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An efficient route for the synthesis of phosphorus–selenium macro-heterocycles†

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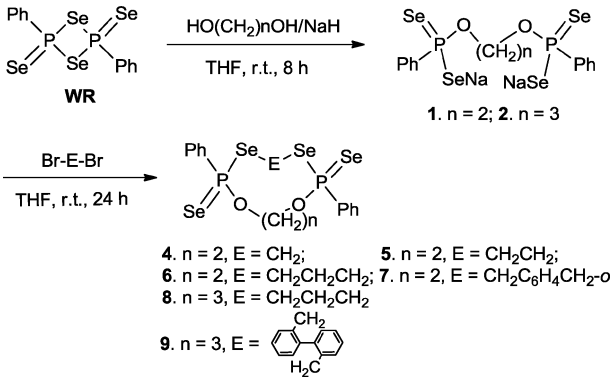
Four-membered ring [PhP(Se)(μ-Se)]$_2$ (Woollins' reagent, WR) reacts with disodium alkenyl-diols followed by *in situ* ring-closure reaction with appropriate dibromoalkanes affording a series of unusual nine- to fifteen-membered organoselenophosphorus macrocycles bearing the O–P–Se–C$_n$–Se–P–O or O–P–Se–C$_n$–O–P–Se linkage.

The synthesis of macrocycles containing heavier elements is challenging and hetero-macrocycles are very rare[1] thus organoselenium heterocycles containing more than eight-membered rings with at least two selenium atoms are limited.[2–7] The known methods to prepare these heterocyclic compounds in general suffer from the use of highly toxic reagents with harsh reaction conditions, low yields or multi-steps. We, and others, have developed and exploited the chemistry of 2,4-bis(phenyl)-1,3-diselenadiphosphetane-2,4-diselenide (Woollins' reagent, **WR**) as a versatile selenation reagent in synthetic chemistry.[8–19]

Recently, we have successfully applied **WR** as an efficient building unit or block to synthesize a series of eight-, nine-, and ten-membered selenophosphorus heterocycles with the P–Se–Se–P linkage,[20] and unique octaselenocyclododecane with four carbon atoms and eight selenium atoms in this fourteen-membered cycle.[21] In this communication, we report a 'one-pot' approach *via* a small ring expansion by consecutively introducing two organic building blocks to construct a series of large organoselenophosphorus heterocycles including two phosphorus atoms and two selenium atoms and two oxygen atoms in the ring. To the best of our knowledge, this is the first synthesis and X-ray structure of such organoselenophosphorus macrocycles consisting of the O–P–Se–C$_n$–Se–P–O linkage or the O–P–Se–C$_n$–O–P–Se linkage.

Cleavage of the four-membered ring P_2S_2 in **WR** by an equimolar amount of disodium ethane-1,2-bis(olate) or disodium propane-1,3-bis(olate) (derived from ethylene glycol or 1,3-propanediol and NaH) led to disodium bis(phenylphosphonodiselenoate)s **1** and **2**, which were converted *in situ* into the corresponding nine- to fifteen-membered phosphorus–selenium macro-heterocycles **4–9** in moderate to good yields (36 to 56%) by further treatment with an equivalent amount of various dibromides (Br–E–Br, E = –(CH$_2$)$_n$– or –CH$_2$C$_6$H$_4$CH$_2$– or –CH$_2$C$_6$H$_4$C$_6$H$_4$CH$_2$–) at ambient temperature for 24 h (Scheme 1). In all the cases, insoluble (in water or normal organic solvent) side products which we were not able to identify were found resulting in the non-quantitative yields arising from the extensive formation of the possible polymers.



Scheme 1 Synthesis of new macroheterocycles **4–9**.

However, analogous routes involving disodium butane-1,4-bis(olate) and 1,4-dibromobutanol gave rise to the surprising fourteen-membered macrocycle **11** along with **10** (Scheme 2, obtained in 36.8% isolated yield). We speculate that **11** is formed by the reaction of 1,4-dibromobutane with an intermediate **3b**, the latter being the intramolecular isomerization product of **3a**. Monitoring the reaction of **WR** with NaO(CH$_2$)$_4$ONa by ^{31}P NMR confirmed the presence of two isomers **3a** and **3b** in the reaction mixture (δ_P = 77.8 and 78.1 ppm).

Preliminary computations at the B3LYP/6-31G* level[22,23] indicate selected stereoisomers of **11** to be slightly more stable in energy than their counterparts **10** (see Fig. S1 and Table S4 in the ESI†). We investigated increased reaction times and higher temperatures for the second stage of the reaction in Scheme 2

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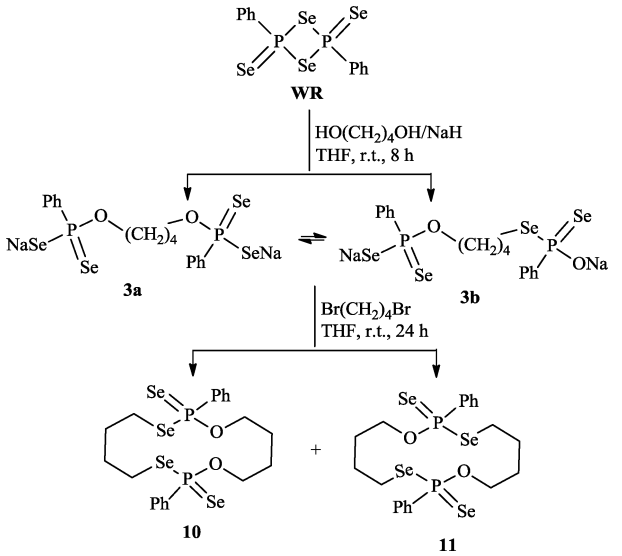

Scheme 2 Synthesis of new 14-membered ring systems **10** and **11**.

but this had no impact suggesting that although **11** is the more stable isomer there is no readily accessible pathway between **10** and **11**.

Macrocycles **4–9** and **11** are soluble in common polar organic solvents and are stable to air and moisture at ambient temperature for several months without any sign of decomposition. All of the new compounds were characterized by standard analytical and spectroscopic techniques. The ^{31}P NMR spectra of **4–9** and **11** exhibit sharp singlets in the range of δ = 67.6 to 82.4 ppm, which are accompanied by two sets of satellites for the endocyclic and exocyclic selenium atoms $^{1}J(\mathrm{P,Se}_{endo})$ and $^{1}J(\mathrm{P,Se}_{exo})$, thus indicating the presence of single and double P=Se bonds in each compound. The results were further confirmed by the ^{77}Se NMR spectra of compounds **4–9** and **11** that contain signals arising from exocyclic selenium in the range of δ = 341.3 to 490.1 ppm and endocyclic selenium atoms in the range of δ = −115.3 to −71.8 ppm with appropriate $^{1}J(\mathrm{P,Se}_{endo})$ and $^{1}J(\mathrm{P,Se}_{exo})$ coupling constants (*ca.* 450 and 830 Hz, respectively).

Macrocycles **5–7**, **9** and **11** were crystallized from dichloromethane solutions with slow diffusion of hexane to give transparent, colorless, cubic crystals. The *R*,*R*/*S*,*S* and the *R*,*S* forms of **11** were crystallised independently. The X-ray structures of **5–7**, **9** and **11** (Fig. 1–4) confirm the presence of nine- to fifteen-membered rings. Within **5–7**, **9** and **11**, the P–Se single bonds are in the range of 2.213–2.251 Å and P=Se double bonds are in the range of 2.078–2.098 Å similar to that in acyclic structures containing the P–Se–Se–P linkage.[20,24] The macrocyclic

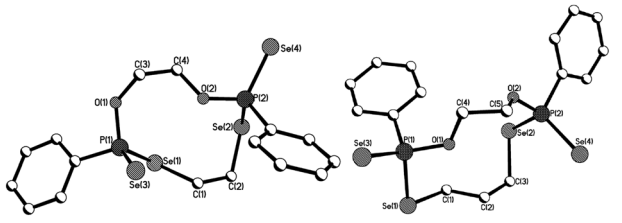

Fig. 1 Molecular structures of **5** (left) and **6** (right) in the crystal.

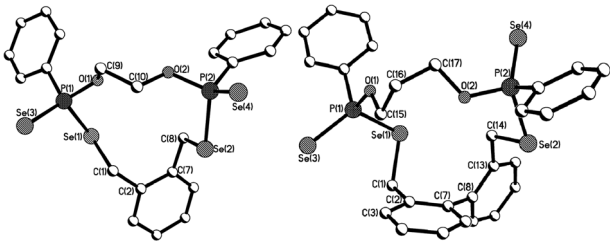

Fig. 2 Molecular structures of **7** (left) and **9** (right) in the crystal.

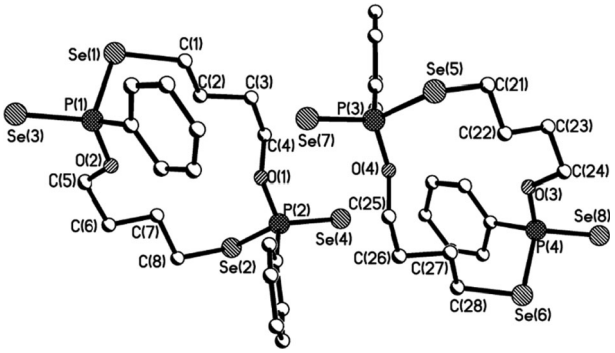

Fig. 3 Molecular structure of **11a** (*R*,*R*/*S*,*S* isomer of **11**) in the crystal.

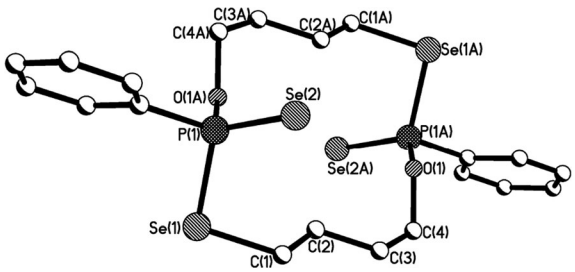

Fig. 4 Crystal structure of **11b** (*R*,*S* isomer of **11**).

frameworks in **5** and **9** are highly puckered with the two phenyl rings on phosphorus atoms on opposite sides of the macro-heterocyclic ring. Table 1 summarises the transannular Se···Se, P···P and O···O distances in the new macro-heterocycles and illustrates the ability to tune the cavity in this new class of macrocycles. The values are as anticipated significantly longer than those observed in the four-membered P_2Se_2 ring system (3.1 Å) and considerably longer than those in the six-membered P_2Se_4 ring system (4.3 Å).[25] The geometry around P(1) and P(2) is distorted tetrahedral (Se(3)–P(1)–Se(1) and Se(4)–P(2)–Se(2): 116.5(6)° and 108.4(6)° for **5**, 115.0(6)° and 116.2(6)° for **9**).

Table 1 Selected cross ring lengths (Å) from the crystal structures

Macrocycle	Ring size & motif	O···O	P···P	Se···Se
R,*S*-**5**	**10** $P_2Se_2O_2C_4$	2.850	5.278	5.119
R,*S*-**6**	**11** $P_2Se_2O_2C_5$	2.768	5.598	4.952
R,*R*-**7**	**12** $P_2Se_2O_2C_6$	3.140	4.793	3.596
R,*R*-**9**	**15** $P_2Se_2O_2C_9$	3.624	6.133	5.422
R,*R*,*S*,*S*-**11**	**14** $P_2Se_2O_2C_8$	4.656 [4.764]	6.890 [6.968]	7.575 [7.528]
R,*S*-**11**	**14** $P_2Se_2O_2C_8$	5.162	6.504	7.561

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Macrocycles **6**, **7** and **11a** (*R*,*R*/*S*,*S* isomer of **11**) contain frameworks similar to **5** and **9**, and are again highly puckered. The geometry around P(1) and P(2) is distorted tetrahedral (Se(3)–P(1)–Se(1) and Se(4)–P(2)–Se(2): 110.5(5)° and 113.7(5)° for **6**, 115.0(6)° and 116.2(6)° for **7**, and 106.7(2) [107.3(2)]° and 108.7(2) [107.5(2)]° for **11a**).

The structure of **11b** (*R*,*S* isomer of **11**) exhibits a distinctly different pattern as shown in Fig. 4, compared with **11a** (Fig. 3). The structure of **11b** adopts a symmetric and puckered macrocyclic framework, with the two phenyl rings directly attached to phosphorus atoms being parallel to each other. The Se–P–Se bite angles are enlarged from ideal tetrahedral (Se(3)–P(1)–Se(1) and Se(4)–P(2)–Se(2): 115.9(8)°), and are considerably larger than those [106.7(2) [107.3(2)]° and 108.7(2) [107.5(2)]°] in **11a**.

To probe the conformational preferences of the diastereomers of **11**, some exploratory optimizations were performed at the B3LYP/6-31G* level of density functional theory. Starting from the relaxed coordinates of **11a** and **11b** with, respectively, (*S*,*S*) and (*S*,*R*) configurations at the stereogenic P centers, Se and Ph moieties were swapped at one P atom, affording the stereoisomers (*S*,*R*)-**11a** and (*S*,*S*)-**11b**. The relative energies of (*S*,*S*)-**11a**, (*S*,*R*)-**11b**, (*S*,*S*)-**11b**, and (*S*,*R*)-**11a** are 4.5, 0.0, 7.4 and 13.5 kJ mol^{-1}, respectively. Thus, only the more stable conformer of each *rac* and *meso* isomer has been observed in the crystals.

Arguably, the flexible linkers will give rise to a plethora of possible conformers, and low kinetic barriers are expected for their interconversion. To confirm this expectation, a representative pathway was characterized leading from (*S*,*S*)-**11a** to (*S*,*S*)-**11b** (*via* one intermediate, see Fig. S1 in the ESI†). The highest barrier along this path is 23.6 kJ mol^{-1} at the B3LYP level (34.6 kJ mol^{-1} at B3LYP-D3). To freeze out such conformers would thus require very low temperatures, and would not seem possible with *e.g.* NMR under ambient conditions.

In summary, an efficient approach has been developed for the synthesis of a series of nine- to fifteen-membered phosphorus–selenium macro-heterocycles by consecutively inserting two difunctional organic units (alkyldiols and dibromoalkanes) into the four-membered ring in Woollins' reagent *via* one-pot reaction. The route is fast and efficient and simple. The demonstrated versatility of synthesis and X-ray structures provide a general and systemic approach to prepare such large phosphorus–selenium heterocyclic compounds. This method allows phosphorus–selenium macro-heterocycles to be easily available for further investigations into their chemical and biological properties.

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