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Stereoselective synthesis of (*Z*)-axino- and (*Z*)-debromoaxinohydantoin

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ABSTRACT

(*Z*)-Axinohydantoin and (*Z*)-debromoaxinohydantoin, two pyrrole–imidazole alkaloids isolated from different marine sponges, possess moderate activities in inhibiting the progress of the cell cycle at different phases. A stereoselective synthesis of both natural products was achieved. The key step in the synthetic pathway was the installation of the hydantoin northern ring by using 1-benzoyl-2-methylsulfanyl-1,5-dihydroimidazol-4-one.

1. Introduction

The increasing number of papers published in the last decade, dealing with the isolation and total synthesis of marine pyrrole–imidazole alkaloids, witnesses the restless attention that this family of alkaloids deserves.[1] The synthetic challenge, sometimes hidden behind apparently simple structures, associated with promising biological activities, justifies this interest. The role of pyrrole–imidazole alkaloids in the sponge economy is far from being completely understood. While the fish feeding deterrent properties of the parent oroidin (**1**, Fig. 1) and some other derivatives[2] have been established, the reasons for the existence of the vast majority of these alkaloids are still obscure. Also their biosynthesis is an open question. Although a number of hypotheses exists,[3,1a] only one experiment on sponge cells culture concerning the incorporation of ^{14}C-labelled amino acids into stevensine biosynthesis has been reported by Kerr et al.[4]

Six different modes of cyclization, seven modes of dimerization [1b] and one mode of tetramerization[5] of the basic skeleton of oroidin have been discovered so far, but a number of potential other architectures is probably waiting to be unveiled.[1a] The growing complexity of the members of this family culminated in the breathtaking structure of palau'amine (**2**, Fig. 1) that has been recently revised.[6,3e,5b] Among the cyclized structures arising from oroidin, hymenialdisines (only (*Z*)-hymenialdisine (**3**, Fig. 1) is depicted for better clarity), and their close analogues, axinohydantoins (**4**–**7**, Fig. 1), represent the tricyclic core most commonly found in

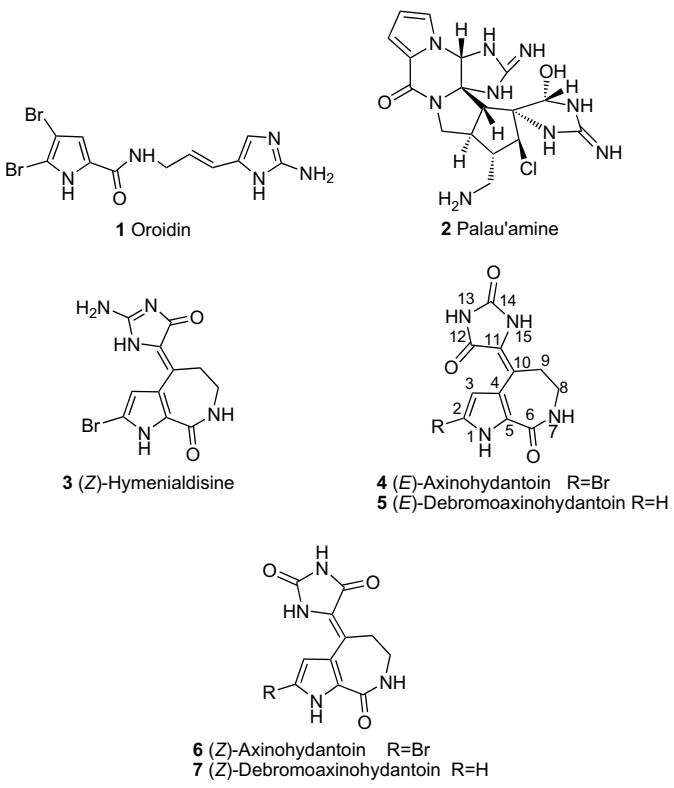

Figure 1. Pyrrole–imidazole alkaloids.

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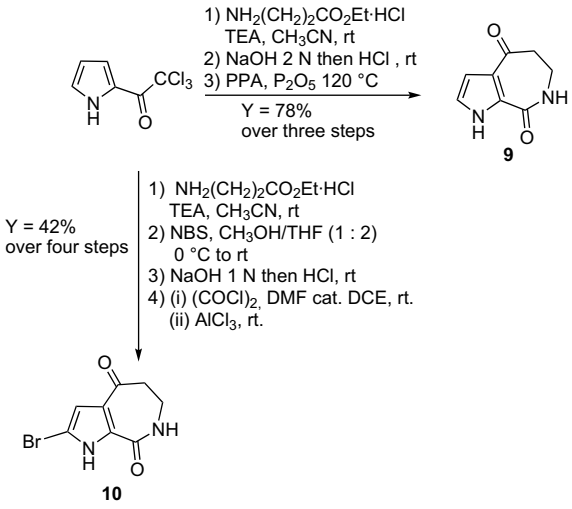
sponges.[1a,7] Moreover, along with agelastatin A,[8] they are the only pyrrole–imidazole alkaloids possessing a single bromine atom at 2-position of the pyrrole ring. Incorporation of the halogen atom is supposed to be catalyzed by a specific pair of haloperoxidase/halogenase enzymes.[9]

(*E*)-Axinohydantoin **4** (from the sponge *Axinella* sp.)[10] and (*E*)-debromoaxinohydantoin **5** (from the sponge *Monanchora* pertaining to the genera *Hymeniacidon*)[11] were the first alkaloids of the quartet to be isolated by Pettit et al. Subsequently, (*Z*)-axinohydantoin **6** and (*Z*)-debromoaxinohydantoin **7** were isolated from the sponge *Stylotella aurantium*[12] and later, christened with the name of spongiacidins D and C, respectively, from *Hymeniacidon* species.[13] Biogenetically, axinohydantoins could arise from different linear precursors.[10,14] (*E*)-Axinohydantoin **4** was only marginally active on murine P388 lymphocytic leukemia (PS system) with an ED_{50} of 18 μg/mL.[10] On the other hand, (*Z*)-axinohydantoin **6** and (*Z*)-debromoaxinohydantoin **7** showed micromolar activities on protein kinase C with IC_{50} values of 9 and 22 μM, respectively.[12,15] Furthermore, (*Z*)-axinohydantoin **6** displayed inhibitory activities on a number of kinases in the micromolar range as well (glycogen synthase kinase-3β, IC_{50}=3 μM; cyclin dependent kinase 1/cyclin B, IC_{50}=4 μM; casein kinase 1, IC_{50}=4.5 μM; cyclin dependent kinase 5/p25, IC_{50}=7 μM).[16] However, an exhaustive investigation of the potential bioactivities of axinohydantoins is far from being achieved. Despite having been isolated more than a decade ago, axinohydantoins **4**–**7** did not significantly raise the interest of the synthetic community. Only a single communication on the synthesis of debromoaxinohydantoins **5** and **7** appeared in 2002 by Horne et al.[14] As a result of this indifference, to date no syntheses of (*Z*)-axinohydantoin **6** and (*E*)-axinohydantoin **4** have been accomplished.

2. Results and discussion

Previous work in our laboratory demonstrated the unprecedented 1-benzoyl-2-methylsulfanyl-1,5-dihydroimidazol-4-one **8** as an effective tool for the construction of the northern ring in (*Z*)-hymenialdisines.[17] In order to test its versatility, we envisioned the chance to capitalize on this reagent to prepare (*Z*)-axinohydantoins **6** and **7**. Herein, the results of our efforts are reported. The planned synthetic strategy towards these alkaloids is depicted in Scheme 1.

Advanced precursors aldisine **9** and 2-bromoaldisine **10** deliver intermediates (**11a** or **11b**) and (**12a** or **12b**) upon reaction with **8**. Conversion of the 2-methylthiodihydroimidazolone ring into the corresponding hydantoin, removal of the *N*-benzoyl protecting group and double bond isomerization (in the case of intermediates **11a** and **12a**) should afford, respectively, (*Z*)-debromoaxinohydantoin **7** and (*Z*)-axinohydantoin **6**. The preparation of aldisine **9** was routinely achieved on a multi-gram scale (Scheme 2). Starting from 2-trichloroacetylpyrrole, **9** was rapidly obtained in a optimized 78% yield over three steps, without the need of any chromatographic purification.[17] The

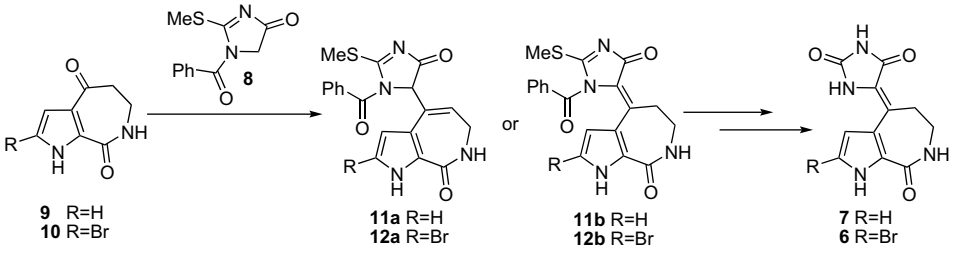


Scheme 2. Synthesis of **9** and **10**.

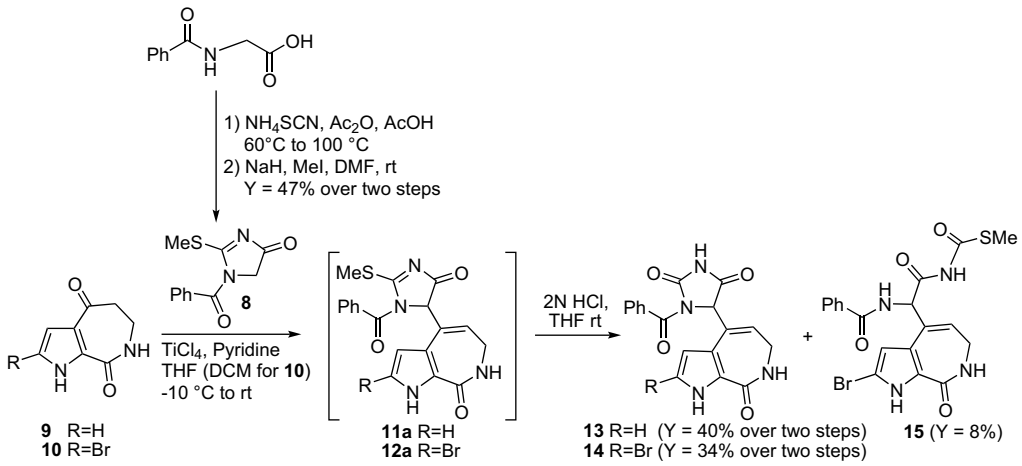
brominated precursor **10** was also prepared from the same starting material (Scheme 2).

However, cyclization of 2-bromopyrrole acid intermediate in the presence of PPA/P_2O_5 suffered from a protic acid-mediated halogen dance on the pyrrole ring, delivering a nearly 1:1 hardly separable mixture of **10** and its corresponding 3-bromo regioisomer.[18] The bromine atom scrambling was effectively suppressed by the use of $AlCl_3$.[17] The yield in this last step was increased up to 69%, delivering **10** with an optimized 42% overall yield.[19] Aldisine **9** and 2-bromoaldisine **10** were subsequently reacted, in the presence of $TiCl_4$ and pyridine, with excess **8**,[17] prepared from hyppuric acid in two steps with an improved 47% overall yield (Scheme 3).

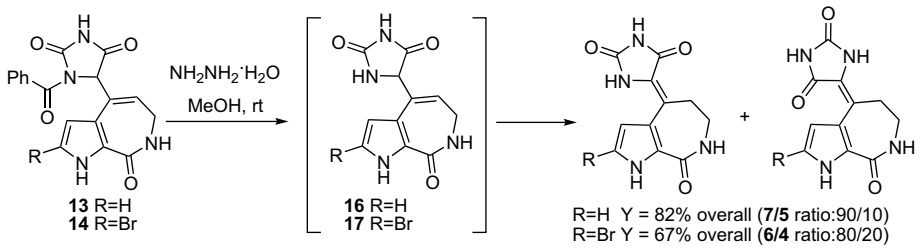
Due to its poor solubility in THF, 2-bromoaldisine **10** required dichloromethane as the solvent for the reaction to proceed. The crude reaction intermediates, whose *endo*-regiochemistry (**11a** and **12a**) or *exo*-regiochemistry (**11b** and **12b**, Scheme 1) was not determined at this stage, were rapidly worked-up and submitted to the next step without any further purification that, as previously investigated,[17] resulted in extensive decomposition. Thus, by exposing the condensation products to aqueous 2 N HCl in THF at room temperature, the corresponding hydantoins **13** and **14** were isolated in, respectively, 40 and 34% yield over two steps along with, in the case of the brominated substrate **12a**, a small amount (8%) of side-product **15** (Scheme 3). The observed endocyclic positioning of the double bond in compounds **13** and **14** allowed us to infer the correct structure of their precursors **11a** and **12a**. The last steps, namely the *N*-benzoyl-protecting group removal and the endocyclic/exocyclic double bond isomerization, were tentatively performed in one pot, in analogy with the synthesis of hymenialdisine,[17] by exposing both **13** and **14** to 7 N ammonia in methanol. However, the reactions proved to be sluggish and poorly



Scheme 1. Synthetic strategy.



Scheme 3. Northern ring installation.



Scheme 4. Benzoyl removal and double bond isomerization.

productive. We then turned to $NH_2NH_2 \cdot H_2O$, which has been reported to cleave *N*-acetyl protecting group on spirohydantoins.[20] Thus, compounds **13** and **14** were reacted with excess of $NH_2NH_2 \cdot H_2O$ in methanol (Scheme 4), delivering debromoaxinohydantoins (82% overall yield, **7**/**5** ratio: 90:10) and axinohydantoins (67% overall yield, **6**/**4** ratio: 80:20), respectively (Scheme 4). (*Z*) and (*E*) isomers were easily separated by reverse phase flash chromatography.

In both cases the protecting group removal/double bond isomerization proceeded stepwise, as judged by changing in the HPLC retention times/UV profiles of same molecular mass peaks over time (see Supplementary data). Detachment of the benzoyl group took place first, affording fast-eluting **16** and **17**, which upon standing in a basic environment, equilibrate towards axinohydantoins (Scheme 4). Endocyclic/exocyclic double bond isomerization could be reasonably justified in terms of shift towards a tetra-substituted and more extensively conjugated alkene. On the other hand, the stereochemical outcome of the last step was anticipated by semiempirical calculations.[14] To experimentally consolidate the predicted[14] different stability of (*Z*) and (*E*) isomers, the isomerization kinetics of axinohydantoins **4** and **6** was monitored at room temperature in MeOH-d_4 through NMR spectroscopy. (*Z*)-Axinohydantoin **6** equilibrated at less than half of the velocity of its (*E*)-isomer **4** (Fig. 2). These data were tentatively rationalized capitalizing on (*E*)-axinohydantoin **4** crystal

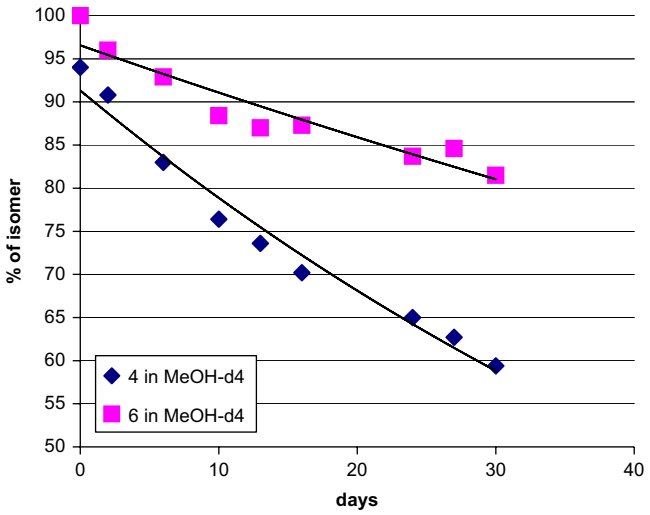


Figure 2. Isomerization of **6** and **4** in MeOH-d_4.

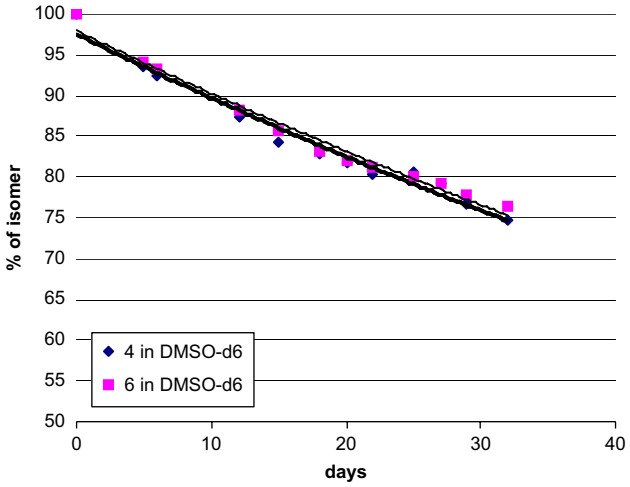


Figure 3. Isomerization of **6** and **4** in DMSO-d_6.

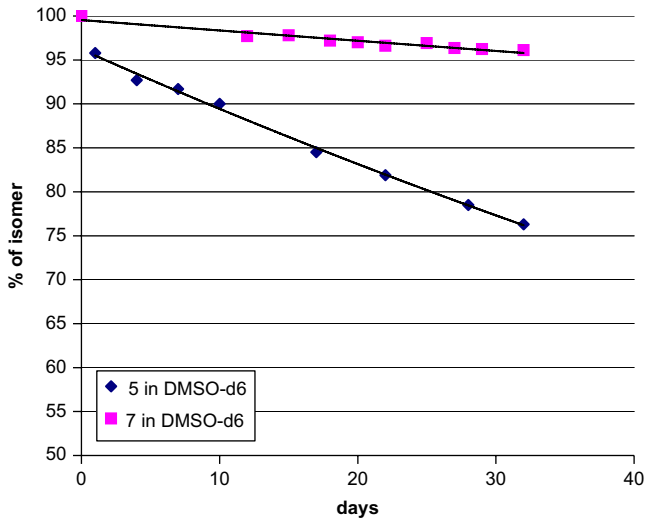


Figure 4. Isomerization of **7** and **5** in DMSO-d_6.

structure, which revealed the C12 carbonyl group being tilted out of the plane of the pyrrole ring by 10° to relieve the steric interaction between O-12 and CH-3.[10] This lack of coplanarity, by preventing the participation of the aforementioned C12 carbonyl group in the conjugated system, may account, along with steric factors, for the lower stability of **4** in MeOH. Surprisingly, however, similar experiments performed in a different solvent (DMSO-d_6) showed the two isomers moving towards each other at the same velocity, mainly due to an increased stability of **4** (Fig. 3). If a solvent effect could then be invoked at this stage, data collected for (*Z*)-debromoaxinohydantoin **7** and (*E*)-debromoaxinohydantoin **5** isomerization in DMSO-d_6 demonstrated also a meaningful negative role of the bromine atom on the stability of the (*Z*)-isomers (Fig. 4). Thus, a complex and elusive to be rationalized interplay of factors seems to govern axinohydantoins isomerization behaviour.

3. Conclusions

In summary, the first total synthesis of (*Z*)-axinohydantoin **6** has been accomplished in a stereoselective fashion, through a seven-step sequence (8% overall). Alongside, (*Z*)-debromoaxinohydantoin **7** was stereoselectively prepared in six steps, with an overall yield of 23%. These achievements demonstrated the versatility of our 1-benzoyl-2-methylsulfanyl-1,5-dihydroimidazol-4-one reagent **8**. The synthesis of both (*Z*)-axinohydantoins **6** and **7** proved to be robust and scalable, thus allowing access to the larger amount of materials required to draw a more complete picture of their bioactivities.

4. Experimental

4.1. General

IR spectra were recorded on a ThermoNicolet Avatar 360 FTIR. NMR spectra (1D, 2D homo H–H and hetero H–C correlated) were recorded at 25 °C in DMSO-d_6 on a Varian Inova 500 spectrometer equipped with a triple resonance cold probe. Residual solvent signal was used as reference; chemical shifts are reported in δ units (ppm). ^{13}C assignments were made using the standard two-dimensional sequences provided by Varian (gradient-enhanced HSQC and HMBC). ESI(+) high-resolution mass spectra (HRMS) were obtained on a Waters Q-Tof Ultima directly connected with micro HPLC 1100 Agilent.[21]

4.2. Experimental procedures

*4.2.1. 1-Benzoyl-5-(8-oxo-1,6,7,8-tetrahydro-pyrrolo[2,3-c]azepin-4-yl)-imidazolidine-2,4-dione (**13**)*

A solution of 1 M $TiCl_4$ in CH_2Cl_2 (7.32 mL, 7.32 mmol) was added to dry THF (30 mL) at −10 °C. Compounds **9** (300 mg, 1.83 mmol) and **8** (864 mg, 3.66 mmol) were subsequently added, the temperature was raised to 0 °C and the mixture stirred for 20 min. After dropwise addition of dry pyridine (1.18 mL, 14.64 mmol) in 30 min, the mixture was stirred at 0 °C for 2 h and at room temperature for additional 2 h. The reaction was quenched with NH_4Cl (30 mL, saturated solution) and stirred for 10 min. After extraction with CH_2Cl_2 (3×60 mL), the organic phases were combined, washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The obtained intermediate was dissolved as crude in THF (35 mL) and treated with aqueous 2 N HCl (10 mL). The solution was stirred overnight at room temperature until HPLC revealed the disappearance of the starting material. Filtration and washing with water of the precipitate afforded the product as a white solid (240 mg, 40% over two steps). ^{1}H NMR (499.75 MHz, DMSO-d_6) δ 3.34–3.38 (signal obscured by water, 1H, CH*H*-8), 3.44 (ddd, *J*=5.1, 6.6, 15.0 Hz, 1H, C*H*H-8), 5.56 (br s, 1H, H-11), 6.08 (t, *J*=6.6 Hz, 1H, H-9), 6.34 (br s, 1H, H-3), 7.05 (t, *J*=2.6 Hz, 1H, H-2), 7.40–7.43 (m, 2H, *m*-Ar–H), 7.52–7.55 (m, 3H, *o*- and *p*-Ar–H), 7.64 (t, *J*=5.1 Hz, 1H, NH-7), 11.83 (s, 1H, NH-1). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 37.4, 63.5, 106.2, 122.2, 122.5, 123.1, 126.1, 127.7, 128.8, 1321.9, 133.2, 163.3, 167.7. HRMS calcd for $C_{18}H_{14}N_4O_4$ [M+H$^+$] 351.1088, found 351.1089.

*4.2.2. (Z)-2-Debromoaxinohydantoin (**7**) and (E)-2-debromoaxinohydantoin (**5**)*

To a suspension of compound **13** (240 mg, 0.69 mmol) in methanol (3.6 mL), $NH_2NH_2\cdot H_2O$ (0.21 mL, 4.14 mmol) was added. The mixture was stirred at room temperature for 48 h yielding the desired products, which precipitated as a white solid. Filtration afforded a mixture of *Z*/*E* isomers (140 mg, 82% overall yield, ratio 9:1 determined by NMR). Purification by reverse phase flash chromatography (eluant 0.1% trifluoroacetic acid in H_2O/acetonitrile 95:5 as mobile phase A and acetonitrile as mobile phase B), afforded **7** (110 mg, 65%) and **5** (10 mg, 6%) as white solids. The separation was performed using a rapid gradient increasing from 0 to 25% B in 15 min followed by a hold at 100% B for 3 min at a flow rate of 20 mL/min. Compound **7**: IR (neat) ν 3269, 3175, 3130, 1744, 1708, 1618 cm^{-1}. ^{1}H NMR (499.75 MHz, DMSO-d_6) δ 3.21–3.25 (m, 2H, CH_2-9), 3.29–3.32 (m, 2H, CH_2-8), 6.54 (t, *J*=2.3 Hz, 1H, H-3), 6.98 (t, *J*=2.9 Hz, 1H, H-2), 7.91 (t, *J*=4.5 Hz, 1H, NH-7), 9.45 (s, 1H, H-13), 11.05 (br s, 1H, H-15), 11.81 (br s, 1H, H-1). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 30.3, 40.2, 110.0, 121.5, 122.2, 122.4, 122.8, 125.6, 154.2, 162.9, 165.5. HRMS calcd for $C_{11}H_{10}N_4O_3$ [M+H$^+$] 247.0826, found 247.0824. Compound **5**: ^{1}H NMR (499.75 MHz, DMSO-d_6) δ 2.69–2.71 (m, 2H, CH_2-9), 3.19–3.23 (m, 2H, CH_2-8), 6.71 (t, *J*=2.5 Hz, 1H, H-3), 6.84 (t, *J*=2.8 Hz, 1H, H-2), 7.84 (t, *J*=5.6 Hz, 1H, NH-7), 9.79 (s, 1H, NH-15), 10.87 (br s, 1H, NH-13), 11.59 (br s, 1H, NH-1). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 35.4, 38.1, 112.7, 119.7, 120.8, 122.1, 124.8, 125.0, 154.0, 162.8, 164.4. HRMS calcd for $C_{11}H_{10}N_4O_3$ [M+H$^+$] 247.0826, found 247.0821.

*4.2.3. 1-Benzoyl-5-(2-bromo-8-oxo-1,6,7,8-tetrahydro pyrrolo[2,3-c]azepin-4-yl)-imidazolidine-2,4-dione (**14**)*

A solution of 1 M $TiCl_4$ in CH_2Cl_2 (4.96 mL, 4.96 mmol) was added to dry CH_2Cl_2 (30 mL) at −10 °C. Compounds **10** (300 mg, 1.24 mmol) and **8** (584 mg, 2.5 mmol) were subsequently added, the temperature was raised to 0 °C and the mixture stirred for

20 min. After dropwise addition of dry pyridine (0.82 mL, 9.92 mmol) in 30 min, the mixture was stirred at 0 °C for 2 h and at room temperature for additional 2 h. The reaction was quenched with NH_4Cl (22 mL, saturated solution) and stirred for 10 min. After extraction with CH_2Cl_2 (3×60 mL), the organic phases were combined, washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The obtained intermediate was dissolved in THF (18 mL), treated with aqueous 2 N HCl (8 mL) and stirred overnight at room temperature until disappearance of the starting material according to HPLC trace. Filtration and washing with water of the precipitate afforded a first aliquot of product **14** as a pale yellow solid. The filtrate was concentrated and purified on silica gel (eluant CH_2Cl_2/MeOH 9:1) yielding a further aliquot of **14** and compound **15** as side product (42 mg, 8%); 175 mg of final compound **14** was recovered (34% over two steps). Compound **14**: ^{1}H NMR (499.75 MHz, DMSO-d_6) δ 3.36 (ddd, J=4.8, 6.7, 15.0 Hz, 1H, CH*H*-8), 3.45 (ddd, J=4.8, 6.7, 15.0 Hz, 1H, C*H*H-8), 5.66 (s, 1H, H-11), 6.18 (t, J=6.7 Hz, 1H, H-9), 6.39 (br s, 1H, H-3), 7.44–7.47 (m, 2H, *m*-Ar–H), 7.57–7.60 (m, 1H, *p*-Ar–H), 7.62–7.64 (m, 2H, *o*-Ar–H), 7.74 (t, J=4.8 Hz, 1H, NH-7), 11.73 (s, 1H, NH-13), 12.71 (s, 1H, NH-1). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 37.4, 62.1, 104.1, 123.6, 124.1, 127.8, 128.1, 128.9, 131.9, 132.6, 154.0, 162.1, 167.3, 170.5. HRMS calcd for $C_{18}H_{13}BrN_4O_4$ [M+H$^+$] 429.0193, found 429.0208. Compound **15**: IR (neat) ν 1625, 1474, 1421, 1196 cm^{-1}. ^{1}H NMR (499.75 MHz, DMSO-d_6) δ 2.22 (s, 3H, SCH_3), 3.46 (dd, J=5.1, 6.7 Hz, 2H, CH_2-8), 5.60 (d, J=7.2 Hz, 1H, NHC*H*CO), 5.82 (t, J=6.7 Hz, 1H, H-9), 6.26 (s, 1H, H-3), 7.45–7.47 (m, 2H, *m*-Ar–H), 7.53–7.56 (m, 1H, *p*-Ar–H), 7.73 (t, J=5.1 Hz, 1H, NH-7), 7.87–7.89 (m, 2H, *o*-Ar–H), 8.94 (d, J=7.2 Hz, 1H, CON*H*CH), 11.72 (br s, 1H, CONHCO), 12.60 (br s, 1H, NH-1). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 11.6, 37.4, 56.3, 104.0, 108.5, 123.2, 123.7, 125.3, 127.8, 128.4, 131.7, 133.6, 162.4, 166.7, 169.7, 170.3. HRMS calcd for $C_{19}H_{17}BrN_4O_4S$ [M+H$^+$] 477.0227, found 477.0215.

*4.2.4. (Z)-Axinohydantoin (**6**) and (E)-axinohydantoin (**4**)*

To a suspension of compound **14** (175 mg, 0.41 mmol) in methanol (2.6 mL), $NH_2NH_2 \cdot H_2O$ (0.1 mL, 2.05 mmol) was added. Removal of benzoyl group followed by two days of *endo*/*exo* isomerization yielded the desired product, which precipitated as a yellow solid. Filtration afforded a mixture of *Z*/*E* isomers (90 mg, 67% overall yield, ratio 8:2 determined by ^{1}H NMR). Purification by reverse phase flash chromatography (eluant 0.1% trifluoroacetic acid in H_2O/acetonitrile 95:5 as mobile phase A and acetonitrile as mobile phase B) afforded **6** (60 mg, 45%) and **4** (10 mg, 8%) as yellow solids. The separation was performed using a rapid gradient increasing from 0 to 30% B in 20 min followed by a hold at 100% B for 3 min at a flow rate of 20 mL/min. Compound **6**: IR (neat) ν 1749, 1732, 1616, 1481, 1442, 1371 cm^{-1}. ^{1}H NMR (499.75 MHz, DMSO-d_6) δ 3.18–3.27 (m, 4H, CH_2-8 and CH_2-9), 6.53 (d, J=1.7 Hz, 1H, H-3), 7.96 (t, J=4.5 Hz, 1H, NH-7), 9.61 (s, 1H, NH-15), 11.09 (s, 1H, NH-13), 11.58 (br s, 1H, NH-1). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 31.2, 39.7, 104.4, 111.6, 121.3, 123.0, 123.7, 127.2, 155.0, 163.7, 165.6. HRMS calcd for $C_{11}H_9BrN_4O_3$ [M+H$^+$] 324.9931, found 324.9931. Compound **4**: IR (neat) ν 1748, 1707, 1613, 1368 cm^{-1}. ^{1}H NMR (499.75 MHz, DMSO-d_6) δ 2.66–2.68 (m, 2H, CH_2-9), 3.18–3.22 (m, 2H, CH_2-8), 6.66 (s, 1H, H-3), 7.92 (t, J=4.7 Hz, 1H, NH-7), 9.85 (s, 1H, NH-15), 10.94 (s, 1H, NH-13), 12.38 (s, 1H, NH-1). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 36.2, 38.4, 101.6, 114.4, 120.1, 121.3, 125.6, 126.6, 153.8, 162.9, 163.5. HRMS calcd for $C_{11}H_9BrN_4O_3$ [M+H$^+$] 324.9931, found 324.9943.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.12.053.

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