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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

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Keywords: Aldehydes / Asymmetric synthesis / Cleavage reactions / Lactams / Spiro compounds

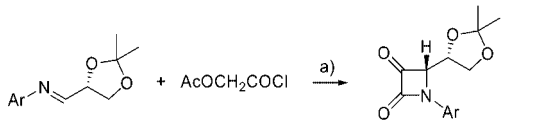
Starting substrates, enantiopure spiranic or 3-substituted 3-alkoxy-4-oxoazetidine-2-carbaldehydes, were prepared from (*R*)-2,3-*O*-isopropylideneglyceraldehyde derived azetidine-2,3-diones by sequential Barbier-type addition reactions followed by hydroxy functionalization and aldehyde unmasking. The reaction between the above β-lactam aldehydes and 2-(trimethylsilyl)thiazole (TMST) gave as major products conformationally constrained α-alkoxy-γ-keto amides, which can be considered both as aldols as well as Passerini-type products, by N1–C4 β-lactam bond cleavage.

Introduction

In addition to being the key structural motif of the β-lactam antibiotics, the 2-azetidinone skeleton has been recognized as a useful building block in the synthesis of pharmaceutically useful products.[1] The strain energy associated with the β-lactam nucleus makes it susceptible to opening through cleavage of any of the single bonds of the four-membered ring.[2] 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 α-amino acids and peptidomimetics.[3] More recently, we and others have established different protocols for the N1–C4 β-lactam bond breakage leading to cyclic and acyclic compounds.[4] In connection with our current research interest in the preparation and synthetic utility of β-lactams,[5] we recently communicated the synthesis of α-alkoxy-γ-keto acid derivatives by N1–C4 bond cleavage when we reacted 2-(trimethylsilyl)thiazole (TMST) with 4-oxoazetidine-2-carbaldehydes.[6] 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 β-lactam aldehydes. Herein we examine the feasibility and efficiency of the reaction between sterically encumbered 4-oxoazetidine-2-carbaldehydes and TMST to obtain enantiopure spiranic and tertiary α-alkoxy-γ-keto acid derivatives.[7]

Results and Discussion

The starting substrates were prepared from azetidine-2,3-diones 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_3N, followed by sequential transesterification and Swern oxidation, following our previously reported procedure (Scheme 1).[8]



(+)-**1a** Ar = 4-$MeOC_6H_4$ (58%)
(–)-**1b** Ar = 2,4-$(OMe)_2C_6H_3$ (81%)

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) $(CO)_2Cl_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C.

The conversion of azetidine-2,3-diones (+)-**1a**[8a] and (–)-**1b** into new spiranic or 3-substituted 3-alkoxy-β-lactam aldehydes (+)-**2a** and (+)-**2b** was carried out through a four-step reaction sequence involving zinc-mediated allylation to give 3-allyl 3-hydroxy-β-lactams (+)-**3a** and (+)-**3b**, hydroxy

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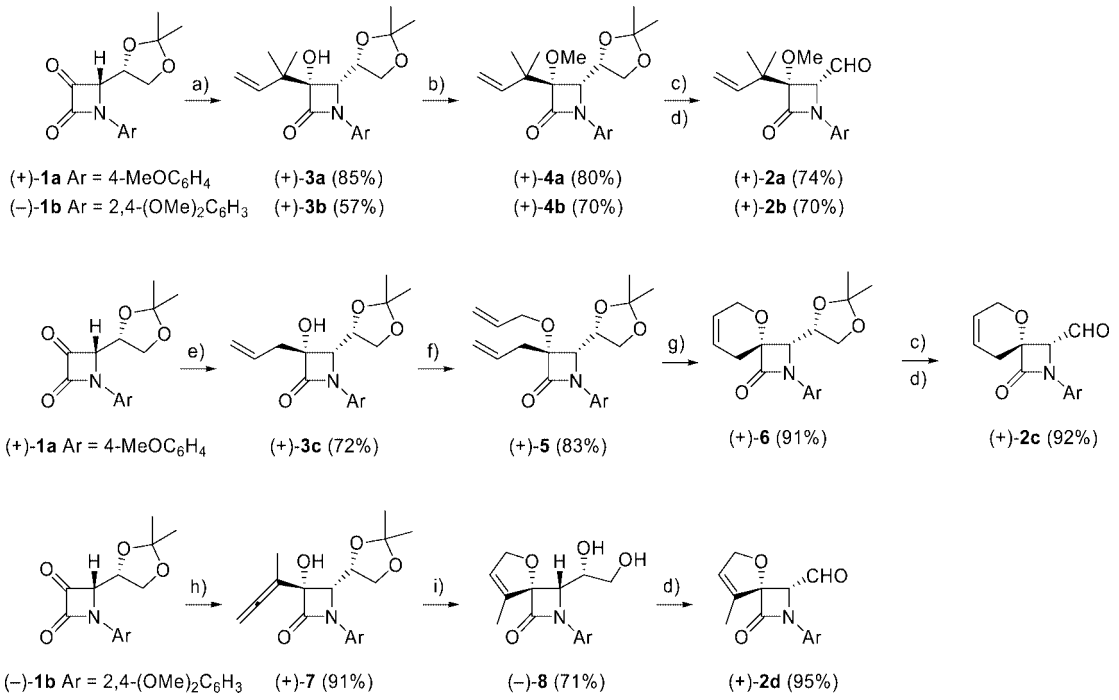
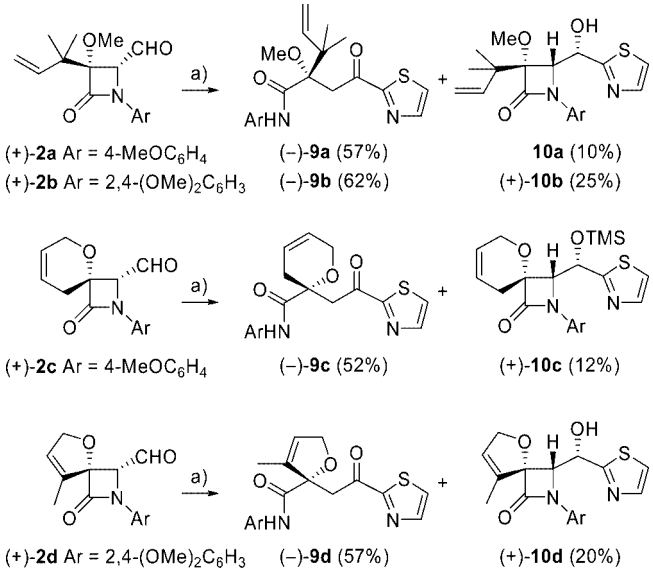


Scheme 2. Preparation of spiranic and 3-substituted 3-alkoxy-β-lactam aldehydes **2**. Reagents and conditions: (a) Prenyl bromide, Zn, THF/NH_4Cl (aq. satd.) (1:5), 0 °C, 1.5 h. (b) Me_2SO_4, TBAI, CH_2Cl_2, NaOH (aq. 50%) (1:1), room temp., 4 h. (c) PTSA, THF/H_2O (1:1), reflux, 2 h. (d) $NaIO_4$, $NaHCO_3$ (aq. satd.), CH_2Cl_2, room temp., 2 h. (e) Allyl bromide, Zn, THF/NH_4Cl (aq. satd.) (1:1), 0 °C, 3 h. (f) Allyl bromide, TBAI, CH_2Cl_2, NaOH (aq. 50%) (1:1), room temp., 16 h. (g) [$Cl_2(PCy_3)_2Ru$ = CHPh], toluene, reflux, 7 h. (h) 1-Bromo-2-butyne, In, THF/NH_4Cl (aq. satd.) (1:5), room temp., 16 h. (i) $AgNO_3$, acetone/H_2O (1:1), reflux, 2 h.

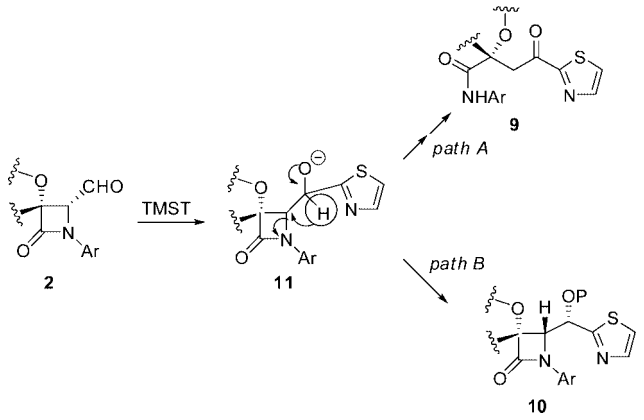
protection to give ethers (+)-**4a** and (+)-**4b**, and aldehyde unmasking by sequential acidic acetonide hydrolysis and oxidative cleavage. Spirocyclic dyhydropyran-β-lactam aldehyde (+)-**2c** was obtained from azetidine-2,3-dione (+)-**1a** by carbonyl allylation to give 3-allyl 3-hydroxy-β-lactam (+)-**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-β-lactam aldehyde (+)-**2d** was obtained from azetidine-2,3-dione (–)-**1b** by indium-mediated carbonyl allenylation to give 3-allenyl 3-hydroxy-β-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 α-hydroxy acid derivatives **9a**–**d** possessing quaternary or spiranic carbon centers in reasonable isolated yields (Scheme 3); addition products[9] **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.[10]

We propose the mechanism shown in Scheme 4 to account for our new ring cleavage. Under the reaction conditions, 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 α-alkoxy-γ-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 3. Preparation of conformationally constrained enantiopure α-alkoxy-γ-keto amides **9**. Reagents and conditions: a) TMST, DCM, 0 °C, 16 h.



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

Conclusions

Spiranic as well as 3-substituted 3-alkoxy-β-lactam aldehydes, which were obtained from enantiopure azetidine-2,3-diones, gave preferentially the N1–C4 β-lactam bond cleavage product rather than the carbonyl addition product by reaction with 2-(trimethylsilyl)thiazole. The resulting optically active spiranic and tertiary α-alkoxy-γ-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: ^{1}H and ^{13}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 $CDCl_3$ solutions, unless otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H NMR, 0.0 ppm), or $CDCl_3$ (^{13}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 $[\alpha]_D$ are given in 10^{-1} °cm^{2}g^{-1} at 20 °C, and the concentration (c) is expressed in g 100 mL^{-1}. All commercially available compounds were used without further purification.

General Procedure for the Synthesis of Spiranic and Tertiary α-Alkoxy-γ-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 4-oxoazetidine-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 $MgSO_4$, filtered, and concentrated under reduced pressure. Chromatography of the residue (ethyl acetate/hexanes) gave a more polar fraction containing the corresponding α-alkoxy-γ-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.[11]

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. $[\alpha]_D$ = +44.2 (c = 0.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.68 (d, J = 3.2 Hz, 1 H), 7.25 (d, 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. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 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 ($CHCl_3$): $\tilde{\nu}$ = 1743 cm^{-1}. MS (ES): m/z (%) = 419 (100) $[M + H]^+$, 418 (17) $[M]^+$. $C_{21}H_{26}N_2O_5S$ (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 α-alkoxy-γ-keto carboxamide (–)-**9b** (47 mg, 62%) as a pale yellow oil. $[\alpha]_D$ = –71.0 (c = 0.6, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 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. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 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 ($CHCl_3$): $\tilde{\nu}$ = 1742, 1726 cm^{-1}. MS (EI): m/z (%) = 419 (8) $[M + H]^+$, 418 (30) $[M]^+$, 153 (100). $C_{21}H_{26}N_2O_5S$ (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 β-lactam (+)-**10c** (13 mg, 12%) as a colorless oil. $[\alpha]_D$ = +28.0 (c = 0.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 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. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 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 ($CHCl_3$): $\tilde{\nu}$ = 1741 cm^{-1}. MS (ES): m/z (%) = 431 (100) $[M + H]^+$, 430 (11) $[M]^+$. $C_{21}H_{26}N_2O_4SSi$ (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 α-alkoxy-γ-keto carboxamide (–)-**9c** (47 mg, 52%) as a pale yellow oil. $[\alpha]_D$ = –44.0 (c = 0.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 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. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 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 ($CHCl_3$): $\tilde{\nu}$ = 1740, 1724 cm^{-1}. 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. $[\alpha]_D$ = +28.0 (c = 0.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 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. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 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 ($CHCl_3$): $\tilde{\nu}$ = 3342, 1742 cm^{-1}. MS (ES): m/z (%) = 389 (100) [M

+ H]$^+$, 388 (7) [M]$^+$. $C_{19}H_{20}N_2O_5S$ (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). $[\alpha]_D$ = –87.0 (c = 1.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 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. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 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 ($CHCl_3$): $\tilde{\nu}$ = 1739, 1725 cm^{-1}. MS (EI): *m/z* (%) = 389 (15) [M + H]$^+$, 388 (54) [M]$^+$, 208 (100). $C_{19}H_{20}N_2O_5S$ (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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