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Tetrahedron: *Asymmetry* 16 (2005) 2429–2435

Synthesis of enantiomerically pure perhydrofuro[2,3-*b*]furans

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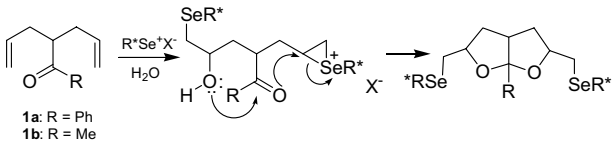
Received 16 May 2005; accepted 15 June 2005

Abstract—Enantiomerically pure 2,5,6a-trisubstituted perhydrofuro[2,3-*b*]furans were obtained by the cyclization of bis-alkenylketones, promoted by camphorselenenyl sulfate produced in situ by oxidation of camphor diselenide with ammonium persulfate in a mixture of water and acetonitrile at room temperature. The cyclization reaction proceeded through a double selenohydroxylation of the two double bonds and produced a mixture of the two diastereoisomers *trans*- and *cis*-2,5-bis[(camphorseleno)methyl] perhydrofuro[2,3-*b*]furans. These were separated by medium pressure liquid chromatography and then deselenenylated with triphenyltin hydride and AIBN.

1. Introduction

The stereoselective syntheses of substituted cyclic ether[1] and perhydrofurofuran derivatives[2] have attracted considerable attention since these heterocyclic compounds are present in several molecules having interesting biological properties.[3,4] In recent years, our research group has been deeply involved in the synthesis of several types of heterocyclic compounds in an enantiomerically enriched or pure form[5] using very efficient organoselenium reagents.[6,7] We have recently reported the synthesis of enantiomerically enriched substituted tetrahydrofurans[8,9] by the cyclization of alkenols promoted by the electrophilic reagents produced from two sulfur containing chiral non-racemic diselenides.[9,10] On the other hand, the synthesis of enantiomerically pure substituted tetrahydrofurans was obtained starting from commercially available enantiopure epoxides[11] and using simple conversions promoted by achiral phenylselenium reagents. A similar multi-step sequence has been employed in the synthesis of more complex molecules. Starting from the commercially available (*R*)-(+)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde, by means of two consecutive selenium promoted cyclizations, the tetrahydrofuro[3,4-*b*]pyrans and tetrahydrofuro[3,4-*b*]furans can be easily obtained as pure enantiomers.[12] The synthesis of related perhydrofuro[2,3-*b*]furans has also attracted considerable attention[13–21] since this structure is encountered in various biologically active natural products. Important compounds are clerodane-type diterpenes, which have potential insect antifeedant[19] and antibacterial activity,[20] and the aflatoxins, which are important mycotoxins with potent toxicity and carcinogenicity that have been detected as contaminants in different types of food.[15] It has been recently reported that a series of very potent non-peptidyl HIV protease inhibitors incorporate a bis-tetrahydrofuranyl structure.[21]

Herein, we report a new and convenient approach for the synthesis of enantiomerically pure 2,5,6a-trisubstituted perhydrofuro[2,3-*b*]furans. As indicated in Scheme 1, this simple method consists of the double cyclization of bis-alkenylketones promoted by a chiral non-racemic electrophilic selenenylating reagent in the presence of water.



Scheme 1.

2. Results and discussion

The starting products **1a** and **1b** were easily prepared according to the procedure described.[22,23] Their

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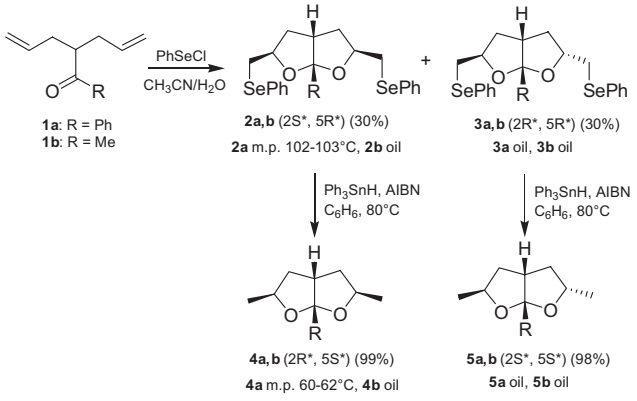
doi:10.1016/j.tetasy.2005.06.016

cyclization reactions were carried out in acetonitrile and water and most likely proceeded through the initial formation of the seleno-hydroxylation products, which are then converted into the perhydrofuro[2,3-*b*]furans by a double cyclization.[22]

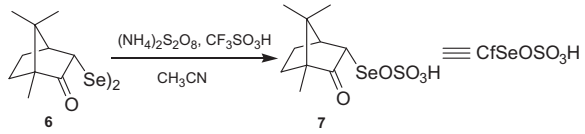
In order to obtain 2,5-dimethyl derivatives **4a**, **4b**, **5a**, and **5b** (Scheme 2) that were to be used as reference compounds in our investigations, we first carried out the cyclization reactions of **1a** and **1b** with the achiral phenylselenenyl chloride and water under the conditions described for the selenohydroxylation of alkenes.[24] As reported in Scheme 2, these reactions produced 1:1 mixtures of the *cis*- and *trans*-isomers **2a**, **3a** and **2b**, **3b**. These results were in good agreement with those reported in the literature.[22,25,26] The two pairs of the diastereoisomers were separated by medium pressure liquid chromatography and then submitted to reductive deselenenylation with Ph_3SnH and AIBN.[11,12] Yields of isolated products are indicated (Scheme 2). The single products **4a**,[27] **4b**, **5a**, and **5b** were examined by GC–MS using a Chirasildex column. As expected, *cis*-isomers **4a** and **4b** appeared as a single peak, while *trans*-isomers **5a** and **5b** appeared as two peaks with the same integrated area corresponding to the two enantiomers.



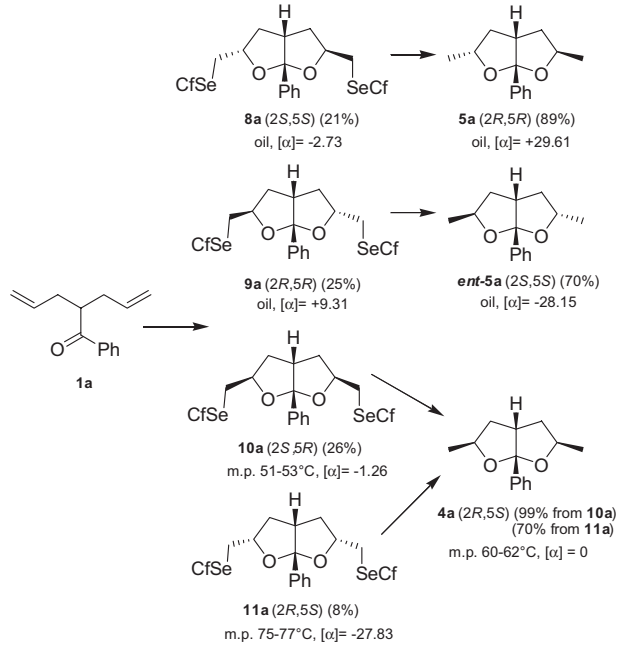
Scheme 2.

The same synthetic sequence was then employed for the cyclizations of **1a** and **1b** promoted by the camphorselenenyl sulfate **7**. This reagent was produced in situ by oxidation of camphor diselenide **6** with ammonium persulfate in the presence of a stoichiometric amount of trifluoromethanesulfonic acid (Scheme 3).[28] The camphor diselenide can be easily obtained in a one-pot reaction from (1*R*)-(+)-camphor and elemental selenium as described by Back.[29]

The results of the cyclization of compound **1a** are reported in Scheme 4. This reaction produced a mixture of the two *trans*-diastereoisomers **8a** and **9a** and the two *cis*-diastereoisomers **10a** and **11a**, which could be separated by medium pressure liquid chromatography. The selenides are presented in the same order in which they are eluted from the chromatographic column. Yields of the isolated products are indicated (Scheme 4). These enantiomerically pure diastereoisomers were



Scheme 3.

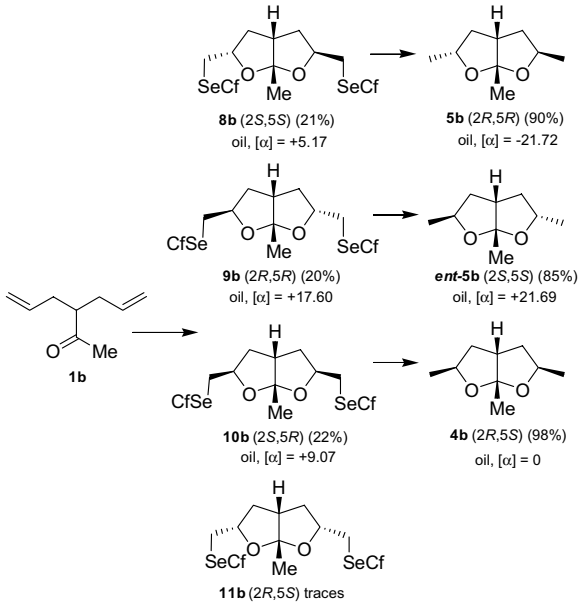


Scheme 4.

then submitted to reductive deselenenylation with Ph_3SnH and AIBN. Compounds **8a** and **9a** afforded the two enantiomeric trisubstituted perhydrofuro[2,3-*b*]furans **5a** and *ent*-**5a**, whereas **10a** and **11a** gave rise to the same compound **4a**.[30] Attribution of structure **5a** and structure *ent*-**5a** to the dextrorotatory and to the levorotatory enantiomers, respectively, and hence to **8a** and **9a**, is only tentative.

As indicated in Scheme 5, in the case of compound **1b**, cyclization gave rise to a mixture of the two *trans*-diastereoisomers **8b** and **9b** and only one *cis*-diastereoisomer **10b**. The *cis*-isomer **11b** was only present in trace amounts. The diastereoisomers **8b**–**10b** could be separated by medium pressure liquid chromatography. After reductive deselenylation, **8b** and **9b** gave the corresponding enantiomerically pure perhydrofuro[2,3-*b*]furans **5b** and *ent*-**5b**. The *cis*-isomer **10b** gave compound **4b**. In this case also the selenides are presented in the same order in which they are eluted from the chromatographic column and structural attributions to compounds **5b** and *ent*-**5b**, and hence **8b** and **9b**, are tentative. Yields of isolated products are indicated in Scheme 5.

The enantiomeric excesses of the deselenylated products **5a**, **5b**, *ent*-**5a**, and *ent*-**5b** were determined by GC–MS experiments using a Chirasildex column. All these isomers appeared as a single peak (ee >98%). The specific rotations of these compounds are indicated in Schemes



Scheme 5.

4 and 5 and are also reported in the Experimental. Obviously, compounds **4a** and **4b** also appeared as single peaks but were optically inactive.

All *trans*-compounds **3a**, **3b**, **8a**, **8b**, **9a**, **9b**, **5a**, **5b**, *ent*-**5a**, and *ent*-**5b** were liquids and in their ^{1}H NMR spectra the hydrogen at the 3a position appeared as a broad quartet because the coupling constant with the proton *anti* in the 3α position (in compounds **8a**, **8b**, **5a**, and **5b**) or in the 4α position (in compounds **3a**, **3b**, **9a**, **9b**, *ent*-**5a**, and *ent*-**5b**) is nearly zero[17] and produces only a line broadening. Molecular models, in fact, indicate that the two protons H_{3a} and $H_{3\alpha}$ in compounds **8a**, **8b**, **5a**, and **5b**, and the two protons H_{3a} and $H_{4\alpha}$ in compounds **3a**, **3b**, **9a**, **9b**, *ent*-**5a**, and *ent*-**5b** are almost orthogonal (Fig. 1).

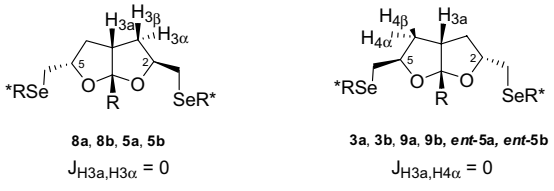


Figure 1.

In the case of **8b**, the *trans* relationship between the two CH_2SeR^* groups was confirmed by the results of NOESY experiments. A strong dipolar effect was in fact observed between the protons at the 5 and 3a positions. The *trans*-configuration of compounds **3a**,[22,25] **3b**, **8a**, **9a**, and **9b** was attributed by analogy. It was also important that, because of the lack of symmetry, all these *trans*-compounds, as well as their deselenenylated derivatives **5a**, **5b**, *ent*-**5a**, and *ent*-**5b**, gave proton and ^{13}C NMR spectra which were more complex than those of the *cis*-isomers.

The *cis*-isomers of the phenyl derivatives **2a**, **10a**, **11a**, and **4a** were solids, while the corresponding isomers of the methyl derivatives **2b**, **10b**, and **4b** were liquids. In the ^{1}H NMR spectra, the hydrogen at the 3a position appeared as a multiplet in compounds **2a**, **2b**, **10a**, and **11a** and as a triplet of triplets in compounds **10b**, **4a**, and **4b**. This indicates that in these *cis*-isomers, the coupling constant between the proton at 3a and the proton at the 3α or 4α positions is not zero. The relative configurations of some *cis*-perhydrofuro[2,3-*b*]furans were also confirmed by the results of NOESY experiments. The protons at the 2 and 5 positions showed a dipolar effect with the proton at the 3a position in compound **11a** while a similar dipolar effect was observed between the protons at the 3a position and the two protons of the CH_2SeR^* group in compound **10a**. This suggests that compounds **11a** and **10a** have the two *cis*-configurations indicated in Scheme 4. The *cis*-configuration of compound **10b** was attributed by analogy. The *cis*-configuration of compounds **2a**,[22,25] **2b**, **4a**, and **4b** was confirmed by the fact that the proton and ^{13}C NMR spectra that resulted were very simple because of the symmetry of the molecules.

3. Conclusions

The herein described camphorselenenyl sulfate promoted double cyclization of bis-alkenylketones favorably compares with previously described methods for the preparation of substituted perhydrofuro[2,3-*b*]furan derivatives.[14–20] The great advantage of the present method consists of the use of chiral non-racemic organoselenium reagents and hence the preparation of the perhydrofuro[2,3-*b*]furans in their enantiomerically pure forms. This simple procedure could have general application since it can be applied to the cyclization of several bis-alkenylketones thus leading to differently substituted perhydrofuro[2,3-*b*]furans. Moreover, the presence of the organoselenium function in the cyclization products facilitates the introduction of several other groups to be easily effected.

4. Experimental

All new compounds were characterized by MS, ^{1}H, 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

Bis-alkenylation of acetophenone with allyl bromide in the presence of sodium hydride in tetrahydrofuran gave rise to 4-benzoylhepta-1,6-diene **1a**.[22] 3-Allylhex-5en-2-one **1b** was obtained by bis-allylation of the ethyl 3-oxobutanoate and subsequently by hydrolysis and decarboxylation.[23] *N*-Phenylseleno phthalimide and triphenyltin hydride were commercial products and used without further purification.

4.2. Cyclization reactions promoted by phenylselenenyl chloride: general procedure

Phenylselenenylchloride[24] (1.5 mmol) was added to a solution of bis-alkenylketones **1a** and **1b** (0.5 mmol) in acetonitrile (5 mL) and water (2 mL). The resulting pale yellow solution was stirred at room temperature for 4 h. The progress of the reaction was monitored by TLC. The reaction mixture was then 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 1:9 mixture of diethyl ether and light petroleum as eluant. The products obtained and the reaction yields are reported in Scheme 2. Physical and spectral data are reported below.

4.2.1. (2*S,5*R**)-6a-Phenyl-2,5-bis[(phenylseleno)methyl]-hexahydrofuro[2,3-*b*]furan, 2a[22,25].** Mp 102–103 °C; ^{1}H NMR: δ 7.70–7.50 (m, 6H), 7.40–7.10 (m, 9H), 4.53–4.46 (m, 2H), 3.24 (dd, 2H, J = 4.5, 12.3 Hz), 3.05 (dd, 2H, J = 7.4, 12.3 Hz), 2.86–2.79 (m, 1H), 1.98–1.93 (m, 4H); ^{13}C NMR: δ 141.7, 132.5 (four carbons), 130.1 (two carbons), 129.0 (four carbons), 127.9 (three carbons), 126.9 (two carbons), 125.8 (two carbons), 117.6, 79.8 (two carbons), 50.6, 39.3 (two carbons), 32.4 (two carbons). Anal. Calcd for $C_{26}H_{26}O_2Se_2$: C, 59.10; H, 4.96. Found: C, 59.08; H, 4.94.

4.2.2. (2*R,5*R**)-6a-Phenyl-2,5-bis[(phenylseleno)methyl]-hexahydrofuro[2,3-*b*]furan, 3a[22,25].** Oil. ^{1}H NMR: δ 7.60–7.52 (m, 4H), 7.50–7.43 (m, 2H), 7.39–7.20 (m, 9H), 4.65 (ddt, 1H, J = 4.5, 7.8, 10.5 Hz), 4.30 (dddd, 1H, J = 5.4, 6.0, 7.2, 10.3 Hz), 3.38 (dd, 1H, J = 4.5, 12.3 Hz), 3.35 (dd, 1H, J = 5.4, 12.3 Hz), 3.18 (dd, 1H, J = 7.8, 12.3 Hz), 3.15 (dd, 1H, J = 7.2, 12.3 Hz), 2.94 (br q, 1H, J = 9.0 Hz), 2.45 (ddd, 1H, J = 6.0, 9.0, 12.6 Hz), 2.03 (dd, 1H, J = 4.5, 12.4 Hz), 1.95 (ddd, 1H, J = 9.0, 10.5, 12.4 Hz), 1.65 (ddd, 1H, J = 9.0, 10.3, 12.6 Hz); ^{13}C NMR: δ 142.4, 132.7 (two carbons), 132.6, 130.0, 129.1 (four carbons), 128.2 (two carbons), 128.1, 128.0, 127.0, 127.9 (two carbons), 125.5 (two carbons), 117.1, 78.9, 77.9, 51.0, 39.3, 38.3, 32.4, 31.3. Anal. Calcd for $C_{26}H_{26}O_2Se_2$: C, 59.10; H, 4.96. Found: C, 59.12; H, 4.94.

4.2.3. (2*S,5*R**)-6a-Methyl-2,5-bis[(phenylseleno)methyl]-hexahydrofuro[2,3-*b*]furan, 2b.** Oil. ^{1}H NMR: δ 7.62–7.49 (m, 4H), 7.25–7.18 (m, 6H), 4.42–4.33 (m, 2H), 3.15 (dd, 2H, J = 4.5, 12.3 Hz), 2.96 (dd, 2H, J = 7.3, 12.3 Hz), 2.70–2.61 (m, 1H), 1.96–1.88 (m, 4H), 1.51 (s, 3H); ^{13}C NMR: δ 132.4 (three carbons), 130.2 (two carbons), 129.0 (four carbons), 126.8 (three carbons), 117.0, 78.8 (two carbons), 47.3, 39.1 (two carbons), 32.7 (two carbons), 25.1; MS *m*/*z* (rel. int.): 468 (23), 297 (100), 279 (12), 207 (27), 157 (28), 121 (29), 91 (28), 77 (17). Anal. Calcd for $C_{21}H_{24}O_2Se_2$: C, 54.09; H, 5.19. Found: C, 54.04; H, 5.03.

4.2.4. (2*R,5*R**)- 6a-Methyl-2,5-bis[(phenylseleno)methyl]-hexahydrofuro[2,3-*b*]furan, 3b.** Oil. ^{1}H NMR: δ 7.55–7.45 (m, 4H), 7.35–7.15 (m, 6H), 4.49–4.39 (m, 1H), 4.19–3.99 (m, 1H), 3.13 (dd, 1H, J = 1.9, 12.3 Hz), 3.11 (dd, 1H, J = 2.0, 12.3 Hz), 2.93 (dd, 1H, J = 1.9, 12.3 Hz), 2.91 (dd, 1H, J = 2.0, 12.3 Hz), 2.50 (br q, 1H, J = 9.0 Hz), 2.35 (ddd, 1H, J = 5.5, 9.0, 12.5 Hz), 1.89 (dd, 1H, J = 4.5, 12.5 Hz), 1.75 (ddd, 1H, J = 9.0, 10.5, 12.5 Hz), 1.55–1.43 (m, 1H), 1.47 (s, 3H); ^{13}C NMR: δ 132.4 (four carbons), 129.9 (two carbons), 128.9 (four carbons), 126.8 (two carbons), 116.6, 77.1, 77.0, 47.6, 38.8, 38.2, 32.2, 31.4, 24.6; MS *m*/*z* (rel. int.): 468 (32), 311 (36), 297 (64), 207 (23), 171 (26), 157 (51), 153 (53), 139 (100), 121 (44), 91 (53), 77 (32). Anal. Calcd for $C_{21}H_{24}O_2Se_2$: C, 54.09; H, 5.19. Found: C, 54.07; H, 5.09.

4.3. Cyclization reactions promoted by camphorselenenyl sulfate: general procedure

Ammonium persulfate (0.75 mmol) and CF_3SO_3H (1.5 mmol) were added to a solution of camphor diselenide **6** (0.75 mmol) in acetonitrile (4 mL) and the resulting red solution stirred at room temperature for 15 min. A solution of bis-alkenylketones **1a** and **1b** (0.5 mmol) in water (2 mL) and acetonitrile (2 mL) was then added and the mixture stirred at room temperature for 16 h. The progress of the reaction was monitored by TLC. The reaction mixture was then 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 chromatography on a silica gel column (Merck, LiChroprep® Si60, 40–63 μm) using a 2:8 mixture of diethyl ether and light petroleum as eluant. The separation in a pure form of the two *trans*-diastereoisomers **8a**, **9a** and **8b**, **9b** was carried out by monitoring the different fractions by ^{1}H NMR. The products obtained and the reaction yields are reported in Schemes 4 and 5. Physical and spectral data are reported below.

4.3.1. (2*S*,5*S*)-2,5-Bis[(camphorseleno)methyl]-6a-phenyl-hexahydrofuro[2,3-*b*]furan, 8a. Oil, $[\alpha]_D^{21} = -2.73$ (*c* 2.76, $CHCl_3$). ^{1}H NMR: δ 7.56–7.51 (m, 2H), 7.39–7.27 (m, 3H), 4.74 (ddt, 1H, J = 4.4, 6.6, 10.1 Hz), 4.38 (ddt, 1H, J = 4.9, 6.1, 10.6 Hz), 3.92 (dd, 1H, J = 1.7, 4.1 Hz), 3.89 (dd, 1H, J = 1.5, 4.1 Hz), 3.28 (dd, 1H, J = 6.1, 13.0 Hz), 3.21 (dd, 1H, J = 6.6, 12.7 Hz), 3.11 (dd, 1H, J = 4.9, 13.0 Hz), 3.08 (dd, 1H, J = 4.4, 12.7 Hz), 3.01 (br q, 1H, J = 8.6 Hz), 2.52–2.42 (m, 1H), 2.31 (t, 1H, J = 4.1 Hz), 2.15 (t, 1H, J = 4.1 Hz), 2.15–1.99 (m, 2H), 1.92–1.63 (m, 7H), 1.52–1.46 (m, 2H), 1.03 (s, 3H), 0.97 (s, 3H), 0.94 (s, 3H), 0.91 (s,

3H), 0.90 (s, 3H), 0.75 (s, 3H); ^{13}C NMR: δ 218.2, 218.1, 142.8, 128.0 (two carbons), 127.8, 125.6 (two carbons), 117.1, 79.4, 78.4, 58.1 (two carbons), 50.8, 48.4, 48.2, 47.4, 47.2, 46.7, 46.6, 39.1, 38.2, 30.5 (two carbons), 28.9, 27.5, 23.4, 23.2, 19.6, 19.5 (two carbons), 19.4, 9.7 (two carbons). Anal. Calcd for $C_{34}H_{46}O_4Se_2$: C, 60.35; H, 6.85. Found: C, 60.21; H, 6.76.

4.3.2. (2*R*,5*R*)-2,5-Bis[(camphorseleno)methyl]-6a-phenylhexahydrofuro[2,3-*b*]furan, 9a. Oil, $[\alpha]_D^{24} = +9.3$ (*c* 2.65, $CHCl_3$) ^{1}H NMR: δ 7.66–7.49 (m, 2H), 7.46–7.19 (m, 3H), 4.68 (ddt, 1H, *J* = 5.4, 5.7, 10.6 Hz), 4.34 (ddt, 1H, *J* = 5.3, 6.2, 10.0 Hz), 4.05 (dd, 1H, *J* = 1.4, 4.7 Hz), 4.03 (dd, 1H, *J* = 1.5, 4.7 Hz), 3.23 (dd, 1H, *J* = 6.2, 12.6 Hz), 3.20–3.12 (m, 2H), 3.10 (dd, 1H, *J* = 5.7, 12.6 Hz), 3.01 (br q, 1H, *J* = 8.6 Hz), 2.52–2.45 (m, 1H), 2.27 (t, 1H, *J* = 4.7 Hz), 2.23 (t, 1H, *J* = 4.7 Hz), 2.14 (ddd, 1H, *J* = 8.6, 10.6, 12.1 Hz), 2.03 (dd, 1H, *J* = 5.3, 12.1 Hz), 1.91–1.83 (m, 4H), 1.78–1.65 (m, 3H), 1.55–1.40 (m, 2H), 1.06 (s, 3H), 1.05 (s, 3H), 0.96 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H), 0.72 (s, 3H); ^{13}C NMR: δ 217.9 (two carbons), 142.6, 128.0 (two carbons), 127.8, 125.6 (two carbons), 117.1, 79.8, 78.8, 58.1 (two carbons), 50.9, 48.4, 48.0, 47.7, 47.4, 46.8, 46.6, 39.4, 38.6, 30.3 (two carbons), 28.8, 27.2, 23.3, 23.1, 19.6 (three carbons), 19.3, 9.7 (two carbons). Anal. Calcd for $C_{34}H_{46}O_4Se_2$: C, 60.35; H, 6.85. Found: C, 60.31; H, 6.78.

4.3.3. (2*S*,5*R*)-2,5-Bis[(camphorseleno)methyl]-6a-phenylhexahydrofuro[2,3-*b*]furan, 10a. Mp 51–53 °C; $[\alpha]_D^{19} = -1.3$ (*c* 3.74, $CHCl_3$) ^{1}H NMR: δ 7.60–7.58 (m, 2H), 7.33–7.30 (m, 3H), 4.78–4.65 (m, 2H), 4.02 (dd, 1H, *J* = 1.1, 4.6 Hz), 3.85 (dd, 1H, *J* = 1.4, 4.1 Hz), 3.22 (dd, 1H, *J* = 6.0, 12.7 Hz), 3.18 (dd, 1H, *J* = 6.5, 12.7 Hz), 3.11 (dd, 1H, *J* = 4.5, 12.7 Hz), 3.02 (dd, 1H, *J* = 5.4, 12.7 Hz), 3.01–2.94 (m, 1H), 2.25–2.22 (m, 2H), 2.17–2.12 (m, 3H), 1.90–1.65 (m, 7H), 1.50–1.40 (m, 2H), 1.03 (s, 3H), 1.01 (s, 3H), 0.94 (s, 3H), 0.93 (s, 3H), 0.84 (s, 3H), 0.78 (s, 3H); ^{13}C NMR: δ 217.6, 217.5, 141.9, 127.7 (three carbons), 125.8 (two carbons), 117.4, 81.1, 80.2, 57.9 (two carbons), 50.3, 48.1, 47.9, 47.0, 46.6 (two carbons), 39.5, 39.1, 30.4 (three carbons), 28.6, 28.3, 23.2 (two carbons), 19.4 (three carbons), 19.3, 9.6 (two carbons). Anal. Calcd for $C_{34}H_{46}O_4Se_2$: C, 60.35; H, 6.85. Found: C, 60.23; H, 6.75.

4.3.4. (2*R*,5*S*)-2,5-Bis[(camphorseleno)methyl]-6a-phenylhexahydrofuro[2,3-*b*]furan, 11a. Mp 75–77 °C; $[\alpha]_D^{20} = -27.8$ (*c* 2.63, $CHCl_3$). ^{1}H NMR: δ 7.77–7.65 (m, 2H), 7.42–7.28 (m, 3H), 4.77–4.65 (m, 2H), 4.02 (dd, 1H, *J* = 1.1, 4.1 Hz), 3.92 (dd, 1H, *J* = 1.6, 4.4 Hz), 3.32 (dd, 1H, *J* = 6.6, 12.9 Hz), 3.22 (dd, 1H, *J* = 6.6, 12.9 Hz), 3.18 (dd, 1H, *J* = 4.8, 12.9 Hz), 3.16–3.15 (m, 1H), 3.06 (dd, 1H, *J* = 5.1, 12.9 Hz), 2.78 (ddd, 2H, *J* = 5.2, 7.7, 13.1 Hz), 2.59 (dd, 1H, *J* = 10.3, 13.1 Hz), 2.44 (dd, 1H, *J* = 10.3, 13.1 Hz), 2.31 (t, 1H, *J* = 4.4 Hz), 2.25 (t, 1H, *J* = 4.1 Hz), 1.96–1.15 (m, 8H), 1.05 (s, 3H), 1.00 (s, 3H), 0.95 (s, 3H), 0.94 (s, 3H), 0.86 (s, 3H), 0.80 (s, 3H); ^{13}C NMR: δ 217.8, 217.4, 139.0, 128.5, 127.6 (two carbons), 127.3 (two carbons), 118.1, 79.8, 78.8, 58.0 (two carbons), 57.8, 49.3, 49.2, 48.5, 48.2, 48.1, 47.1, 47.0, 46.7 (two carbons), 30.4 (two carbons), 28.1, 23.2 (two carbons), 19.6 (three carbons), 19.1, 9.65 (two carbons). Anal. Calcd for $C_{34}H_{46}O_4Se_2$: C, 60.35; H, 6.85. Found: C, 60.27; H, 6.81.

4.3.5. (2*S*,5*S*)-2,5-Bis[(camphorseleno)methyl]-6a-methylhexahydrofuro[2,3-*b*]furan, 8b. Oil, $[\alpha]_D^{17} = +5.2$ (*c* 3.83, $CHCl_3$). ^{1}H NMR: δ 4.42 (ddt, 1H, *J* = 5.5, 5.6, 10.6 Hz), 4.03 (ddt, 1H, *J* = 5.8, 5.9, 10.6 Hz), 3.98 (dd, 1H, *J* = 1.1, 4.7 Hz), 3.88 (dd, 1H, *J* = 1.7, 4.5 Hz), 3.03 (dd, 1H, *J* = 5.9, 12.3 Hz), 2.97 (dd, 1H, *J* = 5.5, 12.3 Hz), 2.94 (dd, 1H, *J* = 5.6, 12.3 Hz), 2.90 (dd, 1H, *J* = 5.8, 12.3 Hz), 2.59 (br q, 1H, *J* = 9.0 Hz), 2.35 (ddd, 1H, *J* = 5.6, 9.0, 12.7 Hz), 2.23–2.15 (m, 2H), 1.93–1.75 (m, 6H), 1.70–1.60 (m, 2H), 1.59–1.47 (m, 1H), 1.42–1.35 (m, 2H), 1.41 (s, 3H), 0.98 (s, 6H), 0.89 (s, 9H), 0.86 (s, 3H); ^{13}C NMR: δ 218.8, 218.7, 117.5, 79.1, 79.0, 59.1, 59.0, 49.3, 49.1, 48.6, 48.5, 48.4, 47.7, 47.6, 39.9, 39.5, 31.5, 31.4, 29.8, 28.7, 25.7, 24.2, 24.1, 20.6 (two carbons), 20.5 (two carbons), 10.6 (two carbons). Anal. Calcd for $C_{29}H_{44}O_4Se_2$: C, 56.67; H, 7.22. Found: C, 56.61; H, 7.19.

4.3.6. (2*R*,5*R*)-2,5-Bis[(camphorseleno)methyl]-6a-methylhexahydrofuro[2,3-*b*]furan, 9b. Oil, $[\alpha]_D^{19} = +17.6$ (*c* 3.35, $CHCl_3$). ^{1}H NMR: δ 4.52–4.49 (m, 1H), 4.17–4.09 (m, 1H), 3.87 (dd, 1H, *J* = 1.1, 4.7 Hz), 3.77 (dd, 1H, *J* = 1.7, 4.5 Hz), 3.10–2.87 (m, 4H), 2.58 (br q, 1H, *J* = 8.6 Hz), 2.45–2.30 (m, 1H), 2.25–2.19 (m, 2H), 1.90–1.57 (m, 10H), 1.49 (s, 3H), 1.48–1.38 (m, 1H), 0.99 (s, 3H), 0.98 (s, 3H), 0.88 (s, 6H), 0.87 (s, 3H), 0.86 (s, 3H); ^{13} C NMR: δ 217.9, 217.8, 116.6, 77.8, 77.5, 58.0 (two carbons), 48.3, 48.2, 47.7, 47.3, 47.2, 46.7 (two carbons), 38.5, 38.1, 30.4 (two carbons), 28.9, 28.0, 24.8, 23.2 (two carbons), 19.6 (two carbons), 19.5 (two carbons), 9.6 (two carbons). Anal. Calcd for $C_{29}H_{44}O_4Se_2$: C, 56.67; H, 7.22. Found: C, 56.58; H, 7.20.

4.3.7. (2*S*,5*R*)-2,5-Bis[(camphorseleno)methyl]-6a-methylhexahydrofuro[2,3-*b*]furan, 10b. Oil, $[\alpha]_D^{20} = +9.1$ (*c* 3.16, $CHCl_3$). ^{1}H NMR: δ 4.53–4.45 (m, 2H), 4.01 (dd, 1H, *J* = 1.8, 4.9 Hz), 3.83 (dd, 1H, *J* = 1.9, 4.6 Hz), 3.05 (dd, 1H, *J* = 6.4, 12.7 Hz), 2.99 (dd, 1H, *J* = 5.6, 12.7 Hz), 2.92 (dd, 1H, *J* = 5.6, 12.7 Hz), 2.91 (dd, 1H, *J* = 4.2, 12.7 Hz), 2.70 (tt, 1H, *J* = 2.5, 8.9 Hz), 2.25–2.22 (m, 2H), 2.12–1.94 (m, 3H), 1.86–1.82 (m, 3H), 1.80–1.62 (m, 4H), 1.52 (s, 3H), 1.50–1.40 (m, 2H), 1.03 (s, 3H), 1.02 (s, 3H), 0.94 (s, 3H), 0.93 (s, 3H), 0.90 (s, 6H); ^{13}C NMR: δ 218.0 (two carbons), 116.9, 79.9, 79.3, 58.0 (two carbons), 48.3, 48.0, 47.3, 47.1 (two carbons), 46.6 (two carbons), 39.2, 38.9, 30.4 (two carbons), 29.1, 28.8, 24.9, 23.2, 23.1, 19.5 (three carbons), 19.4, 9.6 (two carbons). Anal. Calcd for $C_{29}H_{44}O_4Se_2$: C, 56.67; H, 7.22. Found: C, 56.63; H, 7.17.

4.4. Reductive deselenenylations: general procedure

Triphenyltin hydride (2.5 mmol) and a catalytic amount of AIBN were added to a solution of compounds **8a**–**11a** and **8b**–**10b** (0.5 mmol) in dry benzene (5 mL) and the mixture was stirred and refluxed for 1 h. The solvent was then removed under reduced pressure. The perhydrofuro[2,3-*b*]furans **4a**, **5a**, *ent*-**5a**, **4b**, **5b**, *ent*-**5b** were purified by column chromatography on silica gel using

a 2:8 mixture of diethyl ether and light petroleum as eluant. The reaction yields are reported in Schemes 4 and 5. Physical and spectral data are reported below.

4.4.1. (2*R,5*S**)-2,5-Dimethyl-6a-phenylhexahydrofuro[2,3-*b*]furan, 4a.** Mp 60–62 °C. ^{1}H NMR: δ 7.60–7.45 (m, 2H), 7.30–7.10 (m, 3H), 4.45 (dq, 2H, J = 5.8, 10.3 Hz), 2.78 (tt, 1H, J = 1.9, 9.2 Hz), 1.89 (ddd, 2H, J = 1.9, 5.8, 12.7 Hz), 1.80 (ddd, 2H, J = 9.2, 10.3, 12.7 Hz), 1.32 (d, 6H, J = 5.8 Hz); ^{13}C NMR: δ 142.6, 127.8 (two carbons), 127.6, 125.8 (two carbons), 116.8, 76.7 (two carbons), 51.4, 41.3 (two carbons), 21.3 (two carbons); MS *m*/*z* (rel. int.): 218 (15), 203 (42), 174 (69), 105 (100), 77 (31). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.06; H, 8.35.

4.4.2. (2*S,5*S**)-2,5-Dimethyl-6a-phenylhexahydrofuro-[2,3-*b*]furan, 5a.** Oil. ^{1}H NMR: δ 7.65–7.50 (m, 2H), 7.40–7.20 (m, 3H), 4.55–4.45 (m, 1H), 4.15 (m, 1H), 2.92 (br q, 1H, J = 9.0 Hz), 2.39 (ddd, 1H, J = 5.8, 9.0, 12.4 Hz), 1.90 (dd, 1H, J = 4.4, 12.4 Hz), 1.85–1.74 (m, 1H), 1.55–1.45 (m, 1H), 1.44 (d, 3H, J = 6.0 Hz), 1.43 (d, 3H, J = 6.0 Hz); ^{13}C NMR: δ 143.3, 129.3 (two carbons), 128.0, 125.5 (two carbons), 116.4, 75.5, 74.2, 51.8, 41.3, 40.4, 20.6, 19.5; MS *m*/*z* (rel. int.): 218 (7), 203 (34), 174 (58), 105 (100), 77 (27). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.01; H, 8.33.

4.4.3. (2*R*,5*R*)-2,5-Dimethyl-6a-phenylhexahydrofuro[2,3-*b*]-furan, 5a. Oil, $[\alpha]_D^{25} = +29.6$ (c 2.47, $CHCl_3$). Spectral date are identical to those of the racemic sample. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.98; H, 8.29.

4.4.4. (2*S*,5*S*)-2,5-Dimethyl-6a-phenylhexahydrofuro-[2,3-*b*]furan, *ent*-5a. Oil, $[\alpha]_D^{25} = -28.15$ (c 1.91, $CHCl_3$). Spectral date are identical to those of the racemic sample. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.02; H, 8.30.

4.4.5. (2*R,5*S**)-2,5,6a-Trimethylhexahydrofuro[2,3-*b*]-furan, 4b.** Oil. ^{1}H NMR: δ 4.32 (ddq, 2H, J = 5.4, 6.0, 10.2 Hz), 2.65 (tt, 1H, J = 1.8, 9.0 Hz), 1,87 (ddd, 2H, J = 1.8, 5.4, 12.6 Hz), 1.76 (ddd, 2H, J = 9.0, 10.2, 12.6 Hz), 1.54 (s, 3H) 1.25 (d, 6H, J = 6.0 Hz); ^{13}C NMR: δ 115.0, 75.9 (two carbons), 47.9, 41.3 (two carbons), 25.4, 21.0 (two carbons); MS *m*/*z* (rel. int.): 156 (2), 155 (6), 141 (100), 112 (76), 97 (37), 81 (40), 71 (23), 69 (24), 55 (15). Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.05; H, 10.12.

4.4.6. (2*S,5*S**)-2,5,6a-Trimethylhexahydrofuro[2,3-*b*]-furan, 5b.** Oil. ^{1}H NMR: δ 4.31–4.22 (m, 1H), 3.90–3.80 (m, 1H), 2.56 (br q, 1H, J = 9.0 Hz), 2.25 (ddd, 1H, J = 5.1, 9.0, 12.3 Hz), 1.69 (dd, 1H, J = 4.3, 12.3 Hz), 1.56 (ddd, 1H, J = 7.9, 9.0, 12.3 Hz), 1.46 (s, 3H), 1.28 (d, 3H, J = 5.9 Hz), 1.27 (d, 3H, J = 6.0 Hz), 1.27–1.19 (m, 1H); ^{13}C NMR: δ 115.6, 73.4, 73.3, 48.4, 40.9, 40.5, 24.6, 20.2, 19.4; MS *m*/*z* (rel. int.): 156 (1), 155 (5), 141 (100), 112 (84), 97 (37), 81 (41), 71 (24), 69 (25), 55 (17). Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.01; H, 10.16.

4.4.7. (2*R*,5*R*)-2,5,6a-Trimethylhexahydrofuro[2,3-*b*]-furan, 5b. Oil, $[\alpha]_D^{21} = -21.7$ (c 1.20, $CHCl_3$). Spectral date are identical to those of the racemic sample. Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.12; H, 10.27.

4.4.8. (2*S*,5*S*)-2,5,6a-Trimethylhexahydrofuro[2,3-*b*]-furan, *ent*-5b. Oil, $[\alpha]_D^{21} = +21.7$ (c 1.05, $CHCl_3$). Spectral date are identical to those of the racemic sample. Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.15; H, 10.30.

Acknowledgements

Financial support from MIUR, National Projects PRIN2003, FIRB2001 and Consorzio CINMPIS is gratefully acknowledged.

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30. At present, we do not have a reasonable explanation for the formation of **4a** from the deselenenylation of **11a**. One referee suggested that a possible mechanism could be the reversible conversion of acetal with ketone, epimerization via enol and acetal reformation.