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Organoselenium mediated asymmetric cyclizations. Synthesis of enantiomerically pure 1,6-dioxaspiro[4.4]nonanes

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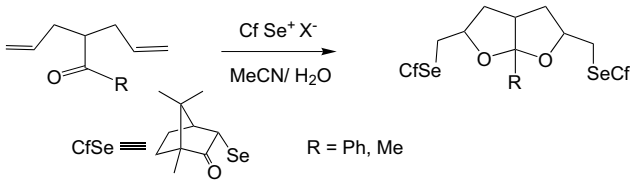
Abstract—The asymmetric cyclization of 1-hydroxyoct-7-en-4-one, promoted by camphorselenenyl tetrafluoroborate, generated from camphor diselenide and silver tetrafluoroborate in dichloromethane at room temperature, afforded a mixture of two diastereoisomeric *E*- and two diastereoisomeric *Z*-2-[(camphorseleno)methyl]-1,6-dioxaspiro[4.4]nonanes. These were separated by medium pressure liquid chromatography and then deselenenylated with triphenyltin hydride and AIBN to give enantiomerically pure 2-methyl-1,6-dioxaspiro[4.4]nonanes. The camphorseleno group was also substituted by an allyl function using allyltributyltin in the presence of AIBN.

1. Introduction

In recent years, we have described the synthesis of different types of heterocyclic compounds, in an enantiomerically enriched or pure form, by means of reagent-controlled or substrate-controlled cyclizations of alkenes containing internal nucleophiles, promoted by electrophilic organoselenium reagents.[1] Several chiral nonracemic selenium reagents have recently been introduced in the literature to effect efficient asymmetric reagent-controlled intramolecular selenocyclization reactions.[2–8] In general the electrophilic selenium reagent is conveniently prepared in situ starting from the corresponding diselenide. Particular attention was devoted to the stereoselective synthesis of substituted cyclic ether derivatives[8,9] since these heterocyclic compounds are present in several molecules having interesting biological properties.[10] Of particular importance are the bicyclic ketal derivatives perhydrofuro[2,3-*b*]furans whose skeleton is encountered in many biologically active natural products.[11] In order to synthesize this kind of substrate we have recently effected the double cyclization of bis-alkenylketones promoted by the electrophilic reagents deriving from the sulfur containing diselenides in the presence of water. These experiments, however, gave unsatisfactory results since an unseparable mixture of diastereoisomers was obtained. When the reaction was repeated using the camphorselenenyl sulfate (Scheme 1), the cyclization reaction was again not stereoselective giving a mixture of all the four possible diastereoisomers. In this case however these diastereoisomers could be separated and the enantiopure perhydrofuro[2,3-*b*]furans derivatives could thus be obtained by deselenenylation.[12]



Scheme 1.

Herein, we report that by using a similar procedure and starting from 1-hydroxyoct-7-en-4-one the synthesis of enantiopure 2-substituted 1,6-dioxaspiro[4.4]nonanes can easily be effected. The enantioselective synthesis of these spiroacetals is of considerable importance since these nuclei are the subunits of many biologically active natural products, for example, insect pheromones, oxygenated terpenoids, polyether antibiotics and antiparasitic agents.[13,14] This has stimulated considerable interest among synthetic organic chemists and several methods to obtain different types of racemic spiroacetals have been reported in the literature.[14–18]

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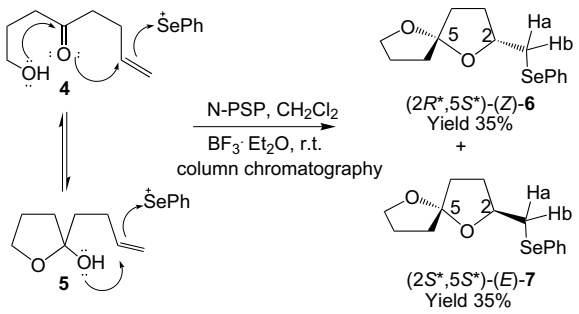
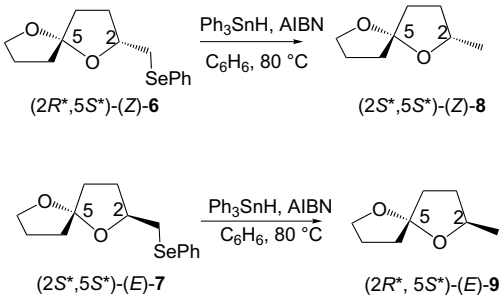
2. Results and discussion

The starting compound necessary for the present investigation was easily prepared from the commercially available ethyl-3-oxobutanoate **1**. As indicated in Scheme 2, this was subjected to two consecutive alkylations to afford ketone **3**, which after hydrolysis and simultaneous removal of the tetrahydropyran-2-yl protecting group gave a 1:2 mixture of hydroxyketone **4** and of hemiacetal **5**. This procedure is shorter than that reported in the literature.[14]

In order to dispose of the two racemic geometrical isomers **6** and **7** and of their deselenenylation products, which were necessary as reference compounds, we carried out the cyclization reaction of the mixture of **4** and **5** with *N*-(phenylseleno)phthalimide (*N*-PSP) in the presence of BF_3 as the catalyst at room temperature. This reaction produced a 1:1 mixture of the two isomeric 2-[(phenylseleno)methyl]-1,6-dioxaspiro[4.4]nonanes **6** and **7**, which were separated by medium pressure liquid chromatography on a silica gel column. In Scheme 3, the two geometrical isomers are presented in the order in which they are eluted from the chromatographic column. This reaction has already been described in the literature.[14] Also in that case a 1:1 mixture was obtained; however, the two racemic geometrical isomers **6** and **7** could not be separated.



Scheme 3.



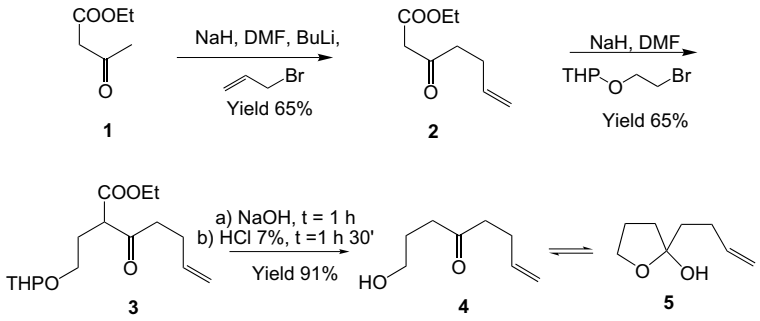
Scheme 4.

The *Z*- and *E*-geometry was attributed to **6** and **7**, respectively, on the basis of their ^1H and ^{13}C NMR spectra. In agreement with the data reported in the literature[17] (see below) for similar 2-substituted-1,6-dioxaspiro[4.4]nonanes the proton at the 2-position is deshielded in the *E*-isomer in respect to the corresponding proton in the *Z*-isomer (4.35 vs 4.22 ppm). At the same time, the absorption of carbon-2 is deshielded in the *Z*-isomer with respect to that of the *E*-isomer (78.9 vs 77.1 ppm). These geometrical attributions were then unambiguously confirmed by the deselenenylation of **6** and **7** to the corresponding racemic 2-methyl-1,6-dioxaspiro[4.4]nonanes, which are described in the literature.[17] It is also noteworthy that the difference in chemical shift between the two diastereotopic protons, Ha and Hb, in the CH_2Se group is greater for the *Z*-isomer than for the *E*-isomer (3.25 and 2.97 ppm, $\Delta\delta = 0.28$ for **6** and 3.10 and 2.98 ppm, $\Delta\delta = 0.12$ for **7**).

As illustrated in Scheme 4, the two diastereoisomers **6** and **7** were then submitted to reductive deselenenylation with Ph_3SnH and AIBN and afforded compounds **8** and **9**, respectively. Owing to their volatility[13b] and to the tendency of the *Z*-isomer to equilibrate on standing or on prolonged contact with silica gel, the benzene was carefully evaporated under reduced pressure and the deselenenylated products were isolated by simple filtration of the reaction mixtures on a deactivated silica gel column.[19] The eluate was carefully evaporated and the resulting crude products were then directly analyzed by NMR. As anticipated above the ^1H and ^{13}C NMR data of the racemic *Z*- and *E*-2-methyl-1,6-dioxaspiro[4.4]nonanes **8** and **9** are in good agreement with those reported in the literature.[17]

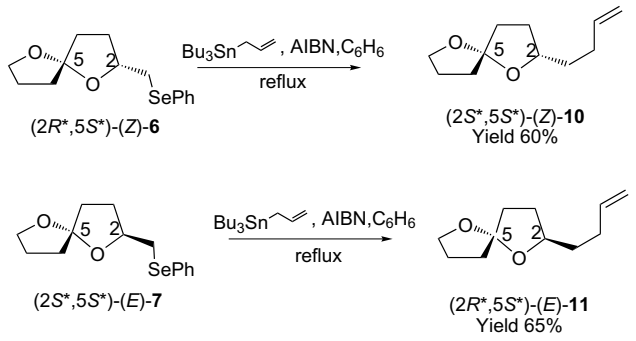
These trends of the ^1H and ^{13}C NMR data were particularly useful to confidently assign either the *Z*- or *E*-configurations to the 1,6-dioxaspiro[4.4]nonanes, which are described below.

Owing to the presence of the arylseleno group, compounds **6** and **7** can be further functionalized. As an example we report that the PhSe can be substituted by an allyl group by



Scheme 2.

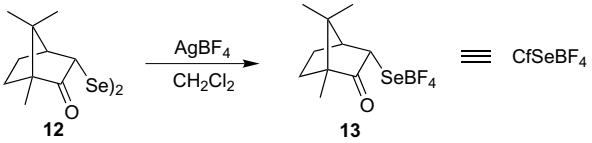
simple treatment with allyltributyltin and AIBN (Scheme 5). In order to minimize the equilibration of the *Z*-isomer, the reaction mixtures were worked up as described above for the deselenenylated products. *Z*-Isomer **10** (δ_{H2} 3.94 ppm, δ_{C2} 79.4 ppm) and *E*-isomer **11** (δ_{H2} 4.04 ppm, δ_{C2} 77.6 ppm) were thus obtained in satisfactory yields from **6** and **7**, respectively.



Scheme 5.

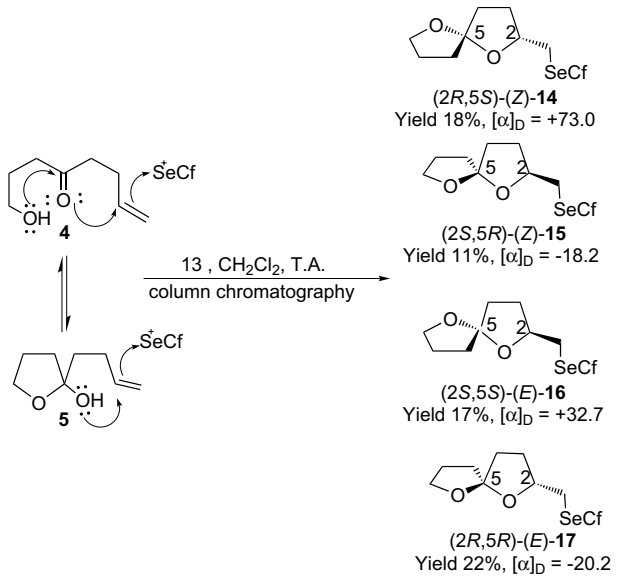
With all these data in hand, we then approached the problem of the asymmetric cyclization reactions of a mixture of **4** and **5** using the camphor diselenide as the precursor of the chiral nonracemic electrophilic selenenylating agent. This diselenide can be easily obtained in a *one-pot* from (1*R*)-(+)-camphor and elemental selenium as described by Back.[20]

Unsatisfactory results were obtained from some preliminary experiments carried out with camphorselenenyl sulfate or triflate, the desired spiro compounds being obtained in very low yields. Only using camphorselenenyl tetrafluoroborate **13**, generated from the reaction of camphor diselenide **12** with silver tetrafluoroborate, could the cyclization products be obtained in a good yield. The electrophilic reagent was formed in dichloromethane at −50 °C, the resulting suspension was stirred at the same temperature for 30 min[21] and then allowed to reach room temperature before adding the starting compounds (Scheme 6).



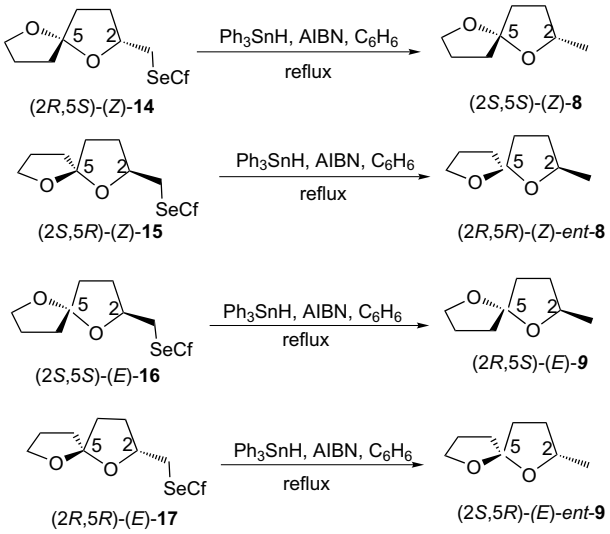
Scheme 6.

As reported in Scheme 7, this reaction afforded a mixture of the two *Z*-diastereoisomers **14** (δ_{H2} 4.21 ppm, δ_{C2} 79.8 ppm) and **15** (δ_{H2} 4.21 ppm, δ_{C2} 80.3 ppm) and of the two *E*-diastereoisomers **16** (δ_{H2} 4.34 ppm, δ_{C2} 78.4 ppm) and **17** (δ_{H2} 4.40 ppm, δ_{C2} 77.6 ppm), which could be separated by medium pressure liquid chromatography. In agreement with what was already observed for the corresponding phenylseleno derivatives, the difference in chemical shift between the two diastereotopic protons in the CH_2Se group is greater for the *Z*-isomer than for the *E*-isomer ($\Delta\delta = 0.25$ and 0.27 for **14** and **15** and $\Delta\delta = 0.16$ and 0.12 for **16** and **17**). The enantiopure selenides are presented in Scheme 7 in the same order in which they are eluted from the chromatographic column. The geometrical structures of the 2-[(camphorseleno)methyl]-1,6-dioxaspiro[4.4]nonanes **14**–**17**, assigned on the basis of their NMR spectra, were also confirmed by the results obtained from their deselenenylation and allylation reactions, which are described below. The yields of isolated products are indicated in Scheme 7.



Scheme 7.

These enantiomerically pure diastereoisomers were then submitted to reductive deselenenylation with Ph_3SnH and AIBN (Scheme 8).

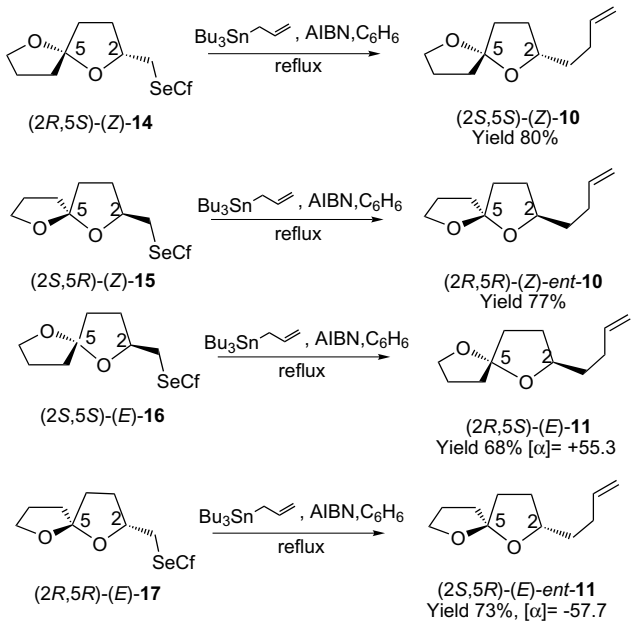


Scheme 8.

The reaction mixtures were carefully worked up as described above for the corresponding racemic compounds. As indicated by the NMR spectra, these products were

slightly contaminated by some unidentified tin compounds and reaction yields and specific rotations were therefore not determined. Isomers **8** and *ent*-**8**, obtained from **14** and **15**, respectively, gave NMR spectra identical to those of the deselenenylated compound obtained from **6**; thus, they are two enantiomers and have the *Z*-configurations. Isomers **9** and *ent*-**9**, obtained from **16** and **17**, respectively, gave NMR spectra, which were identical to those of the deselenenylated compound obtained from **7**; thus, they are two enantiomers and have *E*-configurations. Whereas the *Z*- and *E*-configurations indicated in Schemes 7 and 8 are well established the absolute configurations indicated for compounds **8** and *ent*-**8**, and hence **14** and **15**, and those indicated for compounds **9** and *ent*-**9**, and hence **16** and **17**, are at present only tentative.

Scheme 9 indicates the products, which are obtained from the substitution of the camphorselenyl group with the allyl group. These reactions were carried out and worked up as described above for the racemic phenylseleno derivatives.



Scheme 9.

The two allylation products deriving from **14** and **15** presented NMR spectra identical with those of the allylation product derived from **6**, indicating that they are the two enantiomers **10** and *ent*-**10**, having the *Z*-configuration. The two diastereoisomers **16** and **17** presented NMR spectra identical to those of the corresponding product obtained from **7**, indicating that they are the two enantiomers **11** and *ent*-**11**, having the *E*-configuration. In the latter two cases, the reaction products could be obtained in a pure form and their specific rotations could also be measured.

3. Conclusions

Although several methods have been described for the synthesis of spiroacetals, probably the simplest procedure involves intramolecular cyclizations of suitably substituted hydroxyketones. The considerable advantage of the presently described cyclizations consists of the use of chiral nonracemic organoselenium reagents to promote the one-pot double cyclization reaction and hence to obtain the 1,6-dioxaspiro[4.4]nonane derivatives in an enantiomerically pure form. As already observed in previous cases,[12,22,23] the use of camphorselenenyl reagents produces mixtures of diastereoisomers, which are easily separable by column chromatography. Moreover, the presence of the organoselenium function in the cyclization products allows the introduction of several other groups to be easily effected. The compounds described herein are very similar to several naturally occurring spiro-ketals.[15g,h,24] It can be anticipated that most of these compounds could be prepared with the presently described method by selecting the appropriate starting hydroxyketones.

4. Experimental

All new compounds were characterized by MS, ^{1}H and ^{13}C NMR. GC analyses and MS spectra were carried out with an HP 6890 gas chromatograph (25 m dimethyl silicone capillary column) equipped with an HP 5973 Mass Selective Detector; for the ions containing selenium only the peaks arising from the selenium-80 isotope are given. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100.62 MHz, respectively, on a Bruker DRX 400 instrument; unless otherwise specified, $CDCl_3$ was used as solvent and TMS as the standard. HPLC analyses were performed on an HP 1100 instrument equipped with a Chiracel OD-H column (250 × 4 mm, Daicel), eluent: *i*-PrOH–hexane (1:99), flow rate: 1 mL/min, UV detection at 210 nm. Optical rotations were measured with a Jasco DIP-1000 digital polarimeter. Elemental analyses were carried out on a Carlo Erba 1106 Elemental Analyzer.

4.1. Starting products

Ethyl-3-oxobutanoate, 2-(2-bromoethoxy) tetrahydro-2*H*-pyran, *N*-(phenylseleno)phthalimide, triphenyltin hydride and allyltributyltin are commercial products and were used without further purification.

4.2. Synthesis of ethyl 3-oxo-2-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]hept-6-enoate, 3

Ethyl-3-oxobutanoate, **1**, was submitted to the first alkylation according to the procedure described in the literature.[25] Ethyl 3-oxohept-6-enoate, **2** was obtained in a 65% yield. The second alkylation was effected adding ethyl 3-oxohept-6-enoate, **2** (2.0 g, 12 mmol) to sodium hydride (0.31 g, 13 mmol) in DMF at room temperature. After 15 min, 2-(2-bromoethoxy)tetrahydro-2*H*-pyran (2.45 g, 12 mmol) was added and the mixture warmed up to 70 °C. The progress of the reaction was monitored by TLC. After 20 h, the reaction mixture was diluted with water and extracted with diethyl ether. Compound **3** was isolated in a 65% yield after flash column chromatography on silica gel using a mixture of diethyl ether and light petroleum (from 2:98 to 8:92) as eluant.

4.2.1. Ethyl 3-oxo-2-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-hept-6-enoate, 3. Oil; ^{1}H NMR: δ 5.70 (ddt, 1H, $J = 16.7$, 10.2, 6.5 Hz), 5.01–4.80 (m, 2H), 4.45–4.41 (m, 1H), 4.09 (q, 2H, $J = 7.1$ Hz), 3.75–3.57 (m, 3H), 3.42–3.35 (m, 1H), 3.34–3.27 (m, 1H), 2.70–2.50 (m, 2H) 2.29–2.20 (m, 2H), 2.11–2.01 (m, 2H), 1.82–1.28 (m, 6H), 1.17 (t, 3H, $J = 7.1$ Hz); ^{13}C NMR: δ 204.1, 169.3, 136.6, 115.0, 98.7, 64.6, 62.1, 61.1, 55.8, 41.0, 30.2, 28.0, 27.1, 25.1, 19.3, 13.8.

4.3. Synthesis of 1-hydroxyoct-7-en-4-one, 4, and 2-but-3-enyltetrahydrofuran-2-ol, 5

Sodium hydroxide (1.6 g, 40 mmol) was added at room temperature to a solution (20 mL) of ethyl 3-oxo-2-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]hept-6-enoate, **3** (3.0 g, 10 mmol) in water (20 mL). The mixture was stirred for 1 h and then a 7% solution of hydrochloric acid added. The reaction was stirred for 1 h and then extracted with dichloromethane. The organic solution was dried and evaporated to afford an oil, which was constituted by a 2:1 mixture of hemiacetal **5** and of hydroxyketone, **4** (91% yield), which was sufficiently pure to be directly used for the cyclization reactions. The physical and spectral data of compounds **4** and **5**[14] are reported below.

4.3.1. 1-Hydroxyoct-7-en-4-one, 4. Oil; ^{1}H NMR: δ 5.73 (ddt, 1H, $J = 16.9$, 10.3, 6.7 Hz), 5.10–4.90 (m, 2H), 3.51 (t, 2H, $J = 6.0$ Hz), 2.51–2.40 (m, 5H), 2.23 (quart, 2H, $J = 6.5$ Hz), 1.75 (quint, 2H, $J = 6.7$ Hz); ^{13}C NMR: δ 210.7, 136.8, 115.0, 61.5, 41.7, 39.4, 27.6, 26.2.

4.3.2. 2-But-3-enyltetrahydrofuran-2-ol, 5. Oil; ^{1}H NMR: δ 5.80 (ddt, 1H, $J = 16.9$, 10.3, 6.6 Hz), 5.10–4.90 (m, 2H), 3.88–3.80 (m, 1H), 3.41–3.30 (m, 1H), 2.52–2.49 (m, 2H), 2.35–1.61 (m, 7H); ^{13}C NMR: δ 138.1, 114.2, 109.0, 67.1, 35.1, 33.2, 28.7, 24.0. Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.58; H, 9.91.

4.4. Cyclization reactions promoted by *N*-(phenylseleno) phthalimide

To a stirred solution of the mixture of **4** and **5** (0.29 g, 2 mmol) in dichloromethane (6 mL), *N*-(phenylseleno)-phthalimide (0.86 g, 2.8 mmol) was added at room temperature. A catalytic amount of $BF_3{\cdot}Et_2O$ was added dropwise. The pale yellow solution became orange. The progress of the reaction was monitored by TLC. After 4 h, the reaction mixture was poured into aqueous $NaHCO_3$ solution and extracted with dichloromethane. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered and evaporated. The reaction products were separated by medium pressure liquid chromatography on a silica gel column (Merck, LiChroprep®Si60, 40–63 μm) using a 1:4 mixture of diethyl ether and light petroleum as the eluant. The various fractions were analyzed by TLC. The products obtained are reported in Scheme 3. The physical and spectral data are reported below.

4.4.1. (2*R,5*S**)-2-[(Phenylseleno)methyl]-1,6-dioxa spiro[4.4]-nonane, (*Z*)-6.** Yield 35%. Oil; ^{1}H NMR: δ 7.56–7.50 (m, 2H), 7.30–7.23 (m, 3H), 4.22 (m, 1H), 3.93–3.88 (m, 1H), 3.83–3.78 (m, 1H), 3.25 (dd, 1H, $J = 5.7$, 12.0 Hz), 2.97 (dd, 1H, $J = 8.0$, 12.0 Hz), 2.21–2.13 (m, 1H), 2.07–1.80 (m, 7H); ^{13}C NMR: δ 132.4 (two carbons), 130.0, 128.9 (two carbons), 126.6, 114.8, 78.9, 66.8, 35.6, 34.6, 34.4, 31.0, 24.3; MS *m*/*z* (rel. int.): 298 (14), 157 (5), 127 (100), 85 (18), 55 (9). Anal. Calcd for $C_{14}H_{18}O_2Se$: C, 56.57; H, 6.10. Found: C, 56.64; H, 6.03.

4.4.2. (2*S,5*S**)-2-[(Phenylseleno)methyl]-1,6-dioxa spiro[4.4]-nonane, (*E*)-7.** Yield 35%. Oil; ^{1}H NMR: δ 7.56–7.53 (m, 2H), 7.22–7.15 (m, 3H), 4.35 (m, 1H), 3.93–3.88 (m, 1H), 3.85–3.80 (m, 1H), 3.10 (dd, 1H, $J = 4.7$, 12.2 Hz), 2.98 (dd, 1H, $J = 7.2$, 12.2 Hz), 2.26–2.17 (m, 1H), 2.07–1.95 (m, 4H), 1.91–1.87 (m, 2H) 1.78–1.69 (m, 1H); ^{13}C NMR: δ 132.5 (two carbons), 130.2, 128.9 (two carbons), 126.7, 115.2, 77.1, 67.0, 35.1, 34.5, 33.1, 30.0, 24.5; MS *m*/*z* (rel. int.): 298 (24), 157 (4), 127 (100), 85 (19), 55 (8). Anal. Calcd for $C_{14}H_{18}O_2Se$: C, 56.57; H, 6.10. Found: C, 56.53; H, 6.07.

4.5. Cyclization reactions promoted by camphorselenenyl tetrafluoroborate

Silver tetrafluoroborate (0.44 g, 2.28 mmol) was added to a solution of (*R*)-dicamphor diselenide (0.88 g, 1.9 mmol) in dicholoromethane (5 mL) at −50 °C. The resulting yellow suspension was stirred at the same temperature for 30 min. During this time the reaction mixture progressively turned deep orange.[21] The mixture of hydroxyketone **4** and hemiacetal **5** (0.27 g, 1.90 mmol) was added and the mixture was stirred for 8 h. The reaction mixture was poured into an aqueous $NaHCO_3$ solution and extracted with dicholoromethane. After evaporation of the extracts, the reaction products were separated by medium pressure chromatography on a silica gel column (Merk, LiChroprep®Si60, 40–63 μm) using a mixture of diethyl ether and light petroleum as the eluant (from 10:90 to 20:80). The separation of compounds **14**, **15** and **16**, which by TLC presented the same retention times, was monitored by HPLC; their t_R were 15.6, 16.9 and 20.2 min, respectively. The separation of compound **17** could instead be easily followed by TLC. Its HPLC t_R was 17.5 min. The products obtained are reported in Scheme 7. The physical and spectral data are reported below.

4.5.1. (2*R*,5*S*)-2-[(Camphorseleno)methyl]-1,6-dioxa spiro[4.4]-nonane, (*Z*)-14. Yield 18%. Oil; $[\alpha]_D^{17} = +73.0$ (*c* 1.95, $CHCl_3$). ^{1}H NMR: δ 4.21 (dq, 1H, $J = 7.3$, 6.1 Hz), 3.98–3.88 (m, 1H), 3.80–3.70 (m, 2H), 3.05 (dd, 1H, $J = 5.9$, 12.3 Hz), 2.80 (dd, 1H, $J = 7.3$, 12.3 Hz), 2.30–2.20 (m, 2H), 2.10–1.95 (m, 4H), 1.90–1.85 (m, 2H), 1.84–2.80 (m, 2H), 1.70–1.60 (m, 2H), 1.45–1.37 (m, 1H), 0.96 (s, 3H), 0.86 (s, 3H), 0.83 (s, 3H); ^{13}C NMR: δ 217.9, 115.0, 79.8, 67.0, 58.1, 48.2, 47.2, 46.7, 35.7, 34.8, 31.2, 30.9, 30.4, 24.4, 23.2, 19.6 (two carbons), 9.6; MS *m*/*z* (rel. int.): 372 (22), 141 (19), 127 (100), 123 (12), 85 (12), 55 (10). Anal. Calcd for $C_{18}H_{28}O_3Se$: C, 58.21; H, 7.60. Found: C, 58.13; H, 7.68.

4.5.2. (2*S*,5*R*)-2-[(Camphorseleno)methyl]-1,6-dioxa spiro[4.4]-nonane, (*Z*)-15. Yield 11%. Oil; $[\alpha]_D^{18} = -18.2$ (*c* 2.18, $CHCl_3$). ^{1}H NMR: δ 4.21 (dq, 1H, $J = 7.0$, 6.4 Hz), 3.90–3.82 (m, 1H), 3.80–3.72 (m, 2H,), 3.08 (dd, 1H,

$J = 7.0$, 12.2 Hz), 2.81 (dd, 1H, $J = 6.4$, 12.2 Hz), 2.20–2.10 (m, 2H), 2.02–1.85 (m, 4H), 1.83–1.73 (m, 5H) 1.65–1.58 (m, 1H), 1.41–1.35 (m, 1H), 0.94 (s, 3H), 0.85 (s, 3H), 0.83 (s, 3H); ^{13}C NMR: δ 218.1, 114.9, 80.3, 66.9, 58.0, 48.5, 47.1, 46.7, 35.7, 34.7, 31.5, 31.4, 30.4, 24.4, 23.3, 19.6 (two carbons), 9.7; MS *m*/*z* (rel. int.): 372 (19), 141 (27), 127 (100), 85 (12), 55 (11). Anal. Calcd for $C_{18}H_{28}O_3Se$: C, 58.21; H, 7.60. Found: C, 58.28; H, 7.82.

4.5.3. (2*S*,5*S*)-2-[(Camphorseleno)methyl]-1,6-dioxa spiro[4.4]-nonane, (*E*)-16. Yield 17%. Oil; $[\alpha]_D^{16} = +32.7$ (*c* 2.57, $CHCl_3$). ^{1}H NMR: δ 4.34 (dq, 1H, $J = 7.0$, 6.4 Hz), 3.97–3.89 (m, 2H), 3.87–3.80 (m, 1H), 3.01 (dd, 1H, $J = 5.9$, 12.5 Hz), 2.85 (dd, 1H, $J = 6.1$, 12.5 Hz), 2.30–2.20 (m, 2H), 2.15–1.95 (m, 4H), 1.93–1.88 (m, 2H), 1.87–1.65 (m, 3H), 1.47–1.38 (m, 2H), 0.95 (s, 3H), 0.86 (s, 3H), 0.83 (s, 3H); ^{13}C NMR: δ 218.0, 115.2, 78.4, 67.1, 58.0, 48.4, 47.0, 46.7, 34.8, 34.5, 30.3, 30.2, 29.2, 24.5, 23.0, 19.6 (two carbons), 9.6; MS *m*/*z* (rel. int.): 372 (34), 141 (26), 127 (100), 85 (11), 55 (10). Anal. Calcd for $C_{18}H_{28}O_3Se$: C, 58.21; H, 7.60. Found: C, 58.17; H, 7.50.

4.5.4. (2*R*,5*R*)-2-[(Camphorseleno)methyl]-1,6-dioxa spiro[4.4]-nonane, (*E*)-17. Yield 22%. Oil; $[\alpha]_D^{18} = -20.2$ (*c* 1.82, $CHCl_3$). ^{1}H NMR: δ 4.40 (dq, 1H, $J = 5.95$, 5.05 Hz), 3.92–3.89 (m, 1H), 3.88–3.79 (m, 2H), 3.00 (dd, 1H, $J = 5.9$, 12.5 Hz), 2.88 (dd, 1H, $J = 5.05$, 12.5 Hz), 2.28–2.18 (m, 2H), 2.10–1.98 (m, 4H), 1.95–1.85 (m, 2H), 1.84–1.62 (m, 4H), 1.48–1.40 (m, 1H), 1.00 (s, 3H), 0.91 (s, 3H), 0.88 (s, 3H); ^{13}C NMR: δ 218.0, 115.2, 77.6, 67.0, 58.1, 48.3, 46.8, 46.7, 35.0, 34.6, 30.4, 30.1, 29.5, 24.5, 23.2, 19.6 (two carbons), 9.6; MS *m*/*z* (rel. int.): 372 (30), 141 (24), 127 (100), 85 (14), 55 (12). Anal. Calcd for $C_{18}H_{28}O_3Se$: C, 58.21; H, 7.60. Found: C, 58.11; H, 7.65.

4.6. Reductive deselenenylations. General procedure

Triphenyltin hydride (0.32 g, 0.9 mmol) and a catalytic amount of AIBN were added to a solution of compounds **6** and **7** (0.18 g, 0.6 mmol), or **14**–**17** (0.12 g, 0.32 mmol) in dry benzene (5 mL) and the mixture was stirred and refluxed for 1 h. The solvent was then carefully removed under reduced pressure. The deselenenylated products were isolated after a simple filtration on a deactivated silica gel column using a 10:90 mixture of ethyl ether and light petroleum as the eluant. Deactivated silica gel was prepared by flushing with a 10% solution of triethylamine in light petroleum and then by washing with light petroleum just before use.[19] The eluate was carefully evaporated and the resulting products were then directly analyzed by NMR.

The NMR spectra of the racemic *Z*- and *E*-2-methyl-1,6-dioxaspiro[4.4]nonanes **8** and **9** (Scheme 4) are reported below. These data are in very good agreement with those reported in the literature.[11,14,15] The spectral data of the enantiopure compounds **8**, *ent*-**8** and **9**, *ent*-**9** (Scheme 8) are identical to those of the corresponding racemic compounds.

4.6.1. (2*S,5*S**)-2-Methyl-1,6-dioxaspiro[4.4]nonane, (*Z*)-8.** ^{1}H NMR: δ 4.10 (m, 1H), 4.01–3.94 (m, 1H), 3.82–3.75 (m, 1H), 2.08–1.62 (m, 8H), 1.29 (d, 3H, $J = 6.1$ Hz); ^{13}C NMR: δ 114.7, 75.9, 66.9, 36.2, 35.2, 32.7, 24.4, 22.6. Anal. Calcd for $C_8H_{14}O_2$: C, 65.57; H, 9.92. Found: 65.48; H, 9.85.

4.6.2. (2*R,5*S**)-2-Methyl-1,6-dioxaspiro[4.4]nonane, (*E*)-9.** ^{1}H NMR: δ 4.21 (sex, 1H, $J = 6.2$ Hz), 3.94–3.89 (m, 1H), 3.87–3.81 (m, 1H), 2.13–1.63 (m, 8H), 1.21 (d, 3H, $J = 6.1$ Hz); ^{13}C NMR: δ 114.8, 74.1, 66.9, 35.4, 34.9, 32.0, 24.6, 21.2. Anal. Calcd for $C_8H_{14}O_2$: C, 65.57; H, 9.92. Found: 65.51; H, 9.98.

4.7. Radical allylations. General procedure

Allyltributyltin (0.72 g, 2.3 mmol) and a catalytic amount of AIBN were added to a solution of compounds **6** and **7** (0.1 g, 0.33 mmol) or **14**–**17** (0.11 g, 0.33 mmol), in refluxing dry benzene (8 mL) under nitrogen. The progress of the reactions was monitored by TLC and ^{1}H NMR. After 1 h, a second portion of allyltributyltin (2.3 mmol) and a catalytic amount of AIBN were added. The reactions were stirred for 3 h for the compounds **6** and **7**, and for 6 h for compounds **14**–**17**. The solvent was then carefully evaporated under vacuum. The allylated compounds **11** and *ent*-**11** were isolated in a pure form after column chromatography on silica gel using a mixture of diethyl ether and light petroleum (from 2:98 to 10:90) as the eluant. Column chromatography of compounds **10** and *ent*-**10** was instead carried out on deactivated silica gel. The NMR spectra of the racemic *Z*- and *E*-2-methyl-1,6-dioxaspiro[4.4]nonanes **10** and **11** (Scheme 5) are reported below. The spectral data of compounds **10**, *ent*-**10** and **11**, *ent*-**11** (Scheme 9) are identical to those of the corresponding racemic compounds.

4.7.1. (2*S,5*S**)-2-But-3-enyl-1,6-dioxaspiro[4.4]nonane, (*Z*)-10.** Yield 60%. Oil, ^{1}H NMR δ 5.82 (ddt, 1H, $J = 16.8$, 10.1, 6.5 Hz), 5.06–4.93 (m, 2H), 3.94 (m, 2H), 3.86–3.76 (m, 1H), 2.26–1.23 (m, 12H); ^{13}C NMR: δ 138.5, 114.5, 114.3, 79.4, 66.7, 36.3, 35.7, 34.9, 30.7, 30.2, 24.4. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H 9.95. Found: C, 72.55; H, 9.90.

4.7.2. (2*R,5*S**)-2-But-3-enyl-1,6-dioxaspiro[4.4]nonane, (*E*)-11.** Yield 65%. Oil, ^{1}H NMR: δ 5.82 (ddt, 1H, $J = 16.8$, 10.1, 6.5 Hz), 5.06–4.93 (m, 2H), 4.04 (quint, 1H, $J = 6.6$ Hz), 3.94–3.89 (m, 1H), 3.87–3.79 (m, 1H), 2.15–1.87 (m, 6H), 1.86–1.81 (m, 2H), 1.64–1.60 (m, 1H), 1.58–1.43 (m, 2H), 1.26–1.17 (m, 1H); ^{13}C NMR: δ 138.4, 114.5, 114.4, 77.6, 66.9, 35.2, 34.8, 34.6, 30.1, 30.0, 24.6. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.41; H, 9.88.

4.7.3. (2*R*,5*S*)-2-But-3-enyl-1,6-dioxaspiro[4.4]nonane, (*E*)-11. Yield 68%. Oil, $[\alpha]_D^{16} = +55.3$ (*c* 1.20, $CHCl_3$). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: 72.32; H, 9.78.

4.7.4. (2*S*,5*R*)-2-But-3-enyl-1,6-dioxaspiro[4.4]nonane, (*E*)-*ent*-11. Yield 73%. Oil, $[\alpha]_D^{16} = -57.7$ (*c* 1.25, $CHCl_3$). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: 72.35; H, 9.03.

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