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

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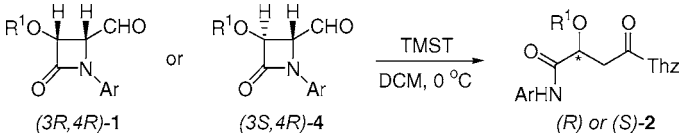
## ABSTRACT




**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-

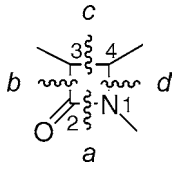



**Figure 1.** Various modes of ring opening of the β-lactam nucleus.

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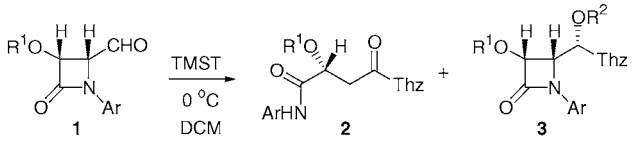
tides, natural products than often exhibit significant biological activity.[6]

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.

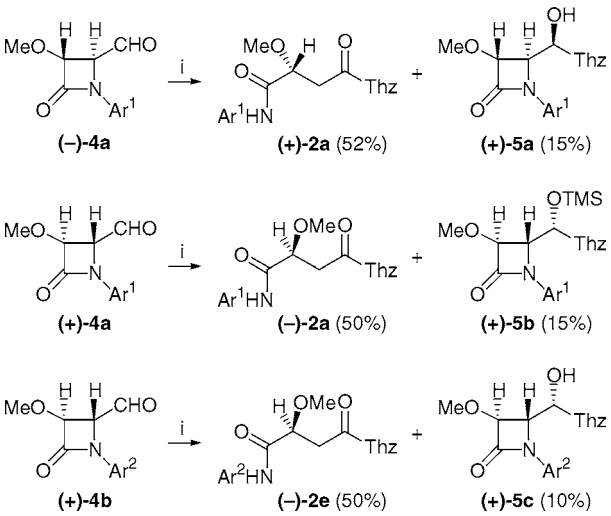
(6) (a) Nicolaou, K. C.; Boddy, C. N. C.; Bräse, S.; Winssinger, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2096. (b) Ballard, C. E.; Yu, H.; Wang, B. *Curr. Med. Chem.* **2002**, *9*, 471.

(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-$\beta$-lactams **4** into $\alpha$-Alkoxy Carboxamides **2**[a]

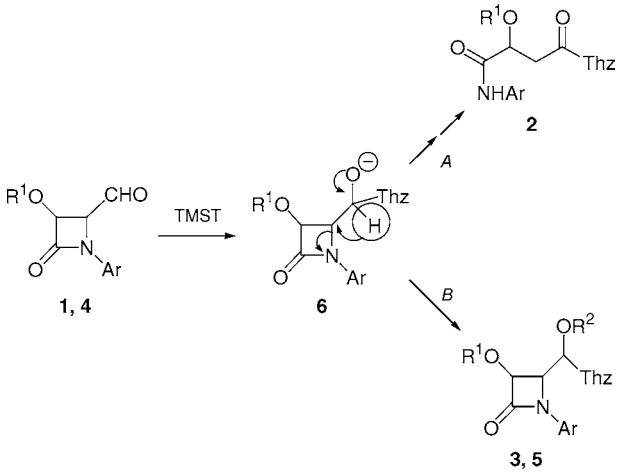



[a] Key: (i) TMST, DCM, 0 °C. Yields are for pure isolated products with correct analytical and spectroscopic data. In all cases, the compounds **2** and **5** could be easily separated by column chromatography. TMST = 2-(trimethylsilyl)thiazole. Thz = 2-thiazolyl. $Ar^1$ = 4-$MeOC_6H_4$. $Ar^2$ = 2,4-di-$MeOC_6H_3$.

bond breakage to afford the $\alpha$-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 $\beta$-lactams lacking an aryl moiety at C4. In addition, the resulting products, possessing simultaneously a $\beta$-alkoxy ketone (aldol-type product) and an $\alpha$-alkoxy carboxamide (Passerini-type product), cannot be easily obtained by alternative means. Studies concerning the

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




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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