Use of the cascade α-oxo-amidoalkylation / transposition / π-cationic cyclization of *N*-acyliminium ions in the synthesis of novel fused heterocyclic *N*,*O*-acetals

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Dedicated to Prof. Bruce E. Maryanoff and his wife, Prof. Cynthia A. Maryanoff, on the occasion of their 65th birthdays

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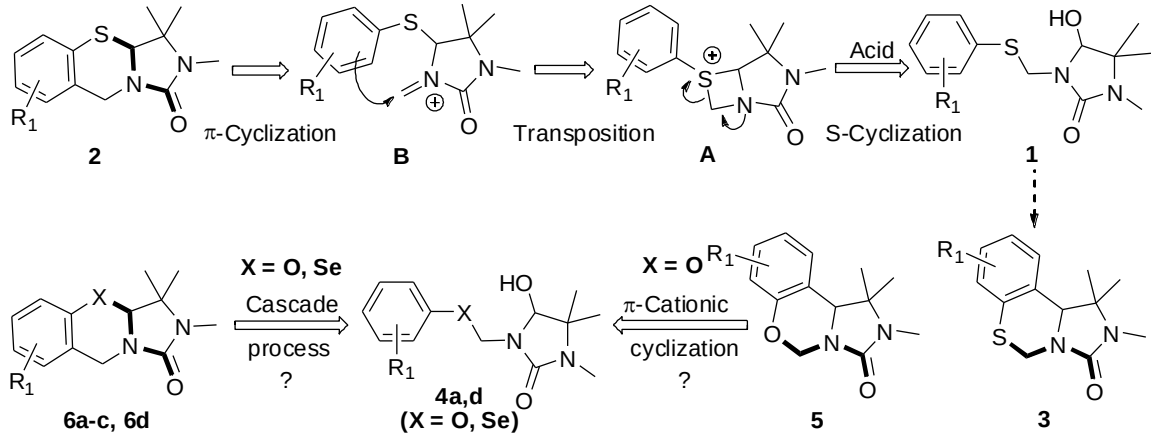
Abstract
Tricyclic *N*,*O*-acetal scaffolds have been prepared easily in few steps starting from cheap reagents in moderate to good yields (40-68%) in which the α-hydroxy lactam intermediates constitute the key substrates. These cyclized products are the result of the exclusive intramolecular attack of the oxygen atom onto the endocyclic *N*-acyliminium ion intermediates leading to the new cyclic aza-oxonium salts, their opening into exocyclic *N*-acyliminium species, followed by their intramolecular arylation. During these investigations, the high level of chemoselectivity during the reduction and cyclization was discussed and the structure of the cyclized products was unequivocally confirmed.

Keywords: *N*-Acyliminium ion, heterocyclization, cationic cyclization, isomerization, *N*,*O*-acetal

Introduction

N-Acyliminium ions are important species in organic synthesis, especially for the elaboration of various nitrogen- containing natural and unnatural products of pharmacological interest.[1,2] *N*-Acyliminium ions also act as more electron-deficient carbocations[3] toward weak nucleophiles, providing exceptionally useful methodologies for carbon-carbon bond (C-C) formation, both in intermolecular and intramolecular processes.[1,2] These intermediates have been generated from amides or lactams bearing a good leaving group in the position α- to the nitrogen atom under acid conditions. The substrates used for this purpose include *N*,*O*-, *N*,*N*-, and *N*,*S*- acetals as well

as α-halo-, α-hydroxy-, and α-acetoxy amides, lactams, carbamates, and isomünchnone cycloadducts. Hence, several Brönsted and Lewis acids have been used as catalysts to effect this transformation. Elsewhere, while the use of π-aromatics, olefins, diolefins, alkynes, allyls, homoallyls, allylsilanes, active methylenes, and π-electron- rich sulfur- or silicon- reagents as nucleophiles has been largely established,[1-3] the use of heteroatom (X = O, N, S and Se) nucleophiles for forming carbon-heteroatom (C-X) linkages either in intermolecular and intramolecular manners has been little explored in organic synthesis.[4]



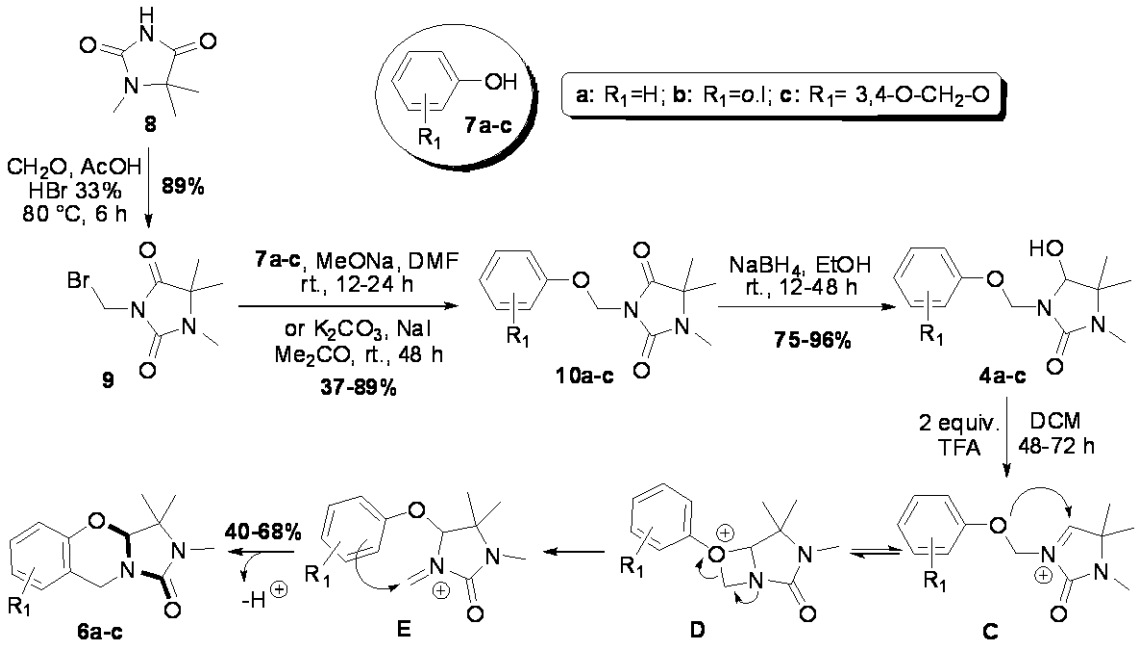
Scheme 1. Tandem cyclization of α-hydroxy lactams **1** with the sulfur atom as internal nucleophile and our *N*-acyliminium ion precursors **4** used during this work.

In the framework of our interest in intramolecular cationic cyclizations based on the formation and cleavage of carbon-heteroatom linkages for the preparation of complex *N*,*X*-containing heterocycles, we have recently demonstrated that in acidic media α-hydroxy lactams of type **1** are effective precursors of the tricyclic *N*,*S*-acetals **2** (Scheme 1).[5] These cyclized products are the result of the exclusive intramolecular attack of the sulfur atom onto the endocyclic *N*-acyliminium ion intermediates into **A**, their opening into **B**, followed by π-cationic cyclization into the polysubstituted tricyclic *N*,*S*-acetals **2**. It is important to note that, whatever the experimental conditions used during these investigations, no formation of the direct π-cationic cyclization products **3** was observed.

Results and Discussion

In the context outlined above, we present herein our findings from a related study dealing with the examination of the impact, during the cyclization process, of the oxygen atom (X = O: which is less nucleophilic than a sulfur atom) on the reactivity of α-hydroxy lactam precursors of type **4** (Scheme 1). Also for comparison reasons, one α-hydroxy lactam of type **4** with X = Se (X = Se: which is more nucleophilic than a sulfur atom) is also considered.

At the outset, the synthesis of the requisite α-hydroxy lactams **4a-c** was accomplished in a three-step sequence, as highlighted in Scheme 2, starting from commercial 1,5,5-trimethylimidazolidine-2,4-dione, **8**. Thus, 3-bromomethyl-1,5,5-trimethylimidazolid-ine-2,4-dione, **9,** was prepared by treatment of imide **8** with paraformaldehyde/HBr in AcOH as solvent at 80 °C for 6 h according to the known procedure[6] (89% yield instead of 88% yield in Ref. 6). This product was O-alkylated with a slight excess of phenol derivatives **7a-c** in an alkaline medium (yield: 37–89%). From these results, it seems that conditions using K_2CO_3 in association with NaI in stoichiometric amounts in dry acetone at room temperature for 48 h are better than those using MeONa in dry DMF at room temperature for 12-24 h. Under the best conditions, theO-alkylated products **10a-c** were isolated as white solids after chromatographic purification (SiO_2, cyclohexane: EtOAc 1:1) in yields of 37%, 89% and 77%, respectively. The mediocre yield in the case of **10a** is probably due to the low solubility of the phenol (**7a**) as the starting material in acetone, and is similar to that observed for the same O-alkylation reaction in the phthalimide series.[7] Later, after optimization work using LAH,[8] $NaBH_4$,[9] etc., the regioselective reduction of the resultant imides **10a-c** was performed with a large excess of $NaBH_4$ (6 equiv.) in analogy to our reports for related structures[5] and others[9] to afford α-hydroxy lactams **4a-c** in good yields (67%, 75% and 96%, respectively; see Scheme 2). In some cases, to avoid the relatively poor solubility of the starting imides **10** and the laborious work-up encountered during these processes, a small quantity of THF was added as co-solvent. Under these conditions, the expected α-hydroxy lactams **4** were isolated with high purity by simple filtration and washing of the solid with diethyl ether and, consequently, were used in the next step without other purification.

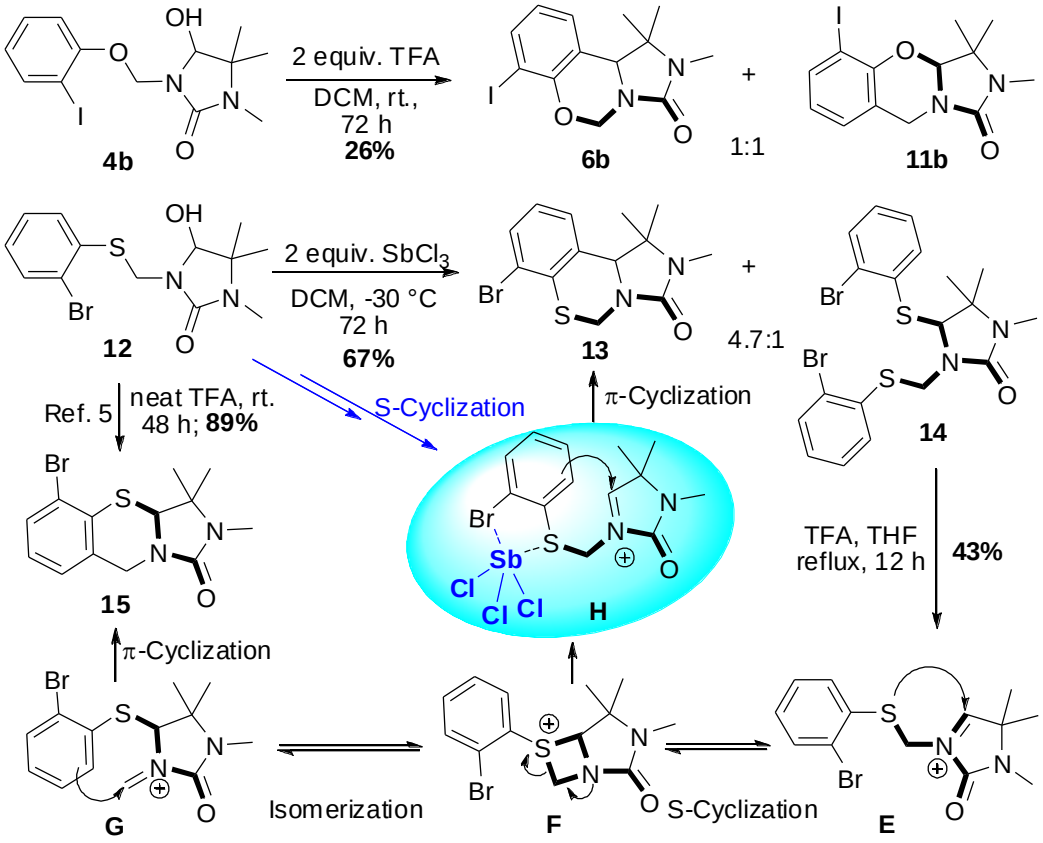


Scheme 2. Scheme leading to the tricyclic targets **6a-c** *via* the effective intramolecular α-oxo-amidoalkylation / isomerization / π-cationic cyclization cascade.

Because of the small body of literature on aryloxymethylimidazolidinols regarding the reactivity of this functionality under acid conditions, an examination of the α-hydroxy lactams **4a-c** was made. Thus, we found that these precursors react under conventional conditions using TFA (2 equiv.) in CH_2Cl_2 at room temperature for 48-72 h to give the cyclized products, analyzed to be components **6**, in moderate to good yields (Scheme 2). Although the reaction provides products **6a** and **6c** in yields of 68% and 40%, respectively, in the case of hydroxyl lactam **4b** an inseparable mixture of two products identified as **6b** and **11b** in a 1:1 ratio was obtained in only 26% yield (Scheme 3). As shown in Schemes 2 and 3, product **6b** and their analogs **6a,c** are the results of the sequence involving O-cyclization of an endocyclic cation **C** being generated in acidic medium into the aza-oxonium species **D**, its isomerization into the exocyclic *N*-acyliminium cation **E**, and followed in the ultimate stage by its ring closure via the π-cationic cyclization. Interestingly, related cations which are generated initially from an atypical heterocyclization were recently put in evidence for the first time by our group. This fact outlined that these cations are in equilibrium via a cyclic aza-oxonium[5] species (type **D**, Scheme 2) and are similar to those observed for related aza-sulfonium[4b,5] species (type **A**, Scheme 1). As for product **11b**, it was obtained by the direct π-cationic cyclization of the *N*-acyliminium ion intermediate **C** formed initially from the starting α-hydroxy lactam **4b**.

Intrigued by this unique behavior of α-hydroxy lactam **4b** in acid media, owing probably to the presence of iodine on the benzene ring at the *ortho*-position, we then planned to explore the reactivity of an equivalent system in the sulfur series. For this purpose, the α-hydroxy lactam **12** that we described recently[5] was considered. Thus, treatment of **12** in neat TFA in precise amount to the reactant (1.5 mL per 1 mmol of **12**) provided the product **15** exclusively. It is worth noting that this reactivity was inverted when **12** was treated with 2 equiv. of $SbCl_3$, as a soft Lewis acid, at -30 °C in dry CH_2Cl_2 for 72 h. Under these conditions, only the direct π-cationic cyclization occurred, providing product **13**, accompanied, however, with the disulfur component **14** in a 4.7:1 ratio and acceptable yield (67%).

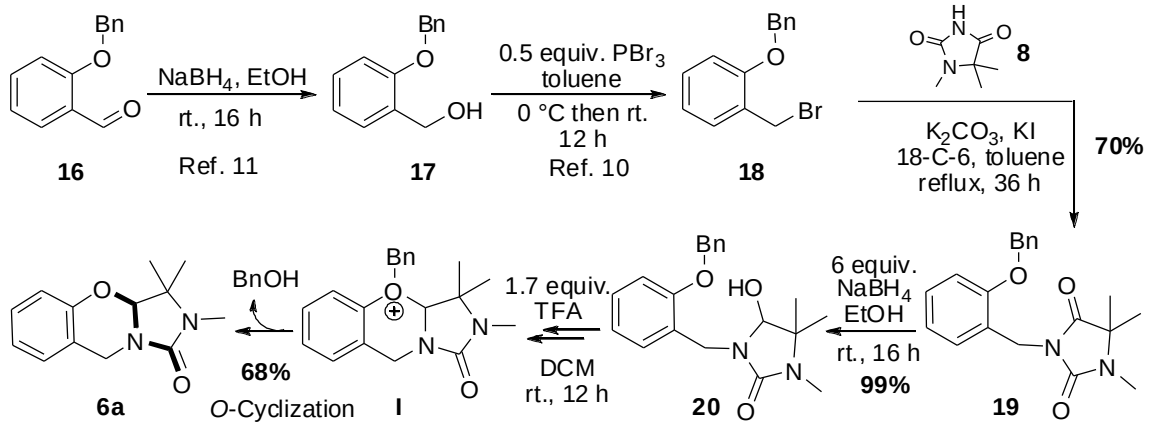
Since the formation of **15** was not observed, we speculated that the origin of the reaction selectivity herein is probably due to the formation of the complex intermediate **H** (Scheme 3) in which the nucleophilicity of the sulfur atom is diminished by the Lewis acid coordination. Otherwise, the formation of **14** could be explained by the formation of an *N*-acyliminium ion intermediate from **12**, followed by the intermolecular nucleophilic attack of the *o*-bromothiophenol being liberated by the cleavage of the exocyclic S-CH_2-N functionality of the *N,S*-acetal derivative. Based on our earlier observations in this field, treatment of phenylthio derivative **14** with TFA in THF at reflux provided a 5.5:4.5 ratio of an inseparable mixture of the cyclized products **13** and **15** in 43% yield. This result confirms the ability of the *N,S*-diacetal **14** to generate, in the same way as α-hydroxy lactam **12**, the intermediate cations **E-G** which are indispensable for the formation of both C-C and C-S linkages of the cyclized products **13** and **15**.[4b] Elsewhere, the ratio obtained in this case for products **13** and **15** is exactly the same as the one obtained in phthalimide and succinimide series starting from related disulfur *N*-acyliminium ion precursors.[4b,c]



Scheme 3. Changes in the cyclization reaction profile of α-hydroxy lactams **4b** and **12**.

Importantly, the structure confirmation of these tricyclic N,O-acetal systems **6** was attempted chemically by an unequivocal approach as shown in Scheme 4. This strategy involves the synthesis from the known *o*-(benzyloxy)-benzyl bromide **18**[10] of the α-hydroxy lactam **20** as a plausible key intermediate to provide the model product **6a** by a direct π-cyclization.

Thus, according to the sequential method illustrated in Scheme 4, reduction of the commercial aldehyde **16** was easily accomplished by sodium borohydride in ethanol at room temperature for 16 h, giving the alcohol derivative **17** in high yield (>98%).[11] The 2-(phenyloxy)-benzyl bromide **18** was then reached by treating **17** with phosphorus tribromide (0.5 equiv. instead of the 1.1 equiv. used in Ref. 10) in toluene at 0 °C, then at room temperature for 12 h. Under these conditions, we isolated the expected product **18**, identical to that mentioned in the literature,[10] in 82% yield (97%, Ref. 10).

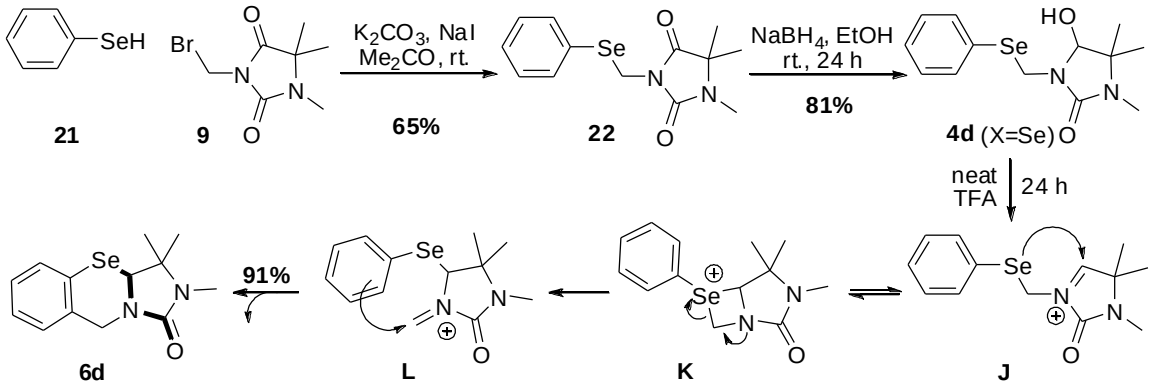


Scheme 4. Chemical confirmation of the targeted tricyclic *N*,*O*-acetal **6a**.

Because the formation of *N*-alkylated imide **19** in one step, by condensation of imide **8** with alcohol **17** in dry THF in the presence of triphenylphosphine and diisopropyl azodicarboxylate according to the Mitsunobu reaction,[12] could not be optimized – no matter what the experimental conditions, another way was used. Thus, exposure of bromide **18** to the imide **8** under solid-liquid phase-transfer catalysis (PTC) conditions,[8,10] using anhydrous potassium carbonate as a base, and a mixture of potassium iodide and crown ether 18-C-6 as catalysts, gave the *N*-alkylated product **19**. This product was isolated as crystalline solids in 70% yield. Reduction of adduct **19** was performed with a large excess of sodium borohydride in dry EtOH and afforded the α-hydroxy lactam **20** as the sole reaction product in nearly quantitative yield.

As expected, the cyclization of the α-hydroxy lactam **20** proceeded with high regioselectivity to provide, *via* the consecutive *N*-acyliminium ion and oxonium species, the tricyclic *N*,*O*-acetal system **6a** in an appreciable, 68% yield. In fact, the cyclized product **6a**, identical to that obtained in Scheme 2 above, is the result of the nucleophilic attack of the oxygen atom onto the endocyclic *N*-acyliminium ion being formed from **20** under acid influence (not shown in the Scheme), followed ultimately by the loss of the stable benzylic cation of the cyclic aza-oxonium salt **I** (Scheme 4). Interestingly, in addition to our recent work demonstrating the effectiveness of this new mechanism, a report concerning a similar phenomenon using a tandem process such as an aza-Cope isomerization / intramolecular *O*-cationic cyclization was pointed out in the literature by Speckamp's group.[14]

With this result in hand, we then planned its extension to the selenium series by targeting first the *N*-acyliminium ion precursor **4d** (X=Se). Thus, this intermediate was prepared as shown in Scheme 5, in two steps starting from bromomethylimide **9**, using the same protocol as for the oxygenated analogs **4a-c** (X = O) described above. Under these conditions, the expected α-hydroxy lactam was isolated in an overall yield of 53% for two steps, in the form of sufficiently pure white crystals as shown with NMR spectroscopy.



Scheme 5. Scheme leading to the target tricyclic *N*,*Se*-acetal **6d**.

As for the oxygenated *N*-acyliminium ion precursors **4a-c** (X = O), the α-hydroxy lactam **4d** (X=Se) was treated with neat TFA according to our standard cyclization protocol outlined above (*e.g.*, TFA, 1.5 mL for 1 mmol of **4d**, R.T, 24 h). After the work- up of the reaction, the 2,3,3*a*,9-tetrahydro-2,3,3-trimethylimidazo[5,1-*b*][1,3]benzoselen-azin-1-one **6d** was obtained as the sole reaction product, in an excellent yield (91%), showing again that the hetero- atom nucleophilicity plays a pivotal role on the cascade α-hetero-amidoalkylation / transposition / π-cationic cyclization of *N*-acyliminium cations.

The structures of all products and intermediates reported herein was confirmed by their ^{1}H- and ^{13}C-NMR spectra, including DEPT programs, NOE measurements, and elemental analyses as well as mass spectra, except for the α-hydroxy lactams which are unstable during the mass measurements. For instance, in the ^{1}H- NMR spectra of the cyclized products **6a-d**, **11b** and **13** the methylene protons (N-CH_2-X with X = O, S, Se) appear as AB systems due to the diastereotopic effect, with a coupling constant *J* ranging from 14 Hz to 17 Hz characteristic of *gem* protons. It is interesting to note that the same fact was observed in their α-hydroxy lactam congeners **4a-d** and **12** with, however, a coupling constant *J* with low values (10-12 Hz). Furthermore, the key feature in the ^{13}C- NMR spectra of the target products **6a-d**, **11b** and **13**, and of the corresponding *N*-acyliminium ion precursors **4a-d** and **12**, was the appearance of the same carbon signals. Moreover, one of these resonances disappears in the DEPT program spectra of **6a,d** and **6c**, as a consequence of the formation of the C-C bond in the ultimate stage both with a direct π-cationic cyclization as well as with the cascade process.

Conclusions

We have shown that aryloxymethylimidazolidinols of type **4,** prepared easily in two steps by *O*-alkylation of phenols followed by a regioselective borohydride reduction, give selectively in acid medium tricyclic *N*,*O*-acetal products in moderate to good yields. These latter, as *N*-acyliminium ion precursors, lead to fused [1,3]oxazines **6** in a one-pot procedure involving an intramolecular

α-oxo-amidoalkylation of an endocyclic *N*-acyliminium species **C**, then its isomerization into a cyclic aza-oxonium ion **D** followed ultimately by its intramolecular arylation through an exocyclic *N*-acyliminium cation **E**. In certain cases, **4b**, the formation of a regioisomer **11b** of **6b** *via* the direct π-cationic cyclization of the endocyclic *N*-acyliminium species **C** was observed. During these investigations, studies towards the inversion of the course of the cyclization reaction were considered and the structure of the cyclized *N,O*-acetals was confirmed chemically.

Experimental Section

General. Melting points are uncorrected. IR spectra of solids (in potassium bromide) were recorded on a Perkin Elmer FTIR Paragon 1000 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were measured on Bruker AC-200 and Bruker 300 instruments (200 and 300 MHz, respectively) and chemical shifts are reported relative to $CDCl_3$ at δ = 7.24 ppm (or to DMSO-d_6 at δ = 2.49 ppm) and tetramethylsilane (TMS) as an internal standard. MS measurements were carried out on an AEI MS 902S instrument (70 eV, electron impact). Reagents were obtained from commercial suppliers and used without further purification. Solvents were dried and purified by standard methods. A Merck silica gel 60 was used for both column chromatography (70-230 mesh) and flash chromatography (230-400 mesh). Ascending TLC was performed on precoated plates of silica gel 60 F 254 (Merck) and the spots visualized using an ultraviolet lamp or iodine vapor. Elemental analyses (C, H, N) were performed by the microanalysis laboratory of INSA at Rouen, F-76130 Mt-St-Aignan, France.

3-Bromomethyl-1,5,5-trimethylimidazolidine-2,4-dione 9. This product was obtained from 1,5,5-trimethylhydantoin (**8**; 21.3 g; 150 mmol) and formaldehyde (5.86 g; 195 mmol) in a solution of HBr/AcOH (33%; 34.8 mL; 195 mmol) at 80 °C for 6 h of reaction according to the protocol reported earlier in the literature.[6] The product was isolated as a white solid after recrystallization from diethyl ether in 89% yield (88%; Lit. 6). MP = 87 °C (86-88 °C; Lit. 6). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.38 (s, 6H, 2 x CH_3); 2.89 (s, 3H, CH_3); 5.26 (s, 2H, CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 21.9 (2x CH_3); 24.6 (CH_3); 32.4 (CH_2); 61.7 (C_q); 152.5 (C_2=O); 174.7 (C_4=O). IR (KBr, cm^{-1}): ν = 1780 (C=O); 1725 cm^{-1} (C=O).

General procedure for N-alkylation of 3-bromomethyl-1,5,5-trimethylimidazoli-dine-2,4-dione 9

To a stirred mixture of 3-bromomethyl-1,5,5-trimethylimidazolidine-2,4-dione (**9**; 2.34 g; 10 mmol) and NaI (1.49 g; 10 mmol) in 50 mL of dry acetone were added solid potassium carbonate (1.38 g; 10 mmol). After stirring for 10 min, 10 mmol of phenols **7a-c** in 50 mL of dry acetone was added dropwise over a period of 20 min. The mixture was then allowed to react at room temperature for 48 h and cooled. After dilution with CH_2Cl_2 (50 mL) and filtration over a

short column of Celite, the organic phase was concentrated under reduced pressure and the crude resulting solid was purified by flash chromatography on silica gel with a mixture of cyclohexane: AcOEt 1:1 as eluent to give *O*-alkylated imides **10a-c**.

1,5,5-Trimethyl-3-phenyloxymethylhydantoin 10a. Obtained as a white solid after recrystallization from diethyl ether in 37% yield. Mp = 94 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.36 (s, 6H, 2x CH_3); 2.88 (s, 3H, CH_3); 5.45 (s, 2H, CH_2); 6.95-7.07 (m, 3H, H_{arom}); 7.23-7.31 (m, 2H, H_{arom}). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 22.0 (2 x CH_3); 24.5 (CH_3); 61.4 (C^q); 66.4 (CH_2); 116.3 (2 x CH_{arom}); 122.4 (CH_{arom}); 129.6 (2 x CH_{arom}); 153.9 (C^q_{arom}-O); 156.4 (C_2=O); 176.1 (C_4=O). IR (KBr, cm^{-1}): ν = 1770 (C=O); 1720 cm^{-1} (C=O). MS (EI): *m*/*z* = 248. Anal. Calcd for $C_{13}H_{16}N_2O_3$ (248.12): C, 62.89; H, 6.50; N, 11.28. Found: C, 62.67; H, 6.29; N, 11.12%.

3-(*o*-Iodophenyl)oxymethyl-1,5,5-trimethylhydantoin 10b. Obtained as a white solid after recrystallization from diethyl ether in 81% yield. Mp = 89 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.37 (s, 6H, 2x CH_3); 2.88 (s, 3H, CH_3); 5.48 (s, 2H, CH_2); 6.72-6.80 (m, 1H, H_{arom}); 7.10-7.15 (m, 1H, H_{arom}); 7.25-7.33 (m, 1H, H_{arom}); 7.70-7.75 (m, 1H, H_{arom}). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 22.1 (2 x CH_3); 24.6 (CH_3); 61.5 (C^q); 67.8 (CH_2); 88.6 (C^q_{arom}-I); 116.7 (CH_{arom}); 124.8 (CH_{arom}); 129.7 (CH_{arom}); 139.6 (CH_{arom}); 153.8 (C^q_{arom}-O); 156.0 (C_2=O); 176.0 (C_4=O). IR (KBr, cm^{-1}): ν = 1769 (C=O); 1722 cm^{-1} (C=O). MS (EI): *m*/*z* = 374. Anal. Calcd for $C_{13}H_{15}IN_2O_3$ (374.01): C, 41.73; H, 4.04; N, 7.49. Found: C, 41.56; H, 3.92; N, 7.27%.

3-(3,4-Dioxymethylenephenyl)oxymethyl-1,5,5-trimethylhydantoin 10c. Obtained as a light-brown solid after recrystallization from diethyl ether in 77% yield. Mp = 89 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.34 (s, 6H, 2 x CH_3); 2.86 (s, 3H, CH_3); 5.33 (s, 2H, CH_2); 5.88 (s, 2H, CH_2); 6,48 (dd, 1H, *J* = 2 and 8 Hz, H_{arom}); 6.59 (d, 1H, *J* = 3 Hz, H_{arom}); 6.65 (d, 1H, *J* = 8 Hz, H_{arom}). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 22.1 (2 x CH_3); 24.5 (CH_3); 61.4 (C^q); 67.7 (CH_2); 100.4 (CH_{arom}); 101.4 (CH_2); 108.0 (CH_{arom}); 108.8 (CH_{arom}); 143.2 (C^q_{arom}-O); 148.3 (C^q_{arom}-O); 151.5 (C^q_{arom}-O); 153.9 (C_2=O); 176.1 (C_4=O). IR (KBr, cm^{-1}): ν = 1765 (C=O); 1722 cm^{-1} (C=O). MS (EI): *m*/*z* = 292. Anal. Calcd for $C_{14}H_{16}N_2O_5$ (292.11): C, 57.53; H, 5.52; N, 9.58. Found: C, 57.39; H, 5.40; N, 9.35%.

1,5,5-Trimethyl-3-phenylselenomethylhydantoin 22. Obtained using the same protocol as above, as a colorless oil after chromatography purification in 65% yield (cyclohexane: AcOEt 1:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.24 (s, 6H, 2 x CH_3); 2.81 (s, 3H, CH_3); 4.87 (s, 2H, CH_2); 7.22-7.25 (m, 3H, H_{arom}); 7.58-7.63 (m, 2H, H_{arom}). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 21.9 (2 x CH_3); 24.4 (CH_3); 33.8 (CH_2); 61.3 (C^q); 128.1 (C^q_{arom}-Se); 128.2 (CH_{arom}); 129.1 (2 x CH_{arom}); 134.8 (2 x CH_{arom}); 153.8 (C_2=O); 175.3 (C_4=O). IR (neat, cm^{-1}): ν = 1769 (C=O); 1710 cm^{-1} (C=O). MS (EI): *m*/*z* = 312. Anal. Calcd for $C_{13}H_{16}N_2O_2Se$ (312.04): C, 50.17; H, 5.18; N, 9.00. Found: C, 50.02; H, 5.00; N, 8.83%.

General procedure for the regioselective reduction of *N*-protected-*N*-aryloxo- (or seleno)-methylhydantoins 10a-c and 22

To a well-stirred solution of 3-protected-1,5,5-trimethyl-hydantoins (**10** or **22**; 6 mmol) in 60 mL of dry ethanol (with addition of 10 mL of THF in certain cases), sodium borohydride (1.37 g; 36

mmol) was added in portions at ambient temperature over a period of 5 up to 10 min. After complete reaction (12 to 48 h; the reaction was monitored by TLC using a precoated plate of silica gel and CH_2Cl_2 as eluent), the excess of sodium borohydride was decomposed by careful addition of 5% HCl solution until pH ≈ 3. After removal of the solvent under reduced pressure, the residue was diluted with H_2O (2 x 20 mL) and extracted with 2 x 30 mL of CH_2Cl_2. The organic phase was separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure, to give the corresponding α-hydroxyl lactam **4** in good yields.

4-Hydroxy-1,5,5-trimethyl-3-phenyloxymethylimidazolidin-2-one 4a. Obtained as a colorless oil in 75% yield. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.00 (s, 3H, CH_3); 1.25 (s, 3H, CH_3), 2.69 (s, 3H, CH_3); 3.60 (d, 1H, *J* = 9 Hz, OH(CH)); 4.81 (d, 1H, *J* = 9 Hz, CH(OH)); 5.22 (d, 1H, *J* = 10 Hz, CH_2); 5.46 (d, 1H, *J* = 10 Hz, CH_2); 6.91-7.00 (m, 3H, H_{arom}); 7.21-7.29 (m, 2H, H_{arom}). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 18.9 (CH_3); 23.3 (CH_3); 24.4 (CH_3); 60.0 (C^q); 69.3 (CH_2); 84.3 (CH); 115.8 (2 x CH_{arom}); 121.6 (CH_{arom}); 129.5 (2 x CH_{arom}); 156.6 (C^q_{arom}-O); 157.1 (C=O). IR (neat, cm^{-1}): ν = 3336 (OH); 1693 cm^{-1} (C=O).

4-Hydroxy-3-(*o*-iodophenyl)oxymethyl-1,5,5-trimethylimidazolidin-2-one 4b. Obtained as a white solid after washing with cold diethyl ether, in 67% yield. Mp = 115 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.02 (s, 3H, CH_3); 1.27 (s, 3H, CH_3); 2.68 (s, 3H, CH_3); 3.85 (d, 1H, *J* = 9 Hz, OH(CH)); 4.90 (d, 1H, *J* = 9 Hz, CH(OH)); 5.28 (d, 1H, *J* = 10 Hz, CH_2); 5.51 (d, 1H, *J* = 10 Hz, CH_2); 6.67-6.74 (m, 1H, H_{arom}); 6.95-7.06 (m, 1H, H_{arom}); 7.22-7.29 (m, 1H, H_{arom}); 7.69-7.73 (m, 1H, H_{arom}). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 19.0 (CH_3); 23.4 (CH_3); 24.6 (CH_3); 60.1 (C^q); 70.6 (CH_2); 84.5 (CH); 87.6 (C^q_{arom}-I); 114.6 (CH_{arom}); 123.7 (CH_{arom}); 129.7 (CH_{arom}); 139.5 (CH_{arom}); 155.2 (C^q_{arom}-O); 156.9 (C=O). IR (KBr, cm^{-1}): ν = 3307 (OH); 1697 cm^{-1} (C=O).

3-(3,4-Dioxymethylenephenyl)oxymethyl-4-hydroxy-1,5,5-trimethylimidazolidin-2-one 4c. Obtained as a white gum after washing with cold diethyl ether followed with cold cyclohexane, in 96% yield. Mp < 40 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.01 (s, 3H, CH_3); 1.23 (s, 3H, CH_3); 2.65 (s, 3H, CH_3); 4.53 (s large, 1H, OH); 4.77 (s, 1H, CH); 5.08 (d, 1H, *J* = 10 Hz, CH_2); 5.32 (d, 1H, *J* = 10 Hz, CH_2); 5.86 (s, 2H, CH_2); 6.40 (dd, 1H, *J* = 2 and 8 Hz, H_{arom}); 6.53 (d, 1H, *J* = 2 Hz, H_{arom}); 6.64 (d, H, *J* = 8 Hz, H_{arom}). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 19.0 (CH_3); 23.5 (CH_3); 24.5 (CH_3); 60.0 (C^q); 70.7 (CH_2); 84.6 (CH); 99.7 (CH_{arom}); 101.3 (CH_2); 107.9 (CH_{arom}); 108.1 (CH_{arom}); 142.5 (C^q_{arom}-O); 148.2 (C^q_{arom}-O); 151.8 (C^q_{arom}-O); 157.1 (C=O). IR (KBr, cm^{-1}): ν = 3326 (OH); 1694 cm^{-1} (C=O).

4-Hydroxy-1,5,5-trimethyl-3-phenylselenomethylimidazolidin-2-one 4d. Obtained in 81% yield as a white solid after washing with cold diethyl ether. Mp = 106 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.94 (s, 3H, CH_3); 1.20 (s, 3H, CH_3); 2.59 (s, 3H, CH_3); 4.27 (d, 1H, *J* = 10 Hz, OH(CH)); 4.55 (d, 1H, *J* = 12 Hz, CH_2); 4.70 (d, 1H, *J* = 10 Hz, CH(OH)); 5.23 (d, 1H, *J* = 12 Hz, CH_2); 7.18-7.23 (m, 3H, H_{arom}); 7.52-7.57 (m, 2H, H_{arom}). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 18.9 (CH_3); 23.7 (CH_3); 24.6 (CH_3); 39.4 (CH_2); 59.7 (C^q); 85.0 (CH); 127.4 (CH_{arom}); 129.1 (C^q_{arom}-Se); 129.2 (2 x CH_{arom}); 133.5 (2 x CH_{arom}); 156.8 (C=O). IR (KBr, cm^{-1}): ν = 3270 (OH); 1682 cm^{-1} (C=O).

General procedure for cyclization of hydroxy lactams 4a-d

To a stirred and cold solution of the hydroxyl lactam **4** (2.5 mmol) in 10 mL of dry CH_2Cl_2 was added TFA (2 equiv.). After 48-72 h of reaction at RT under stirring, the reaction mixture was diluted with 10 mL of water, 10 mL of CH_2Cl_2 and neutralized carefully with 5% NaOH aqueous solution until pH ≈ 6-7. The solution was then extracted twice with CH_2Cl_2 (10 mL). The organic layer was washed with water, then brine, separated, dried over $MgSO_4$ and evaporated under reduced pressure. The resulting residue was finally purified by flash chromatography (SiO_2, cyclohexane: AcOEt 1:1) to give the tricyclic product **6** as white crystals in yields ranging from 40 to 68%.

2,3,3*a*,9-Tetrahydro-2,3,3-trimethylimidazo[5,1-*b*][1,3]benzoxazin-1-one 6a. Obtained as a white solid after washing with cold cyclohexane, in 68% yield. Mp = 84 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.24 (s, 3H, CH_3); 1.42 (s, 3H, CH_3); 2.75 (s, 3H, CH_3); 4.30 (d, 1H, *J* = 17 Hz, CH_2); 4.88 (d, 1H, *J* = 17 Hz, CH_2); 4.89 (s, 1H, CH); 6.77-7.22 (m, 4H, H_{arom}). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 19.1 (CH_3); 22.6 (CH_3); 24.5 (CH_3); 39.8 (CH_2); 59.2 (C^q); 87.3 (CH); 117.8 (CH_{arom}); 120.4 (C^q_{arom}-C); 121.8 (CH_{arom}); 126.7 (CH_{arom}); 127.8 (CH_{arom}); 152.9 (C^q_{arom}-O); 158.4 (C=O). IR (KBr, cm^{-1}): ν = 1709 cm^{-1} (C=O). MS (EI): *m*/*z* = 232. Anal. Calcd for $C_{13}H_{16}N_2O_2$ (232.12): C, 67.22; H, 6.94; N, 12.06. Found: C, 67.06; H, 6.78; N, 12.17%.

2,3,3*a*,9-Tetrahydro-5-iodo-2,3,3-trimethylimidazo[5,1-*b*][1,3]benzoxazine-1-one 6b and 1,2,5,10*b*-tetrahydro-7-iodo-1,1,2-trimethylimidazo[1,5-*c*][1,3]benzoxa-zine-3-one 11b. These products were obtained in 26% yield as an inseparable mixture after chromatographic purification (cyclohexane: AcOEt, 1:1) in a 1:1 ratio. NMR data for isomer **6b**: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.41 (s, 3H, CH_3); 1.53 (s, 3H, CH_3); 2.76 (s, 3H, CH_3); 4.29 (d, 1H, *J* = 16 Hz, CH_2); 4.89 (d, 1H, *J* = 16 Hz, CH_2); 4.96 (s, 1H, CH); 6.79-6.93 (m, 2H, H_{arom}); 7.56 (dd, 1H, *J* = 1.6 and 7.8 Hz, H_{arom}). NMR data for isomer **11b**: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.23 (s, 3H, CH_3); 1.26 (s, 3H, CH_3); 2.74 (s, 3H, CH_3); 4.25 (d, 1H, *J* = 17 Hz, CH_2); 4.85 (d, 1H, *J* = 17 Hz, CH_2); 4.88 (s, 1H, CH); 6.67 (t, 1H, *J* = 7.8 Hz, H_{arom}), 6.99-7.13 (m, 2H, H_{arom}).

6,7-Dioxymethylene-2,3,3*a*,9-tetrahydro-2,3,3-trimethylimidazo[5,1-b][1,3]benzoxazin-1-one 6c. This product was obtained as a white solid after washing with cold cyclohexane in 40% yield. Mp = 139 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.22 (s, 3H, CH_3); 1.38 (s, 3H, CH_3); 2.74 (s, 3H, CH_3); 4.18 (d, 1H, *J* = 16 Hz, CH_2); 4.75 (d, 1H, *J* = 16 Hz, CH_2); 4.82 (s, 1H, CH); 5.86 (s, 2H, CH_2); 6.35 (s, 1H, H_{arom}); 6.46 (s, 1H, H_{arom}). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 19.0 (CH_3); 22.5 (CH_3); 24.5 (CH_3); 39.9 (CH_2); 59.0 (C^q); 87.3 (CH); 99.5 (CH_{arom}); 101.1 (CH_2); 105.4 (CH_{arom}); 112.1 (C^q_{arom}-C); 142.6 (C^q_{arom}-O); 146.8 (C^q_{arom}-O); 147.5 (C^q_{arom}-O); 158.3 (C=O). IR (KBr, cm^{-1}): ν = 1698 cm^{-1} (C=O). MS (EI): *m*/*z* = 276. Anal. Calcd for $C_{14}H_{16}N_2O_4$ (276.11): C, 60.86; H, 5.84; N, 10.14. Found: C, 60.73; H, 5.77; N, 10.01%.

2,3,3*a*,9-Tetrahydro-2,3,3-trimethylimidazo[5,1-*b*][1,3]benzoselenazin-1-one 6d. This product was obtained as a white solid after washing with cold cyclohexane in 91% yield. Mp = 114 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.29 (s, 3H, CH_3); 1.41 (s, 3H, CH_3); 2.70 (s, 3H, CH_3); 4.15 (d, 1H, *J* = 16 Hz, CH_2); 4.78 (d, 1H, *J* = 16 Hz, CH_2); 5.24 (s, 1H, CH); 7.04-7.29 (m, 4H, H_{arom}). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 23.3 (CH_3); 23.6 (CH_3); 24.8 (CH_3); 46.9 (CH_2); 58.9

(C^q); 66.0 (CH); 126.2 (CH_{arom}); 127.6 (CH_{arom}); 128.5 (CH_{arom}); 128.7 (C^q_{arom}-Se); 131.3 (CH_{arom}); 132.2 (C^q_{arom}-C); 158.3 (C=O). IR (KBr, cm^{-1}): ν = 1692 cm^{-1} (C=O). MS (EI): *m*/*z* = 296. Anal. Calcd for $C_{13}H_{16}N_2OSe$ (296.04): C, 52.89; H, 5.46; N, 9.49. Found: C, 52.67; H, 5.29; N, 9.32%.

Cyclization of 3-(*o*-bromophenyl)thiomethyl-4-hydroxy-1,5,5-trimethylimidazolid-in-2-one 12.[5] To a stirred and cold solution of hydroxyl lactam **12** (0.504 g; 1.46 mmol) in 20 mL of dry CH_2Cl_2 was added $SbCl_3$ (0.665 g; 2.92 mmol) at -30 °C. After 72 h of reaction at the same temperature under stirring, the reaction mixture was diluted with water (10 mL) and neutralized carefully with 5% $NaHCO_3$ aqueous solution until pH = 7. The solution was then extracted twice with CH_2Cl_2 (2x10 mL). The organic layer was washed with water, brine, separated, dried over $MgSO_4$ and evaporated under reduced pressure. The resulting residue was finally purified by flash chromatography (SiO_2, cyclohexane: AcOEt 1:1) to give a mixture of two products **13** and **14** separable in a 4.7:1 ratio in 67% yield.

7-Bromo-2,3,3*a*,9-tetrahydro-2,3,3-trimethylimidazo[1,5-*c*][1,3]benzothiazin-1-one 13. Obtained as a colorless oil after chromatographic separation in 47% yield. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.94 (s, 3H, CH_3); 1.17 (s, 3H, CH_3); 2.63 (s, 3H, CH_3); 4.35 (d, 1H, *J* = 14 Hz, CH_2); 4.53 (s, 1H, CH); 5.38 (d, 1H, *J* = 14 Hz, CH_2); 6.97-7.05 (m, 1H, H_{arom}); 7.20-7.28 (m, 1H, H_{arom}); 7.48-7.54 (m, 1H, H_{arom}). IR (neat, cm^{-1}): ν=1698 cm^{-1} (C=O). MS (EI): *m*/*z* = 326-328.

4-(*o*-Bromophenylthio)-1-(*o*-bromophenyl)thiomethyl-1,5,5-trimethylimidazolidin-2-one 14. Obtained as a white solid in 10% yield. Mp = 67 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.09 (s, 3H, CH_3); 1.41 (s, 3H, CH_3); 2.67 (s, 3H, CH_3); 4.55 (d, 1H, *J* = 14 Hz, CH_2); 5.06 (s, 1H, CH); 5.50 (d, 1H, *J* = 14 Hz, CH_2); 6.95-7.32 (m, 4H, H_{arom}); 7.44-7.56 (m, 4H, H_{arom}). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 22.2 (CH_3); 24.4 (CH_3); 24.9 (CH_3); 46.1 (CH_2); 60.3 (C^q); 75.3 (CH); 125.0 (C^q_{arom}-Br); 127.5 (C^q_{arom}-Br); 127.8 (CH_{arom}); 127.9 (CH_{arom}); 128.3 (CH_{arom}); 129.1 (CH_{arom}); 131.1 (CH_{arom}); 133.0 (CH_{arom}); 133.6 (CH_{arom}); 133.9 (CH_{arom}); 135.1 (C^q_{arom}-S); 135.2 (C^q_{arom}-S); 156.6 (C=O). IR (KBr, cm^{-1}): ν = 1704 cm^{-1} (C=O). Anal. Calcd for $C_{19}H_{20}Br_2N_2OS_2$ (513.94): C, 44.20; H, 3.90; N, 5.43. Found: C, 44.08; H, 3.77; N, 5.29%.

Synthesis of 3-(*o*-benzyloxy)benzyl-1,5,5-trimethylimidazolidine-2,4-dione 19. To a stirred mixture of 1,5,5-trimethylimidazolidine-2,4-dione (**8**; 569 mg; 4 mmol) and 18-C-6 (1% *w*/*w*) in 25 mL of dry toluene were added solid potassium carbonate (66.5 mg; 0.4 mmol) and 0.1 equivalent per mmol of potassium iodide. After stirring for 20 min, 4.4 mmol of *o*-(benzyloxy)benzyl bromide (**18**;[10] 1.32 g) in 50 mL of dry toluene was added dropwise over a period of 15 min. The mixture was then refluxed for 36 h and cooled. After filtration over a short column of Celite, the organic phase was concentrated under reduced pressure and the crude resulting solid was purified by flash chromatography on silica gel with CH_2Cl_2 as eluent to give crude product which recrystallized from diethyl ether to provide pure **19** in 70% yield. Mp = 111 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.37 (s, 6H, 2 x CH_3); 2.86 (s, 3H, CH_3); 4.78 (s, 2H, CH_2); 5.09 (s, 2H, CH_2); 6.85-7.46 (m, 9H, H_{arom}). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 22.3 (2 x-CH_3); 24.5 (CH_3); 37.5 (CH_2); 69.9 (C^q), 70.2 (CH_2); 111.9 (CH_{arom}); 120.9 (CH_{arom}); 124.6 (CH_{arom}); 127.4 (CH_{arom}); 127.5 (2 x CH_{arom}); 127.9 (2 x CH_{arom}+(C^q_{arom}-C)); 128.6 (2 x CH_{arom}); 137.1 (C^q_{arom}-

O); 156.1 (C_2=O); 176.7 (C_4=O). IR (KBr, cm^{-1}): ν = 1722 cm^{-1} (C=O). MS (EI): *m*/*z* = 338. Anal. Calcd for $C_{20}H_{22}N_2O_3$ (338.16): C, 70.99; H, 6.55; N, 8.28. Found: C, 70.79; H, 6.41; N, 8.06%.

3-(*o*-Benzyloxy)benzyl-4-hydroxy-1,5,5-trimethylimidazolidine-2-one 20. According to the typical procedure reported above for reduction of *N*-protected imides **10a-c** and **22**, this product was obtained in 99% yield as a white-yellow solid by reduction of 3-(*o*-benzyloxy)benzyl-1,5,5-trimethylimidazolidine-2,4-dione (**19**) with 6 moles equivalent of $NaBH_4$ at room temperature for 17 h in ethanol and melted at 171 °C (ethanol); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.86 (s, 3H, CH_3); 1.02 (s, 3H, CH_3); 2.46 (s, 3H, CH_3); 3.61 (d, 1H, *J* = 7.8 Hz, CH-N); 4.25 (d, 1H, *J* = 14.9 Hz, CH(OH)); 4.30 (d, 1H, *J* = 7.8 Hz, CH-N); 4.44 (d, 1H, *J* = 14.9 Hz, CH-N, broad OH(H)); 4.90 (s, 2H, CH_2-O); 6.75-7.28 (m, 9H, H_{arom}). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 19.1 (CH_3); 23.4 (CH_3); 24.6 (CH_3); 70.6 (CH_2); 73.1 (C^q); 83.3 (CH); 85.7 (CH_2); 111.9 (CH_{arom}); 121.4 (CH_{arom}); 126.4 (C^q_{arom}-C); 127.1 (CH_{arom}); 128.3 (CH_{arom}); 128.7 (CH_{arom}); 128.8 (2xCH_{arom}); 130.2 (2xCH_{arom}); 136.7 (C^q_{arom}-C); 156.6 (C^q_{arom}-O); 158.6 (C=O). IR (KBr, cm^{-1}): ν = 3412 (OH), 1709cm^{-1} (C=O).

2,3,3*a*,9-Tetrahydro-2,3,3-trimethylimidazo[5,1-*b*][1,3]benzoxazin-1-one 6a. This product, which was identical to that described above, was obtained from the hydroxy lactam **20** and TFA (1.7 equiv.) in CH_2Cl_2 at room temperature for 12 h in 68% yield.

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