Stereoselective NaN_3-catalyzed halonitroaldol-type reaction of azetidine-2,3-diones in aqueous media†

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Azetidine-2,3-diones (α-oxo-β-lactams) and bromonitromethane undergo coupling in aqueous media in the presence of catalytic amounts of sodium azide. The stereoselectivity of the process was generally good, proceeding with reasonable *anti* : *syn* ratios under substrate control. On this basis, a simple and fast protocol for the synthesis of the potentially bioactive 3-substituted 3-hydroxy-β-lactam moiety has been developed. Besides, 2-azetidinone-tethered 1-halo-1-nitroalkan-2-ols are quite useful building blocks; for example, reactions of the above nitrobromohydrins provided spiranic and fused bicyclic-β-lactams.

Introduction

β-Lactams are among the most important pharmacophores for treatment of diseases caused by bacterial infections.[1] In addition, there are many important nonantibiotic uses of 2-azetidinones in fields ranging from enzyme inhibition[2] to gene activation.[3] These biological activities, combined with the use of these products as starting materials to prepare α- and β-amino acids, alkaloids, heterocycles, taxoids, and other types of compounds of biological and medicinal interest,[4] provide the motivation to explore new methodologies for the synthesis of substances based on the β-lactam core. In particular, the 3-substituted 3-hydroxy-β-lactam moiety represents an efficient carboxylate mimic,[5] shows promising activity in acyl CoA-cholesterol acyltransferase inhibition assays,[6] and it is present in several pharmacologically active monobactams such as sulfazecin and related products,[7] and in enzyme inhibitors such as tabtoxin and its analogues.[8] Besides, these compounds, with the correct absolute configurations, serve as precursors to the corresponding α-hydroxy-β-amino acids (isoserines), which are key components of a large number of therapeutically important compounds.[9]

Nucleophilic carbonyl addition reactions can be ranked among the premier transformations in organic synthesis for stereoselective carbon–carbon bond formation. In particular, stereoselective addition of nitroalkanes to carbonyls (Henry reaction) plays an important role in organic synthesis.[10] In contrast, the analogous reaction involving halonitroalkanes has remained unexplored despite its ability to provide useful intermediates, the corresponding 1-halo-1-nitroalkan-2-ols;[11] only Concellón *et al.* have recently reported the addition of bromonitromethane to aldehydes promoted by NaI in anhydrous medium.[12] Continuing with our work on the synthesis of nitrogenated compounds of biological interest,[13] herein, we wish to report the efficient NaN_3-catalyzed coupling reaction between α-keto-lactams and bromonitromethane in aqueous media, which resulted in the corresponding 3-[bromonitromethyl]-3-hydroxy-β-lactams.

Results and discussion

Starting substrates, azetidine-2,3-diones **1a–d**, were prepared using our previously described procedure from the appropriate imine, *via* Staudinger reaction with acetoxyacetyl chloride in the presence of Et_3N, followed by sequential transesterification and Swern oxidation.[14] First we studied the effect of different catalysts (15 mol%) on the reaction of azetidine-2,3-dione **1a** with bromonitromethane (1 equiv.) in anhydrous THF as solvent. Despite Concellón's statement that the NaI-catalyzed reaction did not work with highly hindered aldehydes such as pivalaldehyde or ketones,[12] ketone **1a** was found to be a good coupling partner in the halonitroaldol-type reaction (Table 1). LiI, NaI, KI, and NaN_3 promoted the coupling with similar efficiency and selectivity. However, the LiI- and KI-catalyzed processes proceeded more slowly, whereas the NaI-induced reaction yielded appreciable amounts of Henry adduct **3a**. Consequently, we deemed NaN_3 to be the optimal catalyst for the synthesis of 3-[bromonitromethyl]-3-hydroxy-β-lactams **2**. The effect of altering the reaction solvent was then explored (ethanol, acetonitrile, and DMF). Reactions carried out in ethanol, acetonitrile, or *N*,*N*-dimethylformamide yielded lower amounts of **2**, together with considerable amounts of Henry adducts **3**.

The appealing properties of reactions in aqueous media include their synthetic advantages (many reactive functional groups, such as hydroxy and carboxylic functions, do not require the protection–deprotection protocol in such reactions, and many water-soluble compounds do not need to be converted into their derivatives and can be reacted directly) and their potential as environmentally benign chemical processes (the use of anhydrous flammable solvents can be avoided and the burden of solvent disposal may be reduced), as well as unique reactivity and selectivity that are not often attained under dry conditions

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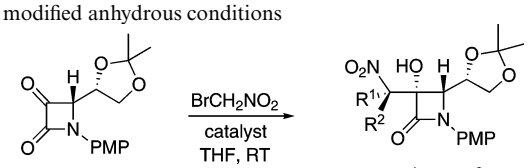
Table 1 Reaction of azetidine-2,3-dione **1a** with bromonitromethane under modified anhydrous conditions



1a

anti-**2a**: R^1 = H, R^2 = Br
syn-**2a**: R^1 = Br, R^2 = H
3a: R^1 = R^2 = H

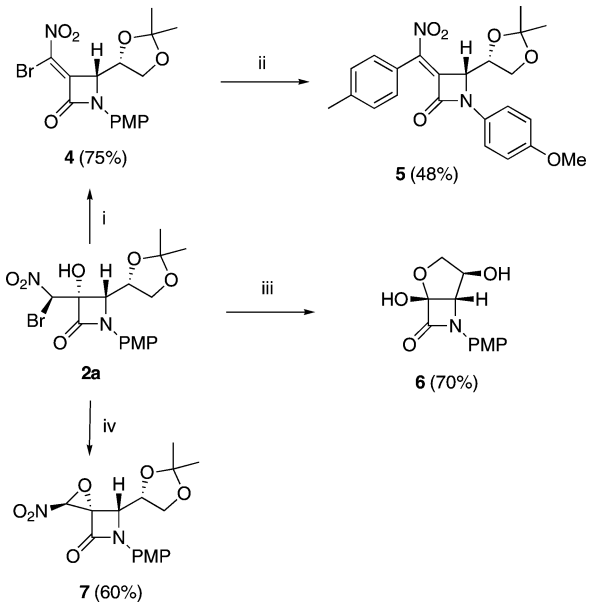
Entry	Catalyst (15 mol%)	*t*/h	**2a**, yield (%)[a]	**2a**, *anti* : *syn*[b]	**3a**, yield (%)[a]
1	NaI	2	56	80 : 20	6
2	LiI	48	54	70 : 30	0
3	KI	6	55	80 : 20	0
4	NaN_3	3	63	85 : 15	0

[a] Yield of pure, isolated product with correct analytical and spectral data. PMP = 4-$MeOC_6H_4$. [b] The ratio was determined by integration of well-resolved signals in the ^{1}H NMR spectra (300 MHz) of the crude reaction mixtures before purification.

(the performance of organic reactions in aqueous conditions might lead to different results as compared with those obtained in purely organic solvents, regardless of whether the reactants are soluble or not in water), making them profitable in many cases.[15]

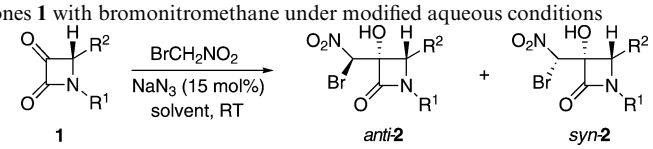
Considering our experience in this field with the application of "on-water chemistry" to the coupling of stabilized organometallic species with carbonylic compounds,[16] we envisaged that the addition of bromonitromethane to carbonyls could be accomplished in the presence of water. To verify this hypothesis, the bromonitroaldol-type reaction of azetidine-2,3-diones **1a–d** was performed in aqueous environment (Table 2). In all cases the NaN_3-catalyzed reactions proceeded well in aqueous media, leading to reasonable yields of products **2a–d** as a mixture of *anti* : *syn* adducts, without the formation of any by-products, such as Henry adducts. No significant difference was observed between using THF–H_2O (1 : 5) and THF–brine (1 : 5) mixtures, the yield being slightly better for the former. When the catalyst loading was lowered to 10% the yield did not change considerably, but the reaction time was increased by 15h. A further decrease in the amount of catalyst used led to a decrease in the yield, but did not affect the degree of stereoselectivity.

Functionalized 1-halo-1-nitroalkan-2-ols are quite useful building blocks in organic synthesis because the haloalkanol moiety can easily be transformed into other functionalities. The usefulness of the 3-[bromonitromethyl]-3-hydroxy-β-lactams **2** becomes much higher by assuming that the 1-bromo-1-nitro-methanol moiety is a placeholder for further conversions. As shown in Scheme 1, water elimination proceeded by treating compound **2a** with *p*-nitrobenzoyl chloride in the presence of triethylamine, affording the α-bromonitroethylene **4**.[17] Owing to the efficacy and functional group tolerance of transition metal catalyzed cross-coupling reactions in forming C–C bonds, we envisioned that such coupling of bromoalkenyl adduct **4** with arylboronic acids (Suzuki–Miyaura reaction) would provide polysubstituted 3-alkylidene-β-lactams.[17]



Scheme 1 Preparation of β-lactams **4–7** from 2-azetidinone-tethered bromonitroalcohols **2**. *Reagents and conditions*: (i) PNPCOCl, Et_3N, CH_2Cl_2, −78 °C, 45 min. (ii) 2.5 mol% $Pd(PPh_3)_4$, 4-$MeC_6H_4B(OH)_2$, $NaHCO_3$, toluene–EtOH–H_2O (18 : 1 : 1), reflux, 4 h. (iii) 5 mol% $BiCl_3$, MeCN–H_2O (1 : 1), rt, 3 d. (iv) K_2CO_3, MeOH, rt, 5 h. PNP = 4-$NO_2C_6H_4$.

Table 2 Reaction of azetidine-2,3-diones **1** with bromonitromethane under modified aqueous conditions



Entry	Ketone	R^1	R^2	Solvent	*t*/h	**2**, yield (%)[a]	**2**, *anti* : *syn*[b]
1	**1a**	PMP[c]	Diox[d]	THF–brine (1 : 5)	2	**2a**, 68	**2a**, 85 : 15
2	**1a**	PMP	Diox[d]	THF–H_2O (1 : 5)	2	**2a**, 77	**2a**, 85 : 15
3	**1b**	Bn	Diox[d]	THF–H_2O (1 : 5)	5	**2b**, 70	**2b**, 80 : 20
4	**1c**	Allyl	Diox[d]	THF–H_2O (1 : 5)	3	**2c**, 72	**2c**, 80 : 20
5	**1d**	PMP	*p*-Tolyl	THF–H_2O (1 : 3)	5	**2d**, 80	**2d**, 85 : 15

[a] Yield of pure, isolated product with correct analytical and spectral data. [b] The ratio was determined by integration of well-resolved signals in the ^{1}H NMR spectra (300 MHz) of the crude reaction mixtures before purification. [c] PMP = 4-$MeOC_6H_4$. [d] (*S*)-2,2-dimethyl-1,3-dioxolan-4-yl.

Indeed, the Pd-catalyzed coupling between electron-deficient bromonitroalkene **4** and *p*-tolylboronic acid afforded product **5** (Scheme 1).

The (*E*)-stereochemistry for compound **5** was established by selective NOE experiments. Surprisingly, treatment of adduct **2a** with aqueous $BiCl_3$ furnished bicyclic β-lactam **6** (Scheme 1), which probably arises from an initial acetonide cleavage followed by a retroaldol-type reaction with concomitant selective cyclization to the five-membered ring.[18] The structure and relative stereochemistry of fused-2-azetidinone **6** was established by X-ray crystallography (Fig. 1).[19]† Next, we studied the reactivity of 2-azetidinone-tethered bromonitroalcohol **2a** with potassium carbonate. Oxacyclopropane formation was observed to give the highly strained oxiranyl-β-lactam **7** (Scheme 1), possessing a spirocyclic structure.[20] The relative stereochemistry of the spirocyclic β-lactam **7** was determined by X-ray crystallography,[21] as is shown in Fig. 2.

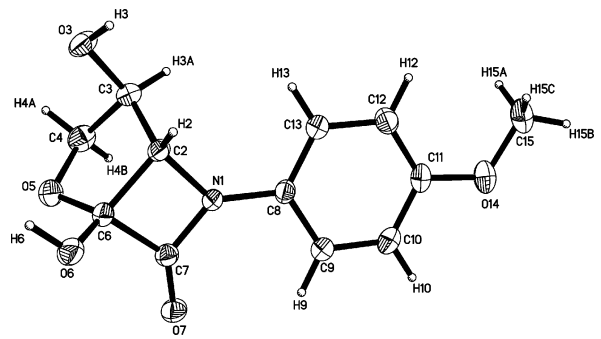


Fig. 1 ORTEP plot of fused β-lactam **6** with thermal ellipsoids with 35% probability.

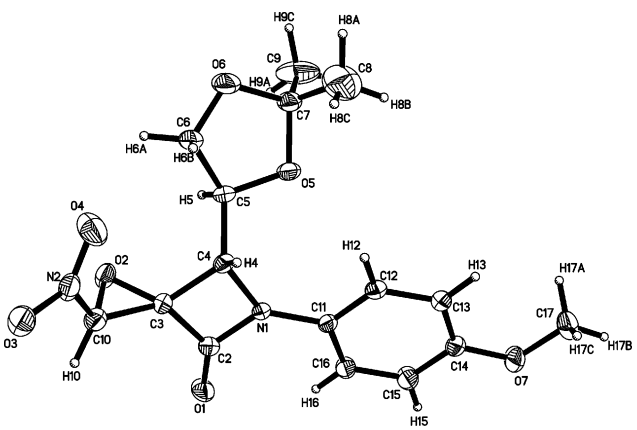
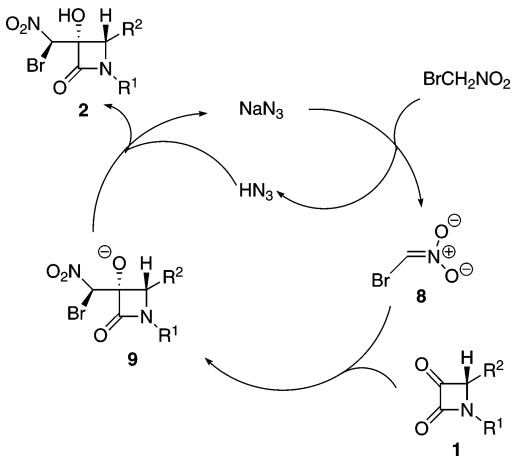


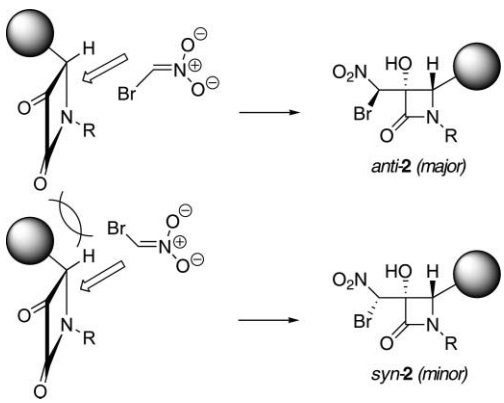
Fig. 2 ORTEP plot of spirocyclic β-lactam **7** with thermal ellipsoids with 25% probability.

The pathway proposed in Scheme 2 looks valid for the formation of products **2**. It involves the nucleophilic addition of bromonitronate **8**, a species generated *in situ* from the exposure of bromonitromethane to the mild azide base, to an α-ketolactam **1**. The addition product, alkoxide **9**, would suffer a protonation which produces the adduct **2** with concomitant liberation of the catalyst. Despite the fact that halonitroaldol-type reaction of ketone acceptors **1** with bromonitromethane generates two new stereocenters, it proceeds with reasonable *anti* : *syn* ratios under



Scheme 2 Mechanistic explanation for the formation of 3-[bromonitromethyl]-3-hydroxy-β-lactams **2**.

substrate chirality control to afford adducts **2**.[22,23] From azetidine-2,3-diones **1**, full stereocontrol at the carbinolic stereocenter was achieved due to the presence of a bulky group at C4, which was able to control the stereochemistry of the new C3-substituted C3-hydroxy quaternary center. One face of the carbonyl group is blocked preferentially, thus the nucleophile species is delivered to the less hindered face, and as a consequence the diastereoselectivity was complete in all cases (Scheme 3). The observed stereochemistry for the second stereocenter can be explained by invoking steric interactions between the bulky group at C4 and the bromine atom of the bromonitronate (Scheme 3).



Scheme 3 Models to explain the observed stereochemistry for the halonitroaldol-type reaction of ketones **1**.

Conclusions

We can conclude that new protocols for the synthesis of 3-substituted 3-hydroxy-β-lactams from azetidine-2,3-diones and bromonitromethane have been developed. This addition reaction proceeds under mild conditions in aqueous media under the presence of a cheap catalyst. Besides the observed reactivity, it has been shown that the resulting 1-bromo-1-nitroalkan-2-ols are not only important end points, but also key intermediates for further manipulations, *i.e.* they are useful building blocks for the preparation of diversely functionalized monocyclic, fused, and spirocyclic 2-azetidinones.

Experimental

Melting points were taken using a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance-300, Varian VRX-300S or Bruker AC-200. NMR spectra were recorded in $CDCl_3$ solutions, except otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm), or $CDCl_3$ (^{13}C, 76.9 ppm). Low and high resolution mass spectra were taken on a HP5989A spectrometer using the electronic impact (EI) or electrospray modes (ES) unless otherwise stated. Optical rotations were measured using a Perkin-Elmer 241 polarimeter. Specific rotation $[\alpha]_D$ is given in deg cm^2 g^{-1} at 25 °C, and the concentration (c) is expressed in g per 100 mL. All commercially available compounds were used without further purification. THF was distilled from Na–benzophenone. Dichloromethane and triethylamine were distilled from CaH_2. Flame-dried glassware and standard Schlenk techniques were used for moisture sensitive reactions. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh).

General procedure for the halonitroaldol-type reaction of azetidine-2,3-diones 1. Preparation of 3-[bromonitromethyl]-3-hydroxy-β-lactams 2

Bromonitromethane (1.0 mmol) was added to a well stirred solution of the corresponding azetidine-2,3-dione **1** (1.0 mmol) and sodium azide (9.7 mg, 0.15 mmol) in THF–H_2O (1 : 5, 12 mL) at room temperature. The mixture was stirred at the same temperature until complete disappearance of the α-keto-β-lactam (TLC). Saturated aqueous ammonium chloride (2.5 mL) was added, before the product was extracted with ethyl acetate (3 × 5 mL). The organic extract was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue, eluting with hexanes–ethyl acetate mixtures, gave analytically pure compounds **2**.[24]

3-[Bromonitromethyl]-3-hydroxy-2-azetidinone 2a

From 185 mg (0.63 mmol) of azetidine-2,3-dione **1a**, 209 mg (77%) of compound *anti*-**2a**, containing *ca.* 15% of its *syn*-**2a** epimer, were obtained as a colorless oil after purification by flash chromatography (hexanes–ethyl acetate, 2 : 1); $[\alpha]_D$ = +116.3 (c 0.8 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.49 (m, 2H), 6.90 (d, J = 9.0 Hz, 2H), 6.34 (s, 0.15H), 6.21 (s, 0.85H), 4.98 (d, J = 4.6 Hz, 1H), 4.68 (m, 0.15H), 4.48 (m, 0.85H), 4.24 (dd, J = 9.0, 6.6 Hz, 0.15H), 4.20 (dd, J = 9.0, 6.6 Hz, 0.85H), 3.92 (dd, J = 9.0, 6.8 Hz, 1H), 3.80 (s, 3H), 1.41 and 1.36 (s, each 3H); ^{13}C NMR ($CDCl_3$): δ = 162.5 (M + m), 157.6 (M + m), 129.0 (M + m), 120.8 (M), 120.0 (m), 114.5 (M + m), 114.4 (m), 110.4 (M + m), 85.5 (M + m), 76.1 (M + m), 74.9 (M + m), 66.1 (M), 65.5 (m), 61.8 (M + m), 55.4 (M + m), 26.4 (M), 26.1 (m), 25.4 (M), 25.2 (m) (M = major product; m = minor); IR ($CHCl_3$): ν = 3320, 1746, 1564 cm^{-1}; MS (EI): m/z (%): 432 (100) $[M + 2]^+$, 430 (98) $[M]^+$.

Dehydration reaction of 2-azetidinone-tethered 1-bromo-1-nitroalkan-2-ol 2a. Preparation of bromoalkenyl-β-lactam 4

4-Nitrobenzoyl chloride (87 mg, 0.47 mmol) and triethylamine (40 mg, 0.39 mmol) were sequentially added dropwise to a stirred solution of bromonitroalcohol **2a** (168 mg, 0.39 mmol) in dichloromethane (4 mL) at −78 °C, and the mixture was stirred for 45 min at this temperature. Saturated aqueous sodium hydrogen carbonate (2 mL) was added, and the mixture was allowed to warm to room temperature, before being partitioned between dichloromethane and water. The organic extract was washed with water (2 × 1 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes–ethyl acetate (2 : 1) gave 121 mg (75%) of compound **4**.

3-[Bromonitromethylene]-2-azetidinone 4

Colorless solid; mp: 161–163 °C (hexanes–ethyl acetate); $[\alpha]_D$ = −5.8 (c 0.6 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.35 and 6.90 (d, J = 9.0 Hz, each 2H), 5.36 (d, J = 2.7 Hz, 1H), 4.74 (td, J = 6.4, 2.7 Hz, 1H), 4.07 (dd, J = 8.9, 6.6 Hz, 1H), 3.92 (dd, J = 8.9, 6.1 Hz, 1H), 3.81 (s, 3H), 1.29 (s, 6H); ^{13}C NMR ($CDCl_3$): δ = 157.7, 156.1, 144.1, 133.8, 129.8, 120.2, 114.6, 110.3, 73.6, 66.0, 64.8, 55.5, 26.0, 25.1; IR ($CHCl_3$): ν = 1746, 1550 cm^{-1}; MS (EI): m/z (%): 414 (100) $[M + 2]^+$, 412 (98) $[M]^+$.

Suzuki–Miyaura cross-coupling reaction of α-bromonitromethylene β-lactam 4 with boronic acids. Preparation of 3-[nitro(*p*-tolyl)-methylene]-2-azetidinone 5

Compound **4** (45 mg, 0.11 mmol) was added under argon to a stirred suspension of the *p*-tolylboronic acid (22.4 mg, 0.16 mmol), sodium bicarbonate (28 mg, 0.33 mmol), in toluene–ethanol–water (18 : 1 : 1) (2.24 mL), and the resulting mixture was stirred for 15 min. Then, $Pd(PPh_3)_4$ (2.5 mol%) was added and the reaction mixture was heated at reflux temperature for 4 h. The reaction mixture was allowed to cool to ambient temperature, before being partitioned between ethyl acetate and water. The organic extract was washed with water (2 × 1 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes–ethyl acetate (3 : 1) gave 22 mg (48%) of compound **5**.

3-[Nitro(*p*-tolyl)methylene]-2-azetidinone 5

Pale orange oil; $[\alpha]_D$ = −1.4 (c 0.5 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.61 and 6.91 (d, J = 8.2 Hz, each 2H), 7.28 and 6.65 (d, J = 9.0 Hz, each 2H), 4.79 (d, J = 3.7 Hz, 1H), 4.35 (m, 1H), 3.68 (dd, J = 8.7, 7.0 Hz, 1H), 3.58 (dd, J = 8.7, 6.5 Hz, 1H), 3.22 (s, 3H), 1.95 (s, 3H), 1.31 and 1.14 (s, each 3H); ^{13}C NMR ($CDCl_3$): δ = 157.7, 157.5, 147.9, 142.1, 136.8, 131.5, 130.2, 129.8, 125.6, 120.2, 115.0, 110.6, 75.3, 66.3, 61.2, 55.3, 26.5, 25.8, 21.6; IR ($CHCl_3$): ν = 1745, 1552 cm^{-1}; MS (EI): m/z (%): 424 (49) $[M]^+$, 135 (100); elemental analysis calcd (%) for $C_{23}H_{24}N_2O_6$ (424.4): C 65.08, H 5.70, N 6.60; found C 64.70, H 5.36, N 6.35.

Retroaldol/cyclization reaction of 3-[bromonitromethyl]-3-hydroxy-β-lactam 2a. Preparation of fused bicyclic β-lactam 6

Bismuth(III) chloride (6 mg, 0.02 mmol) was added to a stirred solution of bromonitroalcohol **2a** (168 mg, 0.39 mmol) in

acetonitrile–water (1 : 1) (6 mL). The reaction mixture was stirred at room temperature for 3 days, before being poured into a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (3 × 5 mL), and the combined organic extracts were dried ($MgSO_4$), and concentrated under reduced pressure. Recrystallization (ethyl acetate–hexanes) of the residue gave 69 mg (70%) of compound **6**.

Fused bicyclic 2-azetidinone 6

Colorless solid; mp: 133–135 °C (hexanes–ethyl acetate); $[\alpha]_D$ = +17.5 (*c* 1.0 in CH_3OH); ^{1}H NMR (300 MHz, acetone-d_6, 25 °C): δ = 7.46 (d, J = 9.2 Hz, 2H), 6.98 (m, 2H), 4.59 (d, J = 3.9 Hz, 1H), 4.45 (t, J = 3.4 Hz, 1H), 4.22 (m, 2H), 3.90 (dd, J = 11.2, 3.4 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (acetone-d_6): δ = 163.9, 157.0, 131.0, 118.6, 114.9, 113.2, 74.2, 70.3, 64.5, 55.3; IR ($CHCl_3$): ν = 3325, 1744 cm^{-1}; MS (EI): *m*/*z* (%): 251 (29) $[M]^+$, 134 (100); elemental analysis calcd (%) for $C_{12}H_{13}NO_5$ (251.1): C 57.37, H 5.22, N 5.58; found C 56.95, H 5.06, N 5.25.

Dehydrobromination reaction of 3-[bromonitromethyl]-3-hydroxy-β-lactam 2a. Preparation of spirocyclic β-lactam 7

Potassium carbonate (65 mg, 0.47 mmol) was added to a stirred solution of bromonitroalcohol **2a** (168 mg, 0.39 mmol) in methanol (5 mL). The reaction mixture was stirred at room temperature for 5 h, before being poured into a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with ethyl acetate (3 × 5 mL), and the combined organic extracts were dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes–ethyl acetate (3 : 1) gave 82 mg (60%) of compound **7**.

Spirocyclic 2-azetidinone 7

Colorless solid; mp: 71–73 °C (hexanes–ethyl acetate); $[\alpha]_D$ = +42.4 (*c* 0.5 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.49 and 6.90 (d, J = 9.3 Hz, each 2H), 5.77 (s, 1H), 4.56 (m, 1H), 4.40 (d, J = 5.4 Hz, 1H), 4.25 and 4.00 (dd, J = 9.3, 6.5 Hz, each 1H), 3.81 (s, 3H), 1.40 and 1.37 (s, each 3H); ^{13}C NMR ($CDCl_3$): δ = 158.9, 157.4, 130.1, 120.0, 114.3, 110.2, 78.4, 75.4, 69.3, 66.1, 60.9, 55.4, 26.2, 25.3; IR ($CHCl_3$): ν = 1745, 1557 cm^{-1}; MS (EI): *m*/*z* (%): 350 (64) $[M]^+$, 101 (100); elemental analysis calcd (%) for $C_{16}H_{18}N_2O_7$ (350.3): C 54.86, H 5.18, N 8.00; found C 54.47, H 5.05, N 7.85.

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20 The spirocyclic β-lactam framework is an important structural motif in biologically relevant compounds as natural products and pharmaceuticals. Spiro-β-lactams behave as β-turn mimetics, as well as enzyme inhibitors; they are precursors of α,α-disubstituted β-amino acids, and the spiranic β-lactam moiety is present in chartellines, a family of marine natural products. For selected references, see: (*a*) A. Macías, A. Morán Ramallal, E. Alonso, C. del Pozo and J. González, *J. Org. Chem.*, 2006, **71**, 7721; (*b*) H. Bittermann, F. Böckler, J. Einsiedel and P. Gmeiner, *Chem.–Eur. J.*, 2006, **12**, 6315; (*c*) P. S. Baran and R. A. Shenvi, *J. Am. Chem. Soc.*, 2006, **128**, 14028; (*d*) C. Sun, X. Lin and S. M. Weinreb, *J. Org. Chem.*, 2006, **71**, 3159; (*e*) P. S. Baran, R. A. Shenvi and C. A. Mitsos, *Angew. Chem., Int. Ed.*, 2005, **44**, 3714; (*f*) A. Macías, E. Alonso, C. del Pozo, A. Venturini and J. González, *J. Org. Chem.*, 2004, **69**, 7004; (*g*) T. Kambara and K. Tomioka, *J. Org. Chem.*, 1999, **64**, 9282.

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22 Although we have tried to separate these diastereomers (*anti*-**2a–d** and *syn*-**2a–d**), we failed to separate them. Therefore, we reported ^{1}H and ^{13}C NMR spectroscopic data for the mixture of diastereomers of **2a–d**. Ratios of diastereomers of *anti*-**2a–d** and *syn*-**2a–d** were determined on the basis of the integration ratio of separated peaks.

23 Taking into account that 3-[bromonitromethyl]-3-hydroxy-β-lactam **2a** could be obtained and cyclized to spirocyclic oxiranyl-β-lactam **6**, the relative stereochemistry at the bromohydrin stereogenic centers for major compounds **2** was immediately deduced because epoxide formation requires an *anti* arrangement of the nucleophile and the leaving group.

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