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Intramolecular addition of carbon radicals to aldehydes: synthesis of enantiopure tetrahydrofuran-3-ols

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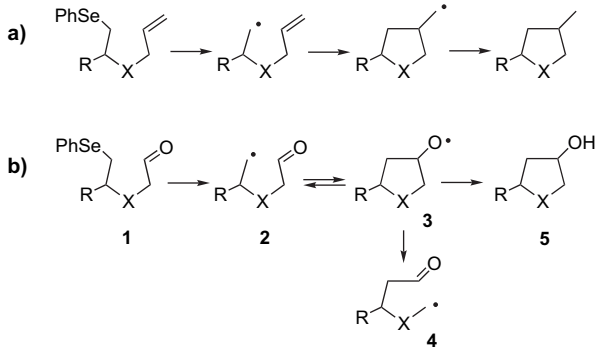
Abstract—A simple and efficient substrate-controlled asymmetric synthesis of enantiopure tetrahydrofuran-3-ols by a 5-*exo-trig* radical cyclization is described. This cyclization occurs when a δ-carbon radical adds intramolecularly to the carbonyl group of an aldehyde. The δ-carbon radicals can be efficiently produced from the tin hydride mediated deselenenylation of 5-phenylseleno-3-oxapentanals, which were easily prepared starting from commercially available enantiopure epoxides or chlorohydrins.

1. Introduction

Several selenium-based methodologies to effect convenient syntheses of a wide variety of heterocyclic compounds have been developed in recent years.[1] The cyclization reactions of alkenes containing internal nucleophiles, promoted by electrophilic selenium reagents, have emerged as a highly efficient method to prepare these compounds in a regio and diastereoselective manner. Of particular importance are the asymmetric versions of these reactions, either reagent-controlled or substrate-controlled, from which enantiomerically enriched or enantiopure heterocycles can be obtained.[1,2] Alternatively, the synthesis of small or medium sized heterocycles can be effected by ring closure reactions, which occur by intramolecular nucleophilic substitution by oxygen, nitrogen or sulfur nucleophiles, after transformation of the organoselenium group into a good leaving-group, like a selenonium ion or a selenone.[3] A further interesting method is represented by the radical cyclization reactions, which take place when a carbon radical intramolecularly adds to a carbon–carbon double or triple bond. The carbon radicals are generally produced by the tin hydrides mediated deselenenylation of properly substituted selenides. This latter approach has been successfully employed by Engman for the preparation of racemic tetrahydrofurans and pyrrolidines in high yields and with a good level of regio and diastereocontrol (Scheme 1, route a).[4] Other cyclizations involving intramolecular radical addition to conjugated carbon–carbon double bonds, allenes or carbon–nitrogen multiple bonds have found useful applications in the stereoselective synthesis of simple heterocycles or of more complex natural and biologically active compounds.[5] Similar cyclizations by addition to carbon–oxygen double bonds (Scheme 1, route b) are much less common. In fact, even if the addition of the carbon radical to a carbonyl group is faster than that to a carbon–carbon double bond the reaction is reversible and it is not always easy to trap the cyclic alkoxy radical before it suffers the β-scission to the open chain carbon radical. The β-scission reactions of the cyclic alkoxy radicals are particularly favored in the cases of poorly substituted five-membered rings.[6] Simple racemic cyclopentanols were prepared from ω-formyl halides by rapid trapping of the cyclic alkoxy radical intermediate using efficient hydrogen donors such as organosilanes,[6c] or radical quenchers, such as Et_3B.[6d] A radical cyclization reaction by addition to a carbon–oxygen double bond has been employed to effect the stereoselective



Scheme 1.

Keywords: Asymmetric synthesis; Organoselenium compounds; Radical cyclizations; Tetrahydrofuranols.
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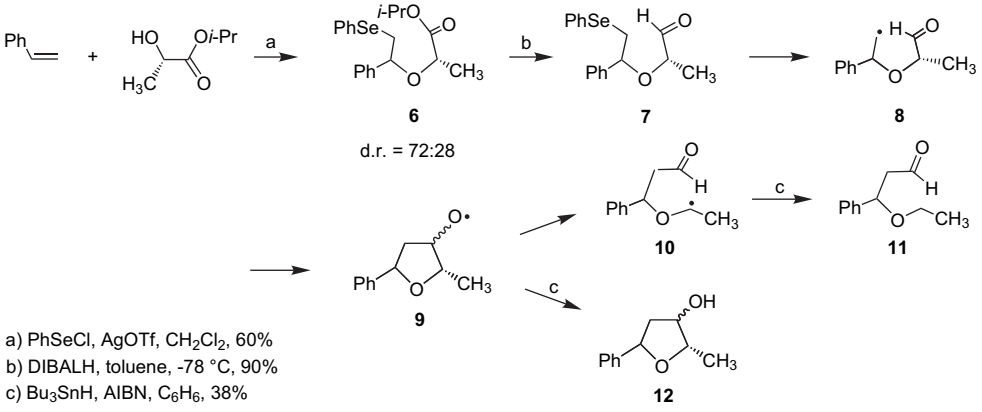
synthesis of optically active perhydrofuro[2,3-*b*]furanols.[7] Our continuous interest in the development of new synthetic methodologies based on the use of versatile organoselenium compounds induced us to investigate the tin hydrides mediated deselenenylation of enantiopure 5-phenylseleno-3-oxapentanals **1** (Scheme 1, path b, X=O) to produce the corresponding δ-carbon radicals **2** and the cyclic alkoxy radicals **3** and to study the competition between the β-scission to afford radicals **2** or **4** and the hydrogen abstraction to give **5** as a function of the structure of compounds **1**. It would be thus possible to develop a new synthetic method for a convenient production of enantiopure tetrahydrofuran-3-ols. Stereocontrolled approaches[8] to these compounds are in fact of considerable importance because tetrahydrofuran-3-ols can be employed as useful reaction intermediates for the preparation of a wide range of biologically active compounds as for instance isonucleosides.[9]

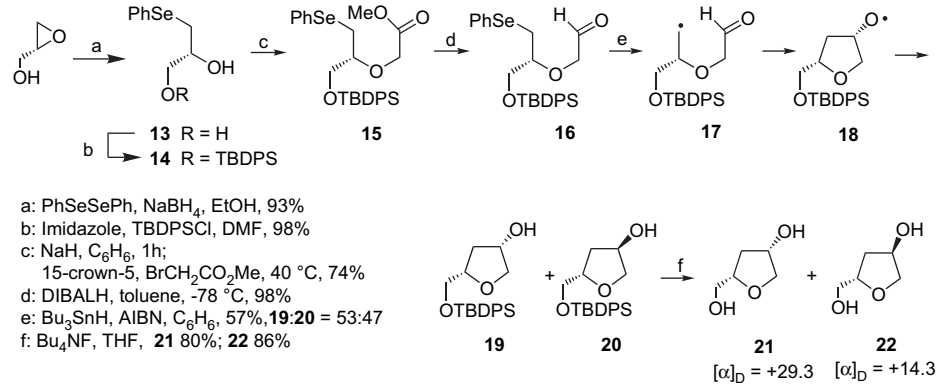
2. Results and discussion

The first experiments were carried out on (2*S*)-2-[1-phenyl-2-(phenylseleno)ethoxy]propanal **7** (Scheme 2). This compound was prepared in two steps starting from styrene and isopropyl (*S*)-lactate. The first step consisted in the alkoxyselenenylation of styrene promoted by the electrophilic phenylselenenyl triflate. The addition of the electrophile produced a seleniranium intermediate, which was regiospecifically trapped by the hydroxy group of the hydroxyester to afford the two diastereomeric alkoxy ester **6** (in the ratio of 72:28), which were separated by column chromatography. The major isomer was then transformed into the corresponding aldehyde **7** by controlled reduction with DIBALH. This compound was then submitted to the radical cyclization. For this purpose it was treated with a slight excess of tributyltin hydride in the presence of a catalytic amount of AIBN in refluxing benzene. The main product of this reaction was identified as the open chain ether **11**. The desired tetrahydrofuran-3-ol **12** was only present in very small amounts. This result can be explained assuming that the β-scission of the alkoxy radical **9** to afford the carbon radical **10** is faster than the hydrogen abstraction from the tributyltin hydride to give the tetrahydrofuran-3-ol **12**. The observed final product **11** is then formed by hydrogen abstraction. Very likely the β-scission is favored by the formation of an α-alkoxy secondary carbon radical. Similar results were also observed when this reaction sequence was carried out starting from 1-octene. If the above reported interpretation is correct then one can expect that starting from a 5-phenylseleno-3-oxapentanal that has no substituents in the α-position, the rate of the β-scission of the cyclic alkoxy radical should be decreased thus favoring the formation of the tetrahydrofuran-3-ols. The cyclization reaction was therefore effected starting from the δ-phenylseleno aldehyde **16**.

This was obtained in four steps starting from the commercially available (*R*)-glycidol. As reported in Scheme 3 the single steps proceeded with good to excellent yields. The



Scheme 2.



Scheme 3.

regioselective ring opening of the epoxide by the phenylselenium anion, generated in situ by treatment of the diphenyl diselenide with sodium borohydride in ethanol, afforded the dihydroxyselenide **13**. The primary alcohol was selectively protected and the resulting hydroxyselenide **14** was transformed into the corresponding alkoxyester **15** by treatment with methyl bromoacetate. Several experiments were carried out in order to find the best experimental conditions to effect this reaction. Good reaction yields were finally obtained by working in the presence of 15-crown-5 in benzene at 40 °C. The controlled reduction with DIBALH generated the desired aldehyde **16**, which was submitted to radical cyclization under the usual reaction conditions. In agreement with expectations no products derived from the β-scission of the cyclic alkoxy radical intermediate **18** were present in the reaction mixture. As indicated in Scheme 3 the only products formed from this reaction in 57% yield and in the ratio of 53:47 were the two enantiopure diastereomeric tetrahydrofuranols **19** and **20** derived from the hydrogen abstraction by the radical **18**. The lack of diastereoselectivity was not surprising since similar results were already observed in the case of other 5-*exo*-cyclizations involving the carbonyl group.[6b] The two diastereoisomers were easily separated by flash column chromatography and their physical and spectroscopical properties could thus be measured. With the aim of optimizing the reaction yield and the diastereoselectivity of the cyclization step, the reaction was repeated under different experimental conditions using Bu_3SnH or other hydrogen donors in refluxing toluene (Table 1). The best chemical yields and diastereoselectivities were obtained by using 2 equiv of Bu_3SnH in one portion (entry 1). As expected, a slow addition of Bu_3SnH by a syringe pump (entry 2) did not produce any increase in the yield of the cyclization and only favored the re-opening of the cyclic alkoxyl radical.[10] The attempt to improve the cyclization step by using a larger excess of Bu_3SnH (entry 3) in order to facilitate the trapping of the cyclic alkoxy radical intermediate failed because of the formation of a consistent amount (25%) of the 1-silyl protected 2-(2-hydroxyethoxy)propan-1-ol deriving from the reduction of the carbonyl group by the stannyl radical. Different hydrogen donors such as Ph_3SnH (entry 4) or tris-trimethylsilylsilane (entry 5) gave similar or lower yields of cyclic products, respectively.

Table 1. Cyclization of **16** under different experimental conditions

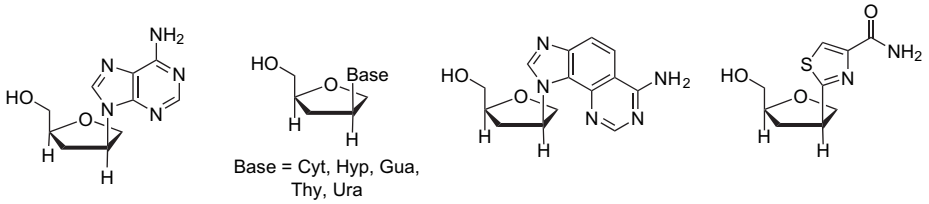
Entry	H-donor	Yield (%)	19:20
1	Bu_3SnH[a]	63	63:37
2	Bu_3SnH[b]	47	60:40
3	Bu_3SnH[c]	37	57:43
4	Ph_3SnH[a]	57	60:40
5	$(Me_3Si)_3SiH$[a]	35	60:40

[a] Hydrogen donor of 2 equiv was added in one portion.
[b] Bu_3SnH of 1.5 equiv was added by a syringe pump in 2 h.
[c] Hydrogen donor 4 equiv was added in one portion.

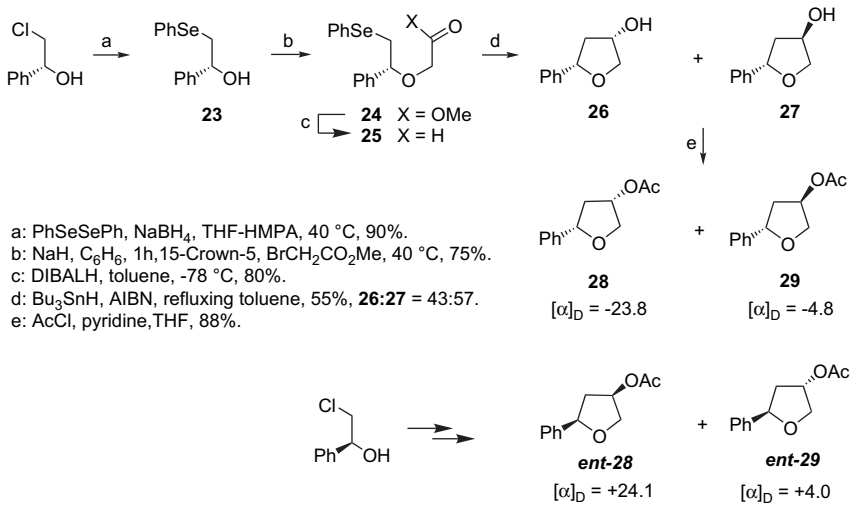
The structural assignment of compounds **19** and **20** was effected after conversion into the known compounds **21** and **22** by treatment with tetrabutylammonium fluoride[9a] (Scheme 3). The tetrahydrofuranols synthesized with the presently described protocol are usually prepared from carbohydrates through multi-steps sequences and are employed as intermediates for further synthetic transformations.

As an example, compound **20** or similar derivatives possessing different protecting groups have been employed in the preparation of interesting antiviral agents such as isodideoxynucleosides, in which the natural or modified base is attached to a non-anomeric carbon atom,[9a,11] or to synthesize C-isodideoxynucleosides.[12] These types of compounds have attracted great interest as anti-HIV agents because of their high stability toward acids and of their resistance to enzymatic deamination.[9,11,12] The strongly active antiviral isoddA and other examples of isodideoxynucleosides and C-isodideoxynucleosides are indicated in Scheme 4.

The presently described procedure was then applied to the aldehyde **25** from which it was expected to produce the two enantiopure phenyl substituted tetrahydrofuranols **26** and **27**. As indicated in Scheme 5 in the present case the hydroxyselenide **23** was not produced by the opening of the corresponding (*R*)-styrene oxide since it is known that this reaction is not regioselective.[13] Compound **23** was instead prepared in good yields by the nucleophilic substitution of the commercially available (*R*)-2-chloro-1-phenylethanol with sodium phenyl selenolate. The conversion of **23** into **24** and the successive reduction to **25** were carried out as described above and proceeded in good yields (see Scheme 5). The deselenenylation and the cyclization of the resulting carbon radical eventually afforded an almost equimolecular mixture of the two enantiomerically pure diastereomeric 5-phenyltetrahydrofuran-3-ols **26** and **27**.[14] These were converted into the corresponding acetates **28** and **29**, which were easily separated by medium pressure liquid chromatography. NOESY experiments confirmed the proposed structures reported in Scheme 5. In the case of compound **28** a strong dipolar interaction was in fact observed between the proton in the 3-position and the proton in the 5-position. A similar interaction was not observed in the case of the diastereoisomer **29**. A similar synthetic sequence was also repeated starting from the (*S*)-2-chloro-1-phenylethanol from which the enantiomeric 5-phenyltetrahydrofuran-3-yl acetates *ent*-**28** and *ent*-**29** were obtained. The four isomeric acetates are reported in Scheme 5 together with their measured optical rotations. HPLC analyses on a chiral column confirmed that the enantiomeric purities of compounds **28**, **29**,



Scheme 4.



Scheme 5.

ent-**28**, and *ent*-**29** are identical to those of the starting chlorohydrins, indicating that no loss of the enantiomeric purity occurred during the various synthetic steps.

3. Conclusions

In conclusion the tin hydride mediated radical 5-*exo-trig* cyclizations of 5-phenylseleno-3-oxapentanals can be efficiently employed for the synthesis of enantiopure tetrahydrofuran-3-ols. The starting aldehydes are easily prepared in few steps from commercially available enantiomerically enriched epoxides or chlorohydrins. The results of the experiments here described allowed the appropriate structural features of the starting aldehydes to be determined in order to obtain good yields of the tetrahydrofuran-3-ols and to minimize the formation of other products deriving from the competitive β-scission of the initially formed cyclic alkoxy radical intermediate. It was observed that these latter compounds are the major reaction products when an alkyl substituent is present in the α-position of the starting aldehyde. Experiments effected to find the best reagents and the best experimental conditions to have a successful hydrogen abstraction reaction by the cyclic alkoxy radical intermediate were also illustrated. Finally it is worth mentioning that the tetrahydrofuran-3-ols here obtained starting from the (*R*)-glycidol are useful intermediates in the preparation of antiviral agents.

4. Experimental

4.1. General

New compounds were characterized by ^{1}H, ^{13}C NMR, and mass spectra. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance-DRX 400 instrument (at 400 and 100.62 MHz, respectively) with $CDCl_3$ as solvent and TMS as internal reference. GC–MS analyses were carried out with an HP 6890 gas chromatograph (HP-5MS capillary column, 30 m i.d., 0.25 mm, film 0.25 μm) equipped with an HP 5973 Mass Selective Detector; for the ions containing selenium only the peaks arising from the selenium-80 isotope are given. HPLC analyses were performed on an HP 1100 instrument equipped with a chiral column and an UV detector. Optical rotations were measured with a Jasco DIP-1000 digital polarimeter. Elemental analyses were carried out on a Carlo Erba 1106 Elemental Analyzer. Commercially available chiral compounds possessed enantiomeric excesses equal or greater than 98%.

4.1.1. Isopropyl (2*S*)-2-[1-phenyl-2-(phenylseleno)ethoxy]propanoate (6). PhSeCl (0.19 g, 1 mmol) was dissolved in CH_2Cl_2 (8 mL) at 0 °C and silver trifluoromethanesulfonate (0.26 g, 1 mmol) was added. After 10 min, styrene (0.26 g, 2.5 mmol) and (*S*)-isopropyl lactate (0.16 g, 1.2 mmol) were added at −78 °C. The reaction temperature was left to gradually reach −50 °C over 30 min. The resulting white suspension was stirred for 1 h and then worked up by treatment with water (30 mL). The mixture was filtered through Celite and extracted with CH_2Cl_2 (3×15 mL). The organic layer was dried over Na_2SO_4 and evaporated. Crude compound **1** was a 72:28 mixture of two diastereoisomers (determined by ^{1}H NMR), which were separated by flash chromatography (light petroleum/dichloromethane 80:20 to 60:40 as eluant). Chemical yields and physical and spectral data of the two compounds are reported below.

Major isomer: 43% yield (0.16 g); oil; R_f: 0.27 (light petroleum/dichloromethane 40:60); $[\alpha]_D^{21}$ −73.8 (*c* 1.5, $CHCl_3$); ^{1}H NMR: δ=7.50–7.45 (m, 2H; SePh), 7.38–7.25 (m, 5H; Ph), 7.22–7.17 (m, 3H; SePh), 5.10 (sept, ^3J=6.3 Hz, 1H; OC*H*Me$_2$), 4.67 (dd, ^3J=7.3, 6.3 Hz, 1H; OC*H*Ph), 3.81 (q, ^3J=6.9 Hz, 1H; OC*H*Me), 3.48 (dd, ^2J=12.0 Hz, ^3J=7.3 Hz, 1H; CH_aH$_b$), 3.16 (dd, ^2J=12.0 Hz, ^3J=6.3 Hz, 1H; CH$_a$*H*$_b$), 1.34 (d, ^3J=6.9 Hz, 3H; OCH*Me*), 1.27 (d, ^3J=6.3 Hz, 6H; OCH*Me*$_2$); ^{13}C NMR: δ=172.6, 140.4, 132.2 (2C), 130.9, 128.9 (2C), 128.5 (2C), 128.3, 127.0 (2C), 126.5, 80.6, 72.3, 68.3, 34.9, 21.7 (2C), 18.8; MS (70 eV, EI) *m*/*z* (%): 392 (23) [M$^+$], 261 (15), 221 (59), 179 (100), 157 (23), 107 (48), 77 (11). Anal. Calcd for $C_{20}H_{24}O_3Se$: C, 61.38; H, 6.18. Found: C, 61.27; H, 6.15.

Minor isomer: 17% yield (67 mg); oil; slightly impure; R_f: 0.20 (light petroleum/dichloromethane 40:60); ^{1}H NMR: δ=7.53–7.48 (m, 2H; SePh), 7.40–7.22 (m, 8H; Ph, SePh),

4.84 (sept, ^3J=6.3 Hz, 1H; OC*H*Me$_2$), 4.59 (dd, ^3J=8.1, 5.4 Hz, 1H; OC*H*Ph), 4.0 (q, ^3J=6.8 Hz, 1H; OC*H*Me), 3.41 (dd, ^2J=12.6 Hz, ^3J=8.1 Hz, 1H; CH_aH$_b$), 3.16 (dd, ^2J=12.6 Hz, ^3J=5.4 Hz, 1H; CH$_a$$H_b$), 1.42 (d, ^3J=6.8 Hz, 3H; OCH*Me*), 1.10 (d, ^3J=6.3 Hz, 3H; OCH*Me*$_2$), 1.08 (d, ^3J=6.3 Hz, 3H; OCH*Me*$_2$); ^{13}C NMR: δ=172.2, 140.7, 132.4 (2C), 130.6, 129.0 (2C), 128.3 (2C), 128.1, 126.9 (2C), 126.8, 81.7, 74.4, 68.1, 35.0, 21.4 (2C), 18.1; MS (70 eV, EI) *m*/*z* (%): 392 (11) [M$^+$], 261 (11), 221 (63), 179 (100), 157 (21), 107 (51), 77 (11).

4.1.2. (2*S*)-2-[1-Phenyl-2-(phenylseleno)ethoxy]propanal (7). The ester **6** (0.13 g, 1 mmol) was dissolved in toluene (8 mL) and treated at −78 °C with 1.1 equiv of DIBALH (1.5 M in toluene) under N$_2$. After 3 h 20 mL of a 7% aqueous solution of HCl was added and the mixture was stirred at room temperature for 3 h. The reaction mixture was extracted with CH$_2$Cl$_2$ (3×15 mL), dried over Na$_2$SO$_4$, and evaporated under reduced pressure. The residue was used without further purification. Chemical yield and physical and spectral data of **7** are reported below.

Yield 98% (0.33 g); oil; ^{1}H NMR: δ=9.64 (d, ^3J=2.1 Hz, 1H; C*H*=O), 7.40–7.35 (m, 2H; SePh), 7.25–7.05 (m, 8H; SePh, Ph), 4.48 (dd, ^3J=8.7, 4.6 Hz, 1H; OC*H*Ph), 3.56 (dq, ^3J=7.0, 2.1 Hz, 1H; OC*H*Me), 3.28 (dd, ^2J=12.6 Hz, ^3J=8.7 Hz, 1H; CH_aH$_b$), 2.99 (dd, ^2J=12.6 Hz, ^3J=4.6 Hz, 1H; CH$_a$$H_b$), 1.06 (d, ^3J=7.0 Hz, 3H; OCH*Me*); ^{13}C NMR: δ=204.0, 140.4, 132.4 (2C), 130.5, 129.0 (2C), 128.6 (2C), 128.4, 127.0, 126.5 (2C), 81.6, 78.0, 36.0, 16.0; MS (70 eV, EI) *m*/*z* (%): 334 (42) [M$^+$], 261 (18), 183 (42), 163 (100), 107 (23), 91 (55), 77 (28).

4.1.3. 3-Ethoxy-3-phenylpropanal (11). Compound **11** was obtained by treatment of **7** (0.1 g, 0.3 mmol) with Bu$_3$SnH and AIBN in benzene under the experimental conditions described in the typical procedure for the cyclization reaction. The crude product was purified by flash chromatography (light petroleum/dichloromethane 70:30 to 50:50). Chemical yield and physical and spectral data of **11** are reported below.

Yield 38% (20 mg); oil; R_f: 0.40 (light petroleum/dichloromethane 20:80); ^{1}H NMR: δ=9.81 (dd, ^3J=2.5, 1.6 Hz, 1H; C*H*=O), 7.48–7.30 (m, 5H; Ph), 4.82 (dd, ^3J=9.0, 4.3 Hz, 1H; C*H*OEt), 3.45 (dq, ^2J=9.3 Hz, ^3J=7.0 Hz, 1H; CH$_3$CH_aH$_b$O), 3.35 (dq, ^2J=9.3 Hz, ^3J=7.0 Hz, 1H; CH$_3$CH$_a$$H_b$O), 2.93 (ddd, ^2J=16.4 Hz, ^3J=9.0, 2.5 Hz, 1H; CH_aH$_b$CH=O), 2.62 (ddd, ^2J=16.4 Hz, ^3J=4.3, 1.6 Hz, 1H; CH$_a$$H_b$CH=O), 1.18 (t, ^3J=7.0 Hz, 3H; Me); MS (70 eV, EI) *m*/*z* (%): 178 (17) [M$^+$], 149 (21), 135 (100), 107 (86), 105 (55), 104 (27), 79 (67), 42 (77). Anal. Calcd for C$_{11}$H$_{14}$O$_2$: C, 74.13; H, 7.92. Found: C, 74.47; H, 8.03.

4.1.4. (2*R*)-3-(Phenylseleno)propane-1,2-diol (13). To a solution of diphenyl diselenide (1.87 g, 6 mmol) in EtOH (20 mL), NaBH$_4$ (0.68 g, 18 mmol) was added at room temperature in small portions. The reaction mixture was warmed to 40 °C for 30 min, then (*R*)-glycidol (0.9 g, 12 mmol) was added to the resulting white suspension. The reaction was monitored by TLC and worked up after 6 h. The reaction was poured into a saturated NH$_4$Cl solution (30 mL) and extracted with diethyl ether (3×20 mL). The ethereal layer was dried over Na$_2$SO$_4$ and evaporated under reduced pressure. The residue was purified by flash chromatography (dichloromethane/MeOH 99:1 to 98:2 as eluant) to afford **13** in 93% yield (2.6 g); R_f: 0.36 (dichloromethane/MeOH 90:10); ([α]$_D^{23}$ −21.7 (*c* 2.7, EtOH)). Spectral data of this compound are in agreement with those already reported in the literature.[15]

4.1.5. (2*R*)-1-{[*tert*-Butyl(diphenyl)silyl]oxy}-3-(phenylseleno)propan-2-ol (14). The diol **13** (2.6 g, 11.2 mmol) was selectively protected by treatment with imidazole (1.14 g, 16.8 mmol) and *tert*-butyl(diphenyl)silyl chloride (TBDPSCl, 4.0 g, 16.8 mmol) in DMF (25 mL) at room temperature. After 4 h the reaction was poured into H$_2$O (50 mL) and extracted with diethyl ether (3×30 mL). The ethereal layer was washed with 20 mL of a 7% aqueous solution of HCl and with 20 mL of water, dried over Na$_2$SO$_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (light petroleum/dichloromethane 70:30 to 50:50 as eluant). Chemical yield and physical and spectral data of **14** are reported below.

Yield 98% (5.16 g); oil; R_f: 0.30 (light petroleum/dichloromethane 40:60); ^{1}H NMR: δ=7.70–7.18 (m, 15H; Ph, SePh), 3.90–3.82 (m, 1H; C*H*OH), 3.75 (dd, ^2J=10.3 Hz, ^3J=4.6 Hz, 1H; CH_aH$_b$COSi), 3.72 (dd, ^2J=10.3 Hz, ^3J=5.6 Hz, 1H; CH$_a$$H_b$CHO), 3.15 (dd, ^2J=12.7 Hz, ^3J=5.7 Hz, 1H; CH_aH$_b$SePh), 3.04 (dd, ^2J=12.7 Hz, ^3J=6.9 Hz, 1H; CH$_a$$H_b$CHO), 2.68 (br s, 1H; O*H*), 1.08 (s, 9H; C*Me*$_3$). ^{13}C NMR: δ=135.5 (4C), 132.9 (2C), 132.5 (2C), 129.8 (3C), 129.1 (2C), 127.8 (4C), 127.0, 70.8, 66.5, 31.5, 26.8 (3C), 19.2. Anal. Calcd for C$_{25}$H$_{30}$O$_2$SeSi: C, 63.95; H, 6.44. Found: C, 63.90; H, 6.42.

4.1.6. Methyl ({(1*R*)-2-{[*tert*-butyl(diphenyl)silyl]oxy}-1-[(phenylseleno)methyl]ethyl}oxy)acetate (15). A solution of **14** (1.88 g, 4 mmol) in dry benzene (15 mL), was treated with NaH (0.11 g, 4.4 mmol) and the reaction mixture was stirred for 1 h at room temperature. 15-Crown-5 (0.88 mL, 4.4 mmol) and methyl bromoacetate (0.4 mL, 4.2 mmol) were added and the reaction mixture was heated at 40 °C overnight. The reaction was quenched with water (30 mL) and extracted with CH$_2$Cl$_2$ (3×15 mL). The organic phase was dried with Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography (light petroleum to light petroleum/diethyl ether 90:10 as eluant). Chemical yield and physical and spectral data of **15** are reported below.

Yield 74% (1.60 g); oil; R_f: 0.60 (light petroleum/diethyl ether 70:30); [α]$_D^{19}$ −14.1 (*c* 2.9, CHCl$_3$); ^{1}H NMR: δ=7.70–7.64 (m, 4H; Ph), 7.58–7.18 (m, 11H; Ph, SePh), 4.22 (d, ^2J=17.8 Hz, 1H; CH_aH$_b$CO$_2$Me), 4.18 (d, ^2J=17.8 Hz, 1H; CH$_a$$H_bCO_2$Me), 3.87 (dd, ^2J=10.8 Hz, ^3J=5.5 Hz, 1H; CH_aH$_b$O), 3.81 (dd, ^2J=10.8 Hz, ^3J=5.0 Hz, 1H; CH$_a$$H_b$O), 3.72 (s, 3H; O*Me*), 3.74–3.66 (m, 1H; C*H*O), 3.24 (dd, ^2J=12.8 Hz, ^3J=5.8 Hz, 1H; CH_aH$_b$-SePh), 3.16 (dd, ^2J=12.8 Hz, ^3J=6.3 Hz, 1H; CH$_a$$H_b$O), 1.07 (s, 9H; C*Me*$_3$); ^{13}C NMR: δ=170.7, 135.5 (2C), 135.4 (2C), 133.0, 132.9, 132.2 (2C), 130.4, 129.7 (2C), 129.0 (2C), 127.7 (4C), 126.4, 80.6, 68.3, 65.1, 51.7, 28.9, 26.7 (3C), 19.1. Anal. Calcd for C$_{28}$H$_{34}$O$_4$SeSi: C, 62.09; H, 6.35. Found: C, 61.79; H, 6.63.

4.1.7. ({(1*R*)-2-{[*tert*-Butyl(diphenyl)silyl]oxy}-1-[(phenylseleno)methyl]ethyl}oxy)acetaldehyde (16). Compound **16** (2.27 g, 4.4 mmol) was prepared according to the procedure described for **7**. In this case also the aldehyde was used without further purification. Chemical yield and physical and spectral data of **16** are reported below.

Yield 98%; oil; ^{1}H NMR: δ=9.66 (t, ^3J=1.0 Hz, 1H; C*H*=O), 7.68–7.62 (m, 4H; Ph), 7.5–7.34 (m, 7H; Ph, SePh), 7.30–7.17 (m, 4H; Ph), 4.13 (dd, ^2J=17.8 Hz, ^3J=1.0 Hz, 1H; CH_aH$_b$CH=O), 4.08 (dd, ^2J=17.8 Hz, ^3J=1.0 Hz, 1H; CH$_a$$H_b$CH=O), 3.85 (dd, ^2J=10.9 Hz, ^3J=5.6 Hz, 1H; CH_aH$_b$OSi); 3.80 (dd, ^2J=10.9 Hz, ^3J=4.8 Hz, 1H; CH$_a$$H_b$OSi), 3.65 (dddd, ^3J=6.9, 5.6, 5.2, 4.8 Hz, 1H; C*H*O), 3.21 (dd, ^2J=13.0 Hz, ^3J=5.2 Hz, 1H; CH_aH$_b$SePh), 3.12 (dd, ^2J=13.0 Hz, ^3J=6.9 Hz, 1H; CH$_a$$H_b$SePh), 1.08 (s, 9H; C$Me_3$); ^{13}C NMR: δ=201.1, 135.6 (2C), 135.5 (2C), 133.1, 133.0, 132.5 (2C), 130.2, 129.9 (2C), 129.2 (2C), 127.8 (4C), 126.7, 81.4, 76.3, 61.9, 28.8, 26.8 (3C), 18.8.

4.1.8. Cyclization reaction of 16: typical procedure. The aldehyde **16** (0.26 g, 0.5 mmol) was dissolved in toluene (5 mL) and Bu_3SnH (0.27 mL, 1 mmol) was added in one portion together with a catalytic amount of AIBN. The reaction mixture was refluxed under N_2 for 2 h. The progress of the reaction was monitored by TLC. The solvent was removed under reduced pressure. The crude mixture of **19** and **20** (dr=53:47) was separated by flash chromatography (light petroleum/diethyl ether 70:30 to 55:45 as eluant). Similar experimental conditions were employed for the reactions effected with other solvents or hydrogen donors (see Table 1).

4.1.8.1. (3*S*,5*S*)-5-({[*tert*-Butyl(diphenyl)silyl]oxy}methyl)tetrahydrofuran-3-ol (19). Yield 40% (72 mg); R_f: 0.27 (light petroleum/diethyl ether 40:60); oil; $[\alpha]_D^{22}$ +16.6 (*c* 4.7, $CHCl_3$); ^{1}H NMR: δ=7.78–7.66 (m, 4H; Ph), 7.49–7.36 (m, 6H; Ph), 4.37–4.30 (m, 1H; C*H*OH), 4.17 (dq, ^3J=10.4, 2.5 Hz, 1H; C*H*OSi), 4.10 (d, ^2J=10.6 Hz, 1H; O*H*), 4.02 (dd, ^2J=9.3 Hz, ^3J=4.7 Hz, 1H; CH_aH$_b$O), 3.88 (dd, ^2J=11.1 Hz, ^3J=2.5 Hz, 1H; CH_aH$_b$OSi), 3.71 (dd, ^2J=9.3 Hz, ^3J=3.0 Hz, 1H; CH$_a$$H_b$O), 3.54 (dd, ^2J=11.1 Hz, ^3J=2.1 Hz, 1H; CH$_a$$H_b$OSi), 2.31 (ddd, ^2J=13.8 Hz, ^3J=10.4, 5.4 Hz, 1H; CHCH_aH$_b$CH), 2.07–2.0 (m, 1H; CHCH$_a$$H_b$CH), 1.09 (s, 9H; C$Me_3$); ^{13}C NMR: δ=135.6 (2C), 135.5 (2C), 132.4, 132.1, 129.9, 129.8, 127.7 (4C), 77.8, 76.7, 71.6, 66.1, 36.7, 26.7 (3C), 19.0. Anal. Calcd for $C_{21}H_{28}O_3Si$: C, 70.74; H, 7.92. Found: C, 70.86; H, 8.01.

4.1.8.2. (3*R*,5*S*)-5-({[*tert*-Butyl(diphenyl)silyl]oxy}methyl)tetrahydrofuran-3-ol (20). Yield 23% (42 mg); R_f: 0.18 (light petroleum/diethyl ether 40:60); oil; $[\alpha]_D^{25}$ +7.2 (*c* 5.6, $CHCl_3$); ^{1}H NMR: δ=7.74–7.68 (m, 4H; Ph), 7.49–7.38 (m, 6H; Ph), 4.62–4.52 (m, 1H; C*H*O), 4.35 (ddt, ^3J=8.6, 6.7, 4.3 Hz, 1H; C*H*OSi), 3.98 (dd, ^2J=9.6 Hz, ^3J=3.8 Hz, 1H; CH_aH$_b$O), 3.82 (dt, ^2J=9.6 Hz, ^3J=1.4 Hz, 1H; CH$_a$$H_b$O), 3.78 (dd, ^2J=10.8 Hz, ^3J=4.3 Hz, 1H; CH_aH$_b$OSi), 3.69 (dd, ^2J=10.8 Hz, ^3J=4.3 Hz, 1H; CH$_a$$H_b$OSi), 2.35 (br s, 1H; O*H*), 2.06 (ddd, ^2J=13.4 Hz, ^3J=8.6, 5.2 Hz, 1H; CHCH_aH$_b$CH), 1.98 (ddt, ^2J=13.4 Hz, ^3J=6.7, 1.5 Hz, 1H; CHCH$_a$$H_b$CH), 1.09 (s, 9H; C$Me_3$); ^{13}C NMR: δ=135.6 (4C), 133.4 (2C), 129.6 (2C), 127.6 (4C), 78.3, 75.7, 72.7, 65.9, 37.2, 26.8 (3C), 19.2. Anal. Calcd for $C_{21}H_{28}O_3Si$: C, 70.74; H, 7.92. Found: C, 70.83; H, 7.78.

4.1.9. Deprotection of tetrahydrofuranols 19 and 20. $Bu_4NF\cdot 3H_2O$ (0.14 g, 0.45 mmol) was added to a solution of **19** or **20** (0.1 g, 0.3 mmol) in THF (4 mL) at room temperature and the resulting mixture was stirred overnight. After addition of 0.1 mL of water and 2 g of silica gel the mixture was evaporated to dryness and purified by flash chromatography (CH_2Cl_2/MeOH 98:2 to 80:20). Spectral data of compounds **21** and **22** reported below are in agreement with those described in the literature.[9a]

4.1.9.1. (3*S*,5*S*)-5-(Hydroxymethyl)tetrahydrofuran-3-ol (21). Yield 80% (28 mg); R_f: 0.43 (dichloromethane/methanol 90:10); oil; $[\alpha]_D^{21}$ +29.3 (*c* 1.2, $CHCl_3$); ^{1}H NMR: δ=4.42–4.36 (m, 1H; C*H*O), 4.25 (dq, ^3J=9.8, 2.5 Hz, 1H; C*H*OSi), 3.98 (dd, ^2J=9.7 Hz, ^3J=1.7 Hz, 1H; CH_aH$_b$O), 3.92 (dd, ^2J=11.7 Hz, ^3J=2.5 Hz, 1H; CH_aH$_b$OSi), 3.75 (dd, ^2J=9.7 Hz, ^3J=3.0 Hz, 1H; CH$_a$$H_b$O), 3.61 (dd, ^2J=11.7 Hz, ^3J=2.5 Hz, 1H; CH$_a$$H_b$OSi), 2.87 (br s, 2H; O*H*), 2.32 (ddd, ^2J=14.1 Hz, ^3J=9.8, 5.7 Hz, 1H; CHCH_aH$_b$CH), 1.99–1.87 (m, 1H; CHCH$_a$$H_b$CH). ^{13}C NMR: δ=78.4, 76.5, 71.4, 63.2, 36.3. Anal. Calcd for $C_5H_{10}O_3$: C, 50.84; H, 8.53. Found: C, 50.99; H, 8.44.

4.1.9.2. (3*R*,5*S*)-5-(Hydroxymethyl)tetrahydrofuran-3-ol (22). Yield 86% (30 mg); oil; R_f: 0.29 (dichloromethane/methanol 90:10); $[\alpha]_D^{24}$ +14.3 (*c* 1.3, $CHCl_3$); ^{1}H NMR: δ=4.56 (dddd, ^3J=4.8, 4.0, 2.0, 1.6 Hz, 1H; C*H*O), 4.33 (dddd, ^3J=9.1, 6.6, 5.4, 3.0 Hz, 1H; C*H*OSi), 3.97 (dd, ^2J=9.7 Hz, ^3J=4.0 Hz, 1H; CH_aH$_b$O), 3.81 (dd, ^2J=9.7 Hz, ^3J=1.6 Hz, 1H; CH$_a$$H_b$O), 3.78 (dd, ^2J=11.8 Hz, ^3J=3.0 Hz, 1H; CH_aH$_b$OSi), 3.53 (dd, ^2J=11.8 Hz, ^3J=5.4 Hz, 1H; CH$_a$$H_b$OSi), 2.10 (br s, 2H; O*H*), 1.96 (dddd, ^2J=13.3 Hz, ^3J=6.6, 2.2 Hz, ^4J=1.0 Hz, 1H; CHCH_aH$_b$CH), 1.92 (ddd, ^2J=13.3 Hz, ^3J=9.1, 4.8 Hz, 1H; CHCH$_a$$H_b$CH); ^{13}C NMR: δ=78.3, 75.5, 72.6, 64.2, 36.7. Anal. Calcd for $C_5H_{10}O_3$: C, 50.84; H, 8.53. Found: C, 50.97; H, 8.50.

4.1.10. (1*R*)-1-Phenyl-2-(phenylseleno)ethanol (23). The β-hydroxyalkyl phenyl selenide **23** was prepared by S_N2 displacement of (*R*)-2-chloro-1-phenylethanol by sodium phenyl selenolate in THF/HMPA (90% yield), as previously described in the literature.[3b,13]

4.1.11. Methyl {[(1*R*)-1-phenyl-2-(phenylseleno)ethyl]oxy}acetate (24). Compound **24** (0.45 g, 1.28 mmol) was prepared as described for **15**. The crude product was purified by medium pressure liquid chromatography with a LiChroprep Si 60 (40–63 μm, 310×25 mm i.d., Merck) and a FMI LAB pump model QSY (light petroleum/diethyl ether 90:10 as eluant). Chemical yield and physical and spectral data of **24** are reported below.

Yield 75%; R_f: 0.53 (light petroleum/diethyl ether 70:30); $[\alpha]_D^{25}$ −49.0 (*c* 2.3, $CHCl_3$); ^{1}H NMR: δ=7.28–7.18 (m, 2H; SePh), 7.13–7.00 (m, 5H; Ph), 7.00–6.90 (m, 3H; SePh), 4.36 (dd, ^3J=7.7, 5.8 Hz, 1H; CHO), 3.76 (d, ^2J=16.3 Hz, 1H; CH_aH$_b$O), 3.63 (d, ^2J=16.3 Hz, 1H; CH$_a$$H_b$O), 3.42 (s, 3H; OMe), 3.18 (dd, ^2J=12.3 Hz, ^3J=7.7 Hz, 1H; CH_aH$_b$SePh), 2.90 (dd, ^2J=12.3 Hz, ^3J=5.8 Hz, 1H;

CH_aH_bSePh); ^{13}C NMR: δ=170.5, 139.6, 132.5 (2C), 130.5, 129.0 (2C), 128.6 (2C), 128.5, 127.0 (2C), 126.8, 81.9, 66.0, 51.8, 34.7; MS (70 eV, EI) *m/z* (%): 350 (16) [M^+], 179 (100), 157 (10), 121 (54), 103 (12), 77 (12). Anal. Calcd for $C_{17}H_{18}O_3Se$: C, 58.46; H, 5.19. Found: C, 58.35; H, 5.38.

4.1.12. {[(1*R*)-1-Phenyl-2-(phenylseleno)ethyl]oxy}acetaldehyde (25). Compound **25** (0.32 g, 1 mmol) was prepared according to the procedure described for **7**. The crude product was purified by column chromatography (light petroleum/diethyl ether 90:10 to 75:25 as eluants). Chemical yield and physical and spectral data of **25** are reported below.

Yield 80%; oil; R_f: 0.20 (light petroleum/diethyl ether 70:30); $[\alpha]_D^{19}$ −56.4 (*c* 2.4, $CHCl_3$); ^1H NMR: δ=9.71 (t, ^3J=1.0 Hz, 1H; C*H*=O), 7.70–7.50 (m, 2H; SePh), 7.50–7.10 (m, 8H; Ph, SePh), 4.60 (dd, ^3J=8.3, 5.2 Hz, 1H; C*H*O), 4.03 (dd, ^2J=17.7 Hz, ^3J=1.0 Hz, 1H; OCH_aH_bCH=O), 3.93 (dd, ^2J=17.7 Hz, ^3J=1.0 Hz, 1H; OCH_aH_bCH=O), 3.49 (dd, ^2J=12.5 Hz, ^3J=8.3 Hz, 1H; CH_aH_bSePh), 3.20 (dd, ^2J=12.5 Hz, ^3J=5.2 Hz, 1H; CH_aH_bSePh); ^{13}C NMR: δ= 200.6, 139.6, 132.6 (2C), 130.3, 129.1 (2C), 128.7 (2C), 128.6, 127.0, 126.8 (2C), 82.8, 74.5, 34.8; MS (70 eV, EI) *m/z* (%): 320 (31) [M^+], 183 (12), 157 (20), 149 (100), 105 (11), 104 (17), 103 (16), 91 (92), 78 (15), 77 (23). Anal. Calcd for $C_{16}H_{16}O_2Se$: C, 60.19; H, 5.05. Found: C, 60.25; H, 4.95.

4.1.13. 5-Phenyltetrahydrofuran-3-ols and their corresponding acetates. Compounds **26** and **27** were obtained from the aldehyde **25** by radical cyclization reaction effected under the reaction conditions described in the typical procedure. The mixture of diastereoisomers could be separated after conversion into the corresponding acetates **28** and **29** by treatment with acetyl chloride and pyridine in THF at 0 °C (flash chromatography, light petroleum/diethyl ether 90:10 as eluant). An identical sequence effected on (*S*)-2-chloro-1-phenylethanol gave compounds *ent*-**28** and *ent*-**29**. The enantiomeric purity of compounds **28**, **29**, *ent*-**28**, and *ent*-**29** was identical to that of the starting products as determined by chiral HPLC (Chiralcel OD-H column (250×4 mm i.d.), eluant: *i*-PrOH/hexane 10:90, flow rate: 1.0 mL/min, UV detection at 210 nm). Chemical yields and physical and spectral data of these compounds are reported below.

4.1.13.1. 5-(3*S*,5*S*)-5-Phenyltetrahydrofuran-3-ol (26) and (3*R*,5*S*)-5-phenyltetrahydrofuran-3-ol (27).[14] Yield 55%; mixture of diastereoisomers, cis/trans=43:57; oil.

4.1.13.2. (3*S*,5*S*)-5-Phenyltetrahydrofuran-3-yl acetate (28). Yield 39%; oil; R_f: 0.36 (light petroleum/diethyl ether 70:30); $[\alpha]_D^{23}$ −23.8 (*c* 1.4, $CHCl_3$); HPLC analysis: t_R 9.6 min; ^1H NMR: δ=7.14–6.97 (m, 5H; Ph), 5.07 (dddd, ^3J=7.7, 4.8, 3.3, 1.8 Hz, 1H; C*H*OAc), 4.58 (t, ^3J=7.7 Hz, 1H; C*H*O), 3.87 (ddd, ^2J=10.6 Hz, ^3J=1.8 Hz, ^4J=1.0 Hz, 1H; CH_aH_bO), 3.68 (dd, ^2J=10.6 Hz, ^3J= 4.8 Hz, 1H; CH_aH_bO), 2.46 (dt, ^2J=13.9 Hz, ^3J=7.7 Hz, 1H; CHCH_aH_bCH), 1.72 (s, 3H; *Me*CO), 1.69 (dddd, ^2J= 13.9 Hz, ^3J=7.7, 3.3 Hz, ^4J=1.0 Hz, 1H; CHCH_aH_bCH); ^{13}C NMR: δ=170.9, 141.6, 128.4 (2C), 127.6, 126.0 (2C), 80.3, 75.2, 73.3, 40.7, 21.0; MS (70 eV, EI) *m/z* (%): 206 (1) [M^+], 146 (63), 145 (41), 117 (34), 106 (12), 105 (100), 91 (17), 77 (20). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.94; H, 6.70.

4.1.13.3. (3*R*,5*R*)-5-Phenyltetrahydrofuran-3-yl acetate (*ent*-28). Yield 35%; oil; $[\alpha]_D^{23}$ +24.1 (*c* 1.0, $CHCl_3$); HPLC analysis: t_R 7.8 min. NMR and MS spectra are identical to those of compound **28**. Anal. Calcd for $C_{12}H_{14}O_3$ (206.2): C, 69.88; H, 6.84. Found: C, 69.90; H, 6.78.

4.1.13.4. (3*R*,5*S*)-5-Phenyltetrahydrofuran-3-yl acetate (29). Yield 49%; R_f: 0.44 (light petroleum/diethyl ether 70:30); $[\alpha]_D^{25}$ −4.8 (*c* 2.7, $CHCl_3$); HPLC analysis: t_R 13.3 min; ^1H NMR: δ=7.37–7.25 (m, 5H; Ph), 5.43–5.39 (m, 1H; C*H*OAc), 5.08 (dd, ^3J=10.2, 5.6 Hz, 1H; C*H*O), 4.36 (dd, ^2J=10.5 Hz, ^3J=4.9 Hz, 1H; CH_aH_bO), 3.95 (ddd, ^2J=10.5 Hz, ^3J=2.0 Hz, ^4J=0.8 Hz, 1H; CH_aH_bO), 2.43 (ddt, ^2J=13.8 Hz, ^3J=5.6 Hz, ^3J=^4J=0.8 Hz, 1H; CHCH_aH_bCH), 2.12 (s, 3H; *Me*CO), 2.05 (ddd, ^2J= 13.8 Hz, ^3J=10.2, 5.9 Hz, 1H; CHCH_aH_bCH); ^{13}C NMR: δ=170.7, 141.4, 128.4 (2C), 127.6, 125.7 (2C), 79.7, 75.3, 73.7, 41.2, 21.1; MS (70 eV, EI) *m/z* (%): 206 (3) [M^+], 146 (41), 145 (25), 117 (18), 106 (12), 105 (100), 91 (13), 77 (15). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.60; H, 6.91.

4.1.13.5. (3*S*,5*R*)-5-Phenyltetrahydrofuran-3-yl acetate (*ent*-29). Yield 44%; $[\alpha]_D^{25}$ +4.0 (*c* 1.3, $CHCl_3$); HPLC analysis: t_R 9.9 min. NMR and MS spectra are identical to those of compound **29**. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.99; H, 6.93.

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