## N1–C4 β-Lactam Bond Cleavage in the 2-(Trimethylsilyl)thiazole Addition to β-Lactam Aldehydes: Asymmetric Synthesis of Spiranic and Tertiary α-Alkoxy-γ-keto Acid Derivatives

Benito Alcaide,\*<sup>[a]</sup> Pedro Almendros,\*<sup>[b]</sup> and María C. Redondo<sup>[a]</sup>

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Starting substrates, enantiopure spiranic or 3-substituted 3alkoxy-4-oxoazetidine-2-carbaldehydes, were prepared from (*R*)-2,3-*O*-isopropylideneglyceraldehyde derived azetidine-2,3-diones by sequential Barbier-type addition reactions followed by hydroxy functionalization and aldehyde unmasking. The reaction between the above  $\beta$ -lactam alde-

#### Introduction

In addition to being the key structural motif of the  $\beta$ lactam antibiotics, the 2-azetidinone skeleton has been recognized as a useful building block in the synthesis of pharmaceutically useful products.<sup>[1]</sup> The strain energy associated with the  $\beta$ -lactam nucleus makes it susceptible to opening through cleavage of any of the single bonds of the fourmembered ring.<sup>[2]</sup> Cleavage of the N1-C4 bond of 4-arylazetidin-2-ones by hydrogenolysis is a very well known methodology developed by Ojima for the synthesis of  $\alpha$ -amino acids and peptidomimetics.<sup>[3]</sup> More recently, we and others have established different protocols for the N1-C4 β-lactam bond breakage leading to cyclic and acyclic compounds.<sup>[4]</sup> In connection with our current research interest in the preparation and synthetic utility of  $\beta$ -lactams,<sup>[5]</sup> we recently communicated the synthesis of  $\alpha$ -alkoxy- $\gamma$ -keto acid derivatives by N1-C4 bond cleavage when we reacted 2-(trimethylsilyl)thiazole (TMST) with 4-oxoazetidine-2-carbaldehydes.<sup>[6]</sup> Our previous report was limited primarily to the use of simple cis- or trans-4-oxoazetidine-2-carbaldehydes as a coupling partner. As such, we have undertaken a study of the potential use of more diverse  $\beta$ -lactam aldehydes. Herein we examine the feasibility and efficiency of the reac-

 [a] Departamento de Química Orgánica I, Facultad de Química, Universidad Complutense de Madrid, 28040 Madrid, Spain Fax: +34-91-3944103

E-mail: alcaideb@quim.ucm.es
[b] Instituto de Química Orgánica General, Consejo Superior de Investigaciones Científicas, CSIC, Juan de la Cierva 3, 28006 Madrid, Spain Fax: +34-91-5644853

- E-mail: iqoa392@iqog.csic.es
- Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

hydes and 2-(trimethylsilyl)thiazole (TMST) gave as major products conformationally constrained  $\alpha$ -alkoxy- $\gamma$ -keto amides, which can be considered both as aldols as well as Passerini-type products, by N1–C4  $\beta$ -lactam bond cleavage. (© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2007)

tion between sterically encumbered 4-oxoazetidine-2-carbaldehydes and TMST to obtain enantiopure spiranic and tertiary  $\alpha$ -alkoxy- $\gamma$ -keto acid derivatives.<sup>[7]</sup>

#### **Results and Discussion**

The starting substrates were prepared from azetidine-2,3diones by metal-mediated Barbier-type carbonyl addition reactions in an aqueous environment followed by functionalization reactions. Azetidine-2,3-diones (+)-1a and (-)-1b, were efficiently obtained in an optically pure form from aromatic (R)-2,3-O-isopropylideneglyceraldehyde derived imines, by the Staudinger reaction with acetoxyacetyl chloride in the presence of Et<sub>3</sub>N, followed by sequential transesterification and Swern oxidation, following our previously reported procedure (Scheme 1).<sup>[8]</sup>



Scheme 1. Stereoselective preparation of azetidine-2,3-diones 1. Reagents and conditions: a) (i)  $Et_3N$ ,  $CH_2Cl_2$ , room temp.; (ii) NaOMe, MeOH, room temp.; (iii) (CO)<sub>2</sub>Cl<sub>2</sub>, DMSO,  $Et_3N$ ,  $CH_2Cl_2$ , -78 °C.

The conversion of azetidine-2,3-diones (+)-1 $a^{[8a]}$  and (-)-1b into new spiranic or 3-substituted 3-alkoxy- $\beta$ -lactam aldehydes (+)-2a and (+)-2b was carried out through a fourstep reaction sequence involving zinc-mediated allylation to give 3-allyl 3-hydroxy- $\beta$ -lactams (+)-3a and (+)-3b, hydroxy





Scheme 2. Preparation of spiranic and 3-substituted 3-alkoxy- $\beta$ -lactam aldehydes 2. Reagents and conditions: (a) Prenyl bromide, Zn, THF/NH<sub>4</sub>Cl (aq. satd.) (1:5), 0 °C, 1.5 h. (b) Me<sub>2</sub>SO<sub>4</sub>, TBAI, CH<sub>2</sub>Cl<sub>2</sub>, NaOH (aq. 50%) (1:1), room temp., 4 h. (c) PTSA, THF/H<sub>2</sub>O (1:1), reflux, 2 h. (d) NaIO<sub>4</sub>, NaHCO<sub>3</sub> (aq. satd.), CH<sub>2</sub>Cl<sub>2</sub>, room temp., 2 h. (e) Allyl bromide, Zn, THF/NH<sub>4</sub>Cl (aq. satd.) (1:1), 0 °C, 3 h. (f) Allyl bromide, TBAI, CH<sub>2</sub>Cl<sub>2</sub>, NaOH (aq. 50%) (1:1), room temp., 16 h. (g) [Cl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub>Ru = CHPh], toluene, reflux, 7 h. (h) 1-Bromo-2-butyne, In, THF/NH<sub>4</sub>Cl (aq. satd.) (1:5), room temp., 16 h. (i) AgNO<sub>3</sub>, acetone/H<sub>2</sub>O (1:1), reflux, 2 h.

protection to give ethers (+)-4a and (+)-4b, and aldehyde unmasking by sequential acidic acetonide hydrolysis and oxidative cleavage. Spirocyclic dyhydropyran- $\beta$ -lactam aldehyde (+)-2c was obtained from azetidine-2,3-dione (+)-1a by carbonyl allylation to give 3-allyl 3-hydroxy- $\beta$ -lactam (+)-3c, treatment with allyl bromide under basic conditions to afford diene (+)-5 and ring-closing metathesis to achieve spiranic 2-azetidinone (+)-6, followed by aldehyde unmasking. Spirocyclic dihydrofuran- $\beta$ -lactam aldehyde (+)-2d was obtained from azetidine-2,3-dione (-)-1b by indiummediated carbonyl allenylation to give 3-allenyl 3-hydroxy- $\beta$ -lactam (+)-7, followed by silver-induced cyclization and oxidative cleavage of the resulting diol (+)-8. Carbaldehydes 2 were obtained as single isomers in reasonable yields (Scheme 2).

TMST addition to 4-oxoazetidine-2-carbaldehydes **2** in dichloromethane resulted in desired enantiopure  $\alpha$ -hydroxy acid derivatives **9a–d** possessing quaternary or spiranic carbon centers in reasonable isolated yields (Scheme 3); addition products<sup>[9]</sup> **10a–d** were also obtained, but as a minor component. Carbinols **10b–d** could be easily separated by gravity flow chromatography. However, compound **10a** could not be isolated as a pure compound. The observed *syn* diastereoselectivity for the TMST addition step might be tentatively explained by invoking the Felkin–Anh model, analogously to related addition processes described in our laboratories.<sup>[10]</sup>

We propose the mechanism shown in Scheme 4 to account for our new ring cleavage. Under the reaction condi-



Scheme 3. Preparation of conformationally constrained enantiopure  $\alpha$ -alkoxy- $\gamma$ -keto amides 9. Reagents and conditions: a) TMST, DCM, 0 °C, 16 h.

tions, intermediate alkoxide **11** may suffer a 1,2-migration of hydrogen with concurrent cleavage of the N1–C4 bond of the 2-azetidinone ring, affording  $\alpha$ -alkoxy- $\gamma$ -keto acid derivatives **9** (Scheme 4, path *A*). Alternatively, species **11** may accept an electrophile (proton or trimethylsilyl group) to give addition products **10** (Scheme 4, path *B*).



Scheme 4. Mechanistic explanation for the N1–C4  $\beta$ -lactam bond breakage of 3-substituted 3-alkoxy- $\beta$ -lactam aldehydes 2 under TMST/carbonyl addition conditions.

#### Conclusions

Spiranic as well as 3-substituted 3-alkoxy- $\beta$ -lactam aldehydes, which were obtained from enantiopure azetidine-2,3diones, gave preferentially the N1–C4  $\beta$ -lactam bond cleavage product rather than the carbonyl addition product by reaction with 2-(trimethylsilyl)thiazole. The resulting optically active spiranic and tertiary  $\alpha$ -alkoxy- $\gamma$ -keto acid derivatives, which can be considered both as conformationally constrained aldols as well as Passerini-type products, cannot be easily achieved by alternative protocols.

#### **Experimental Section**

**General Methods:** <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded with a Bruker Avance-300, a Varian VRX-300S, or a Bruker AC-200 instrument. NMR spectra were recorded in CDCl<sub>3</sub> solutions, unless otherwise stated. Chemical shifts are given in ppm relative to TMS (<sup>1</sup>H NMR, 0.0 ppm), or CDCl<sub>3</sub> (<sup>13</sup>C NMR, 76.9 ppm). Low and high resolution mass spectra were recorded with a HP5989A spectrometer by using the electronic impact (EI) or electrospray modes (ES), unless otherwise stated. Specific rotations  $[a]_D$  are given in  $10^{-1}$  °cm<sup>2</sup>g<sup>-1</sup> at 20 °C, and the concentration (*c*) is expressed in g 100 mL<sup>-1</sup>. All commercially available compounds were used without further purification.

General Procedure for the Synthesis of Spiranic and Tertiary  $\alpha$ -Alkoxy- $\gamma$ -keto Acid Derivatives 9: A solution of TMST (94 mg, 0.60 mmol) in anhydrous dichloromethane (0.35 mL) was added dropwise to a solution cooled to 0 °C of the corresponding 4oxoazetidine-2-carbaldehyde 2 (0.50 mmol) in the same solvent (0.5 mL). The reaction was placed in a 0 °C freezer overnight. The mixture was extracted with EtOAc, washed with water, dried with MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. Chromatography of the residue (ethyl acetate/hexanes) gave a more polar fraction containing the corresponding  $\alpha$ -alkoxy- $\gamma$ -keto amide 9, and a less polar compound, containing the free carbinol or its trimethylsilyl ether 10. Spectroscopic and analytical data for some representative forms of 9 and 10 follow.<sup>[11]</sup>

Tertiary α-Alkoxy-γ-keto Carboxamide (-)-9b and β-Lactam (+)-10b: From 4-oxoazetidine-2-carbaldehyde (+)-2b (63 mg, 0.18 mmol). Chromatography (EtOAc/hexanes, 1:3) gave two fractions. The less polar fraction contained β-lactam (+)-10b (20 mg, 25%) as a colorless oil.  $[a]_D = +44.2$  (c = 0.8, CHCl<sub>3</sub>). <sup>1</sup>H NMR  $(300 \text{ MHz}, \text{CDCl}_3, 25 \text{ °C})$ :  $\delta = 7.68 \text{ (d, } J = 3.2 \text{ Hz}, 1 \text{ H}), 7.25 \text{ (d, } J = 3.2 \text{ Hz}, 1 \text{ H})$ J = 8.8 Hz, 1 H), 7.19 (d, J = 3.2 Hz, 1 H), 6.40 (m, 2 H), 5.78 (dd, J = 22.4, 10.7 Hz, 1 H), 5.19 (d, J = 7.3 Hz, 1 H), 4.91 (m, 2 H), 4.50 (d, J = 7.3 Hz, 1 H), 3.71 and 3.72 (s, each 3 H), 3.69 (s, 3 H), 1.97 (br. s, 1 H), 0.84 and 0.98 (s, each 3 H) ppm. <sup>13</sup>C NMR  $(75 \text{ MHz}, \text{ CDCl}_3, 25 \text{ °C}): \delta = 175.5, 165.3, 156.9, 154.7, 143.0,$ 141.8, 126.5, 121.3, 119.2, 115.1, 104.0, 100.1, 99.5, 72.0, 66.2, 58.2, 56.5, 55.5, 42.1, 23.6, 21.3 ppm. IR (CHCl<sub>3</sub>):  $\tilde{v} = 1743 \text{ cm}^{-1}$ . MS (ES): m/z (%) = 419 (100) [M + H]<sup>+</sup>, 418 (17) [M]<sup>+</sup>. C<sub>21</sub>H<sub>26</sub>N<sub>2</sub>O<sub>5</sub>S (418.2): calcd. C 60.27, H 6.26, N 6.69; found C 60.39, H 6.21, N 6.63. The more polar fraction contained quaternary  $\alpha$ -alkoxy- $\gamma$ keto carboxamide (-)-9b (47 mg, 62%) as a pale yellow oil.  $[a]_D$  =  $-71.0 \ (c = 0.6, \text{ CHCl}_3)$ . <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta =$ 8.90 (br. s, 1 H), 8.25 (d, J = 8.5 Hz, 1 H), 8.00 (d, J = 3.2 Hz, 1 H), 7.66 (d, J = 3.2 Hz, 1 H), 6.47 (m, 2 H), 6.18 (dd, J = 17.5, 10.7 Hz, 1 H), 5.10 (m, 2 H), 3.80 and 3.89 (s, each 3 H), 3.73 and 4.13 (d, J = 19.0 Hz, each 1 H), 3.48 (s, 3 H), 1.06 (s, 6 H) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 190.8, 169.5, 167.1, 156.3, 144.5, 144.0, 126.4, 121.0, 120.5, 113.3, 103.7, 98.7, 85.6, 55.8, 55.7, 54.9, 45.0, 38.1, 23.0, 22.2 ppm. IR (CHCl<sub>3</sub>):  $\tilde{v} = 1742$ , 1726 cm<sup>-1</sup>. MS (EI): m/z (%) = 419 (8) [M + H]<sup>+</sup>, 418 (30) [M]<sup>+</sup>, 153 (100). C21H26N2O5S (418.2): calcd. C 60.27, H 6.26, N 6.69; found C 60.40, H 6.22, N 6.73.

Spiranic α-Alkoxy-γ-keto Carboxamide (-)-9c and β-Lactam (+)-10c: From 4-oxoazetidine-2-carbaldehyde (+)-2c (70 mg, 0.25 mmol). Chromatography (EtOAc/hexanes, 2:3) gave two fractions. The less polar fraction contained  $\beta$ -lactam (+)-10c (13 mg, 12%) as a colorless oil.  $[a]_{D} = +28.0$  (c = 0.8, CHCl<sub>3</sub>). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  = 7.84 (d, J = 3.3 Hz, 1 H), 7.56 (m, 3 H), 6.77 (d, J = 8.9 Hz, 2 H), 5.83 (s, 2 H), 5.50 (d, J = 6.5 Hz, each 1 H), 4.57 (d, J = 6.5 Hz, each 1 H), 4.79 and 4.34 (d, J =16.5 Hz, each 1 H), 3.80 (s, 3 H), 2.63 and 2.36 (d, J = 17.5 Hz, each 1 H), -0.01 (s, 9 H) ppm. 13C NMR (75 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta = 172.3, 165.3, 150.2, 142.7, 131.3, 125.8, 121.0, 120.8, 119.3,$ 113.8, 82.5, 70.5, 67.2, 65.5, 55.6, 55.4, 28.7, 0.00 ppm. IR (CHCl<sub>3</sub>):  $\tilde{v} = 1741 \text{ cm}^{-1}$ . MS (ES): m/z (%) = 431 (100) [M + H]<sup>+</sup>, 430 (11) [M]<sup>+</sup>. C<sub>21</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>SSi (430.6): calcd. C 58.58, H 6.09, N 6.51; found C 58.47, H 6.06, N 6.55. The more polar fraction contained spiranic  $\alpha$ -alkoxy- $\gamma$ -keto carboxamide (–)-9c (47 mg, 52%) as a pale yellow oil.  $[a]_D = -44.0$  (c = 0.3, CHCl<sub>3</sub>). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  = 8.48 (br. s, 1 H), 7.98 (d, J = 3.0 Hz, 1 H), 7.66 (d, J = 3.0 Hz, 1 H), 7.50 and 6.87 (d, J = 9.0 Hz, each 2 H), 5.85 (m, 2 H), 4.37 and 4.32 (d, J = 16.0 Hz, each 1 H), 3.79 (s, 3 H), 4.16 and 3.65 (d, J = 17.0 Hz, each 1 H), 2.50 (m, 2 H) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 189.9, 171.4, 167.0, 156.3, 144.7, 130.7, 126.7, 124.6, 122.4, 121.5, 114.1, 75.3, 62.2, 55.5, 40.2, 32.5 ppm. IR (CHCl<sub>3</sub>):  $\tilde{v} = 1740$ , 1724 cm<sup>-1</sup>. MS (ES): m/z (%) = 359 (100)  $[M + H]^+$ , 358 (23)  $[M]^+$ .  $C_{18}H_{18}N_2O_4S$  (358.4): calcd. C 60.32, H 5.06, N 7.82; found C 60.44, H 5.03, N 7.78.

**Spiranic** *α*-Alkoxy-γ-keto Carboxamide (-)-9d and β-Lactam (+)-10d: From 4-oxoazetidine-2-carbaldehyde (+)-2d (60 mg, 0.19 mmol). Chromatography (EtOAc/hexanes, 1:3) gave two fractions. The less polar fraction contained β-lactam (+)-10d (15 mg, 20%) as a colorless oil.  $[a]_D = +28.0$  (c = 0.8, CHCl<sub>3</sub>). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta = 7.40$  (d, J = 8.5 Hz, 1 H), 7.63 and 7.11 (d, J = 3.4 Hz, each 1 H), 6.37 (dd, J = 8.5, 2.4 Hz, 1 H), 6.15 (d, J = 2.4 Hz, 1 H), 5.83 (q, J = 1.8 Hz, 1 H), 5.39 and 5.02 (d, J = 1.5 Hz, each 1 H), 4.84 (m, 2 H), 3.74 and 3.60 (s, each 3 H), 1.90 (q, J = 1.9 Hz, 3 H) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta =$ 171.2, 167.3, 159.3, 153.3, 139.1, 132.4, 126.9, 124.6, 120.9, 117.1, 103.9, 101.9, 98.6, 75.4, 70.3, 67.0, 55.5, 55.4, 10.9 ppm. IR (CHCl<sub>3</sub>):  $\tilde{v} = 3342$ , 1742 cm<sup>-1</sup>. MS (ES): m/z (%) = 389 (100) [M

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+ H]<sup>+</sup>, 388 (7) [M]<sup>+</sup>. C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub>S (388.4): calcd. C 58.75, H 5.19, N 7.21; found C 58.85, H 5.16, N 7.17. The more polar fraction contained spiranic α-alkoxy-γ-keto carboxamide (–)-**9d** (42 mg, 57%) as a colorless solid. M.p. 118–119 °C (hexanes/ethyl acetate). [a]<sub>D</sub> = -87.0 (c = 1.2, CHCl<sub>3</sub>). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  = 9.07 (br. s, 1 H), 8.22 (d, J = 9.0 Hz, 1 H), 7.99 and 7.66 (d, J= 3.2 Hz, each 1 H), 6.47 (m, 2 H), 5.62 (q, J = 1.8 Hz, 1 H), 4.74 (m, 2 H), 3.86 and 3.80 (s, each 3 H), 4.11 and 3.69 (d, J = 16.8 Hz, each 1 H), 1.95 (q, J = 1.9 Hz, 3 H) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 190.7, 169.5, 167.6, 156.7, 149.8, 145.1, 138.6, 126.9, 122.3, 121.5, 120.3, 104.0, 99.0, 92.8, 75.3, 56.2, 55.9, 43.7, 12.9 ppm. IR (CHCl<sub>3</sub>):  $\tilde{v}$  = 1739, 1725 cm<sup>-1</sup>. MS (EI): m/z (%) = 389 (15) [M + H]<sup>+</sup>, 388 (54) [M]<sup>+</sup>, 208 (100). C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub>S (388.4): calcd. C 58.75, H 5.19, N 7.21; found C 58.63, H 5.17, N 7.25.

Supporting Information (see footnote on the first page of this article): Characterization data and experimental procedures for compounds (-)-1b, 2a-d, 3a-c, (+)-4a, (+)-4b, 5-8, and (-)-9a.

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- [11] Full spectroscopic and analytical data for compounds not included in this Experimental Section are described in the Supporting Information.

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