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Synthesis of enantiomerically pure perhydrofuro[3,4-*b*]pyrans and perhydrofuro[3,4-*b*]furans

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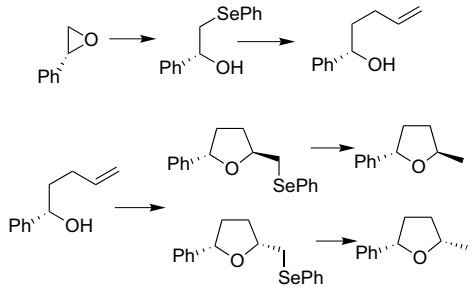
Abstract—Olefinic diols, prepared from (*R*)-(+)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde via olefination and hydrolysis, were converted into enantiomerically pure hydroxy substituted tetrahydrofuran derivatives by cyclization using *N*-phenylselenophthalimide and BF_3. The PhSe group in the C-4 position of these tetrahydrofurans was then substituted by an allyl group using allyltributylstannane in the presence of AIBN. The selenium promoted cyclizations of the allyl tetrahydrofurans in which the OH and the allyl groups are *trans* to each other formed the enantiopure perhydrofuro[3,4-*b*]pyrans, while the cyclization of the allyl tetrahydrofurans in which the OH and the allyl groups are *cis* gave rise to the perhydrofuro[3,4-*b*]furans. These bicyclic products were finally deselenenylated with triphenyltin hydride and AIBN.

1. Introduction

The synthesis of heterocyclic compounds in an enantiomerically enriched or pure form has recently assumed a great importance and several research groups are deeply involved in this problem. Among the various ways in which an heterocyclic compound can be constructed, a very convenient procedure involves the use of the readily available and very versatile organoselenium reagents. In fact, selenium promoted cyclizations of alkenes containing internal nucleophiles in an appropriate position provide an easy access to a wide variety of heterocycles.[1–3] In order to effect the asymmetric synthesis of heterocyclic compounds these cyclization reactions were promoted by electrophilic reagents generated from several types of enantiomerically pure diselenides.[4–13] Using this procedure we have recently reported the synthesis of several heterocycles using two extremely efficient sulfur containing chiral nonracemic diselenides.[14–18] We have also described an alternative approach using achiral phenylselenium reagents and enantiomerically pure substrates.[19,20] In Scheme 1 the reaction sequence employed to effect the synthesis of enantiopure substituted tetrahydrofurans starting from



Scheme 1.

commercially available epoxides is reported.[21] The reaction of epoxides with phenylselenolate anions afforded hydroxyalkyl phenyl selenides. The PhSe group was then substituted by an allyl group and the reaction of these allyl derivatives with electrophilic phenylselenium reagents afforded two enantiomerically pure tetrahydrofurans, which were separated and finally subjected to reductive deselenylation.

This general procedure can find other interesting synthetic applications and it can be employed to effect the synthesis of more complex molecules. We report in this paper that, starting from (*R*)-(+)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde, by means of very simple conversions and of two electrophilic selenium promoted

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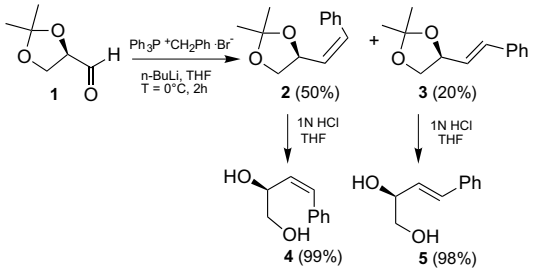
cyclizations the two bicyclic furan derivatives, tetrahydrofuro[3,4-*b*]pyrans and tetrahydrofuro[3,4-*b*]furans can be easily obtained as pure enantiomers.

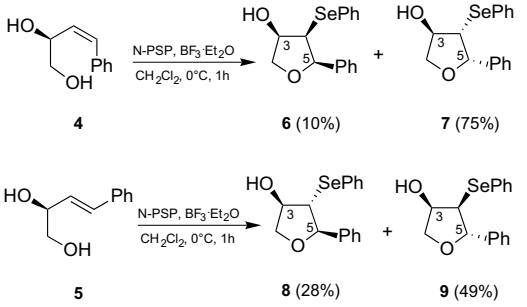
2. Results and discussion

The alkenes necessary for the ring closure reactions were prepared by reacting the phosphorus ylide deriving from triphenyl benzyl phosphonium bromide with the commercially available (*R*)-(+)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde **1**. A mixture of the two geometrical isomers **2** and **3** was obtained from this reaction (Scheme 2). The two *cis*- and *trans*-isomers were easily separated by column chromatography and separately treated with 1 N hydrochloric acid and THF. The two olefinic diols **4** and **5** were thus obtained.[22] The absolute configuration of the *trans*-isomer **5** was confirmed by comparison of its specific rotation with that reported in the literature.[23]



Scheme 2.

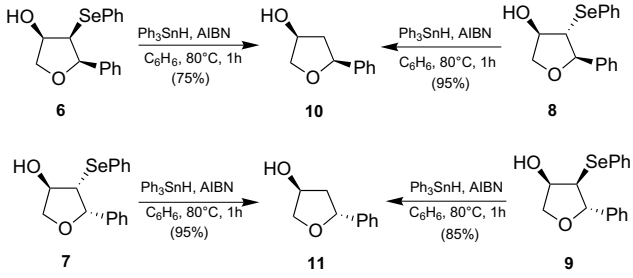
Both the olefinic diols **4** and **5** were converted into a mixture of two enantiomerically pure tetrahydrofurans using *N*-phenylselenophthalimide, as the electrophilic selenenylating reagent, in the presence of BF_3 as catalyst.[19,20] As indicated in Scheme 3 all the products derive from an *endo*-cyclization reaction and are the result of a stereospecific *anti*-addition. The reaction carried out on the *cis*-olefin **4** gave a mixture of the two tetrahydrofurans **6** and **7**, whereas a mixture of the tetrahydrofurans **8** and **9** was obtained starting from the *trans*-olefin **5**. Compounds **6** and **7**, as well as compounds **8** and **9** were separated by column chromatography. Thus, all of the four isomeric trisubstituted tetrahydrofurans could be



Scheme 3.

obtained in an enantiomerically pure form. Phenylselenenyl chloride promoted 5-*endo*-*trig* cyclization of the racemic allyl alcohol **5** has already been described by Landais et al.[24,25] A mixture of **8** and **9**, in the ratio of 28:72, was obtained.

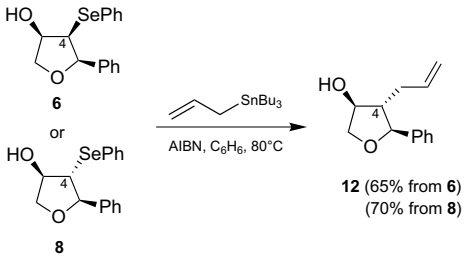
The proposed stereochemistry of these tetrahydrofurans was confirmed by the results of NOESY experiments. The configuration of the carbon atoms in the 3-positions was obviously unchanged with respect to those of the starting diols **4** and **5**. As far as the absolute configuration of the carbon atoms in position 5 is concerned, it was observed that it presented strong dipolar interactions with the proton in position 3 in the cases of compounds **6** and **8** and with the proton of the OH groups in compounds **7** and **9**. Thus, the OH and the Ph groups are *cis* in **6** and **8** and *trans* in compounds **7** and **9**. In all the four tetrahydrofurans, the configurations of the carbons in the 4-positions can be assigned on the basis of the fact that the ring closure reaction is a stereospecific *trans*-addition. These attributions were also confirmed by the NOESY experiments. These stereochemical assignments were also unambiguously confirmed by the structures of the compounds obtained by the reductive deselenenylation reactions indicated in Scheme 4. In fact, under standard conditions (Ph_3SnH and AIBN), the same deselenenylated product **10** was obtained from both the tetrahydrofurans **6** and **8**, while the tetrahydrofurans **7** and **9** gave the deselenenylated product **11**. As demonstrated by GC–MS analysis on chiral column, both **10** and **11** were obviously enantiomerically pure compounds. Compounds **10**[24,25] and **11**[25] have already been obtained by Landais et al.



Scheme 4.

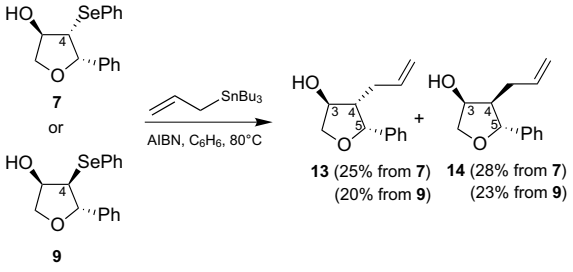
Compounds **6**–**9** can be further functionalized by replacing the PhSe group. By treatment with allyltributyltin and AIBN an allyl chain can be introduced in position 4. As indicated in Scheme 5, in the case of the tetrahydrofurans **6** or **8** this radical reaction afforded the allyl derivative **12** as the sole reaction product. This result can be explained assuming that in these compounds the phenyl group in C-5 and hydroxyl group in C-3, which are *cis* to each other, efficiently direct the incoming allyl group towards the opposite face of the molecule. Compound **12**, in the racemic form, has been already described by Landais et al.[26]

On the contrary, a mixture of the two diastereomeric allyl derivatives **13** and **14** was obtained starting from



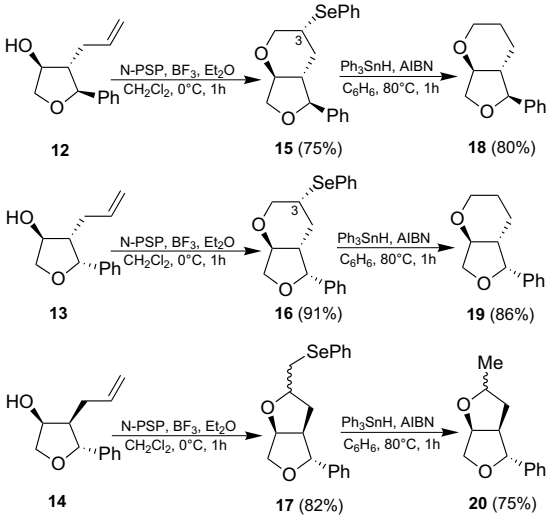
Scheme 5.

the tetrahydrofuran **7**; a mixture of the same two compounds was also obtained starting from **9** (Scheme 6). These two compounds were separated by column chromatography, and were therefore obtained as pure enantiomers. The structures of the allyl tetrahydrofurans **13** and **14** indicated in Scheme 6 were assigned on the basis of the results of NOESY experiments. In compound **13** a strong dipolar interaction was observed between the proton in the 4-position and the proton in the 5-position, indicating that the allyl and the phenyl groups have a *cis* relationship. In compound **14** the strong dipolar interaction was observed between the protons in the 4- and in the 3-positions, indicating that the allyl and the OH group have a *cis* relationship.



Scheme 6.

In this way we have obtained three enantiomerically pure 4-allyl-3-hydroxy-5-phenyl tetrahydrofurans, **12**–**14**, which are alkenes containing a nucleophilic OH group in an appropriate position to give rise to electrophilic selenium promoted cyclization reaction. These ring closure reactions were effected in the usual way by treatment with *N*-phenylselenophthalimide and BF_3. As indicated in Scheme 7, compounds **12** and **13**, in which the hydroxy group and the allyl chain are *trans* to each other, gave rise to a 6-*endo trig* cyclization and the enantiomerically pure perhydrofuro[3,4-*b*]pyrans **15** and **16**, respectively, were obtained as single diastereoisomers and in high yields. Because of the relative geometry of the allyl and the OH groups the addition reaction was forced to take place with an anti-Markovnikov orientation. In compounds **15** and **16** the absolute configurations of C-3 were assigned on the basis of their proton NMR spectra. In both cases the proton in C-3 appeared as a triplet of triplets with coupling constants of 11.7 and 4.5 Hz for compound **15** and of 11.7 and 3.9 Hz for compound **16**. The presence of the large coupling constant clearly indicates that in both compounds the proton is axial and hence the PhSe group occupies an equatorial position, as reported in Scheme 7. On the contrary, in the case of compound **14**, in which the OH group and the allyl chain are in *cis*, a 5-*exo trig* cyclization took place and the reaction product was the perhydrofuro[3,4-*b*]furan **17** (Scheme 7). This was obtained as a 65:35 mixture of two diastereoisomers, which could not be separated by column chromatography. The bicyclic compounds **15**, **16** and **17** were finally submitted to reductive deselenenylation. As reported in Scheme 7 these reactions gave the phenyl derivative **18**, **19** and **20** in excellent yields.



Scheme 7.

3. Conclusions

Starting from the commercially available (*R*)-(+)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde **1**, and using very simple conversions promoted by organoselenium reagents, the two bicyclic compounds perhydrofuro[3,4-*b*]-pyrans and perhydrofuro[3,4-*b*]furans were synthesized. All the steps of the synthetic sequence occurred easily and with good chemical yields. The two furopyran derivatives were isolated in an enantiomerically pure form, whereas in the case of furofurans a mixture of two enantiomerically pure diastereoisomers was obtained. The two types of bicyclic compounds, which have been described in this paper are present in several molecules having interesting biological properties.[27–29]

4. Experimental

All new compounds were characterized by MS, ^1H and ^{13}C NMR spectroscopy. 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. GC chiral analyses and MS

spectra were carried out with an HP 5890 gas chromatograph (25 m Chirasildex capillary column) equipped with an HP 5971 Mass Selective Detector. ^{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 standard. 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

(*R*)-(+)-2,2-Dimethyl-1,3-dioxolane-4-carboxaldehyde **1**, *N*-phenylselenophthalimide, triphenyltin hydride and allyltributyltin were commercial products and were used without further purification.

4.2. Conversion of the (*R*)-(+)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde into the olefinic protected diols 2 and 3[22]

The white suspension of the $Ph_3(PhCH_2)P^+Br^-$ (1.1 mmol) in THF (10 mL) became orange when *n*-BuLi (1.1 mmol) was added dropwise at 0 °C. The temperature was allowed to raise to room temperature over a 30 min period and then (*R*)-(+)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde was added. The suspension immediately became yellow. The progress of the reaction was monitored by TLC and GC–MS and stirring was continued for 2 h. The reaction mixture was then poured into water and extracted with diethyl ether. The organic layer was dried over Na_2SO_4 and evaporated. The isomers **2** and **3** were obtained as a 70:30 mixture of *Z*- and *E*-isomers. These were isolated in a pure form after column chromatography of the residue on silica gel using a 1:9 mixture of diethyl ether and light petroleum as eluent. The products obtained and the reaction yields are reported in Scheme 2. Physical and spectral data are reported below.

4.2.1. (4*S*)-2,2-Dimethyl-4-[(*Z*)-phenylethenyl]-1,3-dioxolane, 2. Oil, $[\alpha]_D^{30} = -41.6$ (*c* 2.15, $CHCl_3$). ^{1}H NMR: δ 7.40–7.20 (m, 5H), 6.72 (d, 1H, $J = 11.5$ Hz), 5.70 (dd, 1H, $J = 8.9$, 11.5 Hz), 4.92 (dddd, 1H, $J = 1.0$, 6.1, 8.0, 8.9 Hz), 4.15 (dd, 1H, $J = 6.1$, 8.1 Hz), 3.68 (dd, 1H, $J = 8.0$, 8.1 Hz), 1.50 (s, 3H), 1.41 (s, 3H); ^{13}C NMR: δ 136.1, 133.8, 129.3, 128.7 (two carbons), 128.3 (two carbons), 127.5, 109.3, 72.4, 69.7, 26.9, 25.9; MS *m*/*z* (rel int.): 204 (18), 174 (13), 146 (30), 129 (80), 115 (72), 104 (100), 91 (19), 77 (12), 72 (56). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.39; H, 7.84.

4.2.2. (4*S*)-2,2-Dimethyl-4-[(*E*)-phenylethenyl]-1,3-dioxolane, 3. Oil, $[\alpha]_D^{20} = +53,5$ (*c* 1.45, $CHCl_3$). ^{1}H NMR: δ 7.47–7.20 (m, 5H), 6.65 (d, 1H, $J = 15.8$ Hz), 6.15 (dd, 1H, $J = 7.5$, 15.8 Hz), 4.68 (dddd, 1H, $J = 0.9$, 6.1, 7.5, 8.0 Hz), 4.16 (dd, 1H, $J = 6.1$, 8.2 Hz), 3.69 (dd, 1H, $J = 8.0$, 8.2 Hz), 1.48 (s, 3H), 1.44 (s, 3H); ^{13}C NMR: δ 136.2, 133.3, 128.5 (two carbons), 127.9, 126.7, 126.6 (two carbons), 109.4, 77.2, 69.5, 26.7, 25.9; MS *m*/*z* (rel int.): 204 (26), 146 (20), 129 (63), 115 (65), 104 (100), 91 (17), 77 (12), 72 (57). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.40; H, 7.85.

4.3. Hydrolysis of the protected diols[22,23]

To a solution of compounds **2** or **3** in THF a 1 N solution of HCl was added and the reaction mixtures were stirred for 30 min below 10 °C. The reaction mixtures were poured into a 10% solution of NaOH and extracted with diethyl ether. The combined organic layers were dried over sodium sulfate, filtered and evaporated. Reaction yields of compounds **4** and **5** are reported in Scheme 2. Physical and spectral data are reported below.

4.3.1. (2*S*,3*Z*)-4-Phenylbut-3-ene-1,2-diol, 4. Mp 70–75 °C; $[\alpha]_D^{22} = +13.0$ (*c* 1.39, $CHCl_3$). ^{1}H NMR: δ 7.38–7.15 (m, 5H), 6.60 (d, 1H, $J = 11.7$ Hz), 5.61 (dd, 1H, $J = 9.1$, 11.7 Hz), 4.70–4.60 (m, 1H), 3.72–3.62 (m, 1H), 3.55 (dd, 1H, $J = 7.7$, 11.4 Hz), 3.20 (br s, 2H); ^{13}C NMR: δ 136.3, 133.0, 129.7, 128.7 (two carbons), 128.4 (two carbons), 127.5, 68.7, 66.1; MS *m*/*z* (rel int.): 146 (M^+-18, 44), 131 (46), 117 (100), 103 (21), 91 (35), 77 (15), 65 (11), 51 (16). Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.10; H, 7.44.

4.3.2. (2*S*,3*E*)-4-Phenylbut-3-ene-1,2-diol, 5. Mp 55–57 °C; $[\alpha]_D^{32} = +33.7$ (*c* 0.95, $CHCl_3$).[23] ^{1}H NMR: δ 7.48–7.18 (m, 5H), 6.72 (d, 1H, $J = 16.0$ Hz), 6.21 (dd, 1H, $J = 6.3$, 16.0 Hz), 4.50–4.30 (m, 1H), 3.78 (dd, 1H, $J = 3.5$, 11.2 Hz), 3.63 (dd, 1H, $J = 7.4$, 11.2 Hz), 2.98 (br s, 1H), 2.78 (br s, 1H); ^{13}C NMR: δ 136.3, 131.8, 128.5 (two carbons), 127.8, 127.6, 126.4 (two carbons), 73.2, 66.4; MS *m*/*z* (rel int.): 146 (M^+-18, 49), 131 (50), 117 (100), 103 (24), 91 (40), 77 (22), 65 (14), 51 (18). Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.19; H, 7.40.

4.4. General procedure for the cyclofunctionalization reactions: synthesis of tetrahydrofurans, perhydrofuro[3,4-*b*]pyrans and perhydrofuro[3,4-*b*]furans

To a solution of *N*-phenylselenophthalimide (1 mmol) in dichloromethane (6 mL) compounds **4**, **5**, **12**, **13** or **14** (1 mmol) were added at 0 °C. A catalytic amount of $BF_3{\cdot}Et_2O$ was added dropwise. The temperature was allowed to raise to room temperature over a 1 h period and the progress of the reaction was monitored by TLC and GC–MS. The reaction mixture was then poured into a 5% aqueous solution of NaOH and extracted with dichloromethane. The organic layer was dried over sodium sulfate, filtered and evaporated. The tetrahydrofurans **6**, **7** and **8**, **9** were separated by medium pressure chromatography on a silica gel column (Merck, LiChroprep® Si60, 40–63 μm) using a 1:1 mixture of diethyl ether and light petroleum as eluent. After col-

umn chromatography of the residue on silica gel using a 3:8 mixture of diethyl ether and light petroleum as eluent, the perhydrofuro[3,4-*b*]pyrans **15** and **16** were obtained in pure form, while the perhydrofuro[3,4-*b*]furans **17** were obtained as a 65:35 mixture of two diastereoisomers. The products obtained and the reaction yields are reported in Schemes 3 and 7. Physical and spectral data, including those of **8** and **9**,[24,25] are reported below.

4.4.1. (3*R*,4*R*,5*R*)-5-Phenyl-4-(phenylseleno)tetrahydrofuran-3-ol, 6. Oil, $[\alpha]_D^{29} = +4.8$ (*c* 0.82, $CHCl_3$). ^1H NMR: δ 7.55–7.40 (m, 4H), 7.35–7.18 (m, 6H), 5.34 (d, 1H, $J = 8.7$ Hz), 4.40 (dd, 1H, $J = 1.7$, 9.8 Hz), 4.28–4.23 (m, 1H), 4.21 (ddd, 1H, $J = 1.4$, 4.5, 8.7 Hz), 3.98 (ddd, 1H, $J = 1.4$, 3.5, 9.8 Hz), 2.89 (br s, 1H); ^{13}C NMR: δ 140.2, 134.4 (two carbons), 129.8 (two carbons), 129.1, 128.5 (two carbons), 128.3 (two carbons), 127.7 (two carbons), 82.4, 74.2, 71.5, 57.0; MS *m*/*z* (rel int.): 320 (30), 214 (13), 158 (100), 145 (62), 115 (26), 105 (31), 91 (34), 77 (55), 57 (18). Anal. Calcd for $C_{16}H_{16}O_2Se$: C, 60.19; H, 5.05. Found: C, 60.14; H, 4.98.

4.4.2. (3*R*,4*S*,5*S*)-5-Phenyl-4-(phenylseleno)tetrahydrofuran-3-ol, 7. Oil, $[\alpha]_D^{22} = +3.9$ (*c* 1.07, $CHCl_3$). ^1H NMR: δ 7.49–7.30 (m, 8H), 7.28–7.18 (m, 2H), 5.53 (d, 1H, $J = 5.1$ Hz), 4.64 (dd, 1H, $J = 4.5$, 9.8 Hz), 4.59–4.51 (m, 1H), 4.02 (d, 1H, $J = 5.1$ Hz), 3.93 (dd, 1H, $J = 1.7$, 9.8 Hz), 2.01 (br s, 1H); ^{13}C NMR: δ 139.2 (two carbons), 134.4 (two carbons), 129.6 (two carbons), 128.5 (two carbons), 128.3, 128.0, 126.4 (two carbons), 81.6, 78.8, 74.6, 53.4; MS *m*/*z* (rel int.): 320 (32), 214 (13), 184 (20), 163 (29), 158 (100), 145 (63), 128 (10), 115 (23), 105 (36), 91 (42), 77 (56), 57 (16). Anal. Calcd for $C_{16}H_{16}O_2Se$: C, 60.19; H, 5.05. Found: C, 60.07; H, 5.10.

4.4.3. (3*R*,4*S*,5*R*)-5-Phenyl-4-(phenylseleno)tetrahydrofuran-3-ol, 8. Oil, $[\alpha]_D^{31} = +6.5$ (*c* 2.46, $CHCl_3$). ^1H NMR: δ 7.52–7.25 (m, 10H), 4.79 (d, 1H, $J = 7.0$ Hz), 4.51–4.46 (m, 1H), 4.09 (dd, 1H, $J = 4.4$, 9.8 Hz), 4.05 (ddd, 1H, $J = 1.0$, 2.9, 9.8 Hz), 3.49 (ddd, 1H, $J = 1.0$, 3.4, 7.0 Hz), 2.08 (d, 1H, $J = 5.7$ Hz); ^{13}C NMR: δ 140.1 (two carbons), 134.9 (two carbons), 129.7 (two carbons), 128.9 (two carbons), 128.5 (two carbons), 126.5 (two carbons), 86.0, 79.3, 74.5, 55.7; MS *m*/*z* (rel int.): 320 (27), 207 (18), 163 (28), 158 (100), 145 (83), 115 (28), 105 (35), 91 (34), 77 (56), 51 (22). Anal. Calcd for $C_{16}H_{16}O_2Se$: C, 60.19; H, 5.05. Found: C, 60.23; H, 5.08.

4.4.4. (3*R*,4*R*,5*S*)-5-Phenyl-4-(phenylseleno)tetrahydrofuran-3-ol, 9. Mp 65–66 °C; $[\alpha]_D^{20} = +70.1$ (*c* 1.69, $CHCl_3$). ^1H NMR: δ 7.50–7.20 (m, 10H), 4.88 (d, 1H, $J = 10.2$ Hz), 4.45–4.39 (m, 1H), 4.32 (ddd, 1H, $J = 1.2$, 4.3, 9.8 Hz), 4.08 (ddd, 1H, $J = 1.2$, 1.8, 9.8 Hz), 3.48 (dd, 1H, $J = 4.7$, 10.2 Hz), 2.91–2.88 (m, 1H); ^{13}C NMR: δ 139.6 (two carbons), 133.8 (two carbons), 129.1 (two carbons), 128.3 (two carbons), 128.1, 127.8, 126.5 (two carbons), 83.1, 74.2, 72.0, 59.0; MS *m*/*z* (rel int.): 320 (27), 207 (14), 163 (30), 158 (100), 145 (85), 115 (30), 105 (36), 91 (34), 77 (59), 51 (17). Anal. Calcd for $C_{16}H_{16}O_2Se$: C, 60.19; H, 5.05. Found: C, 60,21; H, 5.07.

4.4.5. (3*R*,4a*R*,5*S*,7a*S*)-5-Phenyl-3-(phenylseleno)hexahydro-2H-furo[3,4-*b*]pyran, 15. Mp 88–89 °C; $[\alpha]_D^{24} = +20.9$ (*c* 2.91, $CHCl_3$). ^1H NMR: δ 7.57–7.52 (m, 2H), 7.39–7.24 (m, 8H), 4.53 (d, 1H, $J = 10.5$ Hz), 4.18 (t, 1H, $J = 7.1$ Hz), 4.15 (ddd, 1H, $J = 1.5$, 4.5, 11.7 Hz), 3.78 (dd, 1H, $J = 7.1$, 9.7 Hz), 3.69 (ddd, 1H, $J = 7.1$, 9.7, 10.0 Hz), 3.60 (t, 1H, $J = 11.7$ Hz), 3.19 (tt, 1H, $J = 4.5$, 11.7 Hz), 2.34 (dddd, 1H, $J = 1.5$, 3.3, 4.5, 12.0 Hz), 1.89 (dddd, 1H, $J = 3.3$, 10.0, 10.5, 12.0 Hz), 1.60 (dt, 1H, $J = 11.7$, 12.1 Hz); ^{13}C NMR: δ 140.6, 135.0 (two carbons), 129.1 (two carbons), 128.5 (two carbons), 128.0, 127.8, 127.2, 125.6 (two carbons), 82.0, 80.9, 73.3, 68.6, 52.9, 38.4, 32.5; MS *m*/*z* (rel int.): 360 (49), 207 (58), 159 (41), 143 (33), 129 (45), 115 (32), 105 (47), 91 (100), 77 (56), 67 (26), 51 (21). Anal. Calcd for $C_{19}H_{20}O_2Se$: C, 63.51; H, 5.61. Found: C, 63.43; H, 5.68.

4.4.6. (3*R*,4a*R*,5*R*,7a*S*)-5-Phenyl-3-(phenylseleno)hexahydro-2H-furo[3,4-*b*]pyran, 16. Oil, $[\alpha]_D^{21} = -62.4$ (*c* 1.03, $CHCl_3$). ^1H NMR: δ 7.55–7.45 (m, 2H), 7.36–7.20 (m, 6H), 7.20–7.10 (m, 2H) 5.20 (d, 1H, $J = 8.2$ Hz), 4.34 (dd, 1H, $J = 6.9$, 7.4 Hz), 4.07–4.03 (m, 1H), 3.71 (dd, 1H, $J = 7.4$, 9.2 Hz), 3.62 (ddd, 1H, $J = 6.9$, 9.2, 9.9 Hz), 3.37 (t, 1H, $J = 11.7$ Hz), 3.32 (tt, 1H, $J = 3.9$, 11.7 Hz), 2.37–2.29 (m, 2H), 1.10–0.85 (m, 1H); ^{13}C NMR: δ 140.3, 134.5 (two carbons), 129.0 (two carbons), 128.1 (two carbons), 127.8, 127.7, 127.2, 125.2 (two carbons), 80.5, 77.9, 72.9, 69.0, 47.9, 39.0, 32.4; MS *m*/*z* (rel int.): 360 (35), 254 (10), 159 (62), 141 (33), 129 (46), 115 (29), 97 (67), 91 (100), 77 (51), 67 (23), 51 (16). Anal. Calcd for $C_{19}H_{20}O_2Se$: C, 63.51; H, 5.61. Found: C, 63.58; H, 5.65.

4.4.7. (3a*S*,4*R*,6a*S*)-4-Phenyl-2-[(phenylseleno)methyl]-hexahydrofuro[3,4-*b*]furan, 17. Oil; Major diastereoisomer: ^1H NMR: δ 7.55–7.50 (m, 2H), 7.23–7.09 (m, 8H), 4.87 (ddd, 1H, $J = 3.0$, 5.3, 7.0 Hz), 4.63 (d, 1H, $J = 6.6$ Hz), 4.48 (dddd, 1H, $J = 1.1$, 5.6, 6.7, 9.3 Hz), 4.21 (dd, 1H, $J = 5.3$, 10.2 Hz), 3.89 (dd, 1H, $J = 3.0$, 10.2 Hz), 3.21 (dd, 1H, $J = 5.6$, 12.3 Hz), 3.09 (dd, 1H, $J = 6.7$, 12.3 Hz), 2.95–2.87 (m, 1H), 2.18 (ddd, 1H $J = 1.1$, 5.2, 12.7 Hz), 1.88 (ddd, 1H, $J = 7.9$, 9.3, 12.7 Hz); ^{13}C NMR: δ 141.1 (two carbons), 132.7 (two carbons), 129.1 (two carbons), 128.5 (two carbons), 127.6, 127.0, 125.6 (two carbons), 85.9, 84.5, 78.3, 74.2, 52.6, 36.7, 32.1; MS *m*/*z* (rel int.): 360 (51), 203 (60), 189 (57), 173 (27), 157 (31), 143 (61), 129 (38), 117 (31), 115 (31), 105 (67), 91 (100), 77 (47). Anal. Calcd for $C_{19}H_{20}O_2Se$: C, 63.51; H, 5.61. Found: C, 63.53; H, 5.63.

Minor diastereoisomer (distinct signals): ^1H NMR: δ 4.81 (d, 1H, $J = 5.8$ Hz), 4.68 (ddd, 1H, $J = 2.1$, 5.0, 7.0 Hz), 4.26 (dddd, 1H, $J = 5.8$, 6.5, 8.7, 8.9 Hz), 4.12 (dd, 1H, $J = 5.0$, 10.3 Hz), 4.04 (dd, 1H, $J = 2.1$, 10.3 Hz), 3.28 (dd, 1H, $J = 5.8$, 12.3 Hz), 3.19 (dd, 1H, $J = 6.5$, 12.3 Hz), 2.40 (ddd, 1H, $J = 6.4$, 8.9, 12.7 Hz), 1.76 (ddd, 1H, $J = 5.3$, 8.7, 12.7 Hz); ^{13}C NMR: δ 141.0,

128.4 (two carbons), 127.5, 126.9, 125.7 (two carbons), 86.5, 85.5, 81.6, 73.1, 52.5, 36.6; MS m/z (rel int.): 360 (30), 203 (100), 189 (20), 173 (42), 157 (29), 143 (74), 128 (32), 115 (32), 105 (77), 91 (93), 77 (43), 51 (14).

4.5. Reductive deselenenylation. General procedure

Triphenyltin hydride (0.5 mmol) and a catalytic amount of AIBN were added to a solution of compounds **6**, **7**, **8**, **9**, **15**, **16** or **17** (0.3 mmol) in dry benzene (3 mL) and the mixture was stirred and refluxed for 1 h. The solvent was then removed under reduced pressure. The tetrahydrofurans **10** and **11** were obtained in a pure form after column chromatography of the residue on a silica gel column using a 4:6 mixture of diethyl ether and light petroleum as eluent. The perhydrofuro[3,4-*b*]pyrans **18** and **19**, which were present as single enantiomers, and the perhydrofuro[3,4-*b*]furans **20**, which was a mixture of two diastereoisomers, were purified by column chromatography on silica gel using a 2:8 mixture of diethyl ether and light petroleum as eluent. The reaction yields are reported in Schemes 4 and 7. Physical and spectral data of racemic form of the compound **10** are reported in the literature,[26] physical and spectral data of the other compounds are reported below.

4.5.1. (3*S*,5*S*)-5-Phenyltetrahydrofuran-3-ol, 10.[26] Oil, $[\alpha]_D^{22} = -15.0$ (c 0.26, $CHCl_3$).

4.5.2. (3*S*,5*R*)-5-Phenyltetrahydrofuran-3-ol, 11. Oil, $[\alpha]_D^{21} = +34.6$ (c 2.04, $CHCl_3$). ^{1}H NMR: δ 7.45–7.20 (m, 5H), 5.18 (dd, 1H, $J = 5.7$, 10.1 Hz), 4.63–4.58 (m, 1H), 4.24 (dd, 1H, $J = 4.3$, 9.8 Hz), 3.91 (ddd, 1H, $J = 1.1$, 1.8, 9.8 Hz), 2.46 (br s, 1H), 2.34 (ddt, 1H, $J = 1.2$, 5.7, 13.3 Hz), 1.96 (ddd, 1H, $J = 5.2$, 10.1, 13.3 Hz); ^{13}C NMR: δ 142.1, 128.4 (two carbons), 127.4, 125.6 (two carbons), 79.5, 76.2, 72.6, 44.4; MS m/z (rel int.): 164 (74), 163 (90), 146 (15), 120 (34), 115 (16), 105 (100), 92 (64), 91 (51), 79 (43), 77 (44), 51 (16). Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.12; H, 7.40.

4.5.3. (4a*R*,5*S*,7a*S*)-5-Phenyl-hexahydro-2H-furo[3,4-*b*]-pyran, 18. Oil, $[\alpha]_D^{25} = -5.0$ (c 1.11, $CHCl_3$). ^{1}H NMR: δ 7.41–7.27 (m, 5H), 4.55 (d, 1H, $J = 10.2$ Hz), 4.22 (t, 1H, $J = 7.1$ Hz), 4.11 (ddt, 1H, $J = 1.3$, 4.5, 11.5 Hz), 3.84 (dd, 1H, $J = 7.1$, 9.7 Hz), 3.69 (dt, 1H, $J = 7.1$, 9.7 Hz), 3.59 (dt, 1H, $J = 3.1$, 11.5 Hz), 2.10–1.99 (m, 1H), 1.80–1.45 (m, 4H); ^{13}C NMR: δ 141.7, 128.8 (two carbons), 128.1, 126.1 (two carbons), 83.2, 81.9, 69.3, 69.2, 51.9, 25.6, 25.4; MS m/z (rel int.): 204 (100), 173 (12), 159 (25), 145 (83), 131 (12), 119 (23), 115 (26), 105 (34), 98 (32), 91 (35), 83 (76), 77 (20), 69 (12), 55 (12). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 77.38; H, 7.87.

4.5.4. (4a*R*,5*R*,7a*S*)-5-Phenyl-hexahydro-2H-furo[3,4-*b*]-pyran, 19. Mp 69–71 °C; $[\alpha]_D^{23} = -31.9$ (c 2.97, $CHCl_3$). ^{1}H NMR: δ 7.38–7.32 (m, 2H), 7.29–7.24 (m, 1H), 7.20–7.15 (m, 2H) 5.22 (d, 1H, $J = 8.5$ Hz), 4.34 (dd, 1H, $J = 6.8$, 7.4 Hz), 3.98 (ddt, 1H, $J = 1.2$, 4.9, 11.5 Hz), 3.74 (dd, 1H, $J = 7.4$, 9.7 Hz), 3.55 (ddd, 1H, $J = 6.8$, 9.7, 10.5 Hz), 3.32 (ddd, 1H, $J = 2.8$, 11.5, 12.0 Hz), 2.18 (dddd, 1H, $J = 3.3$, 8.5, 10.5, 12.4 Hz), 1.93–1.86 (m, 1H), 1.72–1.60 (m, 1H), 1.58–1.51 (m, 1H), 0.84 (dq, 1H, $J = 4.2$, 12.4 Hz); ^{13}C NMR: δ 141.0, 128.0 (two carbons), 127.0, 125.4 (two carbons), 81.1, 78.3, 69.3, 68.2, 46.2, 25.5, 25.0; MS m/z (rel int.): 204 (69), 173 (11), 159 (25), 145 (79), 129 (11), 119 (29), 105 (39), 98 (41), 91 (47), 83 (100), 77 (32), 69 (19), 55 (19). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 77.36; H, 7.81.

4.5.5. (3a*S*,4*R*,6a*S*)-2-Methyl-4-phenylhexahydrofuro-[3,4-*b*]furan, 20. Oil; major diastereoisomer: ^{1}H NMR: δ 7.40–7.20 (m, 5H), 4.85 (ddd, 1H, $J = 3.5$, 5.6, 7.3 Hz), 4.64 (d, 1H, $J = 6.8$ Hz), 4.36 (ddq, 1H, $J = 4.9$, 5.9, 9.9 Hz), 4.22 (dd, 1H, $J = 5.6$, 10.1 Hz), 3.86 (dd, 1H, $J = 3.5$, 10.1 Hz), 2.93–2.87 (m, 1H), 2.08 (ddd, 1H, $J = 1.2$, 4.9, 12.6 Hz), 1.70 (ddd, 1H, $J = 7.8$, 9.9, 12.6 Hz), 1.34 (d, 3H, $J = 5.9$ Hz); ^{13}C NMR: δ 141.9, 128.9 (two carbons), 128.0, 126.1 (two carbons), 86.5, 84.3, 75.0, 74.7, 53.3, 39.0, 20.5; MS m/z (rel int.): 204 (35), 203 (21), 174 (18), 162 (65), 145 (38), 131 (100), 115 (31), 105 (53), 91 (56), 83 (34), 77 (43), 69 (33), 54 (35). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.43; H, 7.95.

Minor diastereoisomer (distinct signals): ^{1}H NMR: δ 4.78 (d, 1H, $J = 5.7$ Hz), 4.63 (ddd, 1H, $J = 2.1$, 4.9, 7.4 Hz), 4.14 (dd, 1H, $J = 4.9$, 10.2 Hz), 4.10 (dquint, 1H, $J = 6.0$, 9.3 Hz), 4.04 (dd, 1H, $J = 2.1$, 10.2 Hz), 2.34 (ddd, 1H, $J = 6.0$, 8.9, 12.4 Hz), 1.55 (ddd, 1H, $J = 5.8$, 9.3, 12.4 Hz), 1.33 (d, 1H, $J = 6.0$ Hz); ^{13}C NMR: δ 141.5, 128.8 (two carbons), 127.9, 126.2 (two carbons), 87.4, 85.6, 79.1, 73.5, 53.4, 39.2, 20.9; MS m/z (rel int.): 204 (18), 203 (22), 162 (100), 145 (30), 131 (52), 115 (16), 105 (35), 91 (28), 83 (20), 77 (24), 69 (16), 54 (20).

4.6. Radical allylation. General procedure

Allyltributylstannane (7 mmol) and a catalytic amount of AIBN were added to a solution of the tetrahydrofurans **6**, **7**, **8** or **9** (1 mmol) in refluxing dry benzene (8 mL) under nitrogen. The progress of the reaction was monitored by TLC and ^{1}H NMR. After 1 h a second portion of allyltributylstannane (7 mmol) and a catalytic amount of AIBN were then added. The reaction mixtures were stirred for 3 h and then directly evaporated under vacuum. Starting from compounds **6** or **8** the single compound **12** was obtained in a pure form after column chromatography of the residue on a silica gel column using a 6:4 mixture of diethyl ether and light petroleum as eluent. Starting from compound **7** and **9**, compounds **13** and **14**, respectively, were obtained. Their purification required a first column chromatography on silica gel using a 6:4 mixture of diethyl ether and light petroleum as eluent and a second medium pressure chromatography on a silica gel column (Merck, LiChroprep® Si60, 40–63 μm) using a 6:4 mixture of diethyl ether and

light petroleum as eluent. Reaction yields are reported in Schemes 5 and 6. Physical and spectral data of the racemic form of compound **12** are reported in the literature,[26] physical and spectral data of other compounds are reported below.

4.6.1. (3*S*,4*S*,5*S*)-4-Allyl-5-phenyltetrahydrofuran-3-ol, 12.[26] Oil, $[\alpha]_D^{24} = +4.3$ (*c* 1.51, $CHCl_3$).

4.6.2. (3*S*,4*S*,5*R*)-4-Allyl-5-phenyltetrahydrofuran-3-ol, 13. Oil, $[\alpha]_D^{24} = +83.8$ (*c* 0.97, $CHCl_3$). ^{1}H NMR: δ 7.43–7.15 (m, 5H), 5.65 (dddd, 1H, $J = 5.4$, 8.4, 10.2, 17.0 Hz), 5.34 (d, 1H, $J = 5.5$ Hz), 5.02–4.78 (m, 2H), 4.38 (ddd, 1H, $J = 1.8$, 2.1, 4.9 Hz), 4.34 (dd, 1H, $J = 4.9$, 9.7 Hz), 3.86 (dd, 1H, $J = 2.1$, 9.7 Hz), 2.36–2.29 (m, 1H), 2.06 (br s, 1H), 1.74–1.67 (m, 1H), 1.61–1.51 (m, 1H); ^{13}C NMR: δ 139.2, 136.3, 128.1 (two carbons), 127.0, 126.0 (two carbons), 116.4, 81.7, 75.8, 74.2, 51.5, 31.7; MS *m*/*z* (rel int.): 204 (5), 203 (6), 187 (7), 175 (56), 162 (69), 145 (50), 133 (8), 128 (10), 115 (15), 107 (100), 91 (24), 79 (40), 77 (22), 57 (15). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.39; H, 7.88.

4.6.3. (3*S*,4*R*,5*R*)-4-Allyl-5-phenyltetrahydrofuran-3-ol, 14. Oil, $[\alpha]_D^{24} = -36.1$ (*c* 0.77, $CHCl_3$). ^{1}H NMR δ 7.48–7.10 (m, 5H), 5.78 (dddd, 1H, $J = 5.7$, 7.9, 10.1, 17.1 Hz), 5.20–4.99 (m, 2H), 4.63 (d, 1H, $J = 10.0$ Hz), 4.48 (ddd, 1H, $J = 1.2$, 4.1, 4.5 Hz), 4.32 (dd, 1H, $J = 4.1$, 10.0 Hz), 3.96 (dd, 1H, $J = 1.2$, 10.0 Hz), 2.42–2.30 (m, 1H), 2.16–2.08 (m, 1H), 2.07–1.99 (m, 1H), 1.92 (br s, 1H); ^{13}C NMR: δ 141.1, 136.3, 128.4 (two carbons), 127.8, 126.3 (two carbons), 116.2, 83.9, 75.8, 72.9, 52.8, 29.0; MS *m*/*z* (rel int.): 204 (4), 203 (4), 175 (55), 162 (67), 145 (52), 128 (12), 115 (19), 107 (100), 105 (27), 91 (27) 79 (44), 77 (24), 57 (16). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.51; H, 7.96.

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