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Novel N1–C4 β-Lactam Bond Breakage. Synthesis of Enantiopure α-Alkoxy-γ-keto Acid Derivatives†

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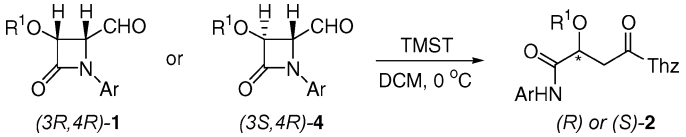
ABSTRACT



Addition reaction of 2-(trimethylsilyl)thiazole (TMST) to *cis*- or *trans*-4-formyl-β-lactams gave enantiopure α-alkoxy-γ-keto acid derivatives via a novel N1–C4 bond breakage of the β-lactam nucleus. This is the first time that the cleavage of the N1–C4 bond on the β-lactam nucleus has been shown to occur in 2-azetidinones lacking an aryl moiety at C4.

In addition to the key role that β-lactams have played in the fight against pathogenic bacteria, the use of 2-azetidinones as chiral building blocks in organic synthesis is now well established.[1] Opening of the β-lactam ring can occur through cleavage of any of the single bonds of the four-membered ring.[2] Cleavage of the amide bond (*a* in Figure 1) has been the subject of many investigations to give β-amino acids, bis-γ-lactams, pyrrolizidines, indolizidines, pyrrolidines, piperidines, cyclic enaminones, pyridones, oxazinones, and complex natural products. *N*-Carboxy anhydrides, α-amino acids, peptides, and haloalkyl isocyanates have been obtained by breakage of the C2−C3 bond (*b* in Figure 1). Pyrazine-2,3-diones, substituted amides, and eight-membered lactams can be prepared through cleavage of the C3−C4 bond on the β-lactam nucleus (*c* in Figure 1). However, little was known about the application in synthesis of the N1−C4 bond breakage of the β-lactam system (*d* in Figure 1), until Ojima and his group entered this field.[3] These authors developed a methodology for the synthesis of α-amino acids and derivatives, based on the hydrogenolytic cleavage of the N1−C4 bond of 4-aryl-β-lactams.[4] In continuation of our efforts on the synthesis and synthetic applications of functionalized β-lactams,[5] herein we report a novel N1−C4 bond breakage of the β-lactam skeleton to yield enantiopure α-hydroxy acid derivatives **2**, an important class of molecules that are building blocks for the synthesis of depsides and depsipep-

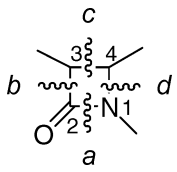


Figure 1. Various modes of ring opening of the β-lactam nucleus.

† Dedicated to Prof. José Luis Soto on the occasion of his retirement.
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(1) For selected reviews, see: (a) Alcaide, B.; Almendros, P. *Chem. Soc. Rev.* **2001**, *30*, 226. (b) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Synlett* **2001**, 1813. (c) Manhas, M. S.; Wagle, D. R.; Chiang, J.; Bose, A. K. *Heterocycles* **1988**, *27*, 1755.

(2) For a review on the selective bond cleavage of the β-lactam nucleus, see: Alcaide, B.; Almendros, P. *Synlett* **2002**, 381.

(3) For reviews, see: (a) Ojima, I.; Delaloge, F. *Chem. Soc. Rev.* **1997**, *26*, 377. (b) Ojima, I. *Adv. Asymmetric Synth.* **1995**, *1*, 95. (c) Ojima, I. *Acc. Chem. Res.* **1995**, *28*, 383.

(4) In addition to Ojima's work, the only available reports on the N1−C4 bond cleavage are: (a) Cabell, L. A.; McMurray, J. S. *Tetrahedron Lett.* **2002**, *43*, 2491. (b) Alcaide, B.; Domínguez, G.; Martín-Domenech, A.; Plumet, J.; Monge, A.; Pérez-García, V. *Heterocycles* **1987**, *26*, 1461.

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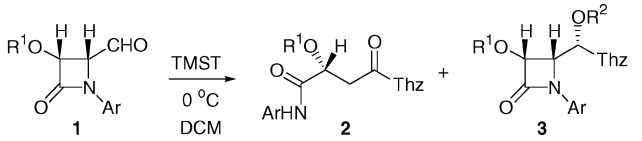
tides, natural products than often exhibit significant biological activity.[6]

The starting substrates, enantiopure 2-azetidinones **1a**−**f**, were prepared using standard methodology as single cis enantiomers from aryl imines of (*R*)-2,3-*O*-isopropylideneglyceraldehyde, through Staudinger reaction with methoxy- or benzyloxyacetyl chloride in the presence of Et_3N, followed by sequential acidic acetonide hydrolysis and oxidative cleavage.[7]

Thiazole-based organometallics are well documented reagents for carbonyl addition.[8] In this context, we began this work by investigating the diastereoselectivity of the addition of *cis*-4-formyl-*β*-lactam (+)-**1a** with 2-(trimethylsilyl)thiazole (TMST) in dichloromethane. The reaction provided the enantiomerically pure α-hydroxy acid derivative (+)-**2a** in a reasonable 58% isolated yield (Table 1, entry 1). The expected addition product, (+)-**3a**, was obtained as a minor component (31%). Polyfunctionalized compound (+)-**2a** can be considered both an aldol as well as a Passerini-type product. Placing a less electron-donating substituent in the para position of the *N*-aryl ring decreased the selectivity of the process (Table 1, entry 2). The NMe_2 analogue was a poor participant (Table 1, entry 3). It was revealed that the introduction of one halogen atom at the 4-position of the aromatic ring was slightly effective (Table 1, entry 4). To further improve the selectivity, we focused on a more electron-rich aromatic ring. Indeed, placing two electron-donating substituents in the ortho and para positions of the aromatic ring at N1 increased the selectivity of the process (Table 1, entry 5). *β*-Lactams bearing a benzyl or an allyl substituent at nitrogen failed to give the α-alkoxy acid derivative, giving the addition product. No advantage is gained from changing the methoxy group at C3 to a benzyloxy (Table 1, entry 6) in the starting (*3R,4R*)-4-formyl-*β*-lactam **1**. Switching solvents (acetonitrile, THF, toluene) had no beneficial effects. In terms of achieving fair yields with reasonable selectivity of reaction, 0 °C seemed to be the temperature of choice for running the experiments.

The susceptibility of the reaction to stereochemically different *β*-lactam aldehydes was next examined, by exploring the possibility of employing *trans*-4-formyl-*β*-lactams **4**. Optically pure 2-azetidinones (+)-**4a**, (−)-**4a**, and (+)-**4b** were prepared adopting literature methodology.[9]

Table 1. Conversion of *cis*-4-Formyl-*β*-lactams **1** into α-Hydroxy Carboxamides **2**[a]



substrate	R^1	Ar	R^2	products	**2**:**3** yields (%)[b]
(+)-**1a**	Me		TMS	(+)-**2a**/(+)-**3a**	58:31
(+)-**1b**	Me		TMS	(+)-**2b**/(+)-**3b**	33:31
(+)-**1c**	Me		TMS	(+)-**2c**/(+)-**3c**	38:20
(+)-**1d**	Me		TMS	(+)-**2d**/(+)-**3d**	46:23
(+)-**1e**	Me		TMS	(+)-**2e**/(+)-**3e**	51:10
(+)-**1f**	Bn		H	(+)-**2f**/(+)-**3f**	55:24

[a] TMST = 2-(trimethylsilyl)thiazole. Thz = 2-thiazolyl. [b] Yields are for pure isolated products with correct analytical and spectroscopic data. In all cases, compounds **2** and **3** could be easily separated by column chromatography.

Gratifyingly, the corresponding enantiopure α-alkoxy carboxamides could be obtained (Scheme 1). The (*3R,4S*)-4-formyl-*β*-lactam (−)-**4a** gave compound (+)-**2a**, while its enantiomer (+)-**4a** gave compound (−)-**2a**. Addition products **5a**−**c** were obtained as minor components in the coupling reactions. The higher ratio of α-alkoxy carboxamide/addition product using aldehydes (−)-**4a** or (+)-**4a** in comparison to (+)-**1a** was mainly due to the inefficiency of the competitive addition reaction in diastereomeric aldehydes **4**, since the opening product accounted as well for a 50% yield in pure product. In each case, the absolute configuration of the α-alkoxy acid product matched that of the corresponding *β*-lactam aldehyde. Therefore, a synthesis of both enantiomers of α-hydroxy acid derivatives was achieved just by a subtle variation in the stereochemistry of the aldehyde component.

It may be possible that, under the reaction conditions, the initially formed adducts **3** or **5** evolve to the corresponding α-hydroxy carboxamides **2**. However, compounds (+)-**3a** or (+)-**3f** remained unaltered after several days in the presence of TMST at the above conditions. At present time, we propose alkoxide **6** as a common intermediate for the thiazole adducts formation (Scheme 2). Alkoxide **6** may suffer a 1,2 migration of hydrogen with concomitant N1−C4 *β*-lactam

(5) See, for instance: (a) Alcaide, B.; Almendros, P.; Alonso, J. M. *J. Org. Chem.* **2004**, *69*, 993. (b) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Rodríguez-Acebes, R. *J. Org. Chem.* **2004**, *69*, 826. (c) Alcaide, B.; Almendros, P.; Alonso, J. M. *Chem. Eur. J.* **2003**, *9*, 5793. (d) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Org. Lett.* **2003**, *5*, 3795. (e) Alcaide, B.; Almendros, P.; Alonso, J. M.; Aly, M. F. *Chem. Eur. J.* **2003**, *9*, 3415.

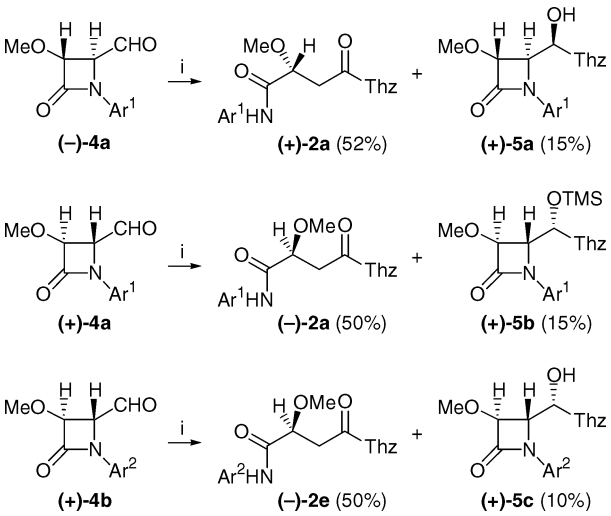
(6) (a) Nicolaou, K. C.; Boddy, C. N. C.; Bräse, S.; Winssinger, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2096. (b) Ballard, C. E.; Yu, H.; Wang, B. *Curr. Med. Chem.* **2002**, *9*, 471.

(7) (a) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Eur. J.* **2002**, *8*, 1719. (b) Alcaide, B.; Almendros, P.; Salgado, N. R. *J. Org. Chem.* **2000**, *65*, 3310.

(8) (a) Dondoni, A.; Marra, A. *Tetrahedron Lett.* **2003**, *44*, 13. (b) Dondoni, A. *Synthesis* **1998**, 1681. (c) Dondoni, A. *Pure Appl. Chem.* **2000**, *72*, 1577.

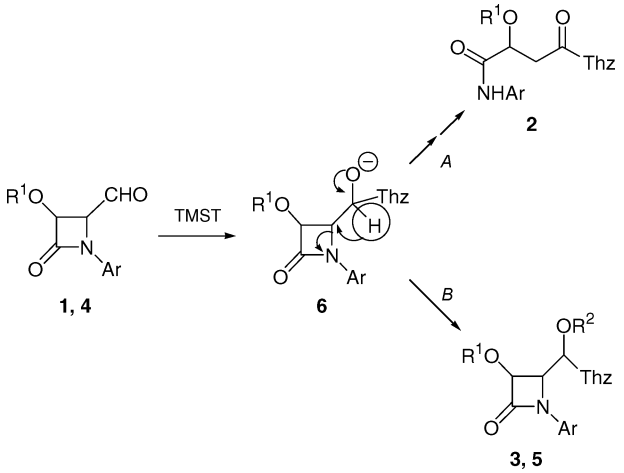
(9) For (−)-**4a**, see: (a) Alcaide, B.; Aly, M.; Rodríguez, C.; Rodríguez-Vicente, A. *J. Org. Chem.* **2000**, *65*, 3453. For (+)-**4a** and (+)-**4b**, see: (b) Wagle, D. R.; Garai, C.; Chiang, J.; Monteleone, M. G.; Kurys, B. E.; Strohmeyer, T. W.; Hedge, V. R.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1988**, *53*, 4227.

Scheme 1. Conversion of *trans*-4-Formyl-β-lactams **4** into α-Alkoxy Carboxamides **2**[a]



[a] Key: (i) TMST, DCM, 0 °C. Yields are for pure isolated products with correct analytical and spectroscopic data. In all cases, the compounds **2** and **5** could be easily separated by column chromatography. TMST = 2-(trimethylsilyl)thiazole. Thz = 2-thiazolyl. Ar^1 = 4-$MeOC_6H_4$. Ar^2 = 2,4-di-$MeOC_6H_3$.

Scheme 2. Proposed Reaction Course for the Formation of α-Alkoxy Carboxamides **2** and Addition Products **3** or **5** from 4-Formyl-β-lactams **1** and **4**



bond breakage to afford the α-alkoxy acid derivatives **2** (*A* in Scheme 2), or it may accept an electrophile to give the addition products **3** or **5** (*B* in Scheme 2).

In conclusion, this is the first report involving the N1−C4 bond breakage in β-lactams lacking an aryl moiety at C4. In addition, the resulting products, possessing simultaneously a β-alkoxy ketone (aldol-type product) and an α-alkoxy carboxamide (Passerini-type product), cannot be easily obtained by alternative means. Studies concerning the scope and generality of this methodology are underway in our laboratory, and further details will be reported in due course.

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Supporting Information Available: General experimental procedures as well as spectroscopic and analytical data for compounds **1a**−**f**, **2a**−**f**, **3a**−**f**, and **5a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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