Electrochemical Phenylselenoetherification as a Key Step in the Synthesis of (±)-Curcumene Ether

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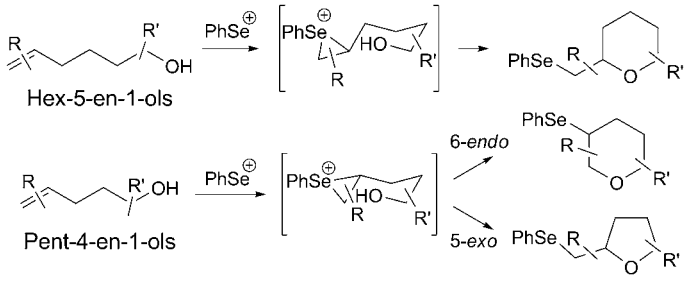
Two variants of a new pathway for the synthesis of (±)-curcumene ether are described. The key steps in these procedures are intramolecular cyclizations of 6-methyl-2-(4-methylphenyl)hept-6-en-2-ol and 2-methyl-6-(4-methylphenyl)hept-6-en-2-ol by means of an electrochemically generated phenylselenyl cation. This synthetic approach provides significantly better yields than the previously reported protocols.

Introduction. – Tetrahydropyrans widely occur in nature, often as the core structural fragment of numerous natural products with antibacterial, antifungal, antiviral, neurotoxic, cytotoxic activities, *etc.* [1]. Many reactions have been applied in the synthesis of these compounds, among which intramolecular cyclizations of the corresponding unsaturated alcohols, by means of diverse electrophilic reagents, are of special importance. Over several decades, electrophilic Se reagents, particularly phenylselenyl halides, have been proven to be quite useful for this purpose [2]. Important advantages of the use of electrophilic Se reagents in these syntheses over other related ones are mild reaction conditions and an easy removal of the Se unit from organic molecules. This removal can be performed in an oxidative manner (by means of H_2O_2), introducing, thus, a C=C bond or by hydrogenolysis (effected by *Ra*-Ni) [2].

As depicted in *Scheme 1*, two types of unsaturated alcohols, *i.e.*, those containing hex-5-en-1-ol and pent-4-en-1-ol systems, can serve as substrates in the synthesis of tetrahydropyran derivatives by the reaction with phenylselenyl halides. Alkenols of the first type undergo the cyclization to give only tetrahydropyrans, whereas the second ones might also afford tetrahydrofurans. Since the reaction obeys *Markovnikov*'s rule, when planning this synthesis, the electronic and steric nature of olefinic C-atoms (or to be more exact those of the intermediary Se cation) must be taken into account. However, the (steric) nature of the carbinol C-atom of the substrate also plays a certain role and must be considered too [2][3].

In continuation of our work on the functionalization of unsaturated compounds by means of electrochemically generated phenylselenyl cation from diphenyl diselenide

Scheme 1. *Cyclo-etherification* via *a Phenylselenyl Cation*



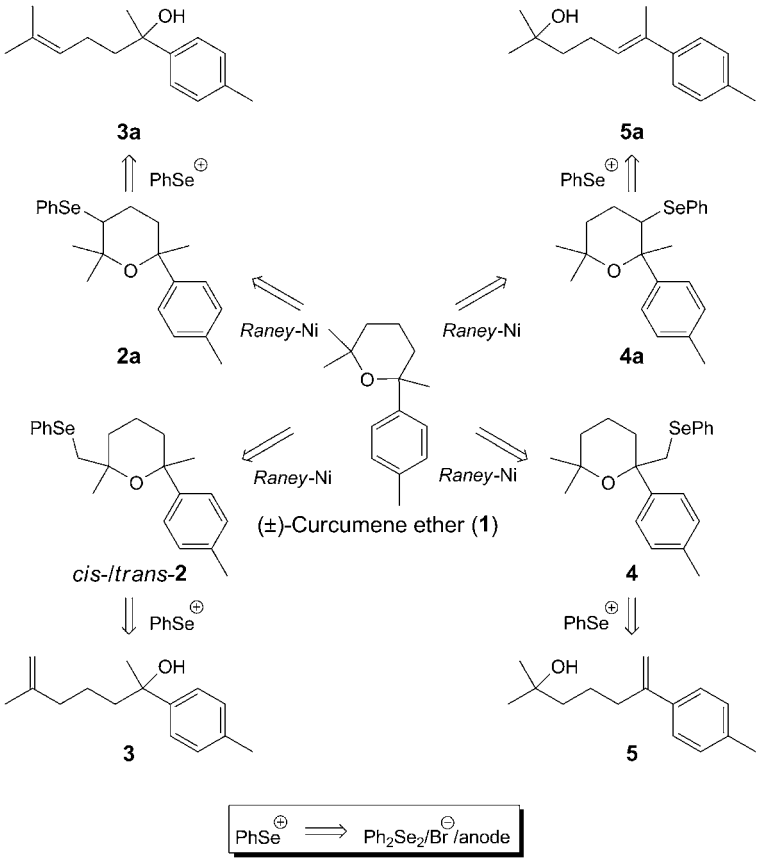
[3], we decided to utilize phenylselenoetherification in the synthesis of a naturally occurring tetrahydropyran, curcumene ether (**1**), isolated from a plant species *Thuja orientalis* [4]. To the best of our knowledge, to date four reports on the synthesis of (±)-**1** appeared in the literature [5][6], among which the first one [5a] could not be reproduced in other laboratories [7]. Key steps of two of the three further syntheses of this compound were the cyclizations of 2-methyl-6-(4-methylphenyl)heptane-2,6-diol [5b] and 2-methyl-6-(4-methylphenyl)-3-phenylthiohept-6-en-2-ol [5c] by treatment with HCOOH and CF_3COOH, respectively, leading to (±)-**1**. The most recently reported synthesis of (±)-**1** was achieved in nine steps (7% overall yield) utilizing an intramolecular *Heck* reaction to generate the stereogenic quaternary center [5d]. A 13-step synthesis of (+)-**1** (involving a resolution of cinenic acid) in an overall yield of 3% was also recently reported [6].

Results and Discussion. – A retrosynthetic analysis of (±)-**1** (*Scheme 2*), with *Markovnikov*'s rule in mind, points to four unsaturated alcohols as the possible starting materials, two of which, *i.e.*, **3** and **5**, possess a hex-5-en-1-ol system, whereas the other two, *i.e.*, **3a** and **5a**, contain a pent-4-en-1-ol scaffold. They are expected to undergo cyclization by means of an electrochemically generated phenylselenyl cation to give *β*-(phenylseleno)tetrahydropyrans **2**, **4**, **2a**, and **4a**, respectively, which could be reduced by *Raney*-Ni to furnish the target molecule. However, we have previously shown that phenylselenoetherification of tertiary pent-4-en-1-ols with a terminally disubstituted C=C bond does not obey *Markovnikov*'s rule and gives derivatives of tetrahydrofuran, or their mixtures with tetrahydropyran derivatives [3c]. Therefore, we abandoned alcohols **3a** and **5a** as possible substrates for the construction of the skeleton of (±)-**1**, and focused our attention on the optimization of synthetic protocols using alkenols **3** and **5**.

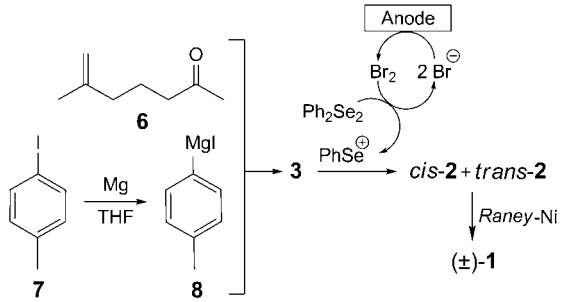
It is apparent that alcohol 6-methyl-2-(4-methylphenyl)hept-6-en-2-ol (**3**) can be easily obtained from the reaction of 6-methylhept-6-en-2-one (**6**), a commercially available material, and the *Grignard* reagent obtained from *p*-halogenotoluenes (*Scheme 3*). Thus, we started with the reaction of Mg mesh with *p*-iodotoluene (**7**) in anhydrous ether, and adding dropwise **6** to the formed *p*-tolylmagnesium iodide (**8**) solution [8]. Alcohol **3** was obtained in a yield of 75%.

The key step of the present synthesis of (±)-**1**, *i.e.*, the construction of the curcumene ether skeleton, was performed by electrolysis of alcohol **3** in an MeCN

Scheme 2. *Retrosynthetic Analysis of* (±)-**1**



Scheme 3. *Synthesis of* (±)-**1** *Based on Alcohol* **3**



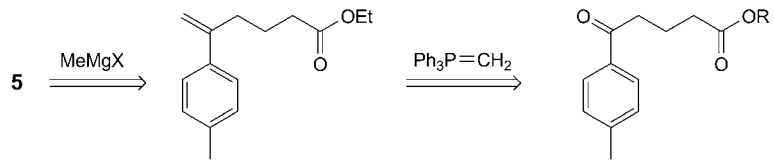
solution of LiBr containing Ph_2Se_2 (in a **3**/Ph_2Se_2 ratio of 1:0.5). As it is known, in this process bromides serve as mediators [3]. The easy oxidation of bromides at the anode provides *in situ* generation of PhSeBr or $PhSe^+$ cation (in the subsequent homogenous

reaction of liberated Br_2 with Ph_2Se_2) capable of reacting with the π-electronic system of **3**. Two diastereoisomeric ethers, *cis*-**2** and *trans*-**2** (*i.e.*, (*R**,*S**) and (*R**,*R**), resp.), were obtained in the overall yield of 61%, and in the *cis*-**2**/*trans*-**2** ratio of 1:1.9 (as estimated by ^{1}H-NMR spectroscopy). The stereoselectivity of this step does not affect the final outcome of the synthesis, since the stereogenic center carrying the Se substituent will be lost during the hydrogenolysis. However, we were able to isolate pure samples of these compounds by column chromatography (SiO_2; hexane/CH_2Cl_2 2:1 (*v*/*v*)), and their structures were confirmed by spectral analysis. A crucial information which enabled the assignment of the selenoethers' configurations came from a conformational analysis of the two compounds and **1**. Molecular modeling at semiempirical level revealed that, in all three cases, the chair conformer with an axial *p*-tolyl group was by far prevailing in the conformational equilibria. The Me group geminal to *p*-tolyl moiety orients the aromatic core in such a way so that it exerts a shielding magnetic anisotropy effect on the other axial substituent. This is quite clear from the upfield shift of the ^{1}H-NMR signals of the axial Me group in *trans*-**2** or axial CH_2 group of $PhSeCH_2$ in *cis*-**2**, when compared with the those of the respective counterpart or with the corresponding chemical shifts of **1**. These assignments were also confirmed by a careful inspection of the cross-peaks in the NOESY spectra of *trans*-**2**.

Reduction of the mixture *cis*-**2**/*trans*-**2**, using a flow reactor (*ThalesNano H-cube*™) with the *Raney*-Ni catalyst cartridge, afforded the target molecule (±)-**1** in 95% yield. Thus, the overall yield of this synthesis, based on the most expensive starting material **6**, was 43%.

The alternative route to (±)-**1** that makes use of the electrochemically generated $PhSe^+$ cation starts with 2-methyl-6-(4-methylphenyl)hept-6-en-2-ol (**5**). However, this alcohol could not be synthesized in such a short way as alcohol **3**, since the corresponding ketone or another substrate suitable for this purpose is not commercially available. A possible retrosynthesis of **5** is depicted in *Scheme 4*, and leads to 5-(4-methylphenyl)-5-oxopentanoic acid (**10**), a compound not available commercially, but well described in the literature [9]. A *Wittig* olefination of the corresponding ethyl ester **11** and a subsequent MeMgCl addition to the obtained ethyl 5-(4-methylphenyl)hex-5-enoate (**9**) should yield alcohol **5**.

Scheme 4. *Retrosynthetic Analysis of Alcohol* **5**

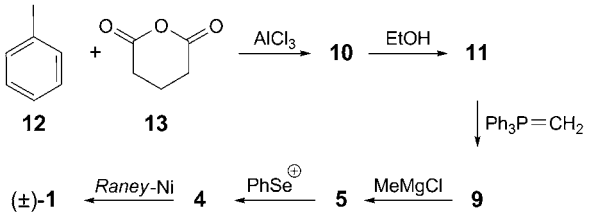


9 **10** R = H, **11** R = Et

We started the synthesis by a *Friedel–Crafts* acylation of toluene (**12**) with glutaric anhydride (**13**; *Scheme 5*) [9]. The obtained keto acid **10** (80%) was esterified with EtOH in the presence of *p*-toluenesulfonic acid as the catalyst [10] to give the keto ester **11** (98%). *Wittig* olefination [11] of **11** gave ethyl 5-(4-methylphenyl)hex-5-enoate (**9**) in a yield of 93%, which, in a subsequent *Grignard* reaction, was transformed to alcohol

5 (89%). Cyclo-etherification of this alcohol was performed under the same conditions as for alcohol **3** and gave β-phenylseleno ether **4** in a yield of 59%. Finally, reduction of **4** using the flow reactor with a *Raney*-Ni catalyst cartridge gave the target (±)-curcumene ether ((±)-**1**) in a yield of 92%. Thus, the overall yield of (±)-**1** achieved in this synthesis was 35%.

Scheme 5. *Synthesis of* (±)-**1** *Based on Alcohol* **5**



Conclusions. – In conclusion, we optimized two new multistep approaches for the synthesis of (±)-curcumene ether ((±)-**1**) leading to 43 and 35% overall yields, respectively. The key step of these protocols, *i.e.*, the construction of the heterocyclic skeleton from aliphatic substrates, involved the cyclization of 6-methyl-2-(4-methylphenyl)hept-6-en-2-ol (**3**) and 2-methyl-6-(4-methylphenyl)hept-6-en-2-ol (**5**) by the electrochemically generated $PhSe^+$ cation (electrochemical phenylselenoetherification).

Financial support from the Ministry of Education, Science and Technological Development of the Republic of Serbia (Grant No. 172034) is gratefully acknowledged.

Experimental Part

General. All the reagents and solvents were obtained from commercial sources (*Aldrich*, USA; *Merck*, Germany; *Fluka*, Germany) and used as received, except that the solvents were purified by distillation or dried when necessary. The electrolysis experiments were performed with a *Uniwatt, Beha Labor-Netzgerät* (NG 394) power supply, and an undivided electrolytic cell (a cylindrical glass vessel) equipped with a magnetic stirrer, a graphite stick (∅ 5 mm) as an anode, and a Cu spiral (∅ 10 mm) as a cathode. Column chromatography (CC): *Merck* silica gel (SiO_2; 70–230 mesh). TLC: silica gel *60* on Al plates; layer thickness, 0.2 mm (*Merck*, Germany). M.p. (uncorrected): *Mel-Temp* cap. melting-points apparatus, model *1001*. IR Spectra: *Perkin-Elmer Spectrum One FT-IR* spectrometer using KBr disks. ^{1}H- and ^{13}C-NMR spectra: in $CDCl_3$; *Varian Gemini 2000* (^{1}H: 200 and ^{13}C: 50 MHz), *Bruker AC 250 E* (^{1}H: 250 and ^{13}C: 62.9 MHz), or *Bruker Avance II+ 600* (^{1}H: 600.13 and ^{13}C: 150.92 MHz) spectrometers; chemical shifts in δ [ppm], relative to TMS and/or residual solvent H-atoms as internal standards (δ 7.26 (^{1}H) and 77 for (^{13}C)). GC/MS: *Hewlett-Packard 6890N* gas chromatograph equipped with a fused silica cap. column *DB-5* (5% phenylmethylsiloxane, 30 m × 0.25 mm, film thickness 0.25 μm, *Agilent Technologies*, USA) and coupled with a *5975B* mass-selective detector from the same company. The injector and interface were operated at 250° and 300°, resp. Oven temp. was raised from 70–290° at a heating rate of 5°/min and then isothermally held for 10 min. As a carrier gas, He at 1.0 ml/min was used. The samples, as solns. in Et_2O (1 mg/ml), were injected in a pulsed split mode (the flow was 1.5 ml/min for the first 0.5 min, and then, it was set to 1.0 ml/min throughout the remainder of the analysis; split ratio, 40:1). MS conditions: ionization voltage, 70 eV; acquisition mass range, 35–500; scan time, 0.32 s. Elemental analyses: *Carlo Erba 1106* microanalyser; results in agreement with the calculated values.

Preparation of 6-Methyl-2-(4-methylphenyl)hept-6-en-2-ol (**3**) [8]. *4-Iodotoluene* (**7**; 3.05 g, 14 mmol) was added dropwise with stirring during 0.5 h to a refluxing slurry of Mg mesh (0.37 g, 15.4 mmol) and anh. Et_2O (50 ml), activated with a few small crystals of I_2. The mixture (which became slightly cloudy after a few min) was stirred for an additional h at reflux, cooled to r.t., and *6-methylhept-6-en-2-one* (**6**; 0.88 g, 7 mmol) was added dropwise during 0.5 h. After stirring for additional 2 h under reflux, sat. aq. NH_4Cl (20 ml) was added, and the resulting mixture was extracted with Et_2O (3×30 ml). The org. layers were combined, dried ($MgSO_4$), and concentrated under reduced pressure. The resulting yellow oil was purified by 'dry flash' CC (hexane/Et_2O 95 : 5 → 85 : 15 (*v*/*v*)) to yield **3** (1.14 g, 75%). Clear colorless oil. IR (KBr): 3411, 3025, 2970, 2941, 1649, 1513, 1452, 1373, 1102, 886, 816, 724. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.36 – 7.25 (*AA′* of *AA′BB′*, 2 arom. H); 7.19 – 7.08 (*BB′* of *AA′BB′*, 2 arom. H); 4.70 – 4.63 (*m*, 1 H of $=CH_2$); 4.63 – 4.57 (*m*, 1 H of $=CH_2$); 2.33 (*s*, *Me*Ar); 1.95 (br. *t*, *J* = 7.4, $=CCH_2CH_2$); 1.81 – 1.67 (*m*, ArC(Me)(O*H*)CH_2); 1.63 (*s*, *Me*C=); 1.54 (*s*, ArC(OH)*Me*); 1.50 – 1.21 (*m*, $CH_2CH_2CH_2$). ^{13}C-NMR (50 MHz, $CDCl_3$): 145.5, 144.9 (*C*=CH_2, 1 arom. C); 136.0 (1 arom. C); 128.8 (2 arom. CH); 124.6 (2 arom. CH); 110.0 (C=*C*H_2); 74.5 (C(OH)); 43.7, 37.8 (*C*H_2CH_2*C*H_2); 30.2, 22.2, 21.8 (C(OH)(*Me*)CH_2*C*H_2CH_2C(=CH_2)*Me*); 20.9 (*Me*Ar). EI-MS (70 eV): 218 (1.3, M^+), 200 (3.1, $[M - H_2O]^+$), 185 (1.9), 172 (1), 147 (1.6), 145 (7.2), 135 (100), 132 (15.5), 119 (19.5), 105 (4.6), 91 (11.2), 77 (2.9), 69 (4.2), 55 (4.2), 43 (52). Anal. calc. for $C_{15}H_{22}O$ (218.33): C 82.52, H 10.16; found: C 82.49, H 10.15.

Electrochemical Phenylselenoetherification of **3** [3c]. A soln. of **3** (0.218 g, 1 mmol), Ph_2Se_2 (156 mg, 0.5 mmol), and LiBr (210 mg, 1 mmol) in MeCN (10 ml) was placed in a cell supplied with an ice-acetone-salt bath (– 10 to – 5°) and electrolyzed at constant current (100 mA, 2 F/mol). The solvent was distilled off, the residue was extracted several times with Et_2O, and the obtained soln. was dried (Na_2SO_4). The solvent was evaporated, and the residue was purified by CC (SiO_2; hexane/CH_2Cl_2 1 : 1 (*v*/*v*)) to afford a mixture of cis- and trans-*tetrahydro-2,6-dimethyl-2-(4-methylphenyl)-6-[(phenylselanyl)-methyl]-2*H-*pyran* (*cis*-**2**/*trans*-**2**; 0.228 g, 0.61 mmol, 61%), a pale yellow oil, which was used in the next step of the synthesis. The anal. samples of *cis*- and *trans*-**2** were obtained from 100 mg (0.268 mmol) of this mixture by CC (silica gel (10 g); hexane/CH_2Cl_2 2 : 1 (*v*/*v*)). The first fraction gave 45 mg of pure *trans*-**2** (a pale yellow oil), the second one gave 30 mg of the mixture of two isomers, whereas the third fraction gave 23 mg of pure *cis*-**2** (a pale yellow oil).

Data of cis-**2**: IR (KBr): 3436, 3056, 2972, 2934, 1637, 1579, 1512, 1478, 1372, 1203, 1073, 1041, 1023, 974, 817, 735, 691. ^{1}H-NMR (250 MHz, $CDCl_3$): 7.59 – 7.38 (overlapped *m*, 2 arom. H of PhSe); 7.36 – 7.14 (overlapped *m*, 3 arom. H of PhSe); 7.12 – 7.04 (overlapped *m*, 4 arom. H of Ar); 2.87 (*d*, ^2J(H,H) = 11.6, ^2J(Se,H) = 7.7, 1 H, $SeCH_2$); 2.79 (*d*, ^2J(H,H) = 11.6, ^2J(Se,H) = 7.0, 1 H, $SeCH_2$); 2.37 (*s*, *Me*Ar); 2.09 – 2.04 (*m*, 1 H); 1.97 – 1.51 (overlapped *m*, 5 H); 1.47 (*s*, Me); 1.40 (*s*, Me). ^{13}C-NMR (62.9 MHz, $CDCl_3$): 145.8 (arom. C); 135.9 (arom. C); 132.0 (arom. C of PhSe); 131.6 (2 arom. CH of PhSe); 128.8, 128.6, 126.1, 125.3 (4 arom. CH of Ar; 3 arom. CH of PhSe); 77.1, 74.5 (COC); 40.7, 34.5, 33.7, 32.9, 28.9 (Me, C*C*H_2*C*H_2*C*H_2*CC*H_2Se); 21.0 (*Me*Ar); 16.8 (Me). EI-MS (70 eV): 374 (0.1, M^+), 313 (0.1), 288 (0.1), 273 (0.1), 248 (0.1), 232 (0.1), 216 (0.3), 203 (100), 185 (30), 171 (0.7), 157 (4.6), 145 (19.2), 129 (5.9), 119 (45.4), 105 (13.4), 91 (22.9), 77 (5.8), 69 (35.7), 55 (5.5), 41 (11.8). Anal. calc. for $C_{21}H_{26}OSe$ (373.39): C 67.55, H 7.02; found: C 67.59, H 6.98.

Data of trans-**2**: IR (KBr): 3436, 3055, 2972, 2936, 1616, 1579, 1512, 1478, 1223, 1074, 1006, 817, 735, 691. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.61 – 7.49 (overlapped *m*, 2 arom. H); 7.41 – 7.31 (overlapped *m*, 3 arom. H); 7.21 – 7.07 (overlapped *m*, 4 arom. H); 3.19 (*d*, ^2J(H,H) = 11.6, ^2J(Se,H) = 8.0, 1 H, $SeCH_2$); 3.07 (*d*, ^2J(H,H) = 11.6, ^2J(Se,H) = 7.2, 1 H, $SeCH_2$); 2.45 – 2.34 (*m*, 1 H); 2.32 (*s*, *Me*Ar); 1.90 – 1.36 (overlapped *m*, 5 H); 1.34 (*s*, Me); 0.84 (*s*, Me). ^{13}C-NMR (50 MHz, $CDCl_3$): 144.5 (arom. C); 135.8 (arom. C); 132.2 (2 arom. CH of PhSe); 131.5 (arom. C of PhSe); 128.8, 128.4, 126.2, 125.9 (4 arom. CH of Ar; 3 arom. CH of PhSe); 77.2, 74.5 (COC); 44.1, 35.4, 34.4, 33.3, 26.0 (Me, C*C*H_2*C*H_2*C*H_2*CC*H_2Se); 21.0 (*Me*Ar); 17.0 (Me). MS: identical to that of *cis*-**2**. Anal. calc. for $C_{21}H_{26}OSe$ (373.39): C 67.55, H 7.02; found: C 67.58, H 7.05.

Preparation of (±)-Curcumene Ether (= *3,4,5,6-Tetrahydro-2,2,6-trimethyl-6-(4-methylphenyl)-2*H-*pyran*; (±)-**1**): *Reduction of* cis- *and* trans-**2**. The reaction was carried out using an H-cube hydrogenation reactor (*Thalesnano*) in continuous-flow mode, and *Raney*-Ni (*CarCart*™ cartridge) was used as a catalyst. To prime the system, the catalyst bed was washed continuously with THF (10 ml) at a flow rate

of 1 ml/min. The pressure was adjusted to full H_2 mode, and the temp. was set at 25°. The mixture *cis*-**2**/*trans*-**2** (200 mg, 0.536 mmol) was dissolved in THF (30 ml) and allowed to flow through the H-cube at 1 ml/min. The collected soln. was concentrated under reduced pressure to afford **1** (111 mg, 95%). Colorless oil. IR (KBr): 2956, 2924, 2853, 1462, 1378, 1365, 1273, 1224, 1119, 1078, 987, 820. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.41 – 7.30 (*AA′* of *AA′BB′*, 2 arom. H); 7.15 – 7.06 (*BB′* of *AA′BB′*, 2 arom. H); 2.32 (*s*, *Me*Ar); 2.31 – 2.20 (*m*, 1 H); 1.33 – 1.84 (overlapped *m*, 5 H); 1.39 (*s*, Me); 1.25 (*s*, Me); 0.78 (*s*, Me); ^{1}H-NMR data are consistent with those reported in [6]. ^{13}C-NMR (50 MHz, $CDCl_3$): 145.5 (arom. C); 135.6 (arom. C); 128.4 (2 arom. CH); 125.7 (2 arom. CH); 73.9, 72.5 (COC); 36.8, 34.8, 34.1, 32.0, 28.3 (*Me*C*C*H$_2$*C*H$_2$*C*H$_2$C*Me*); 21.0 (*Me*Ar); 17.1 (Me). EI-MS (70 eV): 203 (100, $[M - Me]^+$), 185 (22.5), 170 (0.1), 157 (1.6), 145 (44.8), 135 (48.1), 119 (72.3), 105 (13.1), 91 (22.6), 77 (4.2), 69 (22.5), 56 (4.9), 43 (22.4). Anal. calc. for $C_{15}H_{22}O$ (218.33): C 82.52, H 10.16; found: C 82.55, H 10.14.

Preparation of 5-(4-Methylphenyl)-5-oxopentanoic Acid (**10**). Compound **10** was synthesized according to the procedure described in [9] in 80% yield. White solid. M.p. 145 – 147° (146 – 148° [9]). IR (KBr): 3447, 3100, 2967, 1698, 1676, 1607, 1451, 1409, 1287, 1233, 1193, 1185, 1074, 909, 819, 749, 676. The ^{1}H- and ^{13}C-NMR: identical to those reported in [9].

Preparation of Ethyl 5-(4-Methylphenyl)-5-oxopentanoate (**11**). Ester **11** was synthesized from **10** by a modified literature procedure [10] as follows: a 100-ml, single-necked, round-bottomed flask equipped with a magnetic stirring bar, a *Dean–Stark* trap filled with dry toluene, and a H_2O-cooled condenser is charged with **10** (412 mg, 2 mmol), dry toluene (30 ml), abs. EtOH (30 ml), and TsOH · H_2O (150 mg). The mixture was refluxed for 8 h. The solvents were distilled off, and the residue was treated with a NaOH soln. (20 ml, 2 mol/dm^3). The mixture was extracted with Et_2O, org. layers were washed with H_2O and brine, dried (Na_2SO_4), and filtered off. The solvent was evaporated *in vacuo*, and the residue was subjected to CC (SiO_2 (5 g); hexane/AcOEt 9 : 1 (*v*/*v*)) to give **11** (459 mg, 98%). Colorless crystals. M.p. 39 – 40° ([12]: 39 – 40°). IR: identical to that reported in [5a]. ^{1}H-NMR (600 MHz, $CDCl_3$): 7.90 – 7.84 (*m*, H–C(2′), H–(6′)); 7.29 – 7.23 (*m*, H–C(3′), H–C(5′)); 4.14 (*q*, J = 7.2, MeC*H*$_2$O); 3.03 (*t*, J = 7.3, ArCOC*H*$_2$); 2.43 (*t*, J = 7.3, C*H*$_2$COOEt); 2.41 (*s*, *Me*Ar), 2.06 (*quint.*, J = 7.3, CH$_2$C*H*$_2$CH$_2$), 1.26 (*t*, J = 7.2, *Me*CH$_2$O). ^{13}C-NMR (151 MHz, $CDCl_3$): 199.1 (Ar*C*O); 173.3 (*C*OOEt); 143.8 (C(4′)); 134.3 (C(1′)); 129.2 (C(3′), C(5′)); 128.1 (C(2′), C(6′)); 60.3 (Me*C*H$_2$O); 37.3 (ArCO*C*H$_2$); 33.4 (*C*H$_2$COOEt); 21.6 (*Me*Ar); 19.4 (CH$_2$*C*H$_2$CH$_2$); 14.2 (*Me*CH$_2$O).

Preparation of Ethyl 5-(4-Methylphenyl)hex-5-enoate (**9**). *Wittig* olefination of **11** was performed as described in [11]: solid *t*BuOK (0.60 g, 5.34 mmol) was added to a suspension of $MePPh_3Br$ (2.00 g, 5.72 mmol) in dry toluene (35 ml) at 0°, and the mixture was stirred for 20 min at this temp. The soln. of **11** (1.00 g, 4.27 mmol) in dry toluene (15 ml) was added at once. The mixture was stirred for 1.5 h at r.t. Workup: aq. NH_4Cl at r.t., extraction with Et_2O. The org. phase was washed with brine and dried (Na_2SO_4). After evaporation, the crude product was purified by CC (SiO_2 (70 g); 1. petroleum ether (PE), and 2. PE/MeO*t*Bu 10 : 1 (*v*/*v*)) to yield **9** (0.85 g, 86%). Pale-yellow oil. ^{1}H-NMR (600 MHz, $CDCl_3$): 7.32 – 7.28 (*m*, H–C(2′), H–C(6′)); 7.15 – 7.11 (*m*, H–C(3′), H–C(5′)); 5.27 (br. *d*, J = 1.3, C=C*H*$_A$H$_B$, *cis* to Ar); 5.02 (br. *d*, J = 1.3, C=CH$_A$*H*$_B$, *trans* to Ar); 4.11 (*q*, J = 7.1, MeC*H*$_2$O); 2.56 – 2.51 (*m*, ArC(=CH$_2$)C*H*$_2$); 2.43 (*s*, *Me*Ar); 2.33 – 2.28 (*m*, C*H*$_2$COOEt); 1.81 – 1.75 (*m*, CH$_2$C*H*$_2$CH$_2$); 1.25 (*t*, J = 7.1, *Me*CH$_2$O). ^{13}C-NMR (151 MHz, $CDCl_3$): 173.6 (*C*OOEt); 147.2 (*C*=CH$_2$); 137.8 (C(1′)); 137.2 (C(4′)); 129.0 (C(3′), C(5′)); 125.9 (C(2′), C(6′)); 112.1 (C=*C*H$_2$); 60.2 (Me*C*H$_2$O); 34.5 (ArC(=CH$_2$)*C*H$_2$); 33.6 (*C*H$_2$COOEt); 23.4 (*Me*Ar); 21.1 (CH$_2$*C*H$_2$CH$_2$); 14.2 (*Me*CH$_2$O). CI-MS: 233 (13, $[M + 1]^+$), 203 (16, $[M - Et]^+$), 189 (100, $[M - Et - Me]^+$). Anal. calc. for $C_{15}H_{20}O_2$ (232.32): C 77.55, H 8.68; found: C 77.50, H 8.73.

Preparation of 2-Methyl-6-(4-methylphenyl)hept-6-en-2-ol (**5**). MeMgCl in THF (4.59 ml of 3 mol/dm^3 soln., 13.77 mmol) was added to a soln. of **9** (0.80 g, 3.44 mmol) in dry THF at 0°, and the mixture was stirred for 1 h at 0°, and additional 2 h at r.t. Workup: aq. NH_4Cl at 0°, extraction with 3 × 50 ml Et_2O. The org. phase was washed with H_2O and dried (Na_2SO_4). After evaporation, the crude product was purified by CC (SiO_2 (70 g); 1. PE/MeO*t*Bu 10 : 1 and 2. PE/MeO*t*Bu 4 : 1 (each *v*/*v*)) to yield pure **5** (0.67 g, 89%). Pale-yellow oil. IR (KBr): 3365, 3083, 3025, 2968, 2942, 2869, 1626, 1513, 1465, 1377, 1365, 1189, 1148, 1132, 941, 890, 823, 890, 734. ^{1}H-NMR (600 MHz, $CDCl_3$): 7.32 – 7.28 (*m*, H–C(2′), H–C(6′)); 7.15 – 7.11 (*m*, H–C(3′), H–C(5′)); 5.25 (br. *d*, J = 1.5, C=C*H*$_A$H$_B$, *cis* to Ar); 5.02 (br. *q*, J = 1.3, C=CH$_A$*H*$_B$, *trans* to Ar); 2.52 – 2.46 (*m*, C(=CH$_2$)C*H*$_2$); 2.34 (*s*, *Me*Ar); 1.48 – 1.55 (*m*,

$CH_2CH_2C(Me)_2OH$); 1.17 (*s*, 2 Me). ^{13}C-NMR (151 MHz, $CDCl_3$): 148.1 (C=CH_2); 138.2 (C(1′)); 137.0 (C(4′)); 129.0 (C(3′), C(5′)); 125.9 (C(2′), C(6′)); 111.6 (C=CH$_2$); 70.9 (C(Me)$_2$OH); 43.4 ($CH_2C(Me)_2OH$); 35.7 (C(=CH_2)CH_2); 29.2 (C(Me)$_2$OH); 23.0 ($CH_2CH_2CH_2$); 21.1 (MeAr). ESI-MS: 241 (100, $[M+Na]^+$). Anal. calc. for $C_{15}H_{22}O$ (218.33): C 82.52, H 10.16; found: C 82.46, H 10.20.

Electrochemical Phenylselenoetherification of **5** *to Yield 3,4,5,6-Tetrahydro-2,2-dimethyl-6-(4-methylphenyl)-6-[(phenylselanyl)methyl]-2*H*-pyran* (**4**) [3c]. The electrochemical phenylselenoetherification of **5** was performed as described for **3**. From 0.218 g (1 mmol) of **5**, 0.220 g (0.59 mmol) of **4** (a pale-yellow oil) was obtained (59%). IR (KBr): 3055, 3023, 2970, 2937, 2869, 1579, 1510, 1459, 1380, 1364, 1226, 1073, 1032, 1022, 980, 816, 733, 690. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.43 – 7.33 (overlapped *m*, 4 arom. H); 7.18 – 7.05 (overlapped *m*, 5 arom. H); 3.37 (*d*, ^2J(H,H) = 11.6, ^2J(Se,H) = 8.7, 1 H, $SeCH_2$); 3.06 (*dd*, ^2J(H,H) = 11.6, ^2J(Se,H) = 7.5, 1 H, $SeCH_2$); 2.43 (br. *dt*, J = 13.6, 4.1, 1 H); 2.32 (*s*, MeAr); 2.10 – 1.89 (*m*, 1 H); 1.79 – 1.60 (overlapped *m*, 2 H); 1.53 – 1.35 (overlapped *m*, 2 H); 1.24 (*s*, Me); 0.73 (*s*, Me). ^{13}C-NMR (50 MHz, $CDCl_3$): 142.4 (arom. C); 136.5 (arom. C); 132.3 (2 arom. CH of PhSe); 132.0 (arom. C of PhSe); 128.6, 128.5, 126.6 (4 arom. CH of Tol; 2 arom. CH of PhSe); 126.2 (arom. CH of PhSe); 76.1, 73.3 (COC); 46.2, 36.6, 32.0, 30.4, 27.6 (MeC$CH_2CH_2CH_2$CCH_2Se); 21.0 (MeAr); 16.9 (Me). Anal. calc. for $C_{21}H_{26}OSe$ (373.39): C 67.55, H 7.02; found: C 67.50, H, 7.01.

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Received November 12, 2012