An unexpected bicyclic pyrrolidinedione formed by rearrangement of the β-lactam ring under basic conditions

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Dedicated to Prof. Benito Alcaide on the occasion of his 60th birthday

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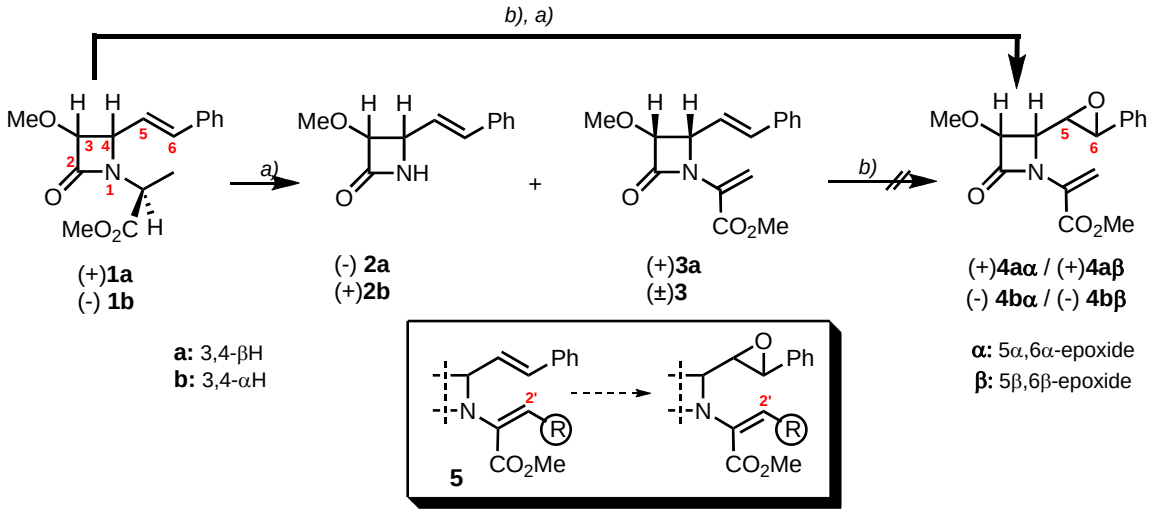
Abstract
During synthetic studies on anti-elastase polycyclic β-lactams from conveniently substituted monolactams, we attempted to obtain an *N*-(1´-methoxycarbonyalkylidene)-β-lactam by α-selenoxide elimination. Although the desired alkenes **5** were obtained, the main products were the N-unsubstituted 2-azetidinone **2** and the bridged bicyclic pyrrolidinedione **7**. The structure of compound **7** was established by spectroscopic methods and confirmed by X-ray crystallography.

Keywords: Anti-elastase, β-lactam rearrangement, pyrrolidinedione, crystallography

Introduction

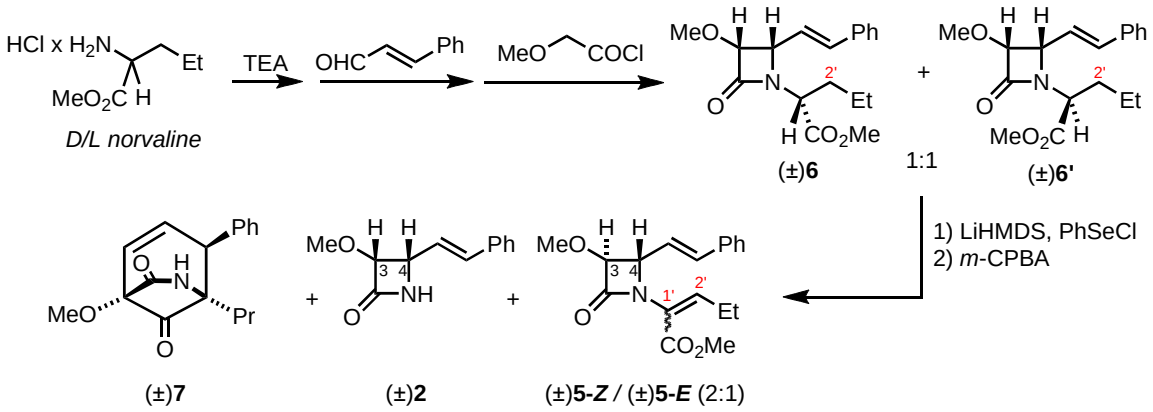
As a part of our studies on the synthesis[1] and anti-elastase activity[2] of β-lactam compounds, we have recently prepared the compounds **3** and **4** (Scheme 1). These substances were active *in vitro* against Human Leukocyte Elastase (HLE), showing the epoxide (-)**4bα** the best inhibition with an IC_{50} = 7μM.[3] Throughout the synthetic process we noticed that the epoxides **4** should be prepared by epoxidation of **1** [*b*)] and then β-elimination [*a*)]. When the β-elimination reaction was carried out before the epoxidation, a 3:2 mixture of the N-unsubstituted compound **2** and the monolactam **3** was obtained, and further epoxidation was not possible.



Scheme 1

Results and Discussion

In order to increase the anti-elastase activity of these β-lactams, we planned the introduction of an alkyl substituent at the C-2' position. The preparation of the *N*-1-ethenyl monolactams **5** were carried out from the precursor monolactam **6** according to the protocol reported by Alcaide and coworkers[4] (Scheme 2).



Scheme 2

The Staudinger reaction between methoxyacetyl chloride and the imine obtained from cinnamaldehyde with D/L-norvaline methyl ester in the presence of TEA afforded a 1:1 mixture of two diastereomers **6** + **6'** in 90% yield after column chromatography. When this mixture was reacted sequentially with LiHMDS, PhSeBr and *m*-CPBA it afforded a 1:3:2 mixture of **5**, **2** and **7** in 75% yield.

Compounds **6**, **5** and **2**[2] displayed IR spectra absorption bands of β-lactam ring (≈1760 cm^{-1}) and the NMR data were in agreement with the proposed structures. The C-3, C-4 configuration shown for these compounds, was clearly established on the basis of their ^{1}H NMR coupling constants between the hydrogen atoms H-3 and H-4 ($J_{cis} \geq 4.0$ Hz, $J_{tras} \leq 2.0$ Hz) but the *Z*/*E* geometry at C1' in compounds **5** we were not able to assign from the available spectroscopic data.

Compound **7** shows spectral data very different from those expected for a β-lactam compound. The IR spectrum of **7** does not show the characteristic β-lactam ring absorption band but other bands at 3200, 1787 and 1722 cm^{-1} were presented. These data together with the signals displayed in ^{13}C-NMR at 204.0 and 169.9 ppm, suggest the presence of ketone and amide functional groups. In addition, the ^{13}C-NMR spectrum agreed with the presence of the phenyl, methoxyl and propyl groups, two quaternary C_{sp3} as well as three methynes (two vinylic and one aliphatic), which were reflected in the ^{1}H-NMR spectrum as an ABX system with coupling constants J_{AB} = 9.6 Hz, J_{AX} = 2.6 Hz and J_{BX} = 2.5 Hz. All these data and those provided by the HMQC and the HMBC spectra prompted us to propose the structure shown in Scheme 2 for the compound (±)**7**, which was confirmed by X-ray crystallography.

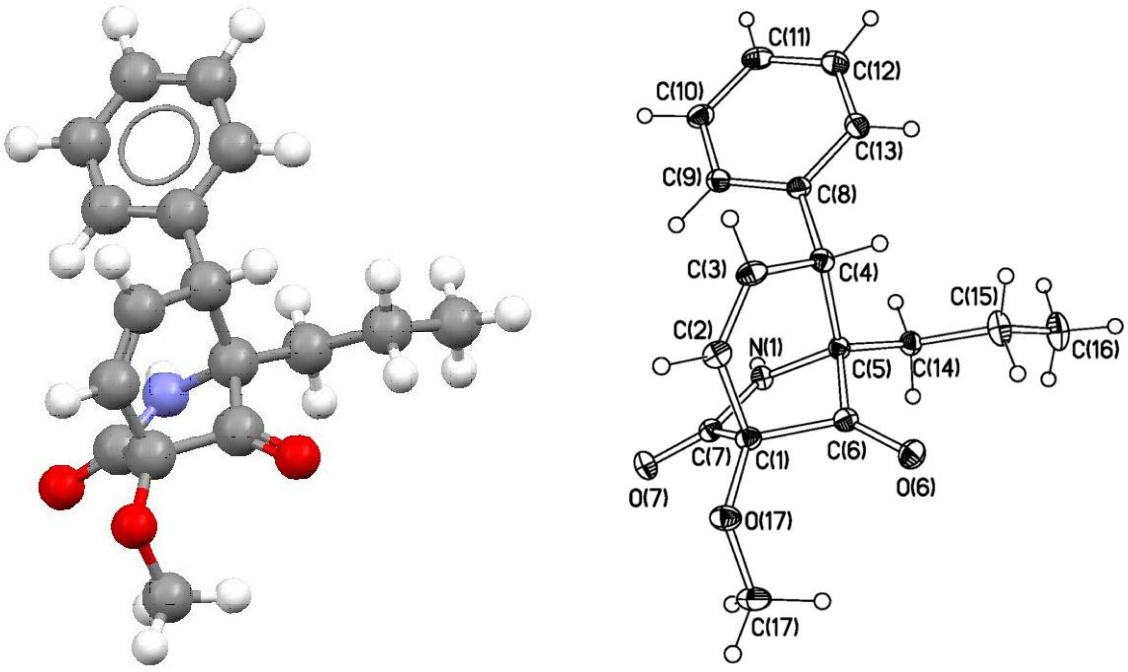


Figure 1. (a) X-ray structure of **7**. (b) ORTEP diagram for **7** showing the atom-labelling scheme.

A view of the crystal structure of this compound is shown in Figure 1 and the most relevant crystallographic data and the hydrogen bond interactions are summarized in Table 1 and Table 2, respectively. There is one molecule in the asymmetric unit and the N-O distances found are on the same order as those reported for other compounds with similar fragments.[5,6] In fact, the N(1)-

C(5) bond 1.484(3) Å is a single bond, where the N(1)-C(7) (1.341(3) Å) is clearly shortened in comparison with a C-N single bond.

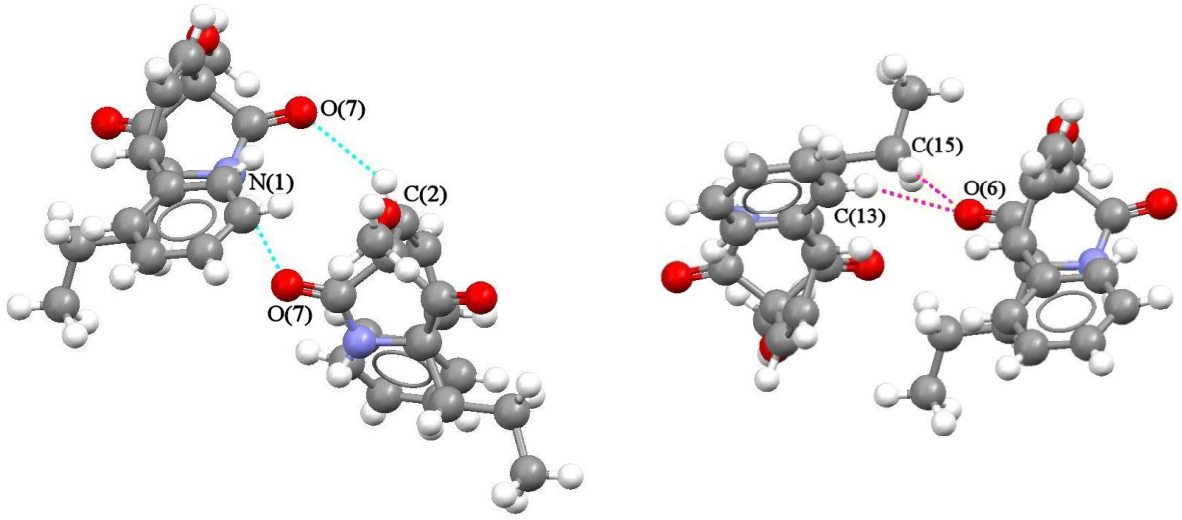


Figure 2. Hydrogen-bond interactions for **7**.

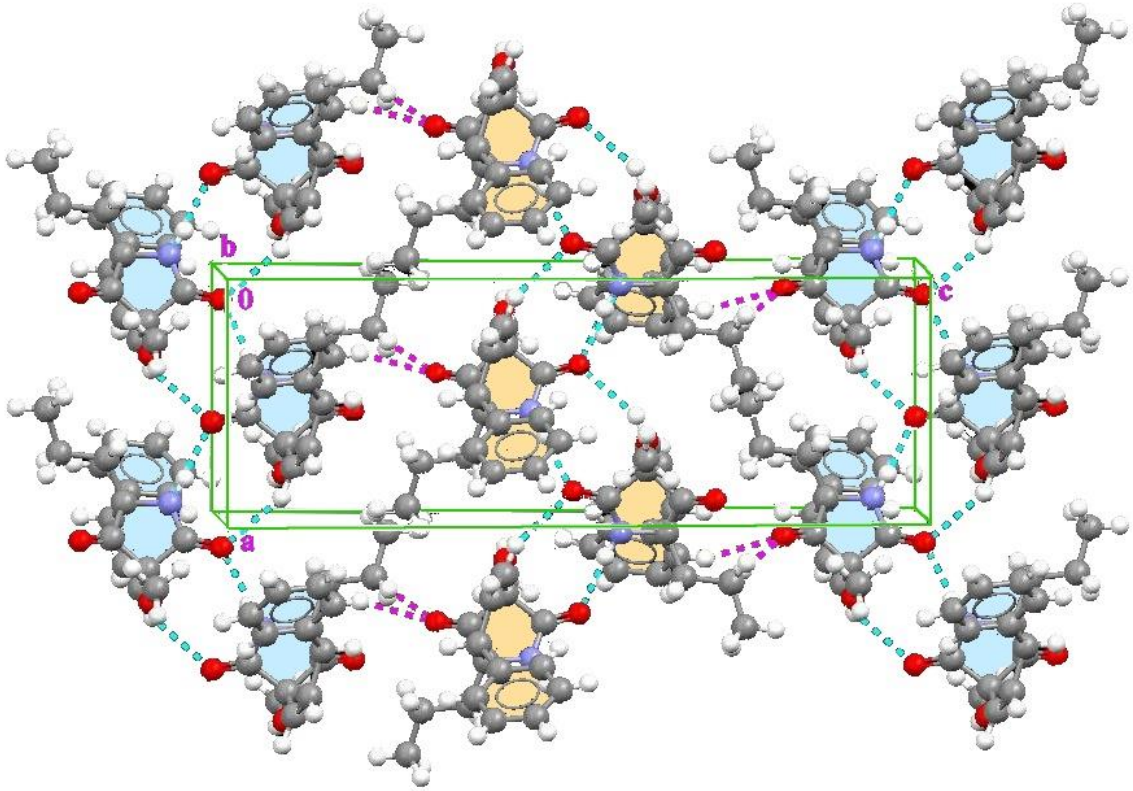
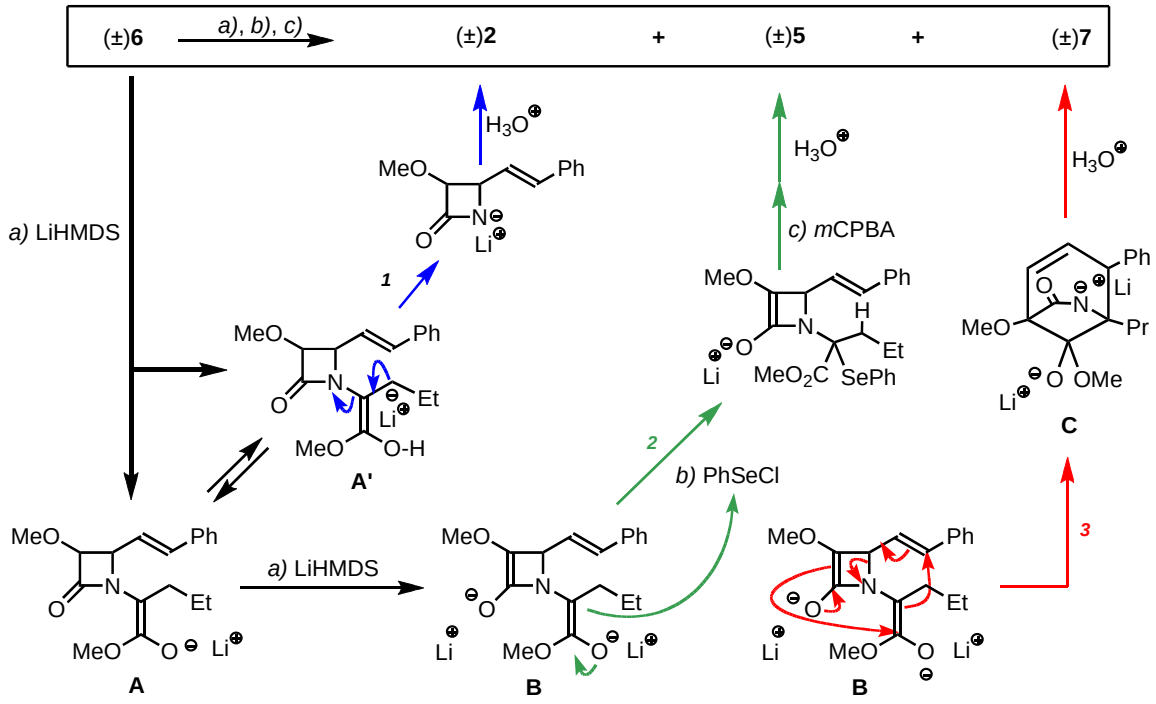


Figure 3. Packing diagram for **7** showing intermolecular hydrogen bonding.

The molecules in the crystal structure are linked by intermolecular N-H···O and C-H···O hydrogen bonding (Table 2), as represented in Figure 2. The packing is stabilized by intermolecular N1-H1N···O7 and C2-H2···O7 hydrogen bonds (dotted light blue lines), which lead to endless associated molecular chains running along the [010] direction. These chains are related *via* a binary axis and are joined to each other along the *c* axis by intermolecular O6-H15···C15 and O6-H13···C13 hydrogen bonds (dotted pink lines) as shown in Figure 3.

The evolution of the diastereomers **6** on reaction with LiHMDS, PhSeCl and *m*-CPBA could be explained as summarized in Scheme 3.



Scheme 3

The carbanion **A'**, in equilibrium with the enolate **A** or directly formed from **6**, can progress by β-elimination and protonation to the N-unsubstituted 3,4-*cis*-2-azetidinone **2** (pathway *1*). An excess of base can drive the reaction to the dianion **B** which after attack by the PhSeCl followed by oxidation with *m*-CPBA and β-elimination of the phenylselenyl-oxo moiety gave the 3,4-*trans* alkenes **5** (pathway *2*). Finally, the dianion **B** can also rearrange to the ketal **C** that will afford after acid work-up, the bicyclic compound **7** (pathway *3*).

Experimental Section

General Procedures. Column chromatographies were run on silica gel (Merck 60 230-400 mesh) and thin layer chromatographies (TLC) on commercial silica gel plates (Merck F-254).

Mass spectra (MS), were recorded on a APPLIED BIOSYSTEMS QSTAR XL (HRMS, 5 kV) spectrometer. IR spectra were recorded as neat film on a NICOLET IR-100 instrument. ^{1}H and ^{13}C NMR spectra were obtained on Bruker instruments WP-200-SY and Avance 400-DRX (200 and 400 MHz respectively) in $CDCl_3$ solutions with tetramethylsilane as internal standard. Solvents and reagents were purified according to standard techniques.

Preparation of monolactams (6). A mixture of D/L-norvaline methyl ester hydrochloride (1.7 g, 10 mmol), TEA (1.7 mL, 12 mmol), *trans*-cinnamaldehyde (1.3 mL, 10 mmol) and molecular sieve 4Å in Et_2O (60 mL), was stirred at room temperature overnight. Then, the mixture was filtered through Celite® and the solvent was removed under reduced pressure. To a solution of the crude imine in anhydrous CH_2Cl_2 (100 mL), dry TEA (2.8 mL, 20 mmol) and methoxyacetyl chloride (1.13 mL, 12 mmol) were successively added under argon. The reaction mixture was stirred at room temperature until the imine disappeared in TLC and then poured into a cold ammonium chloride solution, neutralized to pH 7 and extracted with dichloromethane. The organic layer was washed with brine, dried (anhydrous Na_2SO_4) and concentrated under reduced pressure. Column chromatography of the residue eluting with a 7:3 hexanes/ethyl acetate mixture gave 2.86 g (90%) of a colourless 1:1 mixture of compounds **6** and **6'**: R_f= 0.23 and 0.26 (SiO_2, hexanes/EtOAc 7:3); IR (film, cm^{-1}) ν 1765, 1742, 1651, 1495, 1450, 1394, 1347, 1257, 1207, 1154, 1087, 1024, 971, 756, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ (in parentheses the less polar isomer) 0.86 (0.94) (3H, t, *J* = 7.4 Hz), 1.42 (4H, m), 1.75 (1.93) (2H, m), 3.45 (6H, s), 3.72 (3.66) (3H, s), 4.42 (4.06) (1H, dd, *J* = 5.5, 9.6 (9.8) Hz), 4.65 (4.34) (1H, dd, *J* = 4.7 (4.6), 9.4 (9.3) Hz), 4.65 (2H, d, *J* = 4.7 Hz), 6.31 (2H, dd, *J* = 9.4, 15.9 Hz), 6.73 (6.65) (1H, d, *J* = 15.9 (16.0) Hz), 7.25-7.41 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ (in parentheses the less polar isomer) 13.3, 19.3 (19.6), 32.1 (30.8), 52.2 (52.3), 53.9 (54.7), 58.6 (58.7), 61.5 (60.8), 85.3 (85.0), 124.2 (123.4), 126.6, 128.2, 128.6, 135.9 (136.2), 136.0, 167.4 (166.7), 170.9 (170.5); TOF-HRMS: calcd for $C_{18}H_{23}NNaO_4$ $(M + Na)^+$ 340.1525; found 340.1529.

Transformation of the monolactams 6. To a solution at -78ºC of a 1:1 mixture of compounds **6** (951 mg, 3.0 mmol) in dry THF (15 mL) under argon atmosphere, LiHMDS (1 M in THF, 5.55 mL) was added dropwise during 15 minutes. The reaction mixture was stirred for 1h and then a solution of PhSeCl (652 mg, 3.3 mmol) in dry THF (15 mL) was added. The resulting reaction mixture was stirred from -78ºC to -60ºC during 3h and then poured into a cold ammonium chloride solution. The organic layer was removed and the aqueous layer was extracted with ethylacetate. The combined organic extracts were sequentially washed with saturated solutions of $NaHCO_3$ and NaCl, dried (anhydrous Na_2SO_4), filtered and evaporated to dryness. The crude residue obtained (1.35 g) was dissolved in dry dichloromethane (15 mL), the solution was cooled at -78ºC and then a solution of *m*-CPBA (962 mg, 3.9 mmol) in dry dichloromethane (15 mL) was added. The reaction mixture was stirred at room temperature until the starting material disappeared in TLC and then quenched with 10% v/v aqueous $Na_2S_2O_3$. The aqueous layer was extracted with ethyl acetate (3 x 15 mL). The organic combined extracts were sequentially washed with a saturated solution of $NaHCO_3$ and brine, dried (anhydrous Na_2SO_4),

and concentrated under reduced pressure. Column chromatography of the crude product (700 mg) with hexanes/ethyl acetate mixtures as eluent afforded 118 mg (12.5%) of a 2:1 mixture of 1'-*Z/E*-monolactams **5**, 228 mg (37.5%) of **2** and 214 mg (25.0%) of bicyclic compound **7**.

***Z/E*-monolactams 5.** R_f= 0.28 (SiO_2, hexanes/EtOAc 8:2); IR (film, cm^{-1}) ν 1760, 1729, 1649, 1496, 1449, 1396, 1275, 1216, 1148, 1013, 971, 751, 695; ^{1}H NMR (200 MHz, $CDCl_3$) δ (in parentheses the *E*-isomer) 1.08 (6H, t, *J* = 7.5 Hz), 2.17-2.56 (4H, m), 3.57 (3.54) (3H, s), 3.77 (6H, s), 4.47 (4.41) (1H, d, *J* = 2.0 Hz), 4.82 (4.58) (1H, dd, *J* = 2.0, 8.5 Hz), 6.14 (2H, dd, *J* = 8.5, 15.8 Hz), 6.65 (6.68) (1H, d, *J* = 15.8 Hz), 6,80 (6.28) (1H, t, *J* = 7.5 (7.8) Hz), 7.26-7.43 (10H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ (in parentheses the *E*-isomer) 12.6 (13.7), 22.2 (21.5), 52.1 (51.8), 57.5 (57.7), 63.7 (63.5), 88.6 (88.7), 123.4, 124.9 (124.6), 126.5, 128.3, 128.6, 134.8, 135.6, 144.2 (137.7), 163.6 (163.1), 164.9 (164.5); TOF-HRMS: calcd for $C_{18}H_{21}NNaO_4$ $(M + Na)^+$ 338.1363; found 338.1371.

Compound 2. The physical data for this compound are in agreement with those reported for chiral monolactams **(+)2** and **(-)2**.[2]

Compound 7. R_f= 0.21 (SiO_2, hexanes/EtOAc 8:2); mp 125-7ºC (hexanes/CH_2Cl_2); IR (KBr, cm^{-1}) ν 1787, 1723, 1465, 1265, 1200, 1040, 920, 750, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, t, *J* = 7.1 Hz), 1.23-1.36 (3H, m), 1.92-2.02 (1H, m), 3.58 (3H, s), 3.73 (1H, t, *J* = 2.5 Hz), 3.73 (1H, t, *J* = 2.5 Hz), 5.72 (1H, dd, *J* = 9.6, 2.5 Hz), 5.95 (1H, bs), 6.12 (1H, dd, *J* = 9.6, 2.6 Hz), 7.15 (1H, d, *J* = 7.2 Hz), 7.36-7.40 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 16.6, 31.7, 55.0, 55.6, 68.3, 82.8, 128.3, 128.8, 129.3, 130.8, 132.3, 134.9, 169.9, 204.0; TOF-HRMS: calcd for $C_{17}H_{19}NNaO_3$ $(M + Na)^+$ 308.1263; found 308.1265.

Crystal structure analysis. The compound **7** was dissolved in hexane-dichloromethane at room temperature and suitable crystals for X-ray diffraction studies grew over a period of one week when the solution was exposed to the air. A single crystal was mounted on glass fibre for data collection on a Bruker KAPPA APEX II CCD diffractometer. Data were collected at 293 K using Cu K_α radiation (λ = 1.54178 Å) and *ω* scan technique, and were corrected for Lorentz and polarization effects. A semiempirical absorption correction was applied using SADABS[7], and the program SAINT[8] was used for integration of the diffraction profiles. Structure solution, refinement and data output were carried out with the SHELXTL® program package[9]. The structure was solved by direct methods combined with difference Fourier synthesis and refined by full-matrix least-squares procedures, with anisotropic thermal parameters in the last cycles of refinement for all non-hydrogen atoms. The position of the hydrogen atoms was determined by difference Fourier synthesis and refined, together their isotropic thermal parameter, by least squares procedures. Weighted *R* factors (*ωR*) and all goodness-of-fit (*S*) are based on F^2, conventional *R* factors *(R)* are based on *F*.

Crystallographic data (excluding structure factors) for the structure reported in this paper has been deposited at the Cambridge Crystallographic Data Centre as supplementary material (nº. CCDC-730530).

Table 1. Crystal and experiment data for compound **7**

Crystal data	**7**
Empirical formula	$C_{17}H_{19}NO_3$
Formula weight	285.33
Temperature (K)	293(2)
Wavelength (Å)	1.54178
Crystal system	orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	
a (Å)	7.8605(2)
b (Å)	8.5274(2)
c (Å)	22.2815(4)
α [º], β[º], γ[º]	90, 90, 90
Volume ($Å^3$)	1493.52(6)
Z	4
Calculated density (g cm^{-3})	1.269
Absorption coefficient (mm^{-1})	0.703
F(000)	608
Crystal size (mm)	0.2 x 0.1 x 0.06
θ range for data collection (°)	3.97 - 52.10
Limiting indices	$-6 \leq h \leq 6$, $-7 \leq k \leq 7$, $-22 \leq l \leq 17$
Reflections collected	3454
Reflections independent	1271
Refinement method	full-matrix least-squares on F^2
Data / restraints / parameters	1271 / 0 / 266
Goodness-of-fit on F^2	1.079
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0256, wR2 = 0.0617
R indices (all data)	R_1 = 0.0267, wR2 = 0.0626
Absolute structure parameter	0.0(3)
Largest diff. peak and hole (e $Å^{-3}$)	0.084 and -0.119

Table 2. Hydrogen bonds for compound **7** [Å, º]

D-H···A	D-H	H···A	D···A	<(D-H···A)
N1-H1N···O7	0.92	1.99	2.894(3)	163
C2-H2···O7	1.01	2.57	3.477(2)	148
C13-H13···O6	0.92	2.61	3.479(3)	158
C15-H15···O6	0.97	2.61	3.573(3)	171

Acknowledgements

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