES

(1) Hruby, V. J. *J. Med. Chem.* **2003**, *46*, 4215.
(2) (a) Nicolaou, K. C.; Lizos, D. E.; Kim, D. W.; Schlawe, D.; de Noronha, R. G.; Longbottom, D. A.; Rodriquez, M.; Bucci, M.; Cirino, G. *J. Am. Chem. Soc.* **2006**, *128*, 4460. (b) Yu, S.; Pan, X.; Ma, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 135.
(3) Zlatopolskiy, B. D.; de Meijere, A. *Chem. - Eur. J.* **2004**, *10*, 4718.
(4) Fowler, V. G.; Boucher, H. W.; Corey, G. R. *N. Engl. J. Med.* **2006**, *355*, 653.
(5) Lin, K.; Perni, R. B.; Kwong, A. D.; Lin, C. *Antimicrob. Agents Chemother.* **2006**, *50*, 1813.
(6) For a recent review on stereocontrolled synthesis: Michaux, J.; Niel, G.; Campagne, J.-M. *Chem. Soc. Rev.* **2009**, *38*, 2093.
(7) (a) Burk, M. J.; Gross, M. F.; Martinez, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 9375. (b) Roff, G.; Lloyd, R. C.; Turner, N. J. *J. Am. Chem. Soc.* **2004**, *126*, 4098. (c) Spangenberg, T.; Schoenfelder, A.; Breit, B.; Mann, A. *Org. Lett.* **2007**, *9*, 3881.
(8) For selected allylic substitutions giving branched products, see: (a) Trost, B. M.; Dogra, K. *J. Am. Chem. Soc.* **2002**, *124*, 7256. (b) Kanayama, T.; Yoshida, K.; Miyabe, H.; Kimachi, T.; Takemoto, Y. *J. Org. Chem.* **2003**, *68*, 6197. (c) For a recent review, see: Nájera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584.
(9) (a) Davis, F. A.; Portonovo, P. S.; Reddy, R. E.; Chiu, Y.-h. *J. Org. Chem.* **1996**, *61*, 440. (b) Zhang, M.; Porte, A.; Diamantidis, G.; Sogi, K.; Kubrak, D.; Resnick, L.; Mayer, S. C.; Wang, Z.; Kreft, A. F.; Harrison, B. L. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2401.
(10) (a) Qian, X.; Russell, K. C.; Boteju, L. W.; Hruby, V. J. *Tetrahedron* **1995**, *51*, 1033. (b) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. *J. Am. Chem. Soc.* **1990**, *112*, 4011. (c) Stocking, E. M.; Martinez, R. A.; Silks, L. A.; Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **2001**, *123*, 3391.
(11) (a) Notz, W.; Tanaka, F.; Watanabe, S.; Chowdari, N. S.; Turner, J. M.; Thayumanavan, R.; Barbas, C. F., III. *J. Org. Chem.* **2003**, *68*, 9624. (b) Enders, D.; Grondal, C.; Vrettou, M.; Raabe, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4079.
(12) (a) Quirin, C.; Kazmaier, U. *Synthesis* **2009**, *2009*, 1725. (b) Kazmaier, U. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 998.
(13) Phase-transfer-catalyzed alkylations of glycine imines with racemic secondary alkyl halides have been reported. However, they are limited to activated electrophiles; see: Ooi, T.; Kato, D.; Inamura, K.; Ohmatsu, K.; Maruoka, K. *Org. Lett.* **2007**, *9*, 3945.
(14) Although alkylations of related Li enolates in THF are known, they occur without stereocontrol. See: (a) Sun, L.-Q.; Zhao, Q.; Renduchintala, K. V.; Sarkunam, K.; Nagalakshmi, P.; Gillis, E. P.; Scola, P. M. WO 2014071032, A1, May 08, 2014. (b) Gillis, E. P.; Bowsher, M. S.; Scola, P. M. WO 2014071007, A1, May 08, 2014.
(15) (a) For a recent review highlighting the effect of the metal upon the reactivity of the enolate, see: Bruckner, R. *Organic Mechanisms; Reactions, Stereochemistry and Synthesis*; Harmata, M., Ed.; Springer-Verlag: Berlin, Heidelberg, 2010. (b) K−O bond lengths of potassium enolates are longer than Li−O and Na−O bonds of analogous enolates; see: Williard, P. G.; Carpenter, G. B. *J. Am. Chem. Soc.* **1986**, *108*, 462.
(16) Lucht, B. L.; Collum, D. B. *Acc. Chem. Res.* **1999**, *32*, 1035.
(17) This synthetic sequence was successfully used to produce 12 kg of **8**.
(18) Tally, F. P.; DeBruin, M. F. *J. Antimicrob. Chemother.* **2000**, *46*, 523.
(19) (a) Lam, H. Y.; Zhang, Y.; Liu, H.; Xu, J.; Wong, C. T. T.; Xu, C.; Li, X. *J. Am. Chem. Soc.* **2013**, *135*, 6272. (b) Milne, C.; Powell, A.; Jim, J.; Al Nakeeb, M.; Smith, C. P.; Micklefield, J. *J. Am. Chem. Soc.* **2006**, *128*, 11250. (c) For selective Michael additions affording *anti* $\beta$-substituted pyroglutamic acids, see: Soloshonok, V. A.; Cai, C.; Yamada, T.; Ueki, H.; Ohfune, Y.; Hruby, V. J. *J. Am. Chem. Soc.* **2005**, *127*, 15296.
(20) Structures were fully optimized at the B3LYP/6-31+G(d) level of theory. See Supporting Information for details and references.
(21) For X-ray structures of $\pi$-toluene potassium complexes, see: (a) Honeyman, G. W.; Kennedy, A. R.; Mulvey, R. E.; Sherrington, D. C. *Organometallics* **2004**, *23*, 1197. (b) Schaverien, C. J.; van Mechelen, J. B. *Organometallics* **1991**, *10*, 1704.
(22) Energies in parentheses are normalized to the most stable enolate and transition structure, respectively.
(23) For computational studies endorsing the enhanced stability of (*Z*)-imino ester enolates in the transition structures, see: (a) Aldol condensations of Ag enolates: Lou, S.; Ramirez, A.; Conlon, D. A. *Adv. Synth. Catal.* **2015**, *357*, 28. (b) Alkylation of Li enolates: Nahm, K.; Lee, S. *Bull. Korean Chem. Soc.* **2012**, *33*, 2711. (c) Mannich reaction of Cu enolates: Yan, X.-X.; Peng, Q.; Li, Q.; Zhang, K.; Yao, J.; Hou, X.-L.; Wu, Y.-D. *J. Am. Chem. Soc.* **2008**, *130*, 14362. (d) For a seminal discussion on benzophenone glycine imine enolate conformations using the MM2 force field, see: Lipkowitz, K. B.; Cavanaugh, M. W.; Baker, B.; O'Donnell, M. J. *J. Org. Chem.* **1991**, *56*, 5181.
(24) For a general discussion of cyclic transition structures in the nucleophilic substitution of sulfonate esters, see: Gupta, J.; Ramirez, A.; Collum, D. B. *J. Org. Chem.* **2010**, *75*, 8392 and references cited therein.
(25) Bent transition states are a recurring theme in computational modeling of $S_N2$ ion pair reactions: (a) Li, Q.-G.; Xu, K.; Ren, Y. *J. Phys. Chem. A* **2015**, *119*, 3878. (b) Sato, M.; Yamataka, H.; Komeiji, Y.; Mochizuki, Y.; Ishikawa, T.; Nakano, T. *J. Am. Chem. Soc.* **2008**, *130*, 2396. (c) Zuend, S. J.; Ramirez, A.; Lobkovsky, E.; Collum, D. B. *J. Am. Chem. Soc.* **2006**, *128*, 5939. (d) Harder, S.; Streitwieser, A.; Petty, J. T.; von Schleyer, P. *J. Am. Chem. Soc.* **1995**, *117*, 3253.



DOI: 10.1021/acs.orglett.5b02448
*Org. Lett.* 2015, 17, 5000−5003