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Synthesis of the First Selenium-Containing Acyclic Nucleosides and Anomeric Spironucleosides from Carbohydrate Precursors

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We report the synthesis of acyclic and spiranic imidazole-derived *C*-selenonucleosides. 5-Hydroxy-4-tetrahydroxybutyl imidazolidine-2-selones, a novel class of acyclic selenonucleosides, were transformed into (tetrahydroxybutylimidazol-2-yl)diselenide, by acetylation and chemoselective *N*-deacetylation with methanolic imidazole. Furthermore, the synthesis of a new class of conformationally restricted *arabino*-configured spironucleosides containing an imidazolidine-2-selone unit around the glycosidic bond was achieved, starting from *N*-fructosamines, via 4-hydroxy-4-tetrahydoxybutyl-imidazolidine-2-selones as the key intermediates. Acetylation–deacetylation of these intermediates gave access to stable aromatic imidazoline-2-selones.

Introduction

Nucleoside analogues have proved to exhibit important pharmacological properties, especially as antiviral,[1] antitumor,[2] and antifungal agents.[3] Recent modifications of the nucleoside structure consist of the introduction of a selenium atom, an essential trace element,[4] either by replacing the endocyclic oxygen atom of the carbohydrate residue[5] or as part of the nucleobase.[6–8] The incorporation of 6-selenoguanosine[9] and 4-selenothymidine[10] into DNA to study nucleic acid base pairing by X-ray and for DNA visualization, respectively, has also been described. Furthermore, a series of selenium-containing nucleosides and oligonucleotides have been used for convenient phasing of X-ray crystallographic data.[11–13] Some methylseleno nucleosides were found to inhibit prostatic cancer cells growth.[14] Selenium has not been found in DNA, although its presence in natural uridines from tRNAs has been documented.[15]

Although the synthesis of acyclic nucleosides[1b,16] has generated much interest due to their potent biological activities, no selenium-containing acyclic nucleosides have been reported up to now. The chemistry of organoselenium compounds has been developed to a significant small extent because of the intrinsic instability[17] of some of these compounds. We have devoted our efforts in developing strategies to reach, from carbohydrates, stable and versatile organoselenium templates.[18] In this communication we have explored the access to chiral 2-seleno-1,3-*N*-heterocyclic templates, an attractive challenge from both synthetic and biological points of view.

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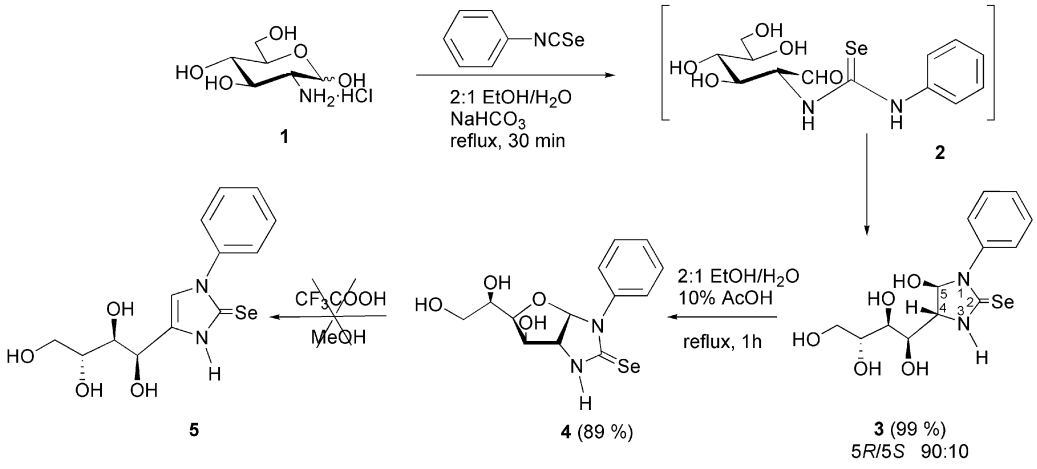
Results and Discussion

Reaction of phenyl isoselenocyanate[18] with D-glucosamine hydrochloride in aqueous ethanol in the presence of $NaHCO_3$ afforded 5-hydroxy-4-polyhydroxyalkylimidazolidine-2-selone **3** in a high yield of 99% after column chromatography (Scheme 1). This reaction must be carried out in the dark, as many selenium-containing compounds undergo UV-induced decomposition.[19]

The reaction might proceed via nondetected selenourea **2**, which could undergo spontaneous cyclization through the carbonyl group of the open chain form to give imidazolidine-2-selone by a 5-*exo*-*trig* cyclization, according to Baldwin's[20] rules. NMR spectroscopic data showed **3** to exist as a nonresolved mixture of 5*R*/5*S* diastereoisomers, in a 90:10 ratio, measured by ^{1}H NMR spectroscopy. The assignment of the 5*R* configuration for the major diastereoisomer was based on the $J_{4,5}$ coupling constant (3.1 Hz), indicating that both protons are in a *trans* arrangement, whereas for the 5*S* derivatives the *J* value was 7.4 Hz, with 4-H and 5-H in a *cis* relationship.

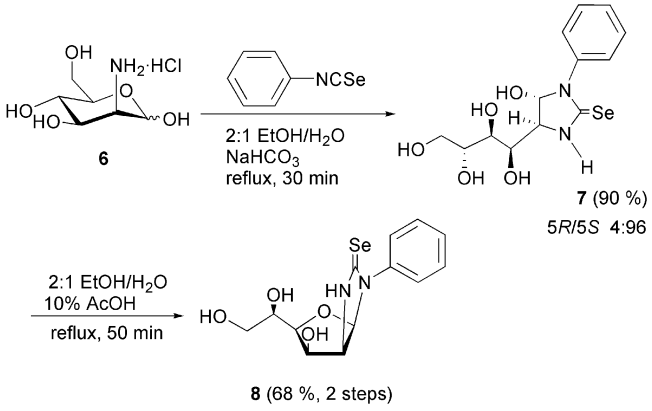
Acid-catalyzed dehydration of **3** with AcOH in a refluxing EtOH/water mixture afforded bicyclic glucofuranosoimidazolidine-2-selone **4** in 89% yield (Scheme 1). The synthesis of **4** was previously reported,[21] but without the isolation of parent selone **3**. Attempts to convert bicyclic derivative **4** into corresponding aromatic imidazoline-2-selone **5** by dehydration under strong acid conditions were



Scheme 1.

unsuccessful, and precipitation of elemental selenium was observed. It has been reported that acidic treatment of a series of selenocarbamates leads to decomposition with the release of elemental selenium.[22]

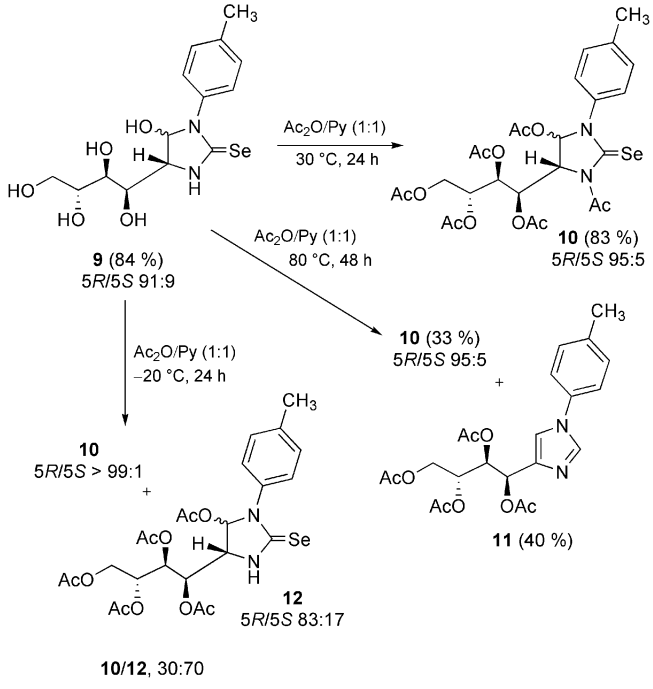
The same reactions were carried out with the use of D-mannosamine hydrochloride and phenyl isoselenocyanate (Scheme 2). In this case, 5-hydroxyimidazolidine-2-selone **7** was obtained in a 90% yield, after chromatographic purification. As indicated above for the D-*gluco*-configured epimer, the ^{1}H NMR spectrum showed the existence of two diastereoisomers at the 5-position in a 5*R*/5*S* ratio of 4:96.



Scheme 2.

Acyclic *C*-pseudonucleoside **7** was subjected, in a one-pot fashion, to acidic treatment to give corresponding bicyclic mannofuranosoimidazolidine-2-selone **8** in 68% yield for the two steps (Scheme 2). The furanoid structure of **8** was evidenced by the observed $J_{1,2}$ and $J_{2,3}$ coupling constants (6.9 and 6.6 Hz, respectively), which are in agreement with the data reported for the only example of a *manno*-configured glycofuranosoimidazolidine-2-one.[23]

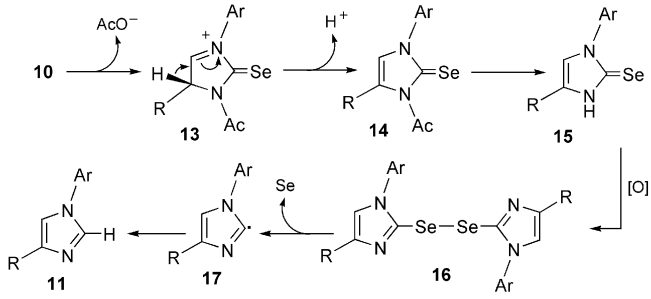
We studied the acetylation of the polyhydroxyalkylimidazolidine-2-selone template; reactions were conducted in a 1:1 Ac_2O/Py mixture at different temperatures and reaction times, leading to different products, as depicted in Scheme 3. We chose **9** as a model compound, obtained by coupling of D-glucosamine hydrochloride **1** and *p*-methylphenyl isoselenocyanate (84% yield), following the same conditions as those used to prepare compound **3**. We observed that at 30 °C for 24 h, the acetylation reaction took place at both the hydroxy groups and the NH group of the heterocyclic moiety to furnish **10** in 83% yield. Moreover, when the acetylation reaction was carried out at 80 °C for 48 h, we obtained a separable mixture of **10** (33%) and imidazole **11** (40%). Imidazoline-2-selone **15** (Scheme 4) was not detected in the mixture.



Scheme 3.

Imidazole **11** could be formed as indicated in Scheme 4, by air oxidation of **15** to give the corresponding transient diselenide **16**, followed by loss of selenium as the key steps. Spontaneous oxidation of imidazoline-2-selone to diselenide has been reported.[24] Imidazole-based compounds are

attractive targets[25] because of their roles in several biological processes,[26] applications in coordination chemistry,[27] and also as an extracellular pH indicator for ^{1}H NMR spectroscopic imaging.[28] Imidazolyl alditols have also been used for the preparation of imidazolo sugars, studied as potential glycosidase inhibitors.[29]



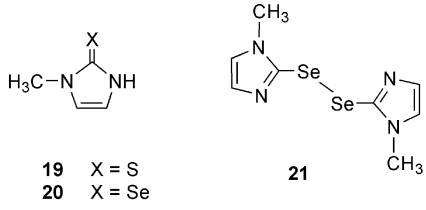
Scheme 4.

When the temperature of the acetylation reaction was decreased to –20 °C, and the acetylation was performed for 24 h (Scheme 3), we obtained a 30:70 mixture of compound **10** (5*R*/5*S* > 99:1) and penta-*O*-acetylated derivative **12** (5*R*/5*S*, 83:17).

Attempts to carry out the chromatographic separation of compounds **10** and **12** on silica gel chromatography led to extensive decomposition, and pure diselenide **16** was isolated as a minor compound (8%). This result demonstrates the higher stability of hexaacetylated derivative **10** in comparison with pentaactylated compound **12**, as the former does not undergo decomposition under chromatographic purification.

We have recently reported a new procedure for the chemoselective *N*-deacetylation of carbohydrate derivatives based on the use of methanolic imidazole.[30] Treatment of the crude mixture of **10** and **12** with methanolic imidazole as a mild base furnished not the expected pentaacetylated derivative **12** but diselenide **16** in a 66% yield (Scheme 5). In compound **12**, the delocalization of the lone pair on N-3 to the selone moiety allows N-1 to contribute more efficiently to the loss of the acetoxy group at C-5. Therefore, we postulate that methanolic imidazole allows conversion of **10** into **12**, which easily undergoes loss of acetic acid to give transient imidazoline-2-selone **15** (Scheme 5). Spontaneous air-promoted oxidation of **15** affords symmetrical diselenide **16** in acceptable yield (66%) after chromatographic purification.

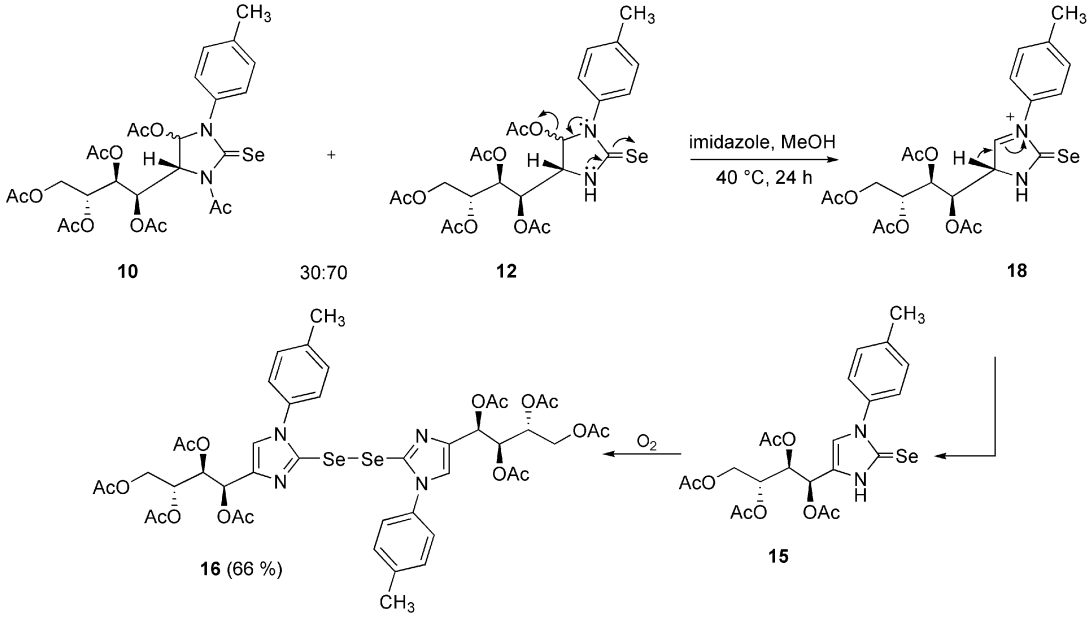
A series of dialkyl and diaryl diselenides were synthesized and found to possess gluthatione-peroxidase-like activity, and thus, are good candidates as antioxidants;[31] for example, diphenyl diselenide is known to be an antioxidant, anti-inflammatory, antinociceptive, and anxyolytic agent.[32] Furthermore, **20**,[24] the selenium isoster of methimazole **19**, one of the most widely used drugs for the treatment of hyperthyroidism, also shows antithyroid activity. Compound **20** is spontaneously oxidized to diselenide **21**, which in turn can be reduced again to selone **20**, so acting as a reversible inhibitor.[33] The inhibitory activity of **20** is due to the reduction of H_2O_2, needed for the first step of the biosynthesis of the thyroid hormone.[34]



19 X = S
20 X = Se

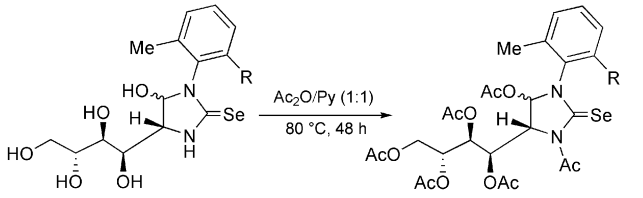
21

In order to check the influence of bulky substituents on the *ortho* positions of the aromatic ring in the acetylation reaction of 5-hydroxyimidazolidine-2-selones, at 80 °C we



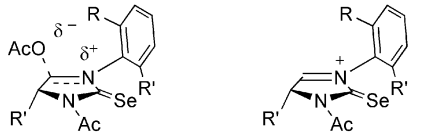
Scheme 5.

acetylated **22** and **23**, obtained from D-glucosamine and the corresponding *o*,*o*′-dialkylphenyl isoselenocyanates (Scheme 6). Surprisingly, no imidazole-derived compounds were obtained, but hexaacetylated imidazolidine-2-selones **24** and **25** (96 and 84%), as a mixture of the 5*R*/5*S* diastereoisomers in a ratio higher than 99:1. Furthermore, the existence of bulky substituents in the *o*,*o*′-positions of the aromatic ring restricts the free rotation of the aromatic ring, giving rise to the presence of atropisomers in the NMR spectra (52:48 and 56:44, respectively for the *5R* diastereoisomers of **24** and **25**).



Scheme 6.

The high steric hindrance in transition state **26** that would furnish cation **27** avoids the loss of the acetoxy group on C-5 (Figure 1), so the corresponding imidazole derivative is not formed; therefore, hexaacetylated derivatives **24** and **25** are obtained in good yields, in comparison with the reaction undergone by *N*-tolyl derivative **9**.

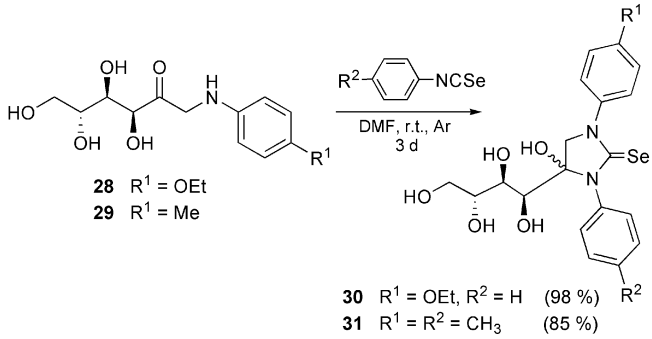


26 **27**

Figure 1. Transition states and intermediates that might be involved in C-5 deacylation of **24** and **25**.

We also investigated the reaction of *N*-arylfructosamines **28** and **29**[35] with phenyl and *p*-tolyl isoselenocyanates, respectively, in DMF at room temperature to afford the corresponding 4-hydroxy-4-polyhydroxyalkylimidazolidine-2-selones **30** and **31** (Scheme 7) in excellent yields after chromatographic purification (98 and 85%, respectively). As previously indicated for the synthesis of 5-hydroxyimidazolidine-2-selones, the reaction must involve a nondetected selenourea that undergoes intramolecular cyclization to give **30** and **31** as a nonresolved mixture of diastereoisomers at C-4 (96:4 and 91:9 ratio, respectively), a diastereoselectivity similar to that found for the 5-hydroxy analogues described above. We could not carry out the unequivocal assignment of the C-4 configuration for compounds **30** and **31**.

Acetylation of imidazolidine-2-selones **30** and **31** provoked aromatization of the heterocyclic moiety ring to give tetra-*O*-acetylated imidazolines **36** and **37** (98 and 83%, respectively). The formation of these derivatives arises from the loss of acetic acid, presumably through stabilized cations **34** and **35** (Scheme 8). ^{1}H and ^{13}C NMR resonances

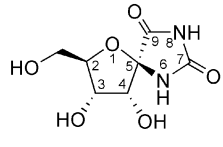


Scheme 7.

at 7.04 ppm (*H*C=) and 160.9–161.1 ppm (C=Se) are consistent with imidazoline-2-selones motifs.[36] Subsequent deacylation gave stable **38** and **39**, acyclic *C*-nucleosides of the imidazoline-2-selone type, in 77 and 91% yield, respectively. *N*,*N*′-Disubstituted imidazoline-2-selones, used in industry as catalysts for the preparation of epoxy resins,[37] were prepared by reaction of nucleophilic carbenes with elemental selenium.[38] *N*,*N*′-Disubstituted imidazoline-2-selones **36**–**39** showed higher stability than *N*-substituted analogue **15**, which is nondetected because of its fast oxidation to imidazol-2-yl diselenide **16**.

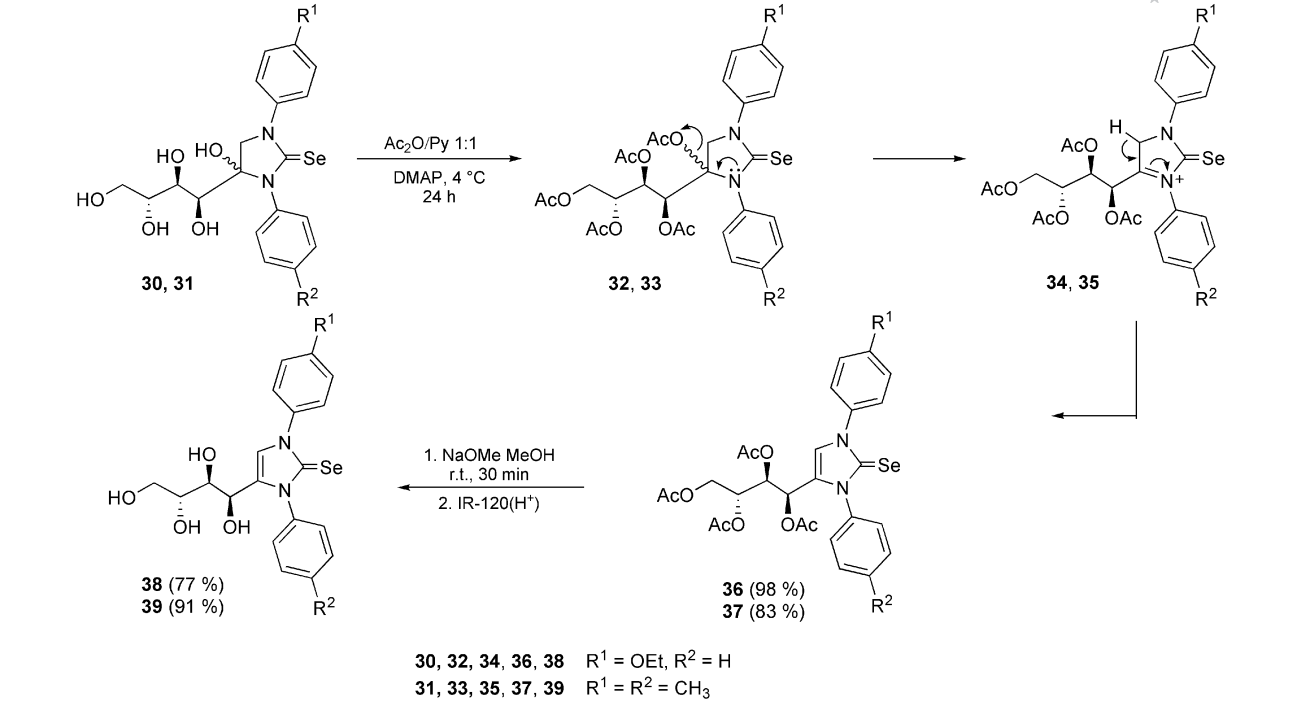
4-Hydroxyimidazolidine-2-selones **30** and **31** underwent dehydration under weak acidic conditions to give a separable mixture of imidazoline-2-selones **38** and **39** (39 and 31% yield, respectively) as minor compounds (Scheme 9), together with the major spiranic derivatives **42** and **43** (60 and 54%, respectively), whose NMR showed signals for a mixture of diastereoisomers on the spiranic carbon C-5 in a 86:14 ratio for **42**, and 89:11 ratio for **43**.

The key synthetic intermediates are stabilized cations **40** and **41** (Scheme 9), obtained by protonation of the hydroxy group on C-4 and subsequent loss of a water molecule. Loss of the proton on C-5 (pathway a) furnished imidazoline-2-selones **38** and **39**, whereas nucleophilic attack of the hydroxy group on C-3′ of the polyhydroxyalkyl chain (pathway b) yielded *arabino*-configured spiranic derivatives **42** and **43**. These derivatives represent the first described selenium-containing spironucleosides, with the additional interest of containing an imidazoline-2-selone unit in a fixed conformation around the glycosidic bond, quite resembling the heterocyclic moiety of (+)-hydantocidin. Hydantocidin, the first natural spironucleoside described,[39] was found to be a plant growth regulator and a potent herbicide, without exerting toxicity to mammals.[40] Since then, many structurally related spiro compounds have been prepared.[41]

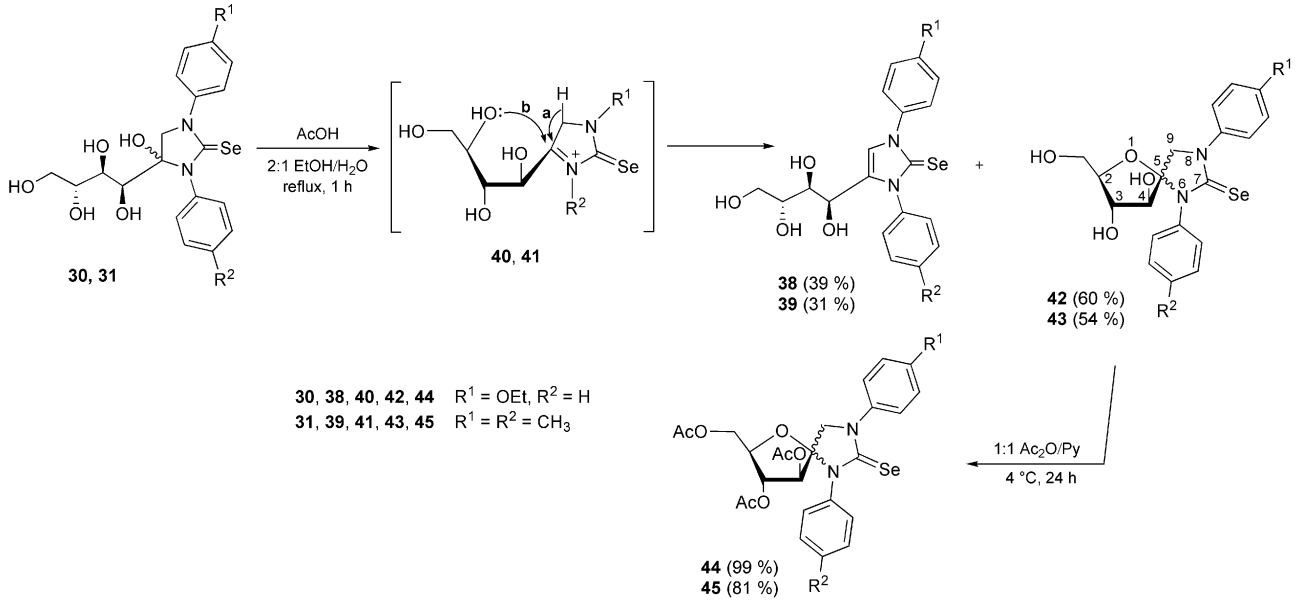


(+)-Hydantocidin

Acetylation of **42** and **43** afforded per-*O*-acetylated derivatives **44** and **45** as a nonresolved mixture of diastereoiso-



Scheme 8.



Scheme 9.

mers on C-5, with the same chromatographic mobility (Scheme 9). Resonances of C-5 (98.7, 100.5 ppm) confirm their spiranic structure.

The major diastereoisomer of nonacetylated derivatives **42** and **43** exhibit high vicinal coupling constants, indicating an almost antiperiplanar disposition of the protons, and thus, confirming the ^3E conformation of the furanoid ring as the major one in solution (Figure 2). The same conclusion can be reached for both, the major ($J_{2,3}$ = 7.4 Hz; $J_{3,4}$ = 7.1, 7.2 Hz) and the minor isomers ($J_{2,3}$ = 7.9, 8.2 Hz; $J_{3,4}$ = 8.1, 8.3 Hz) of acetylated derivatives **44** and **45** (Figure 2).

NOESY experiments on the diastereoisomeric mixture of **44** allowed the unequivocal assignment of the spiranic C-5 configuration. For the major *S* diastereoisomer, strong cross peak correlations were observed between 3-H, 9a-H, and 9b-H. The 5*R* configuration of the minor diastereoisomer was confirmed by a strong cross peak correlation between 4-H and 9a-H.

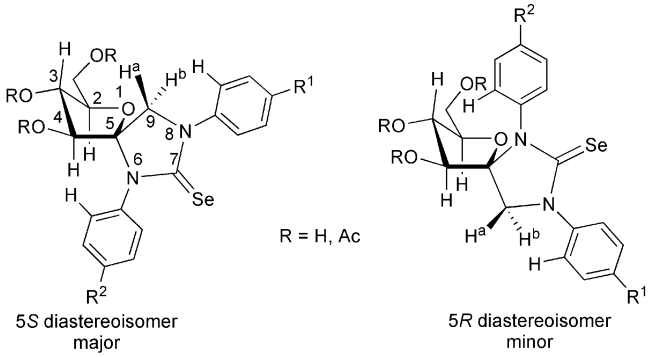


Figure 2. Conformational preferences for compounds **42**–**45**.

Conclusions

In conclusion, the coupling of aryl isoselenocyanates with reducing amino sugars gives access to 5-hydroxy-4-polyhydroxyalkylimidazolidine-2-selones, the acetylation of which allows the synthesis of (polyhydroxyalkylimidazol-2-yl)diselenides, a novel type of acyclic *C*-selenonucleosides. Furthermore, reaction of aryl isoselenocyanates with *N*-arylfructosamines furnishes *N*,*N*′-disubstituted 4-hydroxy-4-polyhydroxyalkylimidazolidine-2-selones, a key intermediate, which can be transformed into stable aromatic imidazoline-2-selones by acetylation or into *arabino*-configured spiranic imidazole-*C*-selenonucleosides upon acid-catalyzed dehydration.

Experimental Section

(4*R*,5*R*/5*S*)-5-Hydroxy-1-phenyl-4-(D-*arabino*-tetritol-1-yl)imidazolidine-2-selone (3): A suspension of D-glucosamine hydrochloride (141 mg, 0.65 mmol), phenyl isoselenocyanate (143 mg, 0.78 mmol, 1.2 equiv.), and $NaHCO_3$ (55 mg, 0.65 mmol) in EtOH/H_2O (2:1, 9 mL) was heated at reflux in the dark for 30 min. Then, the mixture was concentrated to dryness, and the residue was purified by column chromatography (CH_2Cl_2→CH_2Cl_2/MeOH, 5:1) to afford **3** as a syrup. Yield: 221 mg, 99% (5*R*/5*S*, 90:10). R_f = 0.24 (CH_2Cl_2/MeOH, 5:1). $[\alpha]_D^{26}$ = +17 (*c* = 0.8, CH_3OH). Data for the major diastereoisomer: ^{1}H NMR (300 MHz, CD_3OD): δ = 7.47–7.36 (m, 5 H, Ar-H), 5.53 (d, $J_{4,5}$ = 3.1 Hz, 1 H, 5-H), 3.95 (dd, $J_{4,1'}$ = 6.1 Hz, $J_{1',2'}$ = 1.6 Hz, 1 H, 1′-H), 3.89 (dd, 1 H, 4-H), 3.81 (dd, $J_{3',4a'}$ = 2.9 Hz, $J_{4a',4b'}$ = 10.6 Hz, 1 H, 4a′-H), 3.72 (ddd, $J_{2',3'}$ = 8.3 Hz, $J_{3',4b'}$ = 5.5 Hz, 1 H, 3′-H), 3.67 (dd, 1 H, 4b′-H), 3.59 (dd, 1 H, 2′-H) ppm. ^{13}C NMR (75.5 MHz, CD_3OD): δ = 178.9 (C=Se), 140.3, 129.7, 128.8 (Ar), 90.2 (C-5), 72.7 (C-3′), 72.3 (C-2′), 70.9 (C-1′), 68.4 (C-4), 64.8 (C-4′) ppm. Data for the minor diastereoisomer: ^{1}H NMR (300 MHz, CD_3OD): δ = 5.60 (d, $J_{4,5}$ = 7.3 Hz, 1 H, 5-H), 4.33 (d, $J_{4,1'}$ = 7.8 Hz, 1 H, 1′-H), 4.14 (t, 1 H, 4-H), 3.57 (m, 1 H, 2′-H) ppm. ^{13}C NMR (75.5 MHz, CD_3OD): δ = 179.4 (C=Se), 87.3 (C-5) 73.1 (C-3′), 72.8 (C-2′), 68.8 (C-1′), 63.2 (C-4), 58.3 ppm. MS (FAB): *m*/*z* (%) = 385 (77) $[M + Na]^+$. HRMS (FAB): calcd. for $C_{13}H_{18}N_2NaO_5{}^{80}Se$ $[M + Na]^+$ 385.0279; found 385.0277.

1-Phenyl-(1,2-dideoxy-α-D-mannofuranoso)[2,1-*d*]imidazolidine-2-selone (8): A suspension of D-mannosamine hydrochloride (129 mg, 0.60 mmol), phenyl isoselenocyanate (136 mg, 0.75 mmol, 1.25 equiv.), and $NaHCO_3$ (50 mg, 0.60 mmol) in EtOH/H_2O (8 mL, 2:1) was heated at reflux in the dark for 30 min. Then, AcOH (0.8 mL) was added, and the corresponding solution was heated at reflux for 50 min. The reaction mixture was concentrated to dryness coevaporating with EtOH, and the residue was purified by column chromatography (CH_2Cl_2→CH_2Cl_2/MeOH, 10:1) to give **8**. Yield: 142 mg, 68%, R_f = 0.5 (CH_2Cl_2/MeOH, 5:1). $[\alpha]_D^{26}$ = –110 (*c* = 0.6, DMSO). IR: $\tilde{\nu}$ = 3416, 1647, 1507, 698 cm^{-1}. ^{1}H NMR [300 MHz, $(CD_3)_2SO$]: δ = 9.41 (s, 1 H, NH), 7.70–7.38 (m, 5 H, Ar-H), 5.83 (d, $J_{1,2}$ = 6.9 Hz, 1 H, 1-H), 5.48 (d, $J_{H,OH}$ = 5.1 Hz, 1 H, OH-3), 4.70 (d, $J_{H,OH}$ = 3.3 Hz, 1 H, OH-5), 4.46 (t, $J_{H,OH}$ = 5.7 Hz, 1 H, OH-6), 4.42 (m, $J_{2,3}$ = 6.6 Hz, 1 H, 3-H), 4.37 (t, 1 H, 2-H), 3.74 (m, 2 H, 4-H, 5-H), 3.52 (ddd, $J_{5,6a}$ = 4.8 Hz, $J_{6a,6b}$ = 11.1 Hz, 1 H, 6a-H), 3.32 (m, 1 H, 6b-H) ppm. ^{13}C NMR [75.5 MHz, $(CD_3)_2SO$]: δ = 178.2 (C=Se), 139.4, 128.4, 126.7, 126.6 (Ar), 94.5 (C-1), 78.7 (C-4), 71.6 (C-3), 69.8 (C-5), 63.3 (C-6), 62.4 (C-2) ppm. MS (FAB): *m*/*z* (%) = 367 (23) $[M + Na]^+$. $C_{13}H_{16}N_2O_4Se$ (343.24): calcd. C 45.49, H 4.70, N 8.16; found C 45.13, H 4.62, N 8.24.

1-(*p*-Methylphenyl)-4-(1,2,3,4-tetra-*O*-acetyl-D-*arabino*-tetritol-1-yl)imidazole (11): A solution of **9** (75 mg, 0.20 mmol) in Ac_2O/Py (1:1, 2.0 mL) was kept in the dark at 80 °C for 48 h. Then, the mixture was concentrated to dryness coevaporating with toluene and EtOH, and the residue was purified by column chromatography (CH_2Cl_2→CH_2Cl_2/MeOH, 40:1) to give compounds **10** (42 mg, 33%) and **11**. The latter was crystallized from EtOH to give a white solid. Yield: 35 mg, 40%. M.p. 126–128 °C. R_f = 0.38 (CH_2Cl_2/MeOH, 40:1). $[\alpha]_D^{20}$ = –25 (*c* = 1.1, CH_2Cl_2). IR: $\tilde{\nu}$ = 1745, 1520, 1221, 819 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74 (d, $J_{2,5}$ = 1.2 Hz, 1 H, 2-H), 7.25 (m, 5 H, 5-H, Ar-H), 6.15 (d, $J_{1',2'}$ = 5.2 Hz, 1 H, 1′-H), 5.74 (dd, $J_{2',3'}$ = 6.8 Hz, 1 H, 2′-H), 5.28 (td, $J_{3',4a'}$ = 3.0 Hz, $J_{3',4b'}$ = 6.0 Hz, 1 H, 3′-H), 4.29 (dd, $J_{4a',4b'}$ = 12.3 Hz, 1 H, 4a′-H), 4.14 (dd, 1 H, 4b′-H), 2.39 (s, 3 H, CH_3Ar), 2.10, 2.08, 2.07, 2.04 (4 s, 3 H each, 4 OAc) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 170.8, 170.2, 170.0, 169.7 (4 CO), 138.4 (C-4), 137.9 (Ar-C), 135.9 (C-2), 134.7 (Ar-C), 130.6, 121.5 (Ar-CH), 117.4 (C-5), 71.3 (C-2′), 69.2 (C-3′), 67.8 (C-1′), 62.0 (C-4′), 21.1 (CH_3Ar), 21.1, 20.9 (×2), 20.8 (4 CH_3CO) ppm. MS (CI): *m*/*z* (%) = 447 (33) $[M + H]^+$. HRMS (CI): calcd. for $C_{22}H_{27}N_2O_8$ $[M + H]^+$ 447.1767; found 447.1774. $C_{22}H_{26}N_2O_8$ (446.45): calcd. C 59.19, H 5.87, N 6.27; found C 59.10, H 5.89, N 6.38.

Bis[1-(*p*-methylphenyl)-4-(1,2,3,4-tetra-*O*-acetyl-D-*arabino*-tetritol-1-yl)imidazol-2-yl]diselenide (16)

Method A: A solution of **9** (248 mg, 0.66 mmol) in Ac_2O/Py (1:1, 4 mL) was kept in the dark at –20 °C for 30 h. Then, the mixture was poured over water–ice and diluted with CH_2Cl_2. The organic layer was separated, washed with 1 M HCl, saturated aqueous $NaHCO_3$ and H_2O, dried with $MgSO_4$, filtered, and concentrated to dryness to give a 70:30 mixture (357 mg) of pentaacetylated derivative **12** and hexaacetylated derivative **10**. Chromatographic separation (CH_2Cl_2/MeOH, 80:1→40:1) led to extensive decomposition, and the title diselenide was isolated as a minor compound (28 mg, 8%).

Method B: To the crude mixture of compounds **10**/**12** (30:70, 52 mg, 0.09 mmol overall) in MeOH (4 mL) was added imidazole (6 mg, 0.09 mmol), and the corresponding mixture was kept in the dark at 40 °C for 24 h. Then, the mixture was concentrated to dryness, and the residue was purified by column chromatography (CH_2Cl_2/MeOH, 80:1→40:1) to give **16** as a syrup. Yield: 30 mg, 66%. R_f = 0.26 (CH_2Cl_2/MeOH, 40:1). $[\alpha]_D^{20}$ = +10 (*c* = 1.2, CH_2Cl_2). IR: $\tilde{\nu}$ = 1745, 1459, 1218 cm^{-1}. ^{1}H NMR (500 MHz,

$CDCl_3$): δ = 7.12 (m, 3 H, 5-H, Ar-H), 6.91 (m, 2 H, Ar-H), 6.19 (d, $J_{1',2'}$ = 4.3 Hz, 1 H, 1′-H), 5.65 (dd, $J_{2',3'}$ = 7.5 Hz, 1 H, 2′-H), 5.25 (ddd, $J_{3',4a'}$ = 2.9 Hz, $J_{3',4b'}$ = 5.7 Hz, 1 H, 3′-H), 4.23 (dd, $J_{4a',4b'}$ = 12.4 Hz, 1 H, 4a′-H), 4.10 (dd, 1 H, 4b′-H), 2.38 (s, 3 H, C*H*$_3$Ar), 2.11, 2.07, 2.04, 2.03 (4 s, 3 H each, 4 Ac) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 170.8, 170.1, 170.0, 169.6 (4 CO), 139.3 (C-4), 139.1 (C-2), 135.1, 133.4, 129.8, 126.5 (Ar), 123.9 (C-5), 71.0 (C-2′), 69.0 (C-3′), 67.4 (C-1′), 62.1 (C-4′), 21.3 (*C*H$_3$Ar), 21.1, 21.0, 20.9, 20.9 (4 *C*H$_3$CO) ppm. MS (LSI): *m*/*z* (%) = 1051 (7) [M + H]$^+$. HRMS (LSI): calcd. for $C_{44}H_{51}N_4O_{16}{}^{80}Se_2$ [M + H]$^+$ 1051.1630; found 1051.1674.

(4*R*/4*S*)-1-*p*-Ethoxyphenyl-4-hydroxy-3-phenyl-4-(D-*arabino*-tetritol-1-yl)imidazolidine-2-selone (30): To a solution of phenyl isoselenocyanate (100 mg, 0.55 mmol) in DMF (8 mL) was added 1-deoxy-1-*p*-ethoxyphenylamino-D-fructose (**28**,[35] 164 mg, 0.55 mmol), and the resulting mixture was kept in the dark at room temperature for 3 d. Then, the mixture was concentrated to dryness, and the residue was purified by column chromatography (CH_2Cl_2/MeOH, 40:1→10:1) to give **30** as an amorphous solid. Yield: 260 mg, 98% (4*R*/4*S*, 96:4). R_f = 0.20 (CH_2Cl_2/MeOH, 10:1). $[\alpha]_D^{20}$ = +1 (*c* = 0.8, MeOH). IR: $\tilde{\nu}$ = 3283, 1602, 1515, 1242, 1036 cm^{-1}. Data for the major diastereoisomer: ^{1}H NMR (300 MHz, CD_3OD): δ = 7.44 (m, 2 H, Ar-H), 7.43 (m, 5 H, Ar-H), 6.95 (m, 2 H, Ar-H), 4.74 (d, $J_{5a,5b}$ = 12.4 Hz, 1 H, 5a-H), 4.07 (q, $J_{H,H}$ = 7.0 Hz, 2 H, C*H*$_2$CH$_3$), 3.84 (d, 1 H, 5b-H), 3.81 (br. d, $J_{2',3'}$ = 8.1 Hz, 1 H, 2′-H), 3.80 (br. s, 1 H, 1′-H), 3.72 (dd, $J_{3',4a'}$ = 3.7 Hz, $J_{4a',4b'}$ = 10.6 Hz, 1 H, 4a′-H), 3.58 (ddd, $J_{3',4b'}$ = 5.8 Hz, 1 H, 3′-H), 3.53 (dd, 1 H, 4b′-H), 1.40 (t, 3 H, CH$_2$C*H*$_3$) ppm. ^{13}C NMR (75.5 MHz, CD_3OD): δ = 180.7 (CSe), 159.5, 139.2, 135.3 (Ar-C), 132.4, 129.5, 129.3, 129.3, 115.7 (Ar-CH), 95.1 (C-4), 73.0 (C-3′), 71.6 (C-2′), 69.8 (C-1′), 64.9 (C-4′), 64.8 (*C*H$_2$CH$_3$), 61.7 (C-5), 15.1 (CH$_2$*C*H$_3$) ppm. Data for the minor diastereoisomer: ^{1}H NMR (300 MHz, CD_3OD): δ = 4.97 (d, $J_{5a,5b}$ = 11.7 Hz, 1 H, 5a-H) ppm. MS (LSI): *m*/*z* (%) = 483 (48) [M + H]$^+$. HRMS (LSI): calcd. for $C_{21}H_{27}N_2O_6{}^{80}Se$ [M + H]$^+$ 483.1034; found 483.1031.

1-*p*-Ethoxyphenyl-3-phenyl-4-(D-*arabino*-tetritol-1-yl)imidazoline-2-selone (38): To a solution of **36** (176 mg, 0.28 mmol) in dry MeOH (5 mL) was added NaOMe (15.1 mg, 0.28 mmol), and the reaction mixture was kept in the dark at room temperature for 30 min. Then, IR-120(H$^+$) Amberlite resin was added up to neutral pH, which was then washed with hot MeOH, and the solution was concentrated to dryness. The residue was purified by column chromatography (CH_2Cl_2/MeOH, 20:1) to give **38** as an amorphous solid. Yield: 99 mg, 77%. R_f = 0.63 (CH_2Cl_2/MeOH, 5:1). $[\alpha]_D^{20}$ = –38 (*c* = 1.1, MeOH). IR: $\tilde{\nu}$ = 3345, 1600, 1507, 1245, 1038, 830 cm^{-1}. ^{1}H NMR (300 MHz, CD_3OD): δ = 7.59–7.41 (m, 7 H, Ar-H), 7.45 (br. s, 1 H, 5-H), 7.04 (m, 2 H, Ar-H), 4.69 (br. d, $J_{1',2'}$ = 1.8 Hz, 1 H, 1′-H), 4.11 (q, $J_{H,H}$ = 7.0 Hz, 2 H, C*H*$_2$CH$_3$), 3.69 (dd, $J_{3',4a'}$ = 2.8 Hz, $J_{4a',4b'}$ = 10.4 Hz, 1 H, 4a′-H), 3.59 (ddd, $J_{2',3'}$ = 8.1 Hz, $J_{3',4b'}$ = 5.3 Hz, 1 H, 3′-H), 3.55 (dd, 1 H, 4b′-H), 3.50 (dd, 1 H, 2′-H), 1.42 (t, 3 H, CH$_2$C*H*$_3$) ppm. ^{13}C NMR (75.5 MHz, CD_3OD): δ = 160.6 (CSe), 157.9, 136.5, 133.1 (Ar-C), 138.7 (C-4), 130.5, 130.4, 130.2, 129.0, 115.8 (Ar-CH), 121.8 (C-5), 73.8 (C-2′), 72.4 (C-3′), 65.3 (C-1′), 64.9 (*C*H$_2$CH$_3$), 64.8 (C-4′), 15.1 (CH$_2$*C*H$_3$) ppm. MS (LSI): *m*/*z* (%) = 465 (25) [M + H]$^+$. HRMS (LSI): calcd. for $C_{21}H_{25}N_2O_5{}^{80}Se$ [M + H]$^+$ 465.0929; found 465.0926. $C_{21}H_{24}N_2O_5Se{\cdot}H_2O$ (481.40): calcd. C 52.39, H 5.44, N 5.82; found C 52.45, H 5.20, N 5.96.

(2*R*,3*S*,4*S*,5*R*/5*S*)-3,4-Diacetoxy-2-acetoxymethyl-8-(*p*-ethoxyphenyl)-6-phenyl-7-selenoxo-1-oxa-6,8-diazaspiro[4.4]nonane (44): A solution of **42** (40 mg, 0.086 mmol) in Ac_2O/Py (1:1, 2 mL) was kept in the dark at 4 °C for 24 h. Then, the mixture was concentrated to dryness coevaporating with toluene and EtOH, and the residue was purified by column chromatography (CH_2Cl_2) to give **44**. Yield: 50 mg, 99% (5*R*/5*S*, 14:86). R_f = 0.45 (CH_2Cl_2/MeOH, 40:1). IR: $\tilde{\nu}$ = 1749, 1598, 1507, 1229, 1047, 832 cm^{-1}. Data for the major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52–7.38 (m, 7 H, Ar-H), 6.95 (m, 2 H, Ar-H), 5.57 (d, $J_{3,4}$ = 7.1 Hz, 1 H, 4-H), 5.13 (t, $J_{2,3}$ = 7.4 Hz, 1 H, 3-H), 4.40 (d, $J_{9a,9b}$ = 12.0 Hz, 1 H, 9a-H), 4.23 (dd, J_{2,H^a} = 3.1 Hz, J_{H^a,H^b} = 12.3 Hz, 1 H, C*H*^{a}H^{b}OAc), 4.10 (dd, 1 H, J_{2,H^b} = 4.4 Hz, CH^a*H*^{b}OAc), 4.06 (d, 1 H, 9b-H), 4.05 (q, 2 H, $J_{H,H}$ = 7.0 Hz, C*H*$_2$CH$_3$), 3.99 (ddd, 1 H, 2-H), 2.18, 2.10, 1.89 (3 s, 3 H each, 3 Ac), 1.42 (t, 3 H, CH$_2$C*H*$_3$) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 183.1 (CSe), 170.4, 170.2, 169.2 (3 CO), 158.5, 137.0, 132.9 (Ar-C), 131.6, 129.6, 129.5, 127.9, 115.0 (Ar-CH), 99.1 (C-5), 77.0 (C-2), 75.7 (C-4), 74.0 (C-3), 63.9 (*C*H$_2$CH$_3$), 62.7 (CH$_2$OAc), 60.3 (C-9), 20.9 (×2), 20.6 (3 *C*H$_3$CO), 15.0 (CH$_2$*C*H$_3$) ppm. Data for the minor diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.51 (d, $J_{3,4}$ = 8.1 Hz, 1 H, 4-H), 4.67 (t, $J_{2,3}$ = 7.9 Hz, 1 H, 3-H), 4.41 (d, $J_{9a,9b}$ = 11.9 Hz, 1 H, 9a-H), 4.21 (d, 1 H, 9b-H), 4.12 (q, $J_{H,H}$ = 7.0 Hz, 2 H, C*H*$_2$CH$_3$), 4.07 (m, 1 H, 2-H), 3.98 (m, 1 H, C*H*^{a}H^{b}OAc), 3.81 (dd, J_{2,H^b} = 7.4 Hz, J_{H^a,H^b} = 11.9 Hz, 1 H, CH^a*H*^{b}OAc), 2.18, 2.06, 2.01 (3 s, 3 H each, 3 Ac), 1.41 (t, 3 H, CH$_2$C*H*$_3$) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 132.2, 129.0, 128.1, 127.9, 115.0 (Ar-CH), 78.4 (C-4), 76.3 (C-2), 73.1 (C-3), 63.6 (CH$_2$OAc), 63.0 (C-9), 20.8, 20.7, 20.6 (3 *C*H$_3$CO), 14.6 (CH$_2$*C*H$_3$) ppm. MS (LSI): *m*/*z* (%) = 591 (48) [M + H]$^+$. HRMS (LSI): calcd. for $C_{27}H_{31}N_2O_8{}^{80}Se$ [M + H]$^+$ 591.1246; found 591.1239.

Supporting Information (see footnote on the first page of this article)**:** General methods, syntheses, and structural characterization for compounds **7**, **9**, **10**, **12**, **22**–**25**, **31**, **36**, **37**, **39**, **42**–**44**; ^{1}H and ^{13}C NMR spectra for all new compounds; NOESY spectrum of compound **44**.

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[1] a) D. B. Smith, G. Kalayanov, C. Sund, A. Winqvist, P. Pinho, T. Maltseva, V. Morisson, V. Leveque, S. Rajyaguru, S. Le Pogam, I. Najera, K. Benkestock, X.-X. Zhou, H. Maag, N. Cammack, J. A. Martin, S. Swallow, N. G. Johansson, K. Klumpp, M. Smith, *J. Med. Chem.* **2009**, *52*, 219–223; b) E. De Clercq, *Med. Res. Rev.* **2008**, *28*, 929–953; c) E. P. Tchesnokov, A. Obikhod, R. F. Schinazi, M. Gotte, *J. Biol. Chem.* **2008**, *283*, 34218–34228; d) S. S. Carroll, D. B. Olsen, *Infect. Disord. Drug Targets* **2006**, *6*, 17–29.

[2] a) J. Wan, Y. Xia, Y. Liu, M. Wang, P. Rocchi, J. Yao, F. Qu, J. Neyts, J. L. Iovanna, L. Peng, *J. Med. Chem.* **2009**, *52*, 1144–1155; b) B. Ewald, D. Sampath, W. Plunkett, *Oncogene* **2008**, *27*, 6522–6537; c) V. R. Anderson, C. M. Perry, *Drugs* **2007**, *67*, 1633–1655.

[3] C. S. Stauffer, A. Datta, *J. Org. Chem.* **2008**, *73*, 4166–4174.

[4] R. Naithani, *Mini-Rev. Med. Chem.* **2008**, *8*, 657–668.

[5] a) A. L. Braga, W. A. S. Filho, R. S. Schwab, O. E. D. Rodrigues, L. Dornelles, H. C. Braga, D. S. Lüdtke, *Tetrahedron Lett.* **2009**, *50*, 3005–3007; b) D. K. Tosh, W. J. Choi, H. O. Kim, Y. Lee, S. Pal, X. Hou, J. Choi, S. Choi, L. S. Jeong, *J. Org. Chem.* **2008**, *73*, 4259–4262; c) J. K. Watts, B. D. Johnston, K. Jayakanthan, A. S. Wahba, B. M. Pinto, M. J. Damha, *J. Am. Chem. Soc.* **2008**, *130*, 8578–8579; d) K. Sivapriya, P. Suguna, S. Shubashree, P. R. Sridhar, S. Chandrasekaran, *Carbohydr. Res.* **2007**, *342*, 1151–1158.

[6] J. Młochowski, K. Kloc, R. Lisiak, P. Potaczek, H. Wójtowicz, *ARKIVOC* **2007**, 14–46.

[7] a) C. K. Chu, L. Ma, S. Olgen, C. Pierra, J. Du, G. Gumina, E. Gullen, Y.-C. Cheng, R. F. Schinazi, *J. Med. Chem.* **2000**, *43*, 3906–3912; b) J. Du, S. Surzhykov, J. S. Lin, M. G. Newton, Y.-C. Cheng, R. F. Schinazi, C. K. Chu, *J. Med. Chem.* **1997**, *40*, 2991–2993.
[8] Y. Chen, Y. Peng, J. Zhang, L. Fu, *Nucleosides Nucleotides Nucleic Acids* **2008**, *27*, 1001–1008.
[9] J. Salon, J. Jiang, J. Sheng, O. O. Gerlits, Z. Huang, *Nucleic Acids Res.* **2008**, *36*, 7009–7018.
[10] J. Caton-Williams, Z. Huang, *Angew. Chem. Int. Ed.* **2008**, *47*, 1723–1725.
[11] a) B. Puffer, H. Moroder, M. Aigner, R. Micura, *Nucleic Acid Res.* **2008**, *36*, 970–983; b) H. Moroder, C. Kreutz, K. Lang, A. Serganov, R. Micura, *J. Am. Chem. Soc.* **2006**, *128*, 9909–9918; c) C. Höbartner, R. Rieder, C. Kreutz, B. Puffer, K. Lang, A. Polonskaia, A. Serganov, R. Micura, *J. Am. Chem. Soc.* **2005**, *127*, 12035–12045; d) C. Höbartner, R. Micura, *J. Am. Chem. Soc.* **2004**, *126*, 1141–1149.
[12] a) V. Olieric, U. Rieder, K. Lang, A. Serganov, C. Schulze-Briese, R. Micura, P. Dumas, E. Ennifar, *RNA* **2009**, *15*, 707–715; b) S. Freisz, K. Lang, R. Micura, P. Dumas, E. Ennifar, *Angew. Chem. Int. Ed.* **2008**, *47*, 4110–4113.
[13] a) P. S. Pallan, M. Egli, *Nat. Protoc.* **2007**, *2*, 640–646; b) P. S. Pallan, M. Egli, *Nat. Protoc.* **2007**, *2*, 647–651.
[14] L. Lin, J. Sheng, R. K. Momin, Q. Du, Z. Huang, *Nucleosides Nucleotides Nucleic Acids* **2009**, *28*, 56–66.
[15] a) J. Caton-Williams, Z. Huang, *Chem. Biodivers.* **2008**, *5*, 396–407; b) W. M. Ching, B. Alzner-DeWeerd, T. C. Stadtman, *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 347–350.
[16] N. Lougiakis, P. Marakos, N. Poul, J. Balzarini, *Chem. Pharm. Bull.* **2008**, *56*, 775–780.
[17] D. R. Garud, M. Koketsu, H. Ishihara, *Molecules* **2007**, *12*, 504–535.
[18] a) O. López, S. Maza, V. Ulgar, I. Maya, J. G. Fernández-Bolaños, *Tetrahedron* **2009**, *65*, 2556–2566; b) J. G. Fernández-Bolaños, O. López, V. Ulgar, I. Maya, J. Fuentes, *Tetrahedron Lett.* **2004**, *45*, 4081–4084.
[19] T. Wirth, *Tetrahedron* **1999**, *55*, 1–28.
[20] a) J. E. Baldwin, *J. Chem. Soc., Chem. Commun.* **1976**, 734–736; b) J. E. Baldwin, J. Cutting, W. Dupont, L. Kruse, L. Silberman, R. C. Thomas, *J. Chem. Soc., Chem. Commun.* **1976**, 736–738.
[21] J. Fernández-Bolaños Guzmán, T. Skrydstrup, A. López-Castro, M. J. Diánez Millán, M. D. Estrada de Oya, *Carbohydr. Res.* **1992**, *237*, 303–311.
[22] D. H. R. Barton, S. I. Parekh, M. Tajbakhsh, E. A. Theodorakis, C.-L. Tse, *Tetrahedron* **1994**, *50*, 639–654.
[23] M. Ávalos, R. Babiano, P. Cintas, J. L. Jiménez, J. C. Palacios, C. Valencia, *Tetrahedron* **1993**, *49*, 2655–2675.
[24] a) G. Roy, G. Mugesh, *J. Am. Chem. Soc.* **2005**, *127*, 15207–15217; b) V. K. Landry, M. Minoura, K. Pang, D. Buccella, B. V. Kelly, G. Parkin, *J. Am. Chem. Soc.* **2006**, *128*, 12490–12497.
[25] a) N. Xi, S. Xu, Y. Cheng, A. S. Tasker, R. W. Hungate, P. J. Reider, *Tetrahedron Lett.* **2005**, *46*, 7315–7319; b) M. D. Cliff, S. G. Pyne, *J. Org. Chem.* **1997**, *62*, 1023–1032.
[26] M. Boiani, M. González, *Mini-Rev. Med. Chem.* **2005**, *5*, 409–424.
[27] I. Nieto, F. Cervantes-Lee, J. M. Smith, *Chem. Commun.* **2005**, 3811–3813.
[28] J. Soler-Padrós, E. Pérez-Mayoral, L. Domínguez, P. López-Larrubia, E. Soriano, J. L. Marco-Contelles, S. Cerdán, P. Ballesteros, *J. Med. Chem.* **2007**, *50*, 4539–4542.
[29] a) T. Tschamber, F. Gessier, M. Neuburger, S. S. Gurcha, G. S. Besra, J. Streith, *Eur. J. Org. Chem.* **2003**, 2792–2798; b) K. Weinberg, S. Jankowski, D. Le Nouën, A. Frankowski, *Tetrahedron Lett.* **2002**, *43*,1089–1092; c) A. Frankowski, D. Deredas, E. Dubost, F. Gessier, S. Jankowski, *Tetrahedron* **2003**, *59*, 6503–6520.
[30] Ó. López, S. Maza, I. Maya, J. Fuentes, J. G. Fernández-Bolaños, *Tetrahedron* **2005**, *61*, 9058–9069.
[31] a) F. C. Meotti, E. C. Stangherlin, G. Zeni, C. W. Nogueira, J. B. T. Rocha, *Environ. Res.* **2004**, *94*, 276–282; b) G. Mugesh, A. Panda, H. B. Singh, N. S. Punekar, R. J. Butcher, *J. Am. Chem. Soc.* **2001**, *123*, 839–850; c) G. Mugesh, A. Panda, H. B. Singh, N. S. Punekar, R. J. Butcher, *Chem. Commun.* **1998**, 2227–2228.
[32] a) G. Ghisleni, V. Kazlauckas, F. L. Both, N. Pagnussat, S. Mioranzza, J. B. T. Rocha, D. O. Souza, L. O. Porciúncula, *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **2008**, *32*, 1508–1515; b) N. B. Barbosa, J. B. Rocha, D. C. Wondracek, J. Perottoni, G. Zeni, C. W. Nogueira, *Chem. Biol. Interact.* **2006**, *163*, 230–238; c) C. Luchese, R. Brandão, R. de Oliveira, C. W. Nogueira, F. W. Santos, *Toxicol. Lett.* **2007**, *173*, 181–190.
[33] G. Roy, D. Das, G. Mugesh, *Inorg. Chim. Acta* **2007**, *360*, 303–316.
[34] G. Roy, M. Nethaji, G. Mugesh, *J. Am. Chem. Soc.* **2004**, *126*, 2712–2713.
[35] a) J. E. Hodge, B. E. Fisher, *Methods Carbohydr. Chem.* **1963**, *2*, 99–107; b) F. Weygand, *Ber. Dtsch. Chem. Ges.* **1940**, *73B*, 1259–1278.
[36] a) V. K. Landry, M. Minoura, K. Pang, D. Buccella, B. V. Kelly, G. Parkin, *J. Am. Chem. Soc.* **2006**, *128*, 12490–12497; b) D. Fajkusova, P. Pazdera, *Phosphorus Sulfur Silion Relat. Elem.* **2005**, *180*, 1683–1689; c) G. Steiner, H. Kopacka, K.-H. Ongania, K. Wurst, B. Preishuber-Pflügl, B. Bildstein, *Eur. J. Inorg. Chem.* **2005**, 1325–1333.
[37] A. J. Arduengo III, U. S. Patent, 5,104,993, **1992**.
[38] C. J. Carmalt, A. H. Cowley, *Adv. Inorg. Chem.* **2000**, *50*, 1–32.
[39] H. Haruyama, T. Takayama, T. Kinoshita, M. Kondo, M. Nakajima, T. Haneishi, *J. Chem. Soc. Perkin Trans. 1* **1991**, 1637–1640.
[40] S. O. Duke, J. G. Romagni, F. E. Dayan, *Crop. Prot.* **2000**, *19*, 583–589.
[41] a) J. Fuentes, B. A. B. Salameh, M. A. Pradera, F. J. Fernández de Cordoba, C. Gasch, *Tetrahedron* **2006**, *62*, 97–111; b) N. G. Oikonomakos, V. T. Skamnaki, E. Ősz, L. Szilagyi, L. Somsák, T. Docsa, B. Tóth, P. Gergely, *Bioorg. Med. Chem.* **2002**, *10*, 261–268.

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