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Asymmetric selenocyclization with the use of dialkyl monoterpene diselenides

Zbigniew Rafiński, Jacek Ścianowski* and Andrzej Wojtczak

Department of Chemistry, Nicolaus Copernicus University, 7 Gagarin Street, 87-100 Torun, Poland

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Abstract—Selenocyclization with the use of the monoterpene diselenides from menthane, carane and pinane groups has been studied. The conditions for asymmetric selenocyclization have been optimized. It has been established that the best enantiomeric excesses were obtained in the case of selenocyclization for the unsubstituted alkyl diselenides with (+)-dineomenthyl diselenide. The results of the selenocyclization of the (+)-dineomenthyl diselenide with the unsaturated alcohols and acids are presented.

1. Introduction

There is increasing interest in the use of selenoorganic reagents in organic synthesis, which is a consequence of the fact that their reactions can be carried out under mild experimental conditions. Another advantage of selenium-containing groups is their compatibility with most functional groups existing in organic molecules.[1–4]

In recent years the procedures for using selenoorganic compounds in asymmetric syntheses have become of special interest.[5–8] Among them, optically active diselenides have been especially studied. Hitherto, investigations in this group of compounds have been focused on finding convenient methods for the synthesis of optically active diselenides, as well as on their use in asymmetric synthesis.[9–11] Optically active diselenides have been employed as electrophiles in the asymmetric addition to a double bond with the formation of new carbon–oxygen, carbon–nitrogen, or carbon–carbon bonds.[5]

Cyclization reactions with the use of selenoorganic compounds have been widely employed. Many optically active heterocyclic compounds have been obtained with the use of chiral selenoorganic compounds.[12] Selenocyclizations using optically active diselenides proceed as a two-stage process. In the first step of the reaction, addition of the selenium electrophile obtained from the diselenide to a double bond takes place. During the second step, the intramolecular addition of the nucleophile leading to the respective heterocyclic system is observed (Scheme 1).

In our previous papers we described a convenient method for the synthesis of optically active monocyclic and bicyclic terpene diselenides. Diselenide derivatives of menthanes **1** and **2**, caranes **3** and **4** and pinane **5**–**7** groups were obtained in a reaction of sododiselenide with alkyl tosylates and chlorides (Fig. 1). These optically active diselenides have been used in asymmetric additions to a double bond.[10]

Herein we report the influence of the structures of non-substituted optically active monoterpene diselenides **1**–**7** on the diastereomeric excesses of the products of the selenocyclization reactions. Until now, the influence of the reagent structure on the diastereomeric excess of the selenocyclization reaction products for the optically active non-functionalized dialkyl diselenides has not been studied.

2. Result and discussion

The first stage in our research of the selenocyclization reaction of optically active dialkyl diselenides was the optimization of the reaction conditions.

The optimisation was carried out using (+)-dineomenthyl diselenide **1** in the reaction with *o*-allylphenol **8** (Scheme 2).

* Corresponding author. Tel.: +48 56 6114532; fax: +48 56 6542477; e-mail: jsch@chem.uni.torun.pl

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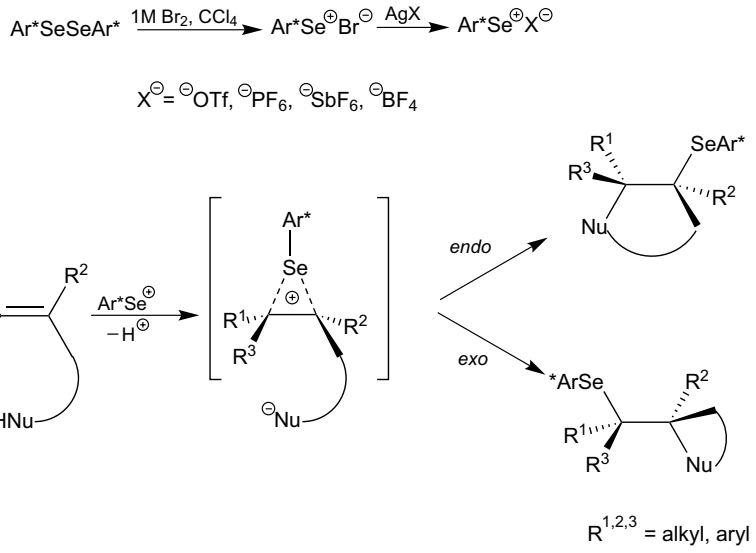


Scheme 1. The mechanism of the selenocyclization reaction.

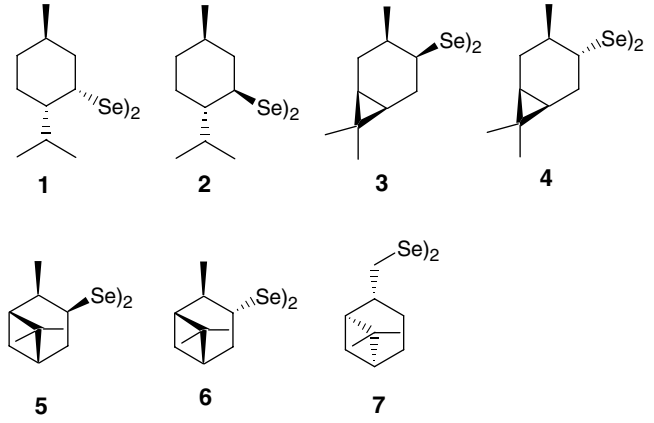


Figure 1. Optically active terpene diselenides.

The respective selenium electrophiles were obtained by the addition of bromine or sulfuryl chloride to a solution of diselenide **1**. We also investigated the possibility of using the triflate and tetrafluoroborane counterions obtained in the reaction of selenoneomenthyl bromide with the corresponding silver salts. A 2.5% additive of methanol or acetic acid was used to dissolve the silver salts. The selenocyclization reactions were conducted for 2 h for the chloride or bromide counterions and 7 h for the triflate or tetrafluoroborane counterions.

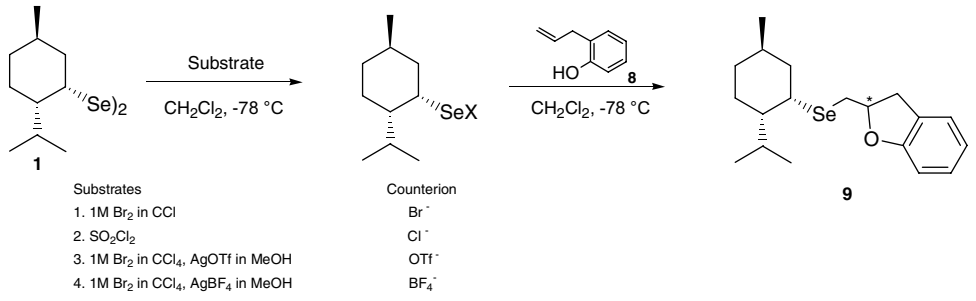
Modification of the counterions and the reaction time indicated that the best diastereomeric ratio (70:30) for dineomenthyl diselenide **1** was obtained with a triflate counterion in the presence of the 2.5% addition of methanol for 7 h (Table 1).

Table 1. Optimization of selenocyclization conditions with (+)-dineomenthyl diselenide **1**

Entry	Counterion	Time [h]	Additive	dr[a]	Yield [%]
1	Br^-	2	—	60:40	89
2	Cl^-	2	—	60:40	73
3	OTf^-	7	2.5% MeOH	70:30	23
4	OTf^-	7	2.5% AcOH	70:30	19
5	BF_4^-	7	2.5% MeOH	62:38	63

[a] dr was estimated on the basis of ^{1}H NMR spectra.

The main, enantiomerically pure product **9** was isolated from a diastereomeric mixture (70:30) by crystallization from *n*-pentane. The structure of **9** was confirmed on the basis of the ^{1}H and ^{13}C NMR spectra and X-ray structure analysis[13] (Fig. 2).



Scheme 2. Selenocyclization reaction with the use of (+)-dineomenthyl diselenide **1**.

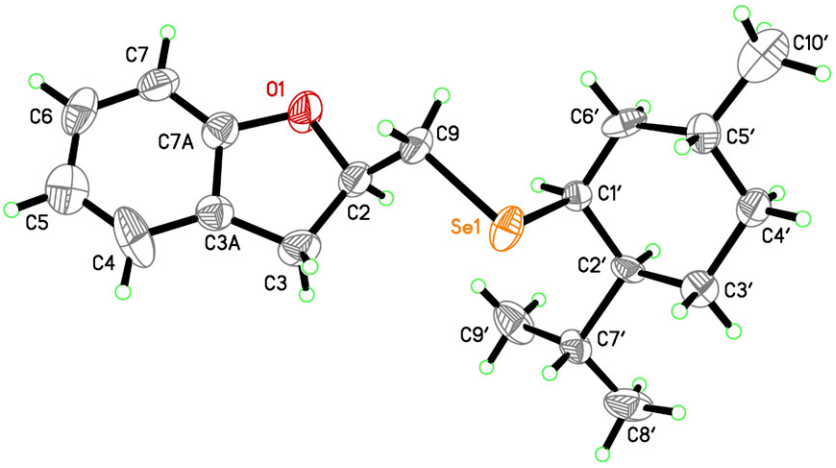
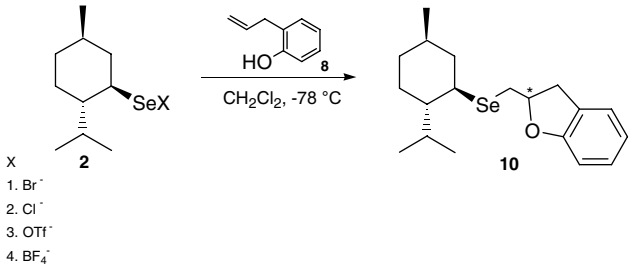


Figure 2. The molecule of (*R*)-2-(((1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexylselanyl)methyl)-2,3-dihydrobenzofuran **9**.

The absolute configuration, as determined by the Flack method,[14] the Flack $x = 0.14(5)$, was (2*R*,1′*S*,2′*S*,5′*R*). A comparison to the known absolute configuration of C1′, C5′ and C2′[10] confirmed the correct solution. Selected distances are Se(1)–C(9) 1.957(15), Se(1)–C(1′) 2.005(12) Å and C(9)–Se(1)–C(1′) and the angle C(9)–Se(1)–C(1′) is 95.8(6)°. Torsion angles describing the molecule conformation: C(3)–C(2)–C(9)–Se(1) 68.0(16)°, C(2)–C(9)–Se(1)–C(1′) 87.0(12)°, C(9)–Se(1)–C(1′)–C(6′) 79.0(11)°. The cyclohexyl ring of the neomenthyl moiety has a chair conformation. The 2,3-dihydrobenzofurane ring is planar, the rms deviation from the best plane being 0.021 Å.

To confirm the choice of the selenocyclization conditions, we carried out an analogous optimization using (−)-dimenthyl diselenide **2** (Scheme 3).



Scheme 3. Selenocyclization reaction with the use of (−)-dimenthyl diselenide **2**.

The best diastereomeric excesses for product **10** formed from (−)-dimenthyl diselenide were also obtained for the reaction carried out with the addition of triflate anion in 2.5% MeOH over 7 h (Table 2).

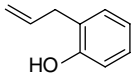
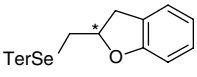
The addition of molecular sieves 4 Å increased the yield of the selenocyclization reaction from 23% to 57% for (+)-dineomenthyl diselenide **1** and from 77% to 92% for (−)-dimenthyl diselenide **2**. By employing the optimized reactions conditions, we conducted the selenocyclization reactions for optically active dialkyl diselenides **1**–**7**, thus obtaining the respective cyclic ethers **9**–**15**. For the reaction of *o*-allylphenol **8**, the best diastereomeric excess dr 70:30 was obtained for (+)-dineomenthyl diselenide **1** (Table 3).

Table 2. Optimization of the selenocyclization conditions with the use of (−)-dimenthyl diselenide **2**

Entry	Counterion	Time [h]	Additive	dr[a]	Yield [%]
1	Br^-	2	—	55:45	86
2	Cl^-	2	—	54:46	97
3	OTf^-	2	2.5% MeOH	63:37	32
4	OTf^-	7	2.5% MeOH	63:37	77
5	BF_4^-	7	2.5% MeOH	60:40	62

[a] dr was estimated on the basis of ^{1}H NMR spectra.

Table 3. Asymmetric selenocyclization with the use of alkyl terpene diselenides

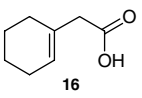
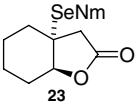
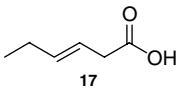
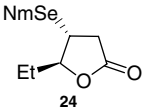
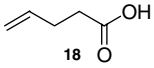
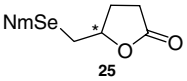
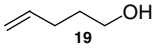
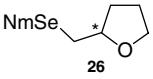
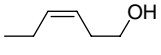
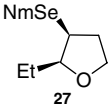
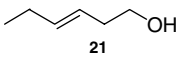
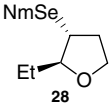
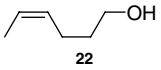
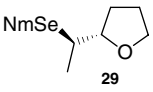
Alkene	Diselenide	Product	dr[a]	Yield [%]
 8	**1**	 9-15	**9** 70:30	57
	2		**10** 63:37	92
	3		**11** 52:48	55
	4		**12** 52:48	64
	5		**13** 52:48	87
	6		**14** 65:35	59
	7		**15** 52:48	83

[a] dr was estimated on the basis of ^{1}H NMR spectra; Ter—terpene moiety.

(+)-Dineomenthyl diselenide **1** has been used as a precursor for further investigations upon selenocyclization reactions with unsaturated acids **16**–**18** and alcohols **19**–**22** (Table 4). The transformations were carried out at −78 °C using the triflate ion as a counterion. The respective lactones **23**–**25** and cyclic ethers **26**–**29** were the products of this selenocyclization. An increase in the reaction temperature to 30 °C and long time of the reaction (24 h) were necessary for compound **20**. It is known that *Z*-disubstituted alkenes tend to react very slowly in selenocyclizations reactions to compare with *E*-disubstituted alkenes.[15]

The cyclization products have been isolated by a column chromatography and their structure was confirmed by

Table 4. The results of the selenocyclization reaction of unsaturated acid and alcohols with the use of (+)-dineomenthyl diselenide **1**

Alkene	Product[a]	Temp. [°C]	Time [h]	dr[b]	Yield [%]
 **16**	 **23**	−78	7	—	—
		−30	3	52:48	18
		0	3	52:48	21
 **17**	 **24**	−78	7	63:37	17
 **18**	 **25**	−78	7	65:35	87
 **19**	 **26**	−78	7	68:32	72
 **20**	 **27**	−78	7	—	—
		0	3	—	—
		30	3	—	—
		30	24	56:44	12
 **21**	 **28**	−78	7	77:23	29
 **22**	 **29**	−78	7	56:44	50

[a] Nm—neomenthyl moiety; the stereochemistry of the main diastereomers have not been determined.
[b] dr was estimated on the basis of ^{1}H and ^{77}Se NMR spectra.

means of the ^{1}H, ^{13}C and ^{77}Se NMR spectra. The diastereomeric excess of the product was estimated on the basis of the ^{1}H and ^{77}Se NMR spectra analysis. The best result 77:23 was achieved for compound **28**.

3. Conclusions

As a result of the conducted investigations, we have established, that terpene alkyl diselenides under the selenocyclization conditions gave the respective heterocyclic products. The best diastereomeric excesses were obtained when using (+)-dineomenthyl diselenide **1** at −78 °C in the presence of a triflate counterion. The use of molecular sieves considerably increased the yield of the selenocyclization reaction. The use of bicyclic systems at the selenocyclization conditions decreased the diastereomeric excess of the product of selenocyclization reaction. For the reaction of the (+)-dineomenthyl diselenide **1** with *o*-allylphenol the preferred diastereomer has an (*R*)-configuration on the newly formed stereogenic centre. The results obtained may be a convenient base for further investigations on functionalized dialkyl diselenides from the terpene group.

4. Experimental

4.1. General

Melting points were measured with a Büchi Tottoli SPM-20 heating unit and are uncorrected. NMR spectra were recorded on Bruker AM-300 at 300 MHz or Varian 200 at 200 MHz for ^{1}H and 75.5 MHz or 50.3 MHz for ^{13}C. Chemical shifts are expressed in parts per million (ppm) relative to TMS. ^{77}Se NMR spectra were recorded on Varian 200, with diphenyl diselenide as the external standard. Elemental analyses were performed on a Vario MACRO CHN analyzer. TLC was conducted on precoated silica gel plates (Merck $60F_{254}$) and the spots were visualized under UV light. Column chromatography was carried out on a column using Silica Gel 60 Merck (70–230 mesh) with the indicated solvents (petroleum ether (Pet ether): 40–60 °C). All reactions requiring anhydrous conditions were conducted in a flame-dried apparatus.

4.2. Asymmetric selenocyclization of olefins with the use of chiral monoterpene diselenides

A typical experimental procedure for the asymmetric cyclization of alkene is as follows. To a CH_2Cl_2 solution

(22.5 mL) of diselenide (250 mg, 0.58 mmol) and powdered molecular sieves (4 Å, 1.7 g) at −78 °C, a CCl_4 (0.6 mL) solution of bromine (96 mg, 0.6 mmol) was slowly added under an argon atmosphere. After 20 min, a solution of silver triflate (320 mg, 1.24 mmol) in methanol (1.0 mL) was added. The resulting heterogeneous mixture was stirred at −78 °C for 20 min. Olefin (1.16 mmol) was then added to the solution and stirred for 7 h at the same temperature. The mixture was treated with an aqueous solution of 10% $NaHCO_3$, extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel, yielding the addition products as yellow oils, and in one case, as white crystals. The diastereomers could not be separated by column chromatography, and diastereomeric ratios were determined after chromatography by ^1H and ^{77}Se NMR spectra analysis.

4.2.1. (*R*)-2-(((1*S*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexylselanyl)methyl)-2,3-dihydrobenzofuran 9. The title compound was obtained as a single diastereomer from the diastereomeric mixture (70:30) by crystallization from *n*-pentane. Yield 40%; white crystals; mp 85–86 °C; $[\alpha]_D^{20} = +80.8$ (*c* 1.48, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.89 (d, $J = 6.3$ Hz, 3H, CH_3), 0.92 (d, $J = 6.6$ Hz, 3H, CH_3), 0.96 (d, $J = 6.6$ Hz, 3H, CH_3), 0.96–1.15 (m, 4H), 1.29–1.38 (m, 1H), 1.57–1.65 (m, 1H), 1.70–1.78 (m, 2H), 1.86–2.03 (m, 2H), 2.76 (dd, $J = 8.1$, 12.3 Hz, 1H, CH_2), 2.95 (dd, $J = 5.7$, 12.3 Hz, 1H, CH_2), 3.04 (dd, $J = 7.2$, 15.9 Hz, 1H, CH_2), 3.38 (dd, $J = 9.0$, 15.9 Hz, 1H, CH_2), 3.49 (m, 1H, CHSe), 6.74 (m, 1H), 6.81–6.87 (m, 1H), 7.09–7.17 (m, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 20.8 (CH_3), 21.0 (CH_3), 22.1 (CH_3), 26.9 (CH_2), 27.6 (CH), 28.2 (CH_2), 31.2 (CH), 35.3 (CH_2), 35.8 (CH_2), 41.8 (CH_2), 45.9 (CH), 49.4 (CH), 82.7 (CH), 109.4 (CH), 120.4 (CH), 125.0 (CH), 126.4 (C), 128.0 (CH), 159.3 (C); ^{77}Se (38.1 MHz, $CDCl_3$): δ 119.6; Anal. Calcd for $C_{19}H_{28}OSe$: C, 64.95; H, 8.03. Found: C, 64.92; H, 7.99.

4.2.2. 2-(((1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexylselanyl)methyl)-2,3-dihydrobenzofuran 10. The title compound was obtained as a mixture of diastereomers. Yield 92%; yellow oil; column chromatography (70–230 mesh silica gel, 5% EtOAc/Pet ether); ^1H NMR (300 MHz, $CDCl_3$): δ major diastereomer 0.78 (d, $J = 6.9$ Hz, 3H, CH_3), 0.87 (d, $J = 7.2$ Hz, 3H, CH_3), 0.91 (d, $J = 7.2$ Hz, 3H, CH_3), 0.97–1.12 (m, 2H), 1.19–1.44 (m, 3H), 1.67–1.78 (m, 2H), 2.16–2.24 (m, 1H), 2.34 (dquin, $J = 3.0$, 6.9 Hz, 1H), 2.77 (dd, $J = 8.1$, 12.3 Hz, 1H, CH_2), 2.82–2.89 (m, 1H), 2.97 (dd, $J = 5.4$, 12.3 Hz, 1H, CH_2), 3.06 (dd, $J = 6.9$, 15.6 Hz, 1H, CH_2), 3.37 (dd, $J = 9.0$, 15.6 Hz, 1H, CH_2), 4.90–5.01 (m, 1H), 6.74 (m, 1H), 6.81–6.87 (m, 1H), 7.09–7.17 (m, 2H); minor diastereomer 0.71 (d, $J = 6.9$ Hz, 3H, CH_3), 2.94 (dd, $J = 5.4$, 12.3 Hz, 1H, CH_2), 3.36 (dd, $J = 9.0$, 15.6 Hz, 1H, CH_2); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ major diastereomer 15.1 (CH_3), 21.4 (CH_3), 22.1 (CH_3), 24.8 (CH_2), 26.2 (CH_2), 28.9 (CH), 34.2 (CH), 34.7 (CH_2), 35.7 (CH_2), 43.6 (CH), 44.9 (CH_2), 47.6 (CH), 82.7 (CH), 109.2 (CH), 120.3 (CH), 124.8 (CH), 126.2 (C), 127.8 (CH), 159.2 (C); minor diastereomer 15.0 (CH_3), 26.5 (CH_2), 35.6 (CH_2), 47.9 (CH), 82.6 (CH), 124.7 (CH), 126.3 (C); ^{77}Se (38.1 MHz, $CDCl_3$): δ major diastereomer 204.7; minor diastereomer 201.6; Anal. Calcd for $C_{19}H_{28}OSe$: C, 64.95; H, 8.03. Found: C, 64.96; H, 7.91.

4.2.3. 2-(((1*R*,3*S*,4*R*,6*S*)-4,7,7-Trimethylbicyclo[4.1.0]heptan-3-ylselanyl)methyl)-2,3-dihydrobenzofuran 11. The title compound was obtained as a mixture of diastereomers. Yield 55%; yellow oil; column chromatography (70–230 mesh silica gel, 10% EtOAc/Pet ether); ^1H NMR (200 MHz, $CDCl_3$): δ major diastereomer 0.66–0.85 (m, 3H), 0.97–1.01 (m, 9H), 1.41–1.59 (m, 1H), 1.78–1.93 (m, 2H), 2.21–2.32 (m, 1H), 2.71–2.81 (m, 1H), 2.97 (dd, $J = 5.7$, 12.4 Hz, 1H, CH_2), 3.09 (dd, $J = 7.2$, 15.9 Hz, 1H, CH_2), 3.19–3.33 (m, 1H), 3.38 (dd, $J = 9.0$, 15.9 Hz, 1H, CH_2), 4.88–5.03 (m, 1H), 6.76 (m, 1H), 6.81–6.87 (m, 1H), 7.09–7.18 (m, 2H); minor diastereomer 0.98 (d, $J = 6.4$ Hz, 3H, CH_3), 2.93 (dd, $J = 5.7$, 12.4 Hz, 1H, CH_2); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ major diastereomer 15.9 (CH_3), 17.6 (C), 20.2 (CH_3), 21.2 (CH), 21.4 (CH), 25.6 (CH_2), 26.5 (CH_2), 28.5 (CH_3), 28.8 (CH_2), 31.1 (CH), 35.7 (CH_2), 43.4 (CH), 82.7 (CH), 109.3 (CH), 120.4 (CH), 124.9 (CH), 126.3 (C), 127.9 (CH), 159.2 (C); minor diastereomer 25.5 (CH_2), 26.2 (CH_2), 29.2 (CH_2), 43.9 (CH); ^{77}Se (38.1 MHz, $CDCl_3$): δ major diastereomer 180.2; minor diastereomer 178.3; Anal. Calcd for $C_{19}H_{26}OSe$: C, 65.32; H, 7.50. Found: C, 65.19; H, 7.26.

4.2.4. 2-(((1*R*,3*R*,4*R*,6*S*)-4,7,7-Trimethylbicyclo[4.1.0]heptan-3-ylselanyl)methyl)-2,3-dihydrobenzofuran 12. The title compound was obtained as a mixture of diastereomers. Yield 64%; yellow oil; column chromatography (70–230 mesh silica gel, 10% EtOAc/Pet ether); ^1H NMR (200 MHz, $CDCl_3$): δ major diastereomer 0.66–0.74 (m, 1H), 0.76–0.94 (m, 2H), 0.96 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 0.99 (d, $J = 6.4$ Hz, 3H, CH_3), 1.12–1.43 (m, 1H), 1.92–2.25 (m, 3H), 2.40–2.59 (m, 1H), 2.80 (dd, $J = 8.1$, 12.3 Hz, 1H, CH_2), 2.97 (dd, $J = 5.4$, 12.3 Hz, 1H, CH_2), 3.09 (dd, $J = 6.9$, 15.6 Hz, 1H, CH_2), 3.38 (dd, $J = 9.0$, 15.6 Hz, 1H, CH_2), 4.88–5.03 (m, 1H), 6.74 (m, 1H), 6.81–6.87 (m, 1H), 7.09–7.17 (m, 2H); minor diastereomer 1.03 (d, $J = 6.4$ Hz, 3H, CH_3), 2.99 (dd, $J = 5.4$, 12.3 Hz, 1H, CH_2); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ major diastereomer 15.5 (CH_3), 17.4 (C), 20.5 (CH), 20.6 (CH), 21.6 (CH_3), 27.2 (CH_2), 28.8 (CH_3), 29.4 (CH_2), 29.8 (CH_2), 35.1 (CH), 35.7 (CH_2), 44.8 (CH), 82.8 (CH), 109.3 (CH), 120.3 (CH), 124.8 (CH), 126.3 (C), 127.9 (CH), 159.1 (C); minor diastereomer 15.6 (CH_3), 27.5 (CH_2), 34.8 (CH), 45.2 (CH), 82.9 (CH), 109.4 (CH), 159.2 (C); ^{77}Se (38.1 MHz, $CDCl_3$): δ major diastereomer 229.0; minor diastereomer 233.2; Anal. Calcd for $C_{19}H_{26}OSe$: C, 65.32; H, 7.50. Found: C, 65.19; H, 7.28.

4.2.5. 2-(((1*R*,2*R*,3*S*,5*S*)-2,6,6-Trimethylbicyclo[3.1.1]heptan-3-ylselanyl)methyl)-2,3-dihydrobenzofuran 13. The title compound was obtained as a mixture of diastereomers. Yield 87%; yellow oil; column chromatography (70–230 mesh silica gel, 5% EtOAc/Pet ether); ^1H NMR (300 MHz, $CDCl_3$): δ major diastereomer 1.01 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.23 (d, $J = 6.9$ Hz, 3H, CH_3), 1.33 (d, $J = 9.9$ Hz, 1H, CH_2), 1.89–2.01 (m, 2H), 2.05–2.25 (m, 2H), 2.38–2.50 (m, 1H), 2.52–2.62 (m, 1H), 2.85

(dd, $J = 7.5$, 12.3 Hz, 1H), 2.76–3.12 (m, 2H), 3.35–3.45 (m, 1H), 3.87–3.99 (m, 1H), 4.94–5.06 (m, 1H), 6.77 (m, 1H), 6.82–6.87 (m, 1H), 7.09–7.18 (m, 2H); minor diastereomer 1.03 (s, 3H, CH_3), 2.80 (dd, $J = 7.5$, 12.3 Hz, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ major diastereomer 19.4 (CH_3), 23.4 (CH_3), 27.4 (CH_3), 27.8 (CH_2), 27.9 (CH_2), 34.3 (CH), 35.7 (CH_2), 36.4 (CH_2), 37.9 (CH), 39.4 (C), 41.8 (CH), 48.7 (CH), 82.6 (CH), 109.2 (CH), 120.3 (CH), 124.8 (CH), 126.2 (C), 127.8 (CH), 159.1 (C); minor diastereomer 27.7 (CH_2), 28.2 (CH_2), 33.7 (CH), 35.8 (CH_2), 36.5 (CH_2), 37.8 (CH), 82.5 (CH), 109.3 (CH), 126.1 (C); ^{77}Se (38.1 MHz, $CDCl_3$): δ major diastereomer 185.4; minor diastereomer 190.3; Anal. Calcd for $C_{19}H_{26}OSe$: C, 65.32; H, 7.50. Found: C, 65.43; H, 7.44.

4.2.6. 2-(((1*R*,2*R*,3*R*,5*S*)-2,6,6-Trimethylbicyclo[3.1.1]heptan-3-ylselanyl)methyl)-2,3-dihydrobenzofuran 14. The title compound was obtained as a mixture of diastereomers. Yield 59%; yellow oil; column chromatography (70–230 mesh silica gel, 5% EtOAc/Pet ether); ^1H NMR (300 MHz, $CDCl_3$): δ major diastereomer 1.05 (s, 3H, CH_3), 1.07 (d, $J = 9.9$ Hz, 1H, CH_2), 1.16 (d, $J = 6.9$ Hz, 3H, CH_3), 1.21 (s, 3H, CH_3), 1.81–1.90 (m, 1H), 1.93–1.98 (m, 1H), (dquin, $J = 1.8$, 7.2 Hz, 1H), 2.20 (ddd, $J = 2.4$, 6.6, 13.8 Hz, 1H), 2.35–2.44 (m, 1H), 2.52–2.65 (m, 1H), 2.83 (dd, $J = 7.8$, 12.3 Hz, 1H), 2.96–3.12 (m, 2H), 3.21–3.45 (m, 2H), 4.97–5.09 (m, 1H), 6.76 (m, 1H), 6.82–6.87 (m, 1H), 7.09–7.18 (m, 2H); minor diastereomer 1.03 (s, 3H, CH_3), 1.09 (d, $J = 6.9$ Hz, 3H, CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ major diastereomer 21.4 (CH_3), 23.2 (CH_3), 27.8 (CH_3), 28.0 (CH_2), 34.0 (CH_2), 35.9 (CH_2), 37.1 (CH), 38.4 (C), 38.5 (CH_2), 42.4 (CH), 45.4 (CH), 48.3 (CH), 82.8 (CH), 109.3 (CH), 120.3 (CH), 124.9 (CH), 126.2 (C), 127.9 (CH), 159.2 (C); minor diastereomer 27.9 (CH_3), 33.9 (CH_2), 35.7 (CH_2), 37.5 (CH), 38.6 (CH_2), 45.6 (CH), 82.6 (CH), 109.2 (CH), 126.3 (C), 127.8 (CH); ^{77}Se (38.1 MHz, $CDCl_3$): δ major diastereomer 292.4; minor diastereomer 287.0; Anal. Calcd for $C_{19}H_{26}OSe$: C, 65.32; H, 7.50. Found: C, 65.13; H, 7.57.

4.2.7. 2-((((1*S*,2*R*,5*S*)-6,6-Dimethylbicyclo[3.1.1]heptan-2-yl)methylselanyl)methyl)-2,3-dihydrobenzofuran 15. The title compound was obtained as a mixture of diastereomers. Yield 83%; yellow oil; column chromatography (70–230 mesh silica gel, 5% EtOAc/Pet ether); ^1H NMR (200 MHz, $CDCl_3$): δ 0.89 (d, $J = 9.6$ Hz, 1H, CH_2), 1.01 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.41–1.61 (m, 1H), 1.83–2.17 (m, 5H), 2.20–2.42 (m, 2H), 2.74–2.84 (m, 3H), 2.95 (dd, $J = 5.8$, 12.4 Hz, 1H, CH_2), 3.07 (dd, $J = 6.9$, 15.9 Hz, 1H, CH_2), 3.40 (dd, $J = 9.0$, 15.9 Hz, 1H, CH_2), 4.88–5.03 (m, 1H), 6.74 (m, 1H), 6.81–6.87 (m, 1H), 7.09–7.17 (m, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ major diastereomer 22.8 (CH_2), 23.1 (CH_3), 27.9 (CH_2), 27.9 (CH_3), 28.5 (CH_2), 32.7 (CH_2), 33.3 (CH_2), 35.8 (CH_2), 38.5 (C), 41.1 (CH), 41.7 (CH), 46.1 (CH), 82.5 (CH), 109.2 (CH), 120.3 (CH), 124.8 (CH), 126.2 (C), 127.8 (CH), 159.1 (C); minor diastereomer 28.6 (CH_2), 32.8 (CH_2), 41.8 (CH), 46.2 (CH), 82.6 (CH), 126.1 (C); ^{77}Se (38.1 MHz, $CDCl_3$): δ major diastereomer 116.1; minor diastereomer 114.9; Anal. Calcd for $C_{19}H_{26}OSe$: C, 65.32; H, 7.50. Found: C, 65.33; H, 7.10.

4.2.8. *trans*-3a-((1*S*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexylselanyl)-hexahydrobenzofuran-2(3*H*)-one 23. The title compound was obtained as a mixture of diastereomers. Yield 21%; yellow oil; column chromatography (70–230 mesh silica gel, 10% EtOAc/Pet ether); ^1H NMR (300 MHz, $CDCl_3$): δ major diastereomer 0.90 (d, $J = 6.4$ Hz, 3H, CH_3), 0.92 (d, $J = 6.4$ Hz, 3H, CH_3), 0.99 (d, $J = 6.2$ Hz, 3H, CH_3), 1.10–1.46 (m, 3H), 1.49–1.68 (m, 5H). 1.70–1.90 (m, 4H), 1.92–2.07 (m, 4H), 2.12–2.33 (m, 1H), 2.56 (d, $J = 16.8$ Hz, 1H), 2.92 (d, $J = 16.8$ Hz, 1H), 3.67–3.71 (m, 1H), 4.49 (t, $J = 3.9$ Hz, 1H); minor diastereomer 0.91 (d, $J = 6.4$ Hz, 3H, CH_3), 0.97 (d, $J = 6.2$ Hz, 3H, CH_3), 2.47 (d, $J = 16.8$ Hz, 1H), 2.98 (d, $J = 16.8$ Hz, 1H), 4.52 (t, $J = 3.9$ Hz, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ major diastereomer 19.6 (CH_2), 20.8 (CH_3), 21.1 (CH_3), 21.8 (CH_2), 21.9 (CH_3), 25.2 (CH_2), 26.2 (CH_2), 27.4 (CH), 31.3 (CH), 33.2 (CH_2), 35.2 (CH_2), 41.8 (CH_2), 45.2 (CH_2), 45.3 (C), 49.6 (CH), 52.6 (CH), 82.8 (CH), 174.9 (C=O); minor diastereomer 20.9 (CH_3), 26.1 (CH_2), 33.1 (CH_2), 41.7 (CH_2), 45.1 (CH_2), 45.4 (C), 52.5 (CH); ^{77}Se (38.1 MHz, $CDCl_3$): δ major diastereomer 282.2; minor diastereomer 282.1; Anal. Calcd for $C_{18}H_{30}O_2Se$: C, 60.50; H, 8.46. Found: C, 60.87; H, 8.62.

4.2.9. *trans*-5-Ethyl-4-((1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexylselanyl)-dihydrofuran-2(3*H*)-one 24. The title compound was obtained as a mixture of diastereomers. Yield 17%; yellow oil; column chromatography (70–230 mesh silica gel, 10% EtOAc/Pet ether); ^1H NMR (200 MHz, $CDCl_3$): δ 0.78–1.01 (m, 9H), 1.08 (t, $J = 7.5$ Hz, 3H, CH_3), 1.15–1.47 (m, 3H), 1.51–1.96 (m, 7H), 2.12–2.26 (m, 1H), 2.55–2.96 (m, 2H), 3.23–3.44 (m, 1H), 3.60–3.68 (m, 1H), 4.27–4.41 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ major diastereomer 9.8 (CH_3), 20.9 (CH_3), 21.0 (CH_3), 22.0 (CH_3), 26.4 (CH_2), 26.8 (CH_2), 27.5 (CH), 31.4 (CH), 35.2 (CH_2), 36.9 (CH), 37.2 (CH_2), 41.7 (CH_2), 49.6 (CH), 53.1 (CH), 88.3 (CH), 174.7 (C=O); minor diastereomer 9.7 (CH_3), 21.1 (CH_3), 27.6 (CH), 36.8 (CH), 37.1 (CH_2), 41.9 (CH_2), 49.7 (CH), 53.3 (CH), 88.2 (CH); ^{77}Se (38.1 MHz, $CDCl_3$): δ major diastereomer 281.6; minor diastereomer 283.5; Anal. Calcd for $C_{16}H_{28}O_2Se$: C, 58.00; H, 8.52. Found: C, 58.23; H, 8.31.

4.2.10. 5-(((1*S*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexylselanyl)methyl)-dihydrofuran-2(3*H*)-one 25. The title compound was obtained as a mixture of diastereomers. Yield 87%; yellow oil; column chromatography (70–230 mesh silica gel, 10% EtOAc/Pet ether); ^1H NMR (200 MHz, $CDCl_3$): δ major diastereomer 0.75 (d, $J = 6.8$ Hz, 3H, CH_3), 0.89 (d, $J = 7.0$ Hz, 3H, CH_3), 0.92 (d, $J = 7.0$ Hz, 3H, CH_3), 0.94–1.13 (m, 1H), 1.17–1.50 (m, 3H), 1.67–1.82 (m, 2H), 1.90–2.08 (m, 2H), 2.10–2.32 (m, 2H), 2.33–3.55 (m, 1H), 2.57–2.98 (m, 5H), 4.11–4.74 (m, 1H); minor diastereomer 0.73 (d, $J = 6.8$ Hz, 3H, CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ major diastereomer 15.1 (CH_3), 21.4 (CH_3), 22.1 (CH_3), 24.8 (CH_2), 25.4 (CH_2), 27.8 (CH_2), 28.7 (CH), 28.9 (CH_2), 34.1 (CH), 34.6 (CH_2), 44.1 (CH), 44.9 (CH_2), 47.7 (CH), 80.0 (CH), 176.6 (C=O); minor diastereomer 25.6 (CH_2), 27.6 (CH_2), 44.5 (CH), 48.0 (CH), 80.1 (CH); ^{77}Se (38.1 MHz, $CDCl_3$): δ major diastereomer 200.1; minor diastereomer

196.5; Anal. Calcd for $C_{15}H_{26}O_2Se$: C, 56.78; H, 8.26. Found: C, 56.60; H, 8.20.

4.2.11. 2-(((1*S*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexylselanyl)methyl)-tetrahydrofuran 26. The title compound was obtained as a mixture of diastereomers. Yield 72%; yellow oil; column chromatography (70–230 mesh silica gel, 5% EtOAc/Pet ether); ^{1}H NMR (300 MHz, $CDCl_3$): δ major diastereomer 0.86 (d, $J = 6.6$ Hz, 3H, CH_3), 0.88 (d, $J = 6.6$ Hz, 3H, CH_3), 0.92 (d, $J = 6.6$ Hz, 3H, CH_3), 1.00–1.13 (m, 1H), 1.26–1.43 (m, 3H), 1.53–1.74 (m, 4H), 1.79–2.09 (m, 5H), 2.63 (dd, $J = 7.2$, 9.6 Hz, 1H), 2.71 (dd, $J = 5.7$, 11.7 Hz, 1H), 3.39 (m, 1H), 3.70–3.78 (m, 1H), 3.85–3.92 (m, 1H), 3.99–4.08 (m, 1H); minor diastereomer 2.58 (dd, $J = 7.2$, 9.6 Hz, 1H), 2.73 (dd, $J = 5.7$, 11.7 Hz, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ major diastereomer 20.7 (CH_3), 20.8 (CH_3), 22.0 (CH_3), 25.8 (CH_2), 26.7 (CH_2), 27.4 (CH), 28.5 (CH_2), 31.0 (CH), 31.6 (CH_2), 35.2 (CH_2), 41.8 (CH_2), 45.5 (CH), 49.3 (CH), 68.1 (CH_2), 79.4 (CH); minor diastereomer 27.5 (CH), 29.0 (CH_2), 42.2 (CH_2), 46.0 (CH), 49.4 (CH), 67.9 (CH_2); ^{77}Se (38.1 MHz, $CDCl_3$): δ 124.4; Anal. Calcd for $C_{15}H_{28}OSe$: C, 59.39; H, 9.30. Found: C, 59.47; H, 9.38.

4.2.12. *cis*-2-Ethyl-3-((1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexylselanyl)-tetrahydrofuran 27. The title compound was obtained as a mixture of diastereomers. Yield 12%; yellow oil; column chromatography (70–230 mesh silica gel, 10% EtOAc/Pet ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88–1.06 (m, 15H), 1.18–1.48 (m, 2H), 1.51–1.82 (m, 4H), 1.86–2.18 (m, 3H), 2.23–2.52 (m, 1H), 3.34–3.45 (m, 2H), 3.75–3.84 (m, 2H), 3.96–4.07 (m, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ major diastereomer 10.9 (CH_3), 20.8 (CH_3), 21.1 (CH_3), 22.1 (CH_3), 25.8 (CH_2), 26.9 (CH_2), 27.8 (CH), 31.1 (CH), 35.3 (CH_2), 35.4 (CH_2), 41.9 (CH), 43.3 (CH_2), 45.9 (CH), 49.8 (CH), 65.9 (CH_2), 83.4 (CH); minor diastereomer 10.8 (CH_3), 20.7 (CH_3), 20.9 (CH_3), 26.1 (CH_2), 27.0 (CH_2), 27.5 (CH), 31.0 (CH), 34.9 (CH_2), 35.5 (CH_2), 40.8 (CH), 41.7 (CH), 44.8 (CH), 49.4 (CH), 66.0 (CH_2), 83.3 (CH); ^{77}Se (38.1 MHz, $CDCl_3$): δ major diastereomer 180.0; minor diastereomer 174.0; Anal. Calcd for $C_{16}H_{30}OSe$: C, 60.55; H, 9.53. Found: C, 60.61; H, 9.22.

4.2.13. *trans*-2-Ethyl-3-((1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexylselanyl)-tetrahydrofuran 28. The title compound was obtained as a mixture of diastereomers. Yield 29%; yellow oil; column chromatography (70–230 mesh silica gel, 10% EtOAc/Pet ether); ^{1}H NMR (300 MHz, $CDCl_3$): δ major diastereomer 0.74–0.84 (m, 2H), 0.87 (d, $J = 6.3$ Hz, 3H, CH_3), 0.89 (d, $J = 6.6$ Hz, 3H, CH_3), 0.92 (d, $J = 6.6$ Hz, 3H, CH_3), 0.98 (t, $J = 7.5$ Hz, 3H, CH_3), 0.99–1.12 (m, 1H), 1.29–1.40 (m, 1H), 1.48–1.64 (m, 2H), 1.70–1.76 (m, 3H), 1.84–2.05 (m, 3H), 2.31–2.44 (m, 1H), 2.84 (m, 1H), 3.42 (m, 1H), 3.59 (dt, $J = 4.2$, 7.5 Hz, 1H), 3.78–3.89 (m, 2H); minor diastereomer 0.91 (d, $J = 6.6$ Hz, 3H, CH_3), 0.97 (t, $J = 7.5$ Hz, 3H, CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ major diastereomer 10.4 (CH_3), 20.8 (CH_3), 20.9 (CH_3), 22.1 (CH_3), 26.9 (CH_2), 27.0 (CH_2), 27.6 (CH), 31.0 (CH), 35.3 (CH_2), 35.8 (CH_2), 39.6 (CH), 42.4 (CH_2), 45.4 (CH), 49.4 (CH), 66.7 (CH_2), 86.4 (CH); minor diastereomer 27.2 (CH_2), 31.1 (CH), 36.2 (CH_2), 40.3 (CH), 43.1 (CH_2), 45.9 (CH), 49.7 (CH), 86.6 (CH); ^{77}Se (38.1 MHz, $CDCl_3$): δ major diastereomer 229.2; minor diastereomer 234.9; Anal. Calcd for $C_{16}H_{30}OSe$: C, 60.55; H, 9.53. Found: C, 60.57; H, 9.08.

4.2.14. 2-(1-((1*S*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexylselanyl)ethyl)-tetrahydrofuran 29. The title compound was obtained as a mixture of diastereomers. Yield 50%; yellow oil; column chromatography (70–230 mesh silica gel, 10% EtOAc/Pet ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.79–1.01 (m, 12H), 1.03–1.21 (m, 1H), 1.28 (t, $J = 7.5$ Hz, 3H, CH_3), 1.35–1.48 (m, 2H), 1.62–1.78 (m, 3H), 1.84–2.16 (m, 4H), 2.81–2.93 (m, 1H), 3.23–3.36 (m, 1H), 3.40–3.62 (m, 2H), 3.86–4.04 (m, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ major diastereomer 20.7 (CH_3), 20.9 (CH_3), 21.0 (CH_3), 22.1 (CH_3), 22.9 (CH_2), 26.9 (CH_2), 27.6 (CH), 31.0 (CH), 31.6 (CH_2), 35.3 (CH_2), 42.2 (CH_2), 45.3 (CH), 45.5 (CH), 49.5 (CH), 67.6 (CH_2), 76.1 (CH); minor diastereomer 26.8 (CH_2), 27.4 (CH), 32.2 (CH_2), 42.8 (CH_2), 45.1 (CH), 45.8 (CH), 49.9 (CH), 67.9 (CH_2), 76.2 (CH); ^{77}Se (38.1 MHz, $CDCl_3$): δ major diastereomer 158.1; minor diastereomer 156.3; Anal. Calcd for $C_{16}H_{30}OSe$: C, 60.55; H, 9.53. Found: C, 60.57; H, 9.12.

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13. Colourless $0.25 \times 0.13 \times 0.06$ mm crystals of (*R*)-2-(((1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexylselanyl)methyl)-2,3-dihydrobenzofuran **9** were obtained from the methanol solution. The compound crystallized in the monoclinic space group C2. The X-ray data were collected at 293(2) K with the Oxford Sapphire CCD diffractometer, graphite monochromator, MoKα radiation ($\lambda = 0.71073$ Å), cell parameters $a = 20.017(4)$, $b = 5.262(1)$, $c = 19.194(4)$ Å, $\beta = 116.92(3)°$, $V = 1802.6(6)$ Å^3, D_{calc} 1.295 Mg/m^3, $Z = 4$, $F(000) = 736$, $\mu = 2.081$ mm^{-1}. The absorption correction was applied (CrysAlis RED 171 package, Oxford Diffraction, 2000), with the maximum and minimum transmissions of 0.8871 and

0.6285. The structure was solved by direct methods and refined with the full-matrix least-squares on F^2 with the use of SHELX-97[16] to $R_1 = 0.1222$, $wR_2 = 0.3021$ for reflections $I > 2\sigma(I)$. The extinction correction applied, extinction coefficient 0.017(4). Absolute structure was determined by the Flack method,[14] $x = 0.14(5)$. Non-hydrogen atoms were refined anisotropically, hydrogen atoms were constrained as riding atoms. The (*R*,*S*,*S*,*R*)—C2, C1′, C2′ and C5′ chirality was determined. The structural data for **9** have been deposited at the Cambridge Crystallographic Data Centre: (CCDC No. 623526).

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