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Expedious synthesis of polyhydroxylated selena and thia-heterocycles via Se and S-ring closure of α,ω-dibromoalditols

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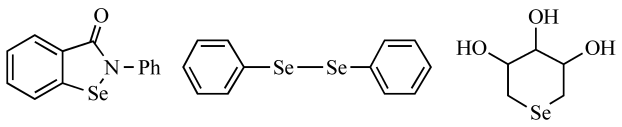
Abstract—The selena and thiaanhydro alditols (with *xylo*, *ribo*, D-*arabino*, *erythro*, D,L-*threo* and D-*manno* configuration) were easily and expeditiously synthesized in good to excellent yields by reaction of selenure and sulfur ions as binucleophiles with α,ω-dibromoalditols as bis-electrophilic substrates. With the 1,6-dibromo-D-glucitol derivative as substrate, only the corresponding thiepane derivative was obtained while the selenaheterocyclistation attempte led to complex mixture.

1. Introduction

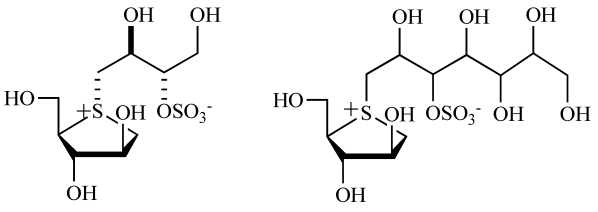
It is well recognised that some diseases such as cancer,[1] aids and the neurodegenerative diseases (e.g. Parkinson and Alzheimer)[2] emerging from abnormally high production of free radicals (oxydatif stress).[3] This is attributed to antioxydants deficiency (free radical scavengers) like vitamins[4] or of enzyme such selenodependent glutathione peroxydase where the sulfur atoms of it's cysteine moieties were replaced by selenium atoms.[5] This enzymatic antioxydant catalysed the hydroperoxyde reduction (reduced metabolite precursor of nossif HO free radical) with concomitante oxydation of a biologically important thiol, the glutathione which transformed in their disulfur.[6]

It was reported that a small organic molecules like Ebselen **A**[7] or the diphenyldiselenide **B**[8] play an important part as glutathione peroxydase mimics. More recently Schiesser and co-workers reported the ten steps synthesis of **C** (discribed in its perbenzylated *xylo*, *ribo* and D-*arabino* configurations) which is an hydrosoluble antioxydant.[9]

In the thiaheterosugars analogues series where the oxygen atom of the monosaccharide ring was replaced by sulfur atom, cyclic tetrahydro thiophene is an important building block of a large number of compounds that are very interesting from the point of view of biological activity. In particular it enters into the structures of nucleoside analogues[10] and certain compounds where the sulfur atom in the ring is in a trivalent state (spirocycle-like), such as the sulfimides,[11] salacinol **D** and kotalanol **E**,[12] which are excellent glycosidase inhibitors. Although analogues with more than six or seven membered rings (tetrahydrothiopyrane and thiepane) generally show weak glycosidase inhibition activity,[13] they are nevertheless excellent precursors for the thiacyclopentane ring through contraction of the ring[13,14] or for conduritol derivatives (from thiepane)[15] which are glycosidase inhibitor and much used as intermediates in the synthesis of inositol[16] and aminocyclitol derivatives.[17]



A **B** **C**



D **E**

The use of alditols as bielectrophilic substrates in heterocyclisation reactions has been reported in the literature. It has been shown, for instance, that the selenepane and thiepane ring are obtained mainly from bis-epoxyhexitol

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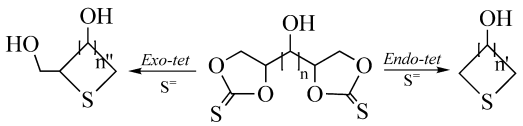
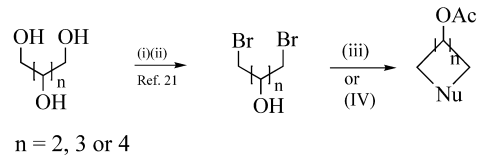
such as D-mannitol always protected in the 3,4 positions.[14b] However, this approach has limitations when applied to other alditols.[18] In our laboratory we have used alditols bis-cyclic-sulfates as bielectrophilic intermediates. Polyhydroxylated tetrahydrothiophene, tetrahydropyrane and thiepane derivatives have been isolated in good yields.[19] Unfortunately, this approach is only applicable to free tetritols and other partially protected alditols carrying only four free hydroxyl groups. Although the alditols cyclic bis-thionocarbonate derivatives formation take place efficiently and directly from umprotected alditols, their use as bis-electrophilic intermediates in thiaheterocyclisation often encountered the *endo-tet* and *exo-tet* competition (Scheme 1).[20] To avoid this competition, the α,ω-dibromoalditols seems to be a judicious alternative (Scheme 2).



Scheme 1. n=0 or 1; n'=2, 3 or 4; n''=2 or 3.



Scheme 2. (i) AcBr, 1,4-dioxane, rt, 16 h; (ii) Ac_2O, pyridine; (iii) Na_2S, DMSO; (iv) Se, $NaBH_4$, H_2O, DMSO, rt, 5 min.

Herein we report a general, short and efficient synthesis affording polyhydroxylated tetrahydroseleno/thiophene, tetrahydroseleno/thiopyrane and selene/thiepane rings from peracetylated α,ω-dibromo-α,ω-dideoxyalditols with *erythro*, D,L-*threo*, *xylo*, *ribo*, D-*arabino*, D-*manno* and D-*gluco* configurations. The latter are obtained directly by bromination of the corresponding alditols.[21]

2. Results and discussion

In the synthesis of thiaheterocycles from bis-electrophilic alditols derivatives, solvents such as EtOH,[13] MeOH[22] or a mixture of acetone–H_2O were used.[19] In the latter case, under mild conditions (rt, 15 min), we showed that cyclic tetritol bis-sulfates reacting with Na_2S, $9H_2O$ leads to corresponding thiacyclopentane derivatives in good yields. Initially, applying these conditions, 2,3,4-tri-*O*-acetyl-1,5-dibromo-1,5-dideoxyxylitol (**8**) (Table 1, entry 3) lead, after flash chromatography, to the xylotetrahydrothiopyrane derivative **9** in only 37% yield. When this reaction is followed by acetylation of the reaction mixture, the yield of compound **9** reaches 90% (entry 3). This is explained by the concomitant deacetylation of the heterocyclisation product.

Under the same conditions, the *S*-cyclisation of α,ω-dibromoalditol derivatives **2**, **5**, **11**, **15**, **18** and **21** followed by acetylation leads to tetrahydrothiophene rings **3** and **6** (entries 1 and 2), tetrahydrothiopyrane **12** and **16** (entries 4 and 5) and thiepane **19** and **23** (entries 6 and 7) in yields from 70 to 95% for a reaction time of 18 h for complete disappearance of substrate.

It is interesting to emphasize that with brominated ribitol **11** and D-glucitol **21** (entries 4 and 7) non-negligible amount of anhydro compounds were isolated (**13** and **25**, respectively). In both cases the formation of these *O*-heterocyclic compounds could be explained by an initial attack at one of the primary sites by S=, followed by transesterification and *O*-heterocyclisation leading to those anhydro derivatives.

For compound **13**, ^{13}C NMR shows both an intra-cyclic secondary carbon atom at 70.82 ppm and another extra-cyclic at 30.9 ppm, plus a signal at 190 ppm shift for thioacetate group. In ^1H NMR, the coupling constant $J_{2,3}$=5.4 Hz is in agreement with a 1,4-anhydroribitol structure.[23]

In the case of the anhydro-D-glucitol derivative **25**, the sequence of coupling constantes $J_{2,3}$=3.48 Hz, $J_{3,4}$=10.96 Hz and $J_{4,5}$=0 Hz favours a 2,6-anhydro-D-glucitol structure. Mechanistically, this requires an initial regioselective attack on the primary C-1 site of disymetrique dibrominated D-glucitol derivative **21** (Scheme 3) followed by competition between *S*-cyclisation (path-a) leading to thiepane **23** and a 1,2-*trans*-esterification (path-b) leading to 2-hydroxy compound **24**. A subsequent *O*-heterocyclisation at 2,6 leads to 2,6-anhydro-D-glucitol derivatives **25**.[24]

To corroborate this higher reactivity of C-1 compared with C-6 in the derivative 1,6-dibromo-D-glucitol **21**, we attempted regioselective nucleophilic substitution using mononucleophiles such as acetate ion (AcO^-) and the alkylthiolate anions (n-$C_4H_9S^-$ and n-$C_8H_{17}S^-$) (Scheme 4).[24] In both cases we confirmed the high reactivity of C-1 leading respectively to 1,2,3,4,5-penta-*O*-acetyl-6-bromo-6-deoxy-D-glucitol (**26**), 2,3,4,5-tetra-*O*-acetyl-6-bromo-6-deoxy-1-thiobutyl-1-deoxy-D-glucitol (**28**) and 2,3,4,5-tetra-*O*-acetyl-6-bromo-6-deoxy-1-thiooctyl-1-deoxy-D-glucitol (**30**) in reasonable yields (50%). Derivatives **26**, **28** and **30** were respectively transformed into the derivatives 6-thiobutyl, 1-thiobutyl and 6-thiobutyl-1-thiooctyl-D-glucitol **27**, **29** and **31** in excellent yields. This regioselective functional transformation then enabled us to synthesise the derivative 1,6-dithioalkyl **31** with two alkyl chains of differing lengths. Note that with an excess of thiolate in the DMSO–THF mixture, the thioalkylation takes place indiscriminately at the two sites C-1 and C-6 to give the disubstituted compound **32**.[24]

Finally, while investigating the influence of the nature of the solvent on thioheterocyclisation, we were able, using DMSO as solvent, to isolate thioheterocyclic compounds in very good yields without subsequent acetylation and in particularly mild conditions (20–45 min, only 1.5 mmol of Na_2S–$9H_2O$ instead of 5 mmol in acetone–H_2O). Furthermore, in the case of ribitol (entry 4) and D-glucitol (entry 7) we noted any amounts of the corresponding anhydro derivatives **13** and **25**.

The above conditions in DMSO could not be applied

directly to selenaheterocyclisation since Na_2Se must be synthesized firstly from metallic selenium and $NaBH_4$ as reducing reagent in aqueous medium.[13] After some attempts, we showed that reaction of peracetylated α,ω-dibromoalditols derivatives in DMSO with a colorless solution obtained by addition of $NaBH_4$ to a suspension of Se in water, gave in less than 10 min the corresponding selenaheterocycles derivatives in good to excellent yields (Table, entries 1–6). Thus, the tetrahydroselenophene **33** (*erythro*, 93%) and **34** (D,L-*threo*, 98%), the tetrahydroselenopyrane **35** (*xylo*, 80%), **36** (*ribo*, 70%), **37** (D-*arabino*, 95%) and manoselenepane **38** (70%) were efficiently obtained. The high rate of *Se*-heterocyclisation could be attributed to both higher nucleophilicity of Se= (comparatively to S=) and to the temperature enhancement (approximately 40 °C) when $NaBH_4$ was added to Se. Farther more we had verify that the addition of the DMSO solution of α,ω-dibromoalditols substrates to the cooled solution of Se and $NaBH_4$ (to 14 °C) increased the reaction temperature of the mixture to 30 °C. Thus both Na_2Se formation and subsequente heterocyclisation were exothermal. We could note also that the peracetylated α,ω-dibromoalditols don't undertake any deacetylation reaction although the temperature enhancement and the basicity of the medium.

In conclusion, this work has led to the short and efficient synthesis in excellent yields of polyhydroxylated tetrahydrothio/selenophene, tetrahydrothio/selenopyrane and thie/selenepane derivatives in various configurations via dibrominated alditol derivatives that are readily prepared from the corresponding alditols. In addition we have shown a higher reaction rate at the primary C-1 compared with the C-6 site of the 2,3,4,5-tetra-*O*-acetyl-1,6-dibromo-D-glucitol (**21**). This opens the way to numerous derivatives of D-glucitol with various functional groups, as well as to a rare sugar, gulose.[25] Finally, it is of interest to emphasise that this strategie from pentitols led to high overal yields in selenaheterocyclic pentitols **35** (*xylo*), **36** (*ribo*) and **37** (D-*arabino*) comparatively to those obtained in the ten steps strategies reported in the literature.[9]

3. Experimental

3.1. General methods

Melting points were determined with a Buchi 535 apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker 300 WB spectrometer; chemical shifts are reported in δ (ppm) relative to Me_4Si. Coupling constants, assigned by double irradiation, are in Hz. All ^{13}C NMR signals were assigned though C,H-correlated spectra with hsqc.grad experiment. TLC was performed on silica Gel 60 F_{254} 230 mesh (E. Merck) with hexane–EtOAc as eluent, and zones were detected by vanillin-H_2SO_4 reagent. The silica gel used in column chromatography was 35–70 m (Amicon). Optical rotations were determined with Jasco Dip 370 electronic micropolarimeter (10 cm cell) for compounds **37** and **38**, and Perkin–Elmer instruments, model 343 polarimeter (1 mL cell) for compounds **16** and, **19** and **23**. Elemental analyses were performed by the 'Service de Microanalyse du CNRS (Laboratoire de Bioorganique, Université de Reims Champagne Ardenne').

3.2. Synthesis of thiahetrocycles 3, 6, 9, 12, 16, 19 and 23

General procedure. To a solution of peracetylated α,ω-dibromoalditols (1 mmol)[21] in DMSO (5 mL), was added Na_2S, $9H_2O$ (1.5 mmol) and the mixture was stirred at rt for the time indicated in table. The extraction was realised with CH_2Cl_2 (30 mL) and H_2O (2×30 mL). The organic layer was concentrated and the products was purified by chromatography on silica gel and mixture of Hexan–EtOAc as eluent.

3.2.1. 2,3-Di-*O*-acetyl-1,4-dideoxy-1,4-thioerythritol (3). 186.7 mg, 92% yield as colorless syrup; R_f 0.44 (6:2, Hexan–EtOAc); ^1H NMR, ($CDCl_3$) δ 2.77 (dd, 2H, $J_{1a,1b}$=$J_{4a,4b}$=11.1 Hz, $J_{1a,2}$=$J_{4a,3}$=5.4 Hz, $H_{1a,4a}$), 3.95 (dd, 2H, $J_{1b,2}$=$J_{4b,3}$=5.6 Hz, $H_{1b,4b}$), 5.21 (m, $H_{2,3}$); 1.98 (s, 6H, CH_3); ^{13}C NMR, δ 31 (C_1=C_4), 74.3 (C_2=C_3), 21.1 (CH_3), 170.2 (CO). Anal. calcd for $C_8H_{12}O_4S$: C, 47.04; H, 5.92; O, 31.33; S, 15.70. Found: C, 47.24; H, 6.11.

3.2.2. 2,3-Di-*O*-acetyl-1,4-dideoxy-1,4-thio-D,L-threitol (6). 193 mg, 95% yield; white solid: mp 43–45 °C; R_f 0.47 (6:2, Hexan–EtOAc); ^1H NMR, ($CDCl_3$) δ 2.70 (dd, 2H, $J_{1a,1b}$=$J_{4a,4b}$=12.2 Hz, $J_{1a,2}$=$J_{4a,3}$=1.3 Hz, $H_{1a,4a}$), 3.17 (dd, 2H, $J_{1b,2}$=$J_{4b,3}$=4.0 Hz, $H_{1b,4b}$), 5.22 (m, 2H, $H_{2,3}$); 2.1 (s, 6H, CH_3); ^{13}C NMR, δ 34 (C_1=C_4), 77.9 (C_2=C_3), 21.2 (CH_3), 170.0 (CO). Anal. calcd for $C_8H_{12}O_4S$: C, 47.04; H, 5.92; O, 31.33; S, 15.70. Found: C, 47.32; H, 6.01.

3.2.3. 2,3,4-Tri-*O*-acetyl-1,5-dideoxy-1,5-thioxylitol (9). 248.7 mg, 90% yield; white solid: mp 120–122 °C; R_f 0.39 (5:2, Hexan–EtOAc); ^1H NMR ($CDCl_3$), δ 2.53 (m, 2H, $J_{1a,1b}$=$J_{5a,5b}$=13.9 Hz, $J_{1a,2}$=$J_{5a,4}$=6.4 Hz, $H_{1a,5a}$), 2.74 (m, $J_{1b,2}$=$J_{5b,4}$=1.8 Hz, H_{1ab5b}), 4.93 (m, 3H, $H_{2,3,4}$), 1.96 (s, 6H, CH_3), 1.99 (s, 3H, CH_3); ^{13}C NMR, δ 30.6 ($C_{1,5}$), 72.7 ($C_{2,4}$), 73.7 (C3), 20.7 (CH_3), 169.7 (CO). Anal. calcd for $C_{11}H_{16}O_6S$: C, 47.82; H, 5.84; O, 34.74; S, 11.61. Found: C, 47.93; H, 6.12.

3.2.4. 2,3,4-Tri-*O*-acetyl-1,5-dideoxy-1,5-thioribitol (12). 215.3 mg, 78% yield; white solid: mp 89–91 °C; R_f 0.36 (5:2, Hexan–EtOAc); ^1H NMR ($CDCl_3$), δ 2.45 (dd, 2H, $J_{1a,1b}$=$J_{5a,5b}$=12.1 Hz, $J_{1a,2}$=$J_{5a,4}$=12.1 Hz, $H_{1a,5a}$), 2.80 (t, 2H, $J_{1b,2}$=$J_{5b,4}$=4.2 Hz, H_{1b5b}), 5.01 (m, 2H, $H_{2,4}$), 5.55 (s, 1H, H_3), 1.96 (s, 6H, CH_3), 2.15 (s, CH_3); ^{13}C NMR δ 25.1 ($C_{1,5}$), 70.9 ($C_{2,4}$), 69.2 (C_3), 20.8 (CH_3), 169.5, 169.7 (CO). Anal. calcd for $C_{11}H_{16}O_6S$: C, 47.82; H, 5.84; O, 34.74; S, 11.61. Found: C, 48.01; H, 5.98.

3.2.5. 2,3-Di-*O*-acetyl-5-*S*-acetyl-1,4-anhydro-5-thio-D,L-ribitol (13). Obtained when the acetone/H_2O mixture was used solvent in the thiaheterocyclisation reaction (Table 1, entry 4). 55.3 mg, 20% yield; colorless syrup; R_f 0.28 (5:2, Hexan–EtOAc); ^1H NMR ($CDCl_3$), δ 3.76 (dd, 1H, $J_{1a,1b}$=10.4 Hz, $J_{1a,2}$=3.4 Hz, H_{1a}), 4.22 (dd, 1H, $J_{1b,2}$=5.1 Hz, H_{1b}), 5.13 (ddd, 1H, $J_{2,3}$=7.3 Hz, H_2), 4.06 (dd, 1H, $J_{3,4}$=5.4 Hz, H_3), 5.28 (dd, 1H, $J_{4,5a}$=6.0 Hz, $J_{4,5b}$=24.4 Hz, H_4), 5.01 (dd, 1H, $J_{5a,5b}$=14.1 Hz, H_{5a}), 3 (dd, 1H, H_{5b}), 2.02 (s, 3H, CH_3), 2.04 (s, 3H, CH_3 (Ac)),

Table 1. Regioselective thia and selenaheterocyclisation of peracetylated α,ω-dibromoalditols derivatives using sodium sulfide and sodium selenide

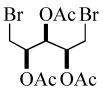
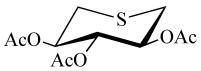
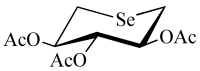
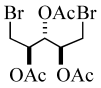
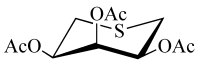
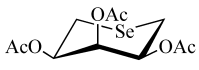
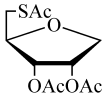
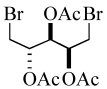
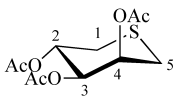
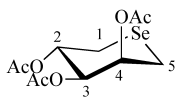
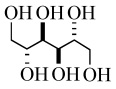
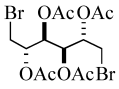
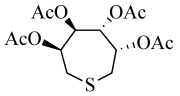
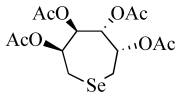
Entry	Substrates	α,ω-Dibromoalditols derivatives (yield (%))[a]	Isolated thiaheterocyclic products	Isolated yields (%) in conditions with acetone–H_2O as solvent[b]		Isolated yields (%) in conditions with DMSO as solvent[c]		Isolated selenahyeterocyclic products after 5 min of reaction time in DMSO/H_2O as solvent	
				Yield (%)[d]	Time (h)	Yield (%) Time (min)	Time (min)	Yield (%)	Time (min)
1				93	18	92	20		<10
	Erythritol (**1**)	**2** (85)	**3**					**33** (93)	
2				95	18	95	20		<10
	D,L-Threitol (**4**)	**5** (86)	**6**					**34** (98)	
3				90[e]	18	87	30		<10
	Xylitol (**7**)	**8** (70)	**9**					**35** (80)	
4				70	18	78	30		<10
	Ribitol (**10**)	**11** (68)	**12**						
				20	18	0	30	**36** (70)	<10
			13						
5				86	18	83	30		<10
	D-Arabinitol (**14**)	**15** (73)	**16**					**37** (95)	
6				82	18	88	45		<10
	D-Mannitol (**17**)	**18** (60)	**19**					**38** (70)	

Table 1 (*continued*)

Entry	Substrates	α,ω-Dibromoalditols derivatives (yield (%))[a]	Isolated thiaheterocyclic products	Isolated yields (%) in conditions with acetone–H_2O as solvent[b]		Isolated yields (%) in conditions with DMSO as solvent[c]		Isolated selenahyeterocyclic products after 5 min of reaction time in DMSO/H_2O as solvent	
				Yield (%)[d]	Time (h)	Yield (%)	Time (min)	Yield (%)	Time (min)
7	D-Glucitol (**20**)	**21** (50)	**23**	75	18	85	45	Complex mixture	
			25 (2,6-Anhydro)	10		0			

[a] Isolated yields from the corresponding aditols.[21]
[b] 5 mmol of Na_2S, $9H_2O$.
[c] Isolated yields from α,ω-dibromoalditols derivatives and after acetylation of crude product.
[d] 1.5 mmol of Na_2S, $9H_2O$.
[e] 37% Yield if separation carryed out without previous acetylation.

Scheme 3. (i) Na_2S, $9H_2O$, Acetone–H_2O (15:1), rt, 18 h.

Scheme 4. R=OAc; (i) AcONa (3 equiv.), 60 °C, 5 h, DMSO; (ii) C_4H_9SH (1.2 equiv.), NaH (1.1 equiv.), DMSO, rt, 15 min; (iii) C_4H_9SH (1.2 equiv.), NaH (1.1 equiv.), DMSO-THF (1:1), rt, 15 min; (iv) AcONa (3 equiv.), 60 °C, 24 h, DMSO; (v) $C_8H_{17}SH$ (1.2 equiv.), NaH (1.1 equiv.), DMSO, TA, 15 min; (vi) C_4H_9SH (2.2 equiv.), NaH (2.4 equiv.) DMSO-THF (1:1), rt, 15 min.

2.33 (s, 3H, CH_3 (SAc)); ^{13}C NMR δ 70.8 (C_1), 78.0 (C_2), 73.5 (C_3), 71.2 (C_4), 30.9 (C_5), 20.5 (CH_3 (OAc)) 30.4 (CH_3 (SAc)), 169.8 (CO, (Ac)), 194.7 (CO (SAc)). Anal. calcd for $C_{11}H_{16}O_6S$: C, 47.82; H, 5.84; O, 34.74; S, 11.61. Found: C, 48.07; H, 5.88.

3.2.6. 2,3,4-Tri-*O*-acetyl-1,5-dideoxy-1,5-thio-D-arabinitol (16). 229.1 mg, 83% yield; $[\alpha]_D=-20.4$ (*c* 3.3; $CHCl_3$); R_f 0.42 (5:2, Hexan–EtOAc); ^1H NMR ($CDCl_3$), δ 2.54 (dd, 1H, $J_{1a,1b}=14$ Hz, $J_{1a,2}=7.7$ Hz, H_{1a}), 2.83 (dd, 1H, $J_{1b,2}=2.2$ Hz, H_{1b}), 5.08 (ddd, 1H, $J_{2,3}=8.1$ Hz, H_2), 4.89 (dd, 1H, $J_{3,4}=2.6$ Hz, H_3), 5.28 (dd, 1H, $J_{4,5a}=7.2$ Hz, $J_{4,5b}=2.6$ Hz, H_4), 2.62 (dd, 1H, $J_{5a,5b}=14$ Hz, H_{5a}), 2.75 (dd, 1H, H_{5b}), 1.98 (s, 3H, CH_3), 1.97 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 2.15 (s, CH_3); ^{13}C NMR δ 28.7 (C_1), 68.9 (C_2), 70.3 (C_3), 68.8 (C_4), 28.6 (C_5), 20.8 (CH_3), 169.5, 169.7, 169.9 (CO). Anal. calcd for $C_{11}H_{16}O_6S$: C, 47.82; H, 5.84; O, 34.74; S, 11.61. Found: C, 48.18; H, 6.22.

3.2.7. 2,3,4,5-Tetra-*O*-acetyl-1,6-dideoxy-1,6-thio-D-mannitol (19). 307.2 mg, 88% yield; white solid: mp 93–95 °C; $[\alpha]_D=-157$ (*c* 3.7; $CHCl_3$); R_f 0.42 (5:3, Hexan–EtOAc); ^1H NMR ($CDCl_3$), δ 2.79 (dd, 2H, $J_{1a,1b}=J_{6a,6b}=14.6$ Hz, $J_{1a,2}=J_{6a,5}=7.0$ Hz, $H_{1a,6a}$), 2.83 (dd, 2H, $J_{1b,2}=J_{6b,5}=4.5$ Hz, $H_{1b,6b}$), 5.28 (m, 2H, $J_{2,3}=J_{4,5}=0.8$ Hz, $H_{2,5}$), 5.28 (m, 2H, $H_{3,4}$),1.96 (s, 6H, CH_3), 1.99 (s, 6H, CH_3); ^{13}C NMR, δ 30.9 ($C_{1,6}$), 70.2 ($C_{2,5}$), 70.9 ($C_{3,4}$), 20.6 (CH_3), 169.3, 169.7 (CO). Anal. calcd for $C_{14}H_{20}O_8S$: C, 48.27; H, 5.79; O, 36.74; S, 9.20. Found: C, 48.32; H, 6.05.

3.2.8. 2,3,4,5-Tetra-*O*-acetyl-1,6-dideoxy-1,6-thio-D-glucitol (23). 296.7 mg; $[\alpha]_D=-0.2$ (*c* 1.6; $CHCl_3$); 85% yield; white solid: mp 76–78 °C; R_f 0.26 (5:3, Hexan–EtOAc); ^1H NMR ($CDCl_3$) (arbitrary numeration), δ 2.69 (dd, 1H, $J_{1a,1b}=14.6$ Hz, $J_{1a,2}=7.2$ Hz, H_{1a}), 2.84 (dd, 1H, $J_{1b,2}=3.9$ Hz, H_{1b}), 5.33 (ddd, 1H, $J_{2,3}=1.4$ Hz, H_2), 5.15 (dd, 1H, $J_{3,4}=8.1$ Hz, H_3), 5.49 (dd, 1H, $J_{4,5}=6$ Hz, H_4), 5.04 (ddd, 1H, $J_{5,6a}=7.4$ Hz, $J_{5,6b}=4.6$ Hz, H_5), 2.74 (dd, 1H, $J_{1a,1b}=15.4$ Hz, H_{6a}), 2.88 (dd, 1H, H_{6b}),1.95 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 2.02 (s,3H, CH_3); ^{13}C NMR δ 33.1 ($C_{1,6}$), 71.3 (C_2), 70.8 (C_3), 70.6 (C_4), 75.2 (C_5), 20.6, 20.8 (CH_3), 169.0, 169.1, 169.5, 169.8 (CO). Anal. calcd for $C_{14}H_{20}O_8S$: C, 48.27; H, 5.79; O, 36.74; S, 9.20. Found: C, 48.63; H, 5.92.

3.2.9. 3,4,5-Tri-*O*-acetyl-1-*S*-acetyl-2,6-anhydro-1-thio-D-glucitol (25). Obtained when the acetone/H_2O mixture was used solvent in the thiaheterocyclisation reaction (Table 1, entry 7). 34.8 mg, 10% yield; Yelow syrup; R_f 0.38 (5:3, Hexan–EtOAc); ^1H NMR ($CDCl_3$), δ 3 (dd, 1H, $J_{1a,1b}=14.5$ Hz, $J_{1a,2}=6.2$ Hz, H_{1a}), 3.52 (dd, 1H, $J_{1b,2}=3.3$ Hz, H_{1b}), 5.13 (ddd, 1H, $J_{2,3}=3.5$ Hz, H_2), 4.06 (dd, 1H, $J_{3,4}=11$ Hz, H_3), 5.38 (dd, 1H, $J_{4,5}=0$ Hz, H_4), 5.01 (ddd, 1H, $J_{5,6a}=1.8$ Hz, $J_{5,6b}=4.7$ Hz, H_5), 3.76 (dd, 1H, $J_{1a,1b}=10.7$ Hz, H_{6a}), 4.22 (dd, 1H, H_{6b}), 1.93 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.29 (s,3H, CH_3 (SAc)); ^{13}C NMR δ 72.3 (C_1), 67.8 (C_2), 79.4 (C_3), 74.5 (C_4), 77.3 (C_5), 30.8 (C_6), 20.7 (CH_3 (Ac)), 30.4 (CH_3 (SAc)), 169.3, 169.6 (CO (OAc)), 194.5 (CH3 (SAc)). Anal. calcd for $C_{14}H_{20}O_8S$: C, 48.27; H, 5.79; O, 36.74; S, 9.20. Found: C, 48.54; H, 5.83.

3.3. Synthesis of selenahetrocycles 33, 34, 35, 36, 37 and 38

General procedure. To a freshly colorless solution obtained from addition of $NaBH_4$ in H_2O to a suspension of Se in H_2O, was added a solution of peracetylated α,ω-dibromoalditols[21] in DMSO (Table 2). The mixture was stirred for <10 min. The extraction was realised with CH_2Cl_2 (20 mL) and H_2O (2×20 mL). The organic layer was concentrated and the products was purified by chromatography on silica gel and mixture of Hexan–EtOAc as eluant.

3.3.1. 2,3-Di-*O*-acetyl-1,4-dideoxy-1,4-selenoerythritol (33). 70.5 mg, 93% yield as yellow syrup; R_f 0.52 (5:2, Hexan–EtOAc); ^1H NMR, ($CDCl_3$) δ 2.92 (dd, 2H, $J_{1a,1b}=J_{4a,4b}=10.3$ Hz, $J_{1a,2}=J_{4a,3}=5.9$ Hz, $H_{1a,4a}$), 3.11 (dd, 2H, $J_{1b,2}=J_{4b,3}=5.6$ Hz, $H_{1b,4b}$), 5.42 (m, $H_{2,3}$); 2.04 (s, 6H, CH_3); ^{13}C NMR, δ 21.9 (C_1=C_4), 75.9 (C_2=C_3), 21.4 (CH_3), 170.6 (CO). Anal. calcd for $C_8H_{12}O_4Se$: C, 38.26; H, 4.82; O, 25.48; Se, 31.44. Found: C, 38.43; H, 4.85.

3.3.2. 2,3-Di-*O*-acetyl-1,4-dideoxy-1,4-seleno-D,L-threitol (34). 74.3 mg, 98% yield; yellow syrup; R_f 0.55 (5:2, Hexan–EtOAc); ^1H NMR, ($CDCl_3$) δ 2.93 (dd, 2H, $J_{1a,1b}=J_{4a,4b}=11.0$ Hz, $J_{1a,2}=J_{4a,3}=2.4$ Hz, $H_{1a,4a}$), 3.20 (dd, 2H, $J_{1b,2}=J_{4b,3}=4.0$ Hz, $H_{1b,4b}$), 5.33 (m, 2H, $H_{2,3}$); 2.05 (s, 6H, CH_3); ^{13}C NMR, δ 24.80 (C_1=C_4), 78.5 (C_2=C_3), 21.4 (CH_3), 170.2 (CO). Anal. calcd for $C_8H_{12}O_4Se$: C, 38.26; H, 4.82; O, 25.48; Se, 31.44. Found: C, 38.75; H, 5.01.

3.3.3. 2,3,4-Tri-*O*-acetyl-1,5-dideoxy-1,5-selenoxylitol (35). 64 mg, 80% yield; red solid: mp 110–112 °C; R_f 0.46 (5:2, Hexan–EtOAc); ^1H NMR ($CDCl_3$), δ 2.64 (d, 2H, $J_{1a,1b}=J_{5a,5b}=12.1$ Hz, $J_{1a,2}=J_{5a,4}=0$ Hz, $H_{1a,5a}$), 2.72 (dd, $J_{1b,2}=J_{5b,4}=4.8$ Hz, H_{1ab5b}), 5.07 (m, 2H, $H_{2,4}$), 4.95 (d, H_3, 1.96 (s, 6H, CH_3), 1.99 (s, 3H, CH_3); ^{13}C NMR, δ 21.4 ($C_{1,5}$), 74.1 ($C_{2,4}$), 74.3 (C3), 20.9, 21.2 (CH_3), 169.9, 170.1 (CO). Anal. calcd for $C_{11}H_{16}O_6Se$: C, 40.88; H, 4.99; O, 29.70; Se, 24.43. Found: C, 40.93; H, 5.12.

3.3.4. 2,3,4-Tri-*O*-acetyl-1,5-dideoxy-1,5-selenoribitol (36). 56 mg, 70% yield; pink solid: mp 128–130 °C; R_f 0.46 (5:2, Hexan–EtOAc); ^1H NMR ($CDCl_3$), δ 2.45 (dd, 2H, $J_{1a,1b}=J_{5a,5b}=11.7$ Hz, $J_{1a,2}=J_{5a,4}=4.1$ Hz, $H_{1a,5a}$), 2.97 (t, 2H, $J_{1b,2}=J_{5b,4}=11.7$ Hz, H_{1b5b}), 5.15 (m, 2H, $H_{2,4}$), 5.53 (s, 1H, H_3), 2.01 (s, 6H, CH_3), 2.19 (s, 3H, CH_3); ^{13}C NMR δ 16.2 ($C_{1,5}$), 72.7 ($C_{2,4}$), 70.1 (C_3), 21.2 (CH_3), 170.2, 169.9 (CO). Anal. calcd for $C_{11}H_{16}O_6Se$: C, 40.88; H, 4.99; O, 29.70; Se, 24.43. Found: C, 41.04; H, 5.23.

3.3.5. 2,3,4-Tri-*O*-acetyl-1,5-dideoxy-1,5-seleno-D-arabinitol (37). 76 mg, 95% yield; yellow syrup; $[\alpha]_D^{22}=-84.8$ (*c* 1.2, CH_2Cl_2); R_f 0.37 (5:2, Hexan–EtOAc); ^1H NMR ($CDCl_3$), δ 2.86–2.94 (m, 2H, $H_{1a,1b}$), 5.27 (ddd, 1H, $J_{2,3}=7.5$ Hz, H_2), 4.99 (dd, 1H, $J_{3,4}=2.8$ Hz, H_3), 5.43 (m, 1H, $J_{4,5a}=7.3$ Hz, $J_{4,5b}=3.1$ Hz, H_4), 2.67 (dd, 1H, $J_{5a,5b}=13.2$ Hz, H_{5a}), 2.70 (dd, 1H, H_{5b}), 1.98 (s, 3H, CH_3), 1.97 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 2.11 (s, 9H, CH_3); ^{13}C NMR δ 19.2 (C_1), 69.7 (C_2), 71.0 (C_3), 69.8 (C_4), 19.5 (C_5), 20.4, 21.3, 21.2 (CH_3), 170.4, 170.2, 171.0 (CO). Anal. calcd for $C_{11}H_{16}O_6Se$: C, 40.88; H, 4.99; O, 29.70; Se, 24.43. Found: C, 40.73; H, 5.02.

3.3.6. 2,3,4,5-Tetra-*O*-acetyl-1,6-dideoxy-1,6-seleno-D-mannitol (38). 58 mg, 70% yield; white solid: mp 93–95 °C; $[\alpha]_D^{22}=-21.0$ (*c* 0.55, CH_2Cl_2); R_f 0.42 (5:3,

Table 2. Selenaheterocyclisation conditions of peracetylated α, ω-dibromoalditol derivatives

α,ω-Dibromoalditol	M (g mol^{-1})	m (g)	N (mol)	Se		$NaBH_4$		V_{H2O} (mL)	V_{DMSO} (mL)
				m (mg)	equiv.	m (mg)	equiv.		
Tetritol	332	0.100	0.3×10^{-3}	71	3	68	6	2×290 μL	1.10 mL
Pentitol	404	0.100	0.25×10^{-3}	59	3	56	6	2×230 μL	930 μL
Hexitol	476	0.100	0.2×10^{-3}	50	3	48	6	2×200 μL	790

Hexan–EtOAc); ^{1}H NMR ($CDCl_3$), δ 2.79 (dd, 2H, $J_{1a,1b}$=$J_{6a,6b}$=14.6 Hz, $J_{1a,2}$=$J_{6a,5}$=7.0 Hz, $H_{1a,6a}$), 2.83 (dd, 2H, $J_{1b,2}$=$J_{6b,5}$=4.5 Hz, $H_{1b,6b}$), 5.28 (m, 2H, $J_{2,3}$=$J_{4,5}$=0.8 Hz, $H_{2,5}$), 5.28 (m, 2H, $H_{3,4}$),1.96 (s, 6H, CH_3), 1.99 (s, 6H, CH_3); ^{13}C NMR, δ 30.9 ($C_{1,6}$), 70.2 ($C_{2,5}$), 70.9 ($C_{3,4}$), 20.6 (CH_3), 169.3, 169.7 (CO). Anal. calcd for $C_{14}H_{20}O_8Se$: C, 42.54; H, 5.10; O, 32.38; Se, 19.98. Found: C, 42.72; H, 5.55.

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