Conjugated Additions of Selenium Containing Enolates to Enones – Enantioselective Synthesis of δ-Oxo-α-Seleno Esters and Their Facile Transformations

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Titanium enolates derived from methyl phenylselenoacetate and other acetates bearing a selenium containing chiral auxiliary have been employed to bring about 1,4-addition reactions to enones. These reactions generate δ-oxo-α-seleno esters in good yields and with excellent regio- and diastereoselectivities. The results obtained clearly indicate that the Lewis acids, employed to activate the starting enones towards addition, greatly influence reactivity as well as the stereochemical outcomes of these reactions. $TiCl_4$ complexation resulted in particularly efficient promotion of the 1,4-addition. Simple manipulations of the organoselenium moiety allowed some enantiomerically pure δ-oxo-α-camphorseleno esters to be transformed into the corresponding δ-oxo-α-hydroxy or δ-oxo-α-allyl esters or into trisubstituted tetrahydrofurans.

Introduction

Organoselenium compounds are commonly employed as useful and powerful reagents in organic synthesis.[1] They allow the chemo, regio and stereoselective introduction of new functional groups into organic substrates to be carried out. Recently, enantiopure diselenides have been extensively employed in asymmetric electrophilic addition reactions to carbon-carbon double bonds. Highly stereoselective seleno-alkoxylations, seleno-hydroxylations[2] and seleno-azidations[3] or selenium-induced cyclisations,[2,4] which afford various heterocyclic compounds, have been extensively studied by us and by other research groups. On the other hand, a careful analysis of the literature revealed that the use of enantiopure selenium containing nucleophiles in asymmetric additions remains largely unexplored.[5] In this field, we have successfully investigated asymmetric aldol condensations between (*R*)-camphorselenoacetone or methyl (*R*)-camphorselenoacetate and aromatic or aliphatic aldehydes. These reactions proceed with satisfactory to good yields giving, predominantly, mixtures of diastereomeric *syn* aldols which could be separated by chromatography.[6]

These interesting results prompted us to evaluate the use of similar nucleophiles to effect conjugate additions to α,β-unsaturated carbonyl compounds. This process is a fundamental method for carbon–carbon bond formation since it generates highly functionalised compounds. In recent years, many asymmetric variants of this important reaction have been developed. Efficient methods for the control of diastereo- and enantioselectivity include the use of a chiral auxiliary in the Michael acceptor or in the Michael donor or the employment of chiral catalysts.[7]

We report herein that α-selenoenolates containing a chiral auxiliary linked to the selenium atom can be efficiently employed as Michael donors for the stereoselective preparation of enantiomerically pure δ-oxo-α-seleno esters. It has been found that the chiral selenium containing group can transfer the chirality to the 1,4-addition products affording δ-oxo-α-seleno esters with a high level of diastereoselectivity and facial selectivity. Moreover, the organoselenium moieties in the reaction products can be stereospecifically substituted to afford useful multifunctional derivatives not easily available by other methods.

Results and Discussion

The reactions of chalcone with the methyl selenoacetates **1a**–**1c** are indicated in Scheme 1.

In order to choose the best conditions for high conversion and good regio- (1,4 vs. 1,2 selectivity) and diastereocontrol (*syn* vs. *anti*) and to evaluate the effects of some Lewis acids, preliminary experiments were carried out with chalcone and the methyl phenylselenoacetate **1a**.[8] In fact, it is well known that Lewis acids can affect the reactivity and the selectivity of Michael-type reactions.[9] Compound

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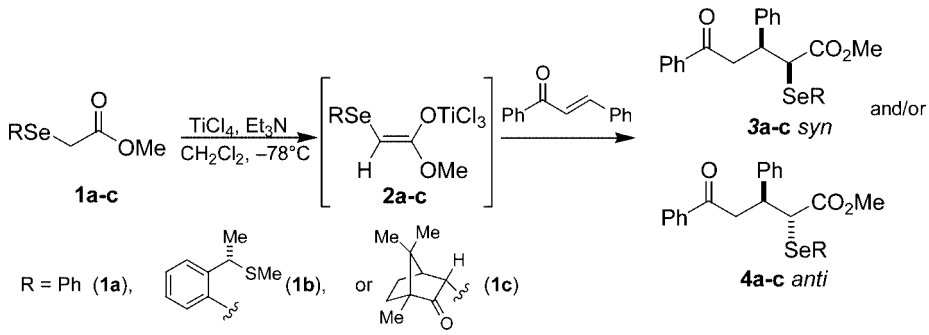


Scheme 1. Reactions of chalcone with the methyl selenoacetates **1a**–**1c**

Table 1. Nucleophilic additions of the selenoacetates **1a–c** to chalcone

	Acetate	Lewis acid[a]	1,4 vs. 1,2[b]			1,4 Adducts[c]		3:4[b]
1	**1a**	$TiCl_4$	98:2	**3a**	78%	**4a**	4%	95:5
2	**1a**	$Ti(OiPr)_4$	76:24	**3a**	–	**4a**	54%	<1:99
3	**1a**	$BF_3 \cdot Et_2O$	87:13	**3a**	17%	**4a**	46%	27:73
4	**1a**	none	82:18	**3a**	–	**4a**	67%	<1:99
5	**1b**	$TiCl_4$	90:10	**3b**	29% *dr* 58:42[b]	**4b**	13% *dr* 57:43[b]	69:31
6	**1c**	$TiCl_4$	98:2	**3c**	69%[d] *dr* >99:1[b]	**4c**	trace	>98:2
7	**1c**	none	98:2	**3c**	–	**4c**	25%[d] *dr* >99:1[b]	<1:99

[a] An equimolar amount of the indicated Lewis acid was used to activate the chalcone. [b] The diastereomeric ratios were determined by ^1H NMR spectroscopy of the crude mixtures and confirmed after chromatographic separation. [c] Yields determined after column chromatographic separation. [d] The absolute configuration of the β-carbon atom in **3c** and **4c** was determined after removal of the organoselenium moiety by reductive deselenenylation with Ph_3SnH and by comparing the optical rotations of the resultant esters with those already reported in the literature.

1a was treated with 1.1 equivalents of $TiCl_4$ and 2 equivalents of Et_3N at –78 °C under nitrogen in order to prepare the titanium enolate **2a**. The (*Z*) geometry was assigned to this titanium enolate on the basis of its ^1H NMR spectrum and the results of NOESY experiments recorded on a sample of the enolate generated in CD_2Cl_2 at –40 °C in an NMR tube.

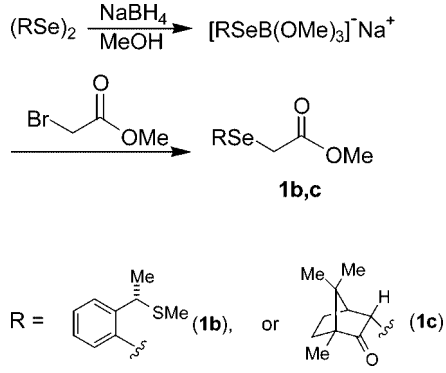
After 1 hour, 1.5 equivalents of chalcone, complexed or not with 1.5 equivalents of a Lewis acid [$TiCl_4$, $Ti(iPrO)_4$ or $BF_3 \cdot Et_2O$], were added and the reaction mixtures were stirred at the same temperature for 3–5 h. The reaction products, yields and the observed diastereomeric ratios are reported in Table 1 (entries 1–4).

The results obtained from these reactions indicate that the precomplexation of the enone with an equimolar amount of a Lewis acid dramatically influences the outcome of the addition. In fact, by activating chalcone with $TiCl_4$ (entry 1), it was possible to obtain the 1,4 adduct **3a**, having *syn* stereochemistry, in high yield and with excellent regio- and diastereoselectivity.

In all the other cases, i.e. in the presence of other Lewis acids such as $Ti(OiPr)_4$ or $BF_3 \cdot Et_2O$ or without complexation, not only were greater amounts of the 1,2-addition products formed but the *anti* product **4a** was also present as the major or even as the sole isomer (entries 2–4).

The last three experiments of Table 1 (entries 5–7) refer to the reactions carried out on chalcone with the enantiomerically pure α-selenoacetates **1b** and **1c**.

The methyl selenoacetates **1b** and **1c** [6] were prepared as indicated in Scheme 2 from the reaction of the nucleophilic selenium species (generated in situ by treatment of the bis{2-[(1*S*)-1-(methylthio)ethyl]phenyl} diselenide[10] or the (*R*)-dicamphor diselenide[11] with sodium borohydride in methanol) with methyl bromoacetate.

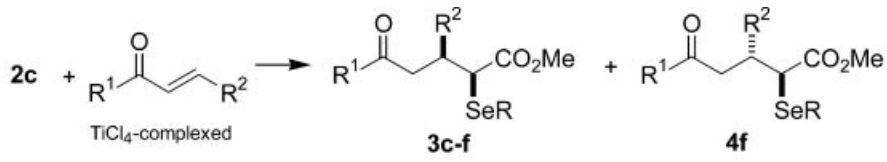


Scheme 2. Synthesis of the methyl [{2-[(1*S*)-1-(methylthio)ethyl] phenyl}seleno]acetate (**1b**) and the methyl (*R*)-camphorseleno acetate **1c**

The α-selenoacetate **1b** (entry 5) reacted with $TiCl_4$-complexed chalcone without any selectivity, giving rise to mixtures of diastereomeric *syn* and *anti* 1,4-addition products.

On the other hand, the selenoacetate **1c**, both in the presence or in the absence of $TiCl_4$ (entries 6 and 7), gave rise to 1,4-addition products with excellent diastereoselectivities

Table 2. $TiCl_4$-activated nucleophilic 1,4-additions of the titanium enolate **2c** to enones



	R^1	R^2	T	1,4 vs 1,2[a]		1,4-adducts[b]			3:4[a]
1[c]	Ph	Ph	–78 °C	98:2	**3c**[d]	69%	–	–	>99:1
2	Me	Ph	–50 °C	>99:1	**3d**[d]	61%	–	–	>99:1
3	Me		–50 °C	>99:1	**3e**[d]	60%	–	–	>99:1
4	Ph	Me	–50 °C	>99:1	**3f**[d]	30%	**4f**[d]	7%	81:19[e]

[a] The diastereomeric ratios were determined by ^1H NMR of the crude mixtures. [b] Yields determined after column chromatography separation. [c] These results have already been described in Table 1 (entry 6) and are reported here for comparison. [d] The products have diastereomeric excesses >98% as determined by ^1H NMR spectroscopy of the crude mixtures and confirmed after chromatographic separation. [e] Mixture of two diastereoisomers which were not separated.

and facial selectivities. In fact, in the former case, only the *syn* product **3c** was isolated in good yield whereas in the latter case, the *anti* **4c** was present as the sole reaction product although in poor yield (25%).

The excellent results obtained from the $TiCl_4$-activated reaction between chalcone and the chiral α-seleno ester **1c** prompted us to carry out similar reactions with other (*E*)-enones. The reaction products, yields and the diastereomeric ratios obtained are reported in Table 2.

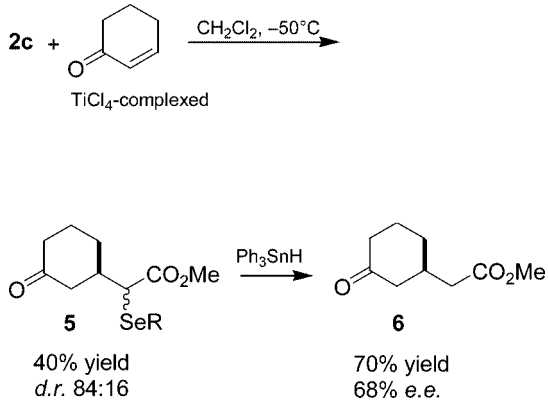
As already observed in the case of chalcone, all reactions proceeded with high regio- and stereocontrol. The best results in terms of yield and stereoselectivity were those obtained starting from enones having an aryl-substituted carbon-carbon double bond. In these cases, the *syn* adducts **3c**–**3e** were the sole reaction products (Table 2, entries 1–3).

A decrease in the yield and diastereoselectivity was observed in the presence of the methyl-substituted enone (Table 2, entry 4).

Similar results were obtained in another experiment carried out with cyclohex-2-en-1-one. In fact, in this case, the reaction gave rise to the 1,4-addition product **5** which was an 84:16 mixture of two diastereoisomers (Scheme 3).

The relative stereochemistry in compounds **3a**–**3e** and **4a**–**4c** was determined on the basis of their ^1H NMR spectra.[12] The configurations of **3a** and **4a** were also confirmed by the *J* values of the corresponding δ-lactones obtained by reduction and cyclisation.

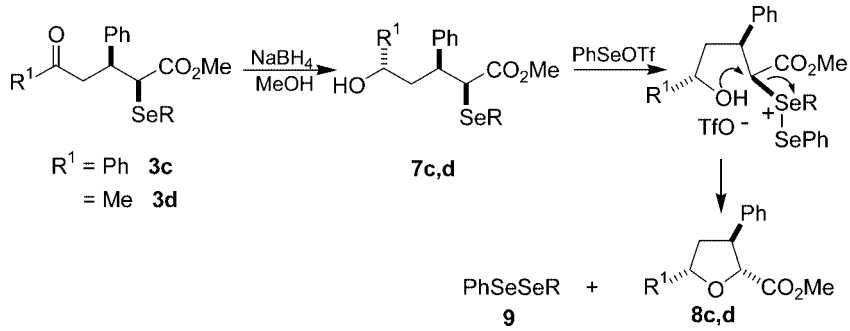
The absolute configurations of the β-carbon atoms of the α-seleno-δ-oxo esters **3c** and **3d** were assigned after removal of the camphorseleno group by reductive deselenenylations with Ph_3SnH[6] and comparison of the optical rotations of the resultant esters with those already reported in the literature. The deselenenylation of the mixture of **3f** and **4f** afforded the corresponding ester in an enantiomerically enriched form (*ee,* 62%). Similarly, compound **5** gave **6** (*ee,* 68%).[13] The configuration of the β-carbon atom of **3e** was assigned by analogy with **3c** and **3d**. The formation of the *syn* enantiomers **3c**–**3f** suggests that (*Z*)-enolate **2c** [14] reacts with the *Si* face and that the addition takes place on the same diastereotopic face of the (*E*)-enones.



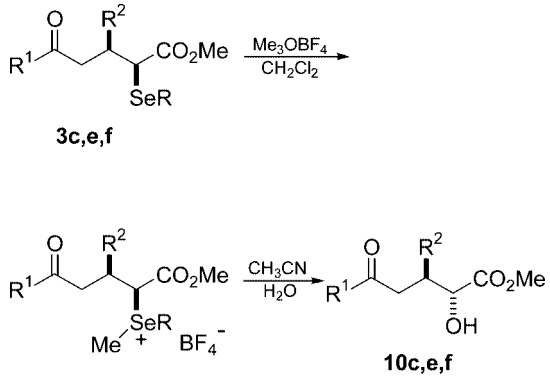
Scheme 3. Nucleophilic addition of the titanium enolate **2c** to cyclohex-2-en-1-one

The enantiomerically pure α-seleno-δ-oxo esters obtained in the present work can be employed as useful intermediates for further synthetic transformations. The first application investigated concerns the conversion of **3c** and **3d** into the enantiomerically pure trisubstituted tetrahydrofurans **8c** and **8d**, respectively.

As indicated in Scheme 4, the α-seleno-δ-hydroxy esters **7c** and **7d** obtained from **3c** and **3d** by reduction with $NaBH_4$ in MeOH gave, after treatment with phenylse-



Scheme 4. Synthesis of enantiomerically pure trisubstituted tetrahydrofurans **8c,d**

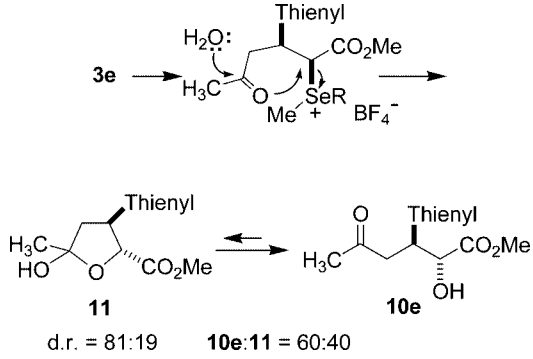


Scheme 5. Synthesis of α-hydroxy esters from α-seleno esters

lenenyl triflate, the tetrahydrofurans **8c** and **8d**. The attack of the electrophilic selenenylating agent on the selenium atom of **7c** or **7d** generates the intermediate selenonium salts in which the diselenide **9** acts as a good leaving group. The ring closure reactions proceeded in both cases with good yields giving **8c** and **8d** in yields of 55% and 61%, respectively. The stereochemistries of **8c** and **8d** were determined by NOESY experiments. The formation of **8c** and **8d** clearly indicates that the intramolecular nucleophilic substitution is a stereospecific process which occurs with inversion of configuration[1] and that the absolute configurations of **7c** and **7d** are those indicated in Scheme 4. During the workup most of the mixed diselenide **9** was converted into a mixture of (*R*)-dicamphor diselenide and diphenyl diselenide which was separated by column chromatography. Thus, with this deselenenylation procedure, the chiral auxiliary can be recovered.

Other nucleophilic substitutions of the camphorseleno group were also studied. It is known that trimethyloxonium tetrafluoroborate can react with the selenides to generate the corresponding selenonium salts.[15] These reactions were employed to effect the synthesis of several heterocyclic compounds by ring closure reactions.[16] We observed that using the trimethyloxonium tetrafluoroborate, the organoselenium group can also be substituted by a hydroxyl group. As indicated in Scheme 5, the α-seleno esters **3c**, **3e** and the diastereomeric mixture of **3f** and **4f** could be converted into the enantiomerically pure α-hydroxy esters **10c**, **10e** and **10f** in yields of 68, 70 and 71%, respectively, based on the converted (79–68%) starting materials. The hydroxy ester **10f** was contaminated by a small amount of the *syn* diastereoisomer.

The conversion of compounds **3** into the hydroxy esters **10** is an interesting process which probably does not takes place by a simple substitution of the selenonium group by water. We have in fact observed that α-seleno esters which do not contain a δ-carbonyl moiety, such as the methyl (*R*)-camphorselenoacetate or the diastereomeric mixture of methyl 2-[(*R*)-camphorseleno]propanoate, could not be transformed into the corresponding hydroxy esters under the same reaction conditions. A possible explanation for the course of these reactions can be deduced from the results obtained in the case of compound **3e**. It can be proposed (Scheme 6) that the substitution is actually an intramolecular process promoted by the oxygen atom of the carbonyl group which generates the cyclic hemiacetal **11** as a mixture of two diastereoisomers. These hemiacetals are in equilibrium with the hydroxy ester **10e**. All the other α-seleno esters gave the α-hydroxy esters directly and the cyclic hemiacetals could not be detected.



Scheme 6. Reaction of the δ-oxo-α-seleno ester **3e** with trimethyloxonium tetrafluoroborate

Finally, a radical process was used in order to convert the organoselenium moiety into an allyl group. Compound **3c** reacted (Scheme 7) with triphenylallyltin and AIBN in C_6H_6 at reflux to afford, after column chromatography, the enantiomerically pure substitution products **12**.[17] These were isolated in high yields (82%) and good diastereoselectivities (*syn*/*anti* = 85:15).

In conclusion, this paper describes 1,4-addition reactions, to enones, of titanium enolates derived from methyl phenylselenoacetate and other easily available selenoacet-

ates containing a chiral auxiliary linked to the selenium atom. The reactions result in good yields and excellent regio- and diastereoselectivities. The results obtained from the reactions between methyl (*R*)-camphorselenoacetate **1c** and different enones indicate that this new strategy for controlling the diastereoselectivity and facial selectivity of the Michael addition reactions is particularly efficient. Moreover, this method provides access to enantiomerically pure δ-oxo-α-seleno esters which are useful synthetic intermediates since they contain a versatile organoselenium moiety. The synthetic applications of these compounds include stereospecific transformations into enantiomerically pure trisubstituted tetrahydrofurans or methyl α-hydroxy esters. Enantiopure methyl α-allyl esters were also prepared by a stereoselective radical reaction.

Experimental Section

General: New compounds were characterized by MS, ^{1}H and ^{13}C NMR spectroscopy. ^{1}H NMR 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. *J* values are given in Hz. GC-MS analyses were carried out with an HP-6890 gas chromatograph (25m dimethyl silicone capillary column) equipped with an HP-5973 mass selective detector at an ionising voltage of 70 eV. For the ions containing selenium only, the peaks arising from the ^{80}Se isotope are given. Optical rotations were measured in a 50 mm cell with a Jasco DIP-1000 digital polarimeter. Enantiomeric excesses were determined by chiral GC-MS performed on an HP 5890 gas chromatograph (25 m Chirasildex capillary column) equipped with an HP 5971 mass selective detector or by chiral HPLC performed on an HP 1100 [(*R*,*R*)-Whelk-O 1 column]. Elemental analyses were carried out on a Carlo Erba 1106 elemental analyser. Flash column chromatography was performed with Merck silica gel 60 (230–400 mesh).

Starting Products: With the exception of (2*E*)-1-phenyl-2-buten-1-one (Table 2, entry 4), which was prepared as described in the literature,[18] the starting enones employed in this investigation are commercially available. The α–seleno esters **1a**,[19] **1b** and **1c** [6] were prepared according to a literature procedure[8] starting from commercial diphenyl diselenide or from the easily available bis{2-[(1*S*)-1-(methylthio)ethyl]phenyl} diselenide[10] or (*R*)-dicamphor diselenide[11] as reported in Scheme 2.

Methyl ({2-[(1*S*)-1-(Methylthio)ethyl]phenyl}seleno)acetate (1b): Yield 92% based on the converted diselenide, (1.60 mmol, 490 mg), oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.64 (dd, $^3J_{H,H}$ = 7.7, $^4J_{H,H}$ = 1.4 Hz, 1 H, CH), 7.48 (dd, $^3J_{H,H}$ = 7.7, $^4J_{H,H}$ = 1.4 Hz, 1 H, CH), 7.30 (dd, $^3J_{H,H}$ = 7.7, $^4J_{H,H}$ = 1.4 Hz, 1 H, CH), 7.16 (dd, $^3J_{H,H}$ = 7.7, $^4J_{H,H}$ = 1.4 Hz, 1 H, CH), 4.52 (q, $^3J_{H,H}$ = 7.0 Hz, 1 H, CH), 3.65 (s, 3 H, OCH_3), 3.60–3.40 (m, 2 H, CH_2), 1.94 (s, 3 H, SCH_3), 1.58 ppm (d, $^3J_{H,H}$= 7.0 Hz, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 170.9, 145.1, 134.3, 130.3, 128.3, 127.6, 126.9, 52.2, 44.0, 27.6, 21.2, 13.8 ppm. Elemental analysis for $C_{12}H_{16}O_2SSe$ (303.3): calcd. C 47.52, H 5.32; found: C 47.68, H 5.41.

General Procedure for Conjugated Additions to Enones: The α-seleno ester **1a–c** (0.5 mmol) dissolved in CH_2Cl_2 (5 mL) was treated with a 1 M solution of $TiCl_4$ in CH_2Cl_2 (0.55 mmol) and Et_3N (1 mmol) at –78 °C under nitrogen. After 1 h, the appropriate enone (0.75 mmol or 1.5 mmol for (3*E*)-4-phenyl-but-3-en-2-one, (3*E*)-4-(thien-2-yl)-but-3-en-2-one and cyclohex-2-en-1-one), complexed or not with the Lewis acid indicated in Tables 1 and 2, was added at the same temperature and the reaction mixture was stirred at –78 or at –50 °C for 3–5 h. The reaction was then quenched with a saturated solution of NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and the solvent evaporated. The crude mixture was purified by flash chromatography using mixtures of diethyl ether and light petroleum as the eluent. Physical and spectroscopic data of the reaction products are reported below.

Methyl (2*S,3*S**)-5-Oxo-3,5-diphenyl-2-(phenylseleno)pentanoate (3a):** Yield 78% (0.39 mmol, 171 mg, Table 1, entry 1), m.p. 93 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.85–7.78 (m, 2 H, CH), 7.53–7.50 (m, 1 H, CH), 7.49–7.40 (m, 4 H, CH), 7.35–7.20 (m, 8 H, CH), 4.12 (d, $^3J_{H,H}$ = 9.6 Hz, 1 H, CH), 3.98 (ddd, $^3J_{H,H}$ = 9.6, 8.5 and 4.0 Hz, 1 H, CH), 3.59 (s, 3 H, OCH_3), 3.58 (dd, $^2J_{H,H}$ = 16.5, $^3J_{H,H}$ = 8.5 Hz, 1 H, CH_2), 3.48 ppm (dd, $^2J_{H,H}$ = 16.5, $^3J_{H,H}$ = 4.0 Hz, 1 H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 197.0, 172.0, 140.1, 136.3, 135.4 (2C), 132.6, 128.6 (2C), 128.2, 128.1 (3C), 128.0 (2C), 127.8 (2C), 127.7 (2C), 126.9, 51.7, 50.0, 43.0, 42.6 ppm. MS (70 eV, EI): *m*/*z* (%): 438 (1) [M^+], 318 (10), 281 (47), 249 (7), 157 (3), 105 (100), 77 (24). Elemental analysis for $C_{24}H_{22}O_3Se$ (437.4): calcd. C 65.90, H 5.07; found: C 66.08, H 5.13.

The δ-oxo ester **3a** was converted into the corresponding δ-lactones by $NaBH_4$ reduction and cyclisation of the crude products from the treatment with TFA in toluene at reflux.[20] The spectroscopic data of the two lactones are reported below.

(3*S,4*S**,6*R**)-4,6-Diphenyl-3-(phenylseleno)tetrahydro-2*H*-pyran-2-one:** Yield 51% (0.05 mmol, 21 mg), oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.85–7.75 (m, 2 H, CH), 7.60–7.25 (m, 13 H, CH), 5.37 (dd, $^3J_{H,H}$ = 11.9 and 2.1 Hz, 1 H, CH), 4.12 (d, $^3J_{H,H}$ = 6.4 Hz, 1 H, CH), 3.54 (ddd, $^3J_{H,H}$ = 11.9, 6.4 and 5.9 Hz, 1 H, CH), 2.42 (ddd, $^2J_{H,H}$ = 14.4, $^3J_{H,H}$ = 5.9 and 2.1 Hz, 1 H, CH_2), 2.15 (dt, $^2J_{H,H}$ = 14.4, $^3J_{H,H}$ = 11.9 Hz, 1 H, CH_2). Elemental analysis for $C_{23}H_{20}O_2Se$ (407.4): calcd. C 67.81, H 4.95; found: C 67.65, H, 4.90.

(3*S,4*S**,6*S**)-4,6-Diphenyl-3-(phenylseleno)tetrahydro-2*H*-pyran-2-one:** Yield 46% (0.04 mmol, 19 mg), oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.80–7.73 (m, 2 H, CH), 7.50–7.20 (m, 13 H, CH), 5.35 (dd, $^3J_{H,H}$ = 10.2 and 3.8 Hz, 1 H, CH), 4.31 (dd, $^3J_{H,H}$ = 4.1, $^4J_{H,H}$= 1.5 Hz, 1 H, CH), 3.69 (ddd, $^3J_{H,H}$ = 5.3, 4.3 and 4.1 Hz, 1 H, CH), 2.64 (ddd, $^2J_{H,H}$ = 14.5, $^3J_{H,H}$ = 10.2 and 4.3 Hz, 1 H, CH_2), 2.29 (dddd, $^2J_{H,H}$ = 14.5, $^3J_{H,H}$ = 5.3 and 3.8, $^4J_{H,H}$ = 1.5 Hz, 1 H, CH_2). Elemental analysis for $C_{23}H_{20}O_2Se$ (407.4): calcd. C 67.81, H 4.95; found: C 67.91, H 4.89.

Methyl (2*S*,3*S*)-2-({2-[(1*S*)-1-(Methylthio)ethyl]phenyl}seleno)-5-oxo-3,5-diphenylpentanoate and Methyl (2*R*,3*R*)-2-({2-[(1*S*)-1-(Methylthio)ethyl]phenyl}seleno)-5-oxo-3,5-diphenylpentanoate (3b): Yield 29% (0.14 mmol, 74 mg), mixture of diastereoisomers 58:42, oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.90–7.80 (m, 4 H, CH), 7.60–7.03 (m, 24 H, CH), 4.46 (q, $^3J_{H,H}$ = 7.0 Hz, 1 H, CH), 4.17 (d, $^3J_{H,H}$ = 9.5 Hz, 1 H, CH), 4.15 (q, $^3J_{H,H}$ = 7.0 Hz, 1 H, CH), 4.11 (d, $^3J_{H,H}$ = 9.5 Hz, 1 H, CH), 4.03 (td, $^3J_{H,H}$ = 9.5 and 3.9 Hz, 1 H, CH), 4.0 (td, $^3J_{H,H}$ = 9.5 and 3.9 Hz, 1 H, CH), 3.65 (s, 3 H, OCH_3), 3.62 (dd, $^2J_{H,H}$ = 16.4, $^3J_{H,H}$ = 9.5 Hz, 1 H, CH_2), 3.57 (dd, $^2J_{H,H}$ = 16.4, $^3J_{H,H}$ = 9.5 Hz, 1 H, CH_2), 3.55(s, 3 H, OCH_3), 3.53 (dd, $^2J_{H,H}$ = 16.4, $^3J_{H,H}$ = 3.9 Hz, 1 H, CH_2), 3.46 (dd, $^2J_{H,H}$ = 16.4, $^3J_{H,H}$ = 3.9 Hz, 1 H, CH_2), 1.90 (s, 3 H, SCH_3), 1.88 (s, 3 H, SCH_3), 1.53 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_3), 1.47 ppm (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 197.3 (2C), 172.5 (2C), 146.7, 146.6, 140.7, 140.6, 137.0, 136.8 (2C), 136.5, 133.0 (2C), 130.9, 129.8, 129.2, 128.9, 128.5 (6C),

128.3 (2C), 128.2 (2C), 128.1 (4C), 127.3 (2C), 127.2, 127.1 (2C), 127.0, 126.7 (2C), 52.1, 51.9, 51.3, 50.4, 44.1, 44.0 (2C), 43.4, 43.2, 43.0, 21.4, 21.1, 13.9 ppm (2C). Elemental analysis for $C_{27}H_{28}O_3SSe$ (511.5): calcd. C 63.40, H 5.52; found: C 63.54, H 5.68.

Methyl (2*S*,3*S*)-2-(Camphorseleno)-5-oxo-3,5-diphenylpentanoate (3c): Yield 69% (0.35 mmol, 178 mg), oil. $[\alpha]_D^{20} = -52.0$ (c = 3.2 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.0–7.90 (m, 2 H, CH), 7.62–7.58 (m, 1 H, CH), 7.52–7.45 (m, 2 H, CH), 7.39–7.22 (m, 5 H, CH), 4.27 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H, CH), 4.05 (ddd, $^3J_{H,H}$ = 9.6, 8.8 and 4.1 Hz, 1 H, CH), 3.83 (dd, $^3J_{H,H}$ = 4.3, $^4J_{H,H}$ = 2.2 Hz, 1 H, CH), 3.82 (s, 3 H, OCH_3), 3.71 (dd, $^2J_{H,H}$ = 16.8, $^3J_{H,H}$ = 9.6 Hz, 1 H, CH_2), 3.51 (dd, $^2J_{H,H}$ = 16.8, $^3J_{H,H}$ = 4.1 Hz, 1 H, CH_2), 2.20 (t, $^3J_{H,H}$ = 4.3, 1 H, CH), 1.90–1.60 (m, 3 H, CH_2), 1.42–1.30 (m, 1 H, CH_2), 1.05 (s, 3 H, CH_3), 0.95 (s, 3 H, CH_3), 0.92 ppm (s, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 216.9, 197.5, 173.0, 140.7, 136.8, 133.1, 128.5 (2C), 128.4 (2C), 128.3 (2C), 128.1 (2C), 127.2, 58.1, 52.5, 48.2, 47.7, 46.8, 44.6, 43.1, 42.8, 30.4, 23.5, 19.6, 19.5, 9.6 ppm. MS (70 eV, EI): *m*/*z* (%): 512 (4) [M$^+$], 392 (8), 360 (3), 311 (8), 281 (33), 249 (21), 221 (4), 209 (5), 163 (7), 121 (7), 120 (12), 105 (100), 77 (18), 55 (5). Elemental analysis for $C_{28}H_{32}O_4Se$ (511.5): calcd. C 65.75, H 6.31; found: C 65.50, H 6.15.

Methyl (2*S*,3*S*)-2-(Camphorseleno)-5-oxo-3-phenylhexanoate (3d): Yield 61% (0.30 mmol, 137 mg), oil. $[\alpha]_D^{30} = -56.0$ (c = 4.81 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.40–7.15 (m, 5 H, CH), 4.11 (d, $^3J_{H,H}$ = 8.6 Hz, 1 H, CH), 3.78 (ddd, $^3J_{H,H}$ = 9.2, 8.6 and 4.8 Hz, 1 H, CH), 3.74 (s, 3 H, OCH_3), 3.72 (dd, $^3J_{H,H}$ = 4.3, $^4J_{H,H}$ = 2.2 Hz, 1 H, CH), 3.05 (dd, $^2J_{H,H}$ = 16.6, $^3J_{H,H}$ = 9.2 Hz, 1 H, CH_2), 2.94 (dd, $^2J_{H,H}$ = 16.6, $^3J_{H,H}$ = 4.8 Hz, 1 H, CH_2), 2.13 (t, $^3J_{H,H}$ = 4.3 Hz, 1 H, CH), 2.03 (s, 3 H, CH_3CO), 1.82–1.72 (m, 1 H, CH_2), 1.68–1.52 (m, 2 H, CH_2), 1.38–1.28 (m, 1 H, CH_2), 0.99 (s, 3 H, CH_3), 0.89 (s, 3 H, CH_3), 0.86 ppm (s, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 216.8, 206.0, 172.7, 140.4, 128.7 (2C), 128.3 (2C), 127.1, 57.9, 52.2, 48.1, 47.5, 47.4, 46.6, 44.4, 42.6, 30.3, 30.2, 23.3, 19.5, 19.3, 9.5 ppm. MS (70 eV, EI): *m*/*z* (%): 450 (19) [M$^+$], 418 (7), 392 (5), 360 (4), 311 (9), 279 (8), 231 (20), 219 (60), 187 (100), 177 (41), 163 (60), 145 (17), 121 (37), 107 (10), 83 (13), 55 (15). Elemental analysis for $C_{23}H_{30}O_4Se$ (449.4): calcd. C 61.46, H 6.73; found: C 61.40, H 6.59.

Methyl (2*S*,3*S*)-2-(Camphorseleno)-5-oxo-3-(thien-2-yl)hexanoate (3e): Yield 60% (0.30 mmol, 137 mg), oil. $[\alpha]_D^{27} = -71.9$ (c = 3.9 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.17 (dd, $^3J_{H,H}$ = 5.1, $^4J_{H,H}$ = 1.2 Hz, 1 H, CH), 6.96 (dd, $^3J_{H,H}$ = 3.6, $^4J_{H,H}$ = 1.2 Hz, 1 H, CH), 6.92 (dd, $^3J_{H,H}$ = 5.1 and 3.6 Hz, 1 H, CH), 4.22–4.16 (m, 2 H, CH), 3.83 (dd, $^3J_{H,H}$ = 4.3, $^4J_{H,H}$ = 2.2 Hz, 1 H, CH), 3.76 (s, 3 H, OCH_3), 3.12–3.02 (m, 2 H, CH_2), 2.20 (t, $^3J_{H,H}$ = 4.3, 1 H, CH), 2.15 (s, 3 H, CH_3CO), 1.85–1.78 (m, 1 H, CH_2), 1.73–1.58 (m, 2 H, CH_2), 1.42 (ddd, $^2J_{H,H}$ = 13.5, $^3J_{H,H}$ = 8.9, 4.4 Hz, 1 H, CH_2), 1.01 (s, 3 H, CH_3), 0.92 (s, 3 H, CH_3), 0.89 ppm (s, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 216.6, 205.3, 172.1, 143.0, 125.8, 125.3, 123.5, 57.4, 51.7, 47.6, 47.5, 46.8, 46.1, 44.4, 36.9, 29.8, 29.7, 22.7, 18.9, 18.7, 8.9 ppm. MS (70 eV, EI): *m*/*z* (%): 456 (1) [M$^+$], 425 (1), 225 (95), 193 (100), 183 (13), 153 (20), 137 (8), 123 (14), 109 (9), 83 (5), 69 (2), 55 (6). Elemental analysis for $C_{21}H_{28}O_4SSe$ (455.5): calcd. C 55.38, H 6.20; found: C 55.25, H 6.26.

Methyl (2*S*,3*R*)-2-(Camphorseleno)-3-methyl-5-oxo-5-phenylpentanoate (3f) and Methyl (2*S*,3*S*)-2-(Camphorseleno)-3-methyl-5-oxo-5-phenylpentanoate (4f): Yield 37% (0.18 mmol, 83 mg), mixture of isomers *syn*:*anti* = 81:19, oil. *syn* isomer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.1–8.0 (m, 2 H, CH), 7.63–7.50 (m, 1 H, CH), 7.50–7.41 (m, 2 H, CH), 3.97 (dd, $^3J_{H,H}$ = 4.4, $^4J_{H,H}$ = 2.3 Hz, 1 H, CH), 3.94 (d, $^3J_{H,H}$ = 6.8 Hz, 1 H, CH), 3.78 (s, 3 H, OCH_3), 3.30 (dd, $^2J_{H,H}$ = 16.6, $^3J_{H,H}$ = 4.3 Hz, 1 H, CH_2), 3.0 (dd, $^2J_{H,H}$ = 16.6, $^3J_{H,H}$ = 8.7 Hz, 1 H, CH_2), 2.80–2.67 (m, 1 H, CH), 2.24 (t, $^3J_{H,H}$ = 4.4 Hz, 1 H, CH), 1.98–1.52 (m, 3 H, CH_2), 1.50–1.40 (m, 1 H, CH_2), 1.19 (d, $^3J_{H,H}$ = 7.7 Hz, 3 H, CH_3), 1.03 (s, 3 H, CH_3), 0.93 (s, 3 H, CH_3), 0.92 ppm (s, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 216.9, 198.6, 173.3, 136.8, 132.9, 128.4 (2C), 128.0 (2C), 57.9, 53.0, 48.2, 47.5, 46.6, 45.7, 43.1, 31.0, 30.5, 23.3, 19.4, 19.3, 18.1, 9.4 ppm. MS (70 eV, EI): *m*/*z* (%): 450 (16) [M$^+$], 418 (7), 400 (4), 331 (23), 299 (14), 267 (10), 231 (12), 219 (95), 187 (25), 159 (19), 120 (47), 105 (100), 77 (30), 55 (12). Elemental analysis for $C_{23}H_{30}O_4Se$ (449.4): calcd. C 61.46, H 6.73; found: C 61.35, H 6.82. *anti* isomer (distinct signals): ^{1}H NMR: δ = 4.0 (dd, $^3J_{H,H}$ = 4.5, $^4J_{H,H}$ = 2.3 Hz, 1 H, CH), 3.77 (s, 3 H, OCH_3), 3.68 (dd, $^2J_{H,H}$ = 17.0, $^3J_{H,H}$ = 4.1 Hz, 1 H, CH_2), 2.91 (dd, $^2J_{H,H}$ = 17.0, $^3J_{H,H}$ = 8.6 Hz, 1 H, CH_2), 2.26 (t, $^3J_{H,H}$ = 4.5 Hz, 1 H, CH), 1.13 (d, $^3J_{H,H}$ = 6.5 Hz, 3 H, CH_3), 0.96 (s, 3 H, CH_3), 0.94 (s, 3 H, CH_3).

Methyl (2*R,3*S**)-5-Oxo-3,5-diphenyl-2-(phenylseleno)pentanoate (4a):** Yield 67% (0.34 mmol, 147 mg, Table 1, entry 4), m.p. 88 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.90–7.82 (m, 2 H, CH), 7.68–7.61 (m, 2 H, CH), 7.56–7.50 (m, 1 H, CH), 7.45–7.10 (m, 10 H, CH), 4.04 (d, $^3J_{H,H}$ = 11.2 Hz, 1 H, CH), 4.03 (dd, $^2J_{H,H}$ = 16.7, $^3J_{H,H}$ = 3.6 Hz, 1 H, CH_2), 3.95 (ddd, $^3J_{H,H}$ = 11.2, 9.2 and 3.6 Hz, 1 H, CH), 3.47 (dd, $^2J_{H,H}$ = 16.7, $^3J_{H,H}$ = 9.2 Hz, 1 H, CH_2), 3.43 ppm (s, 3 H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 197.4, 171.5, 140.7, 136.6, 134.8 (2C), 132.6, 128.9 (2C), 128.2 (2C), 128.1 (2C), 128.0 (2C), 127.6 (4C), 126.7, 51.5, 50.4, 43.1, 42.1 ppm. MS (70 eV, EI): *m*/*z* (%): 438 (1) [M$^+$], 318 (18), 281 (45), 249 (12), 105 (100), 77 (26). Elemental analysis for $C_{24}H_{22}O_3Se$ (437.4): calcd. C 65.90, H 5.07; found: C 66.0, H 5.18.

The δ-oxo ester **4a** was converted into the following δ-lactone by $NaBH_4$ reduction followed by cyclisation by treatment with TFA in toluene at reflux.[20]

(3*R,4*S**,6*R**)-4,6-diphenyl-3-(phenylseleno)tetrahydro-2*H*-pyran-2-one:** Yield 51% (0.05 mmol, 21 mg), oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.48–7.20 (m, 15 H, CH), 5.52 (dd, $^3J_{H,H}$ = 11.8 and 4.2 Hz, 1 H, CH), 4.19 (dd, $^3J_{H,H}$ = 4.2, $^4J_{H,H}$ = 1.5 Hz, 1 H, CH), 3.84 (dt, $^3J_{H,H}$ = 11.8 and 4.2 Hz, 1 H, CH), 2.54 (dt, $^2J_{H,H}$ = 14.0, $^3J_{H,H}$ = 11.8 Hz, 1 H, CH_2), 2.45 ppm (dtd, $^2J_{H,H}$ = 14.0, $^3J_{H,H}$ = 4.2, $^4J_{H,H}$ = 1.5 Hz, 1 H, CH_2). Elemental analysis for $C_{23}H_{20}O_2Se$ (407.4): calcd. C 67.81, H 4.95; found: C 67.75, H 5.0.

Methyl (2*R*,3*S*)-2-({2-[(1*S*)-1-(methylthio)ethyl]phenyl}seleno)-5-oxo-3,5-diphenylpentanoate and Methyl (2*S*,3*R*)-2-({2-[(1*S*)-1-(methylthio)ethyl]phenyl}seleno)-5-oxo-3,5-diphenylpentanoate (4b): Yield 13% (0.07 mmol, 33 mg), mixture of diastereoisomers 57:43, oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.02–7.05 (m, 28 H, CH), 4.65 (q, $^3J_{H,H}$ = 7.0 Hz, 1 H, CH), 4.54 (q, $^3J_{H,H}$ = 7.0 Hz, 1 H, CH), 4.24–3.90 (m, 6 H, CH, CH_2), 3.62–3.40 (m, 2 H, CH_2), 3.49 (s, 3 H, OCH_3), 3.44 (s, 3 H, OCH_3), 2.0 (s, 3 H, SCH_3), 1.99 (s, 3 H, SCH_3), 1.64 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_3), 1.60 ppm (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 198.6, 197.7, 172.0, 171.9, 146.0, 145.7, 141.1, 141.0, 136.9 (2C), 136.1, 135.6, 133.1 (2C), 130.8, 130.1, 129.1, 128.8, 128.7 (2C), 128.6 (2C), 128.5 (3C), 128.4 (3C), 128.1, 128.0 (3C), 127.9 (2C), 127.8, 127.7 127.5, 127.2, 127.0, 126.7, 52.0, 51.9, 51.6 (2C), 44.1 (2C), 43.5, 43.3, 43.0, 42.7, 21.3, 21.2, 14.0,

13.9 ppm. Elemental analysis for $C_{27}H_{28}O_3SSe$ (511.5): calcd. C 63.40, H 5.52; found: C 63.59, H 5.33.

Methyl (2*R*,3*S*)-2-(Camphorseleno)-5-oxo-3,5-diphenylpentanoate (4c): Yield 25% (0.13 mmol, 64 mg), oil. $[\alpha]_D^{31}$ = –86.3 (*c* = 4.37 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.98–7.92 (m, 2 H, CH), 7.58–7.52 (m, 1 H, CH), 7.48–7.42 (m, 2 H, CH), 7.40–7.32 (m, 2 H, CH), 7.32–7.22 (m, 2 H, CH), 7.22–7.16 (m, 1 H, CH), 4.30 (d, $^3J_{H,H}$ = 11.5 Hz, 1 H, CH), 4.04 (dd, $^2J_{H,H}$ = 17.3, $^3J_{H,H}$ = 4.7 Hz, 1 H, CH_2), 4.01 (dd, $^3J_{H,H}$ = 4.2, $^4J_{H,H}$ = 2.5 Hz, 1 H, CH), 3.97 (ddd, $^3J_{H,H}$ = 11.5, 8.0 and 4.7 Hz, 1 H, CH), 3.55 (s, 3 H, OCH_3), 3.44 (dd, $^2J_{H,H}$ = 17.3, $^3J_{H,H}$ = 8.0 Hz, 1 H, CH_2), 2.29 (t, $^3J_{H,H}$ = 4.2, 1 H, CH), 1.95–1.80 (m, 1 H, CH_2), 1.68–1.58 (m, 1 H, CH_2), 1.49 (ddd, $^2J_{H,H}$ = 12.9, $^3J_{H,H}$ = 9.2 and 4.2 Hz, 1 H, CH_2), 1.27 (ddd, $^2J_{H,H}$ = 16.1, $^3J_{H,H}$ = 9.2 and 5.0 Hz, 1 H, CH_2), 1.05 (s, 3 H, CH_3), 0.95 (s, 3 H, CH_3), 0.92 ppm (s, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 217.5, 198.3, 173.3, 141.9, 137.1, 132.9, 128.5 (4C), 128.1 (2C), 128.0 (2C), 127.0, 58.2, 52.1, 48.3, 47.7, 47.0, 45.7, 43.8, 41.7, 30.2, 23.6, 19.7, 19.4, 9.7 ppm. MS (70 eV, EI): *m*/*z* (%): 512 (4) [M^+], 392 (5), 360 (3), 329 (2), 311 (7), 281 (31), 249 (21), 231 (3), 207 (7), 163 (8), 120 (14), 105 (100), 77 (19), 55 (5). Elemental analysis for $C_{28}H_{32}O_4Se$ (511.5): calcd. C 65.75, H 6.31; found: C 65.91, H 6.19.

Methyl (Camphorseleno)(3-oxocyclohexyl)acetate (5): Yield 40% (0.20 mmol, 80 mg), mixture of diastereoisomers 84:16, oil. Major isomer: ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.91 (dd, $^3J_{H,H}$ = 4.5, $^4J_{H,H}$ = 2.2 Hz, 1 H, CH), 3.78 (d, $^3J_{H,H}$ = 7.9 Hz, 1 H, CH), 3.73 (s, 3 H, OCH_3), 2.50–2.02 (m, 8 H, CH, CH_2), 1.90–1.80 (m, 1 H, CH_2), 1.75–1.55 (m, 3 H, CH_2), 1.55–1.38 (m, 2 H, CH_2), 1.02 (s, 3 H, CH_3), 0.92 (s, 3 H, CH_3), 0.91 ppm (s, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 217.3, 209.8, 172.8, 58.1, 52.3, 48.3, 47.4, 46.8, 45.7, 44.5, 40.9, 39.9, 30.4, 29.2, 24.4, 23.6, 19.6, 19.4, 9.6 ppm. MS (70 eV, EI): *m*/*z* (%): 400 (29) [M^+], 368 (7), 341 (6), 249 (10), 231 (44), 217 (13), 203 (16), 169 (100), 152 (64), 137 (97), 124 (64), 109 (53), 97 (19), 81 (33), 79 (22), 71 (14), 69 (11), 67 (17), 55 (30). Elemental analysis for $C_{19}H_{28}O_4Se$ (399.4): C 57.14, H 7.07; found: C 57.26, H 6.91. Minor isomer (distinct signals): ^{13}C NMR: δ = 210.2, 47.1, 46.0, 44.7, 41.0, 39.7, 29.7, 24.7 ppm. MS (70 eV, EI): *m*/*z* (%): 400 (40) [M^+], 368 (5), 341 (6), 249 (12), 231 (64), 217 (13), 203 (21), 169 (96), 152 (78), 137 (100), 124 (79), 109 (65), 97 (28), 81 (47), 79 (30), 71 (20), 69 (15), 67 (24), 55 (46).

General Procedure for the Preparation of 7c and 7d by Reduction of 3c and 3d with $NaBH_4$: To a solution of **3c** or **3d** (0.5 mmol) in methanol (5 mL) was added $NaBH_4$ (0.55 mmol) and the mixture was stirred for 1–3 h. The reaction mixture was then poured into water and extracted with diethyl ether. The organic layers were dried over Na_2SO_4 and the solvents evaporated. The crude mixture containing two diastereomeric alcohols was purified by flash chromatography using mixtures of diethyl ether and light petroleum as the eluent. The physical and spectroscopic data of the alcohols **7c** and **7d** are reported below.

Methyl (2*S*,3*S*,5*S*)-2-(Camphorseleno)-5-hydroxy-3,5-diphenylpentanoate (7c): Yield 47%[21] (0.23 mmol, 120 mg), oil. $[\alpha]_D^{31}$ = –12.4 (*c* = 3.11 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.48–7.20 (m, 10 H, CH), 4.42 (dd, $^3J_{H,H}$ = 8.4 and 5.8 Hz, 1 H, CH), 4.06 (d, $^3J_{H,H}$ = 10.3 Hz, 1 H, CH), 3.75 (s, 3 H, OCH_3), 3.59 (dd, $^3J_{H,H}$ = 4.3, $^4J_{H,H}$ = 2.5 Hz, 1 H, CH), 2.95 (td, $^3J_{H,H}$ = 10.3 and 3.9 Hz, 1 H, CH), 2.39 (ddd, $^2J_{H,H}$ = 13.4, $^3J_{H,H}$ = 10.3 and 5.8 Hz, 1 H, CH_2), 2.22 (ddd, $^2J_{H,H}$ = 13.4, $^3J_{H,H}$ = 8.4 and 3.9 Hz, 1 H, CH_2), 2.02 (t, $^3J_{H,H}$ = 4.3 Hz, 1 H, CH), 1.97 (br.s, 1 H, OH), 1.80–1.68 (m, 1 H, CH_2), 1.65–1.50 (m, 2 H, CH_2), 1.30–1.20 (m, 1 H, CH_2), 0.98 (s, 3 H, CH_3), 0.88 (s, 3 H, CH_3), 0.81 ppm (s, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 216.0, 172.2, 142.3, 140.0, 127.8 (4C), 127.7 (2C), 127.3, 126.6, 125.9 (2C), 72.2, 57.3, 51.6, 47.4, 46.9, 46.0, 44.4, 43.9, 42.3, 29.7, 22.6, 18.8 (2C), 8.9 ppm. Elemental analysis for $C_{28}H_{34}O_4Se$ (513.5): calcd. C 65.49, H 6.67; found: C 65.39, H 6.60.

Methyl (2*S*,3*S*,5*R*)-2-(Camphorseleno)-5-hydroxy-3-phenylhexanoate (7d): Yield 59%[22] (0.29 mmol, 133 mg), oil. $[\alpha]_D^{21}$ = –38.0 (*c* = 4.72 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.35–7.10 (m, 5 H, CH), 3.98 (d, $^3J_{H,H}$ = 10.2 Hz, 1 H, CH), 3.72 (s, 3 H, OCH_3), 3.54 (dd, $^3J_{H,H}$ = 4.6, $^4J_{H,H}$ = 3.7 Hz, 1 H, CH), 3.53 (dqd, $^3J_{H,H}$ = 7.0, 6.2 and 5.9 Hz, 1 H, CH), 3.13 (td, $^3J_{H,H}$ = 10.2 and 4.3 Hz, 1 H, CH), 2.0 (t, $^3J_{H,H}$ = 4.6, 1 H, CH), 1.97 (ddd, $^2J_{H,H}$ = 13.5, $^3J_{H,H}$ = 10.2 and 5.9 Hz, 1 H, CH_2), 1.71 (ddd, $^2J_{H,H}$ = 13.5, $^3J_{H,H}$ = 7.0 and 4.3 Hz, 1 H, CH_2), 1.70–1.62 (m, 1 H, CH_2), 1.58–1.43 (m, 2 H, CH_2), 1.24–1.14 (m, 2 H, CH_2, OH), 1.08 (d, $^3J_{H,H}$ = 6.2, Hz, 3 H, CH_3), 0.91 (s, 3 H, CH_3), 0.80 (s, 3 H, CH_3), 0.76 ppm (s, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 216.9, 173.3, 140.9, 128.6 (2C), 128.2 (2C), 127.3, 66.3, 58.0, 52.4, 48.1, 47.6, 46.7, 45.2, 45.1, 44.1, 30.4, 23.3, 22.6, 19.6, 19.5, 9.5 ppm. Elemental analysis for $C_{23}H_{32}O_4Se$ (451.5): calcd. C 61.19, H 7.14; found: C 61.23, H 7.10.

General Procedure for the Synthesis of the Trisubstituted Tetrahydrofurans 8c and 8d: To a solution of PhSeBr (0.3 mmol) in acetonitrile (5 mL) at 0 °C was added silver trifluoromethansulfonate (0.3 mmol). The resultant orange suspension was stirred for 15 min and then **7c** or **7d** (0.25 mmol) was added. Upon completion of the reaction (monitoring by TLC) the reaction mixture was poured into a 10% Na_2CO_3 solution and was then extracted with dichloromethane. The organic layer was filtered through celite, dried over Na_2SO_4 and the solvents evaporated. The crude residue was separated by flash column chromatography. Diphenyl diselenide and dicamphor diselenide were also recovered. The physical and spectroscopic data for **8c** and **8d** are given below.

Methyl (2*R*,3*S*,5*S*)-3,5-Diphenyltetrahydrofuran-2-carboxylate (8c): Yield 55% (0.14 mmol, 39 mg), oil. $[\alpha]_D^{29}$ = –43.3 (*c* = 1.6 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.66–7.58 (m, 2 H, CH), 7.46–7.30 (m, 8 H, CH), 5.34 (dd, $^3J_{H,H}$ = 7.9 and 6.8 Hz, 1 H, CH), 4.76 (d, $^3J_{H,H}$ = 5.6 Hz, 1 H, CH), 3.83 (s, 3 H, OCH_3), 3.75 (dt, $^3J_{H,H}$ = 7.9 and 5.6 Hz, 1 H, CH), 2.51 (ddd, $^2J_{H,H}$ = 12.7, $^3J_{H,H}$ = 6.8 and 5.6 Hz, 1 H, CH_2), 2.43 ppm (dt, $^2J_{H,H}$ = 12.7, $^3J_{H,H}$ = 7.9 Hz, 1 H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 172.5, 141.8, 140.9, 128.7 (2C), 128.2 (2C), 127.4, 127.1 (2C), 126.9, 125.9 (2C), 83.4, 81.7, 52.0, 48.8, 42.6 ppm. MS (70 eV, EI): *m*/*z* (%): 282 (7) [M^+], 223 (80), 205 (87), 193 (38), 176 (57), 163 (30), 145 (25), 131 (19), 117 (60), 105 (81), 91 (100), 77 (20). Elemental analysis for $C_{18}H_{18}O_3$ (282.3): calcd. C 76.57, H 6.43; found: C 76.68, H 6.50.

Methyl (2*R*,3*S*,5*R*)-5-Methyl-3-phenyltetrahydrofuran-2-carboxylate (8d): Yield 61% (0.15 mmol, 34 mg), oil. $[\alpha]_D^{19}$ = –85.0 (*c* = 1.3 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.32–7.17 (m, 5 H, CH), 4.44 (d, $^3J_{H,H}$ = 5.9 Hz, 1 H, CH), 4.40 (sext, $^3J_{H,H}$ = 6.4 Hz, 1 H, CH), 3.68 (s, 3 H, OCH_3), 3.58 (dt, $^3J_{H,H}$ = 8.5 and 5.9 Hz, 1 H, CH), 2.14 (ddd, $^2J_{H,H}$ = 12.6, $^3J_{H,H}$ = 6.4 and 5.9 Hz, 1 H, CH_2), 2.02 (ddd, $^2J_{H,H}$ = 12.6, $^3J_{H,H}$ = 8.5 and 6.4 Hz, 1 H, CH_2), 1.35 ppm (d, $^3J_{H,H}$ = 6.4 Hz, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 172.8, 141.8, 128.7 (2C), 127.2 (2C), 126.8, 83.7, 76.7, 52.1, 49.1, 41.3, 21.2 ppm. MS (70 eV, EI): *m*/*z* (%): 220 (1) [M^+], 176 (64), 161 (100), 143 (30), 131 (12), 117 (37), 105 (60), 91 (67), 77 (8). Elemental analysis for $C_{13}H_{16}O_3$ (220.3): calcd. C 70.89, H 7.32; found: C 70.76, H 7.39.

General Procedure for the Synthesis of 2-Hydroxy esters 10c, 10e and 10f: Trimethyloxonium tetrafluoroborate (0.4 mmol) was added, under nitrogen, to a solution of the adduct **3c**, **3e** or the diastereomeric mixture of **3f** and **4f** (0.2 mmol) in dichloromethane (5 mL) at room temperature and the mixture was stirred for 2h. After evaporation of the dichloromethane under reduced pressure, the residue was dissolved in a 1:1 mixture of CH_3CN and H_2O and stirred overnight. The reaction was then poured into a 10% $NaHCO_3$ solution and extracted with CH_2Cl_2. Flash chromatography was used to purify the hydroxy esters **10c**, **10e** or **10f**. The physical and spectroscopic data of these products are reported below.

Methyl (2*R*,3*S*)-2-Hydroxy-5-oxo-3,5-diphenylpentanoate (10c): Yield 68% based on the converted (79%) starting material (0.11 mmol, 33 mg), m.p. 108 °C. $[\alpha]_D^{22} = -37.9$ ($c = 0.81$ in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.0–7.90 (m, 2 H, CH), 7.55–7.50 (m, 1 H, CH), 7.48–7.43 (m, 2 H, CH), 7.42–7.22 (m, 5 H, CH), 4.43 (dd, $^3J_{H,H}$ = 5.9 and 4.2 Hz, 1 H, CH), 3.94 (ddd, $^3J_{H,H}$ = 7.1, 6.5 and 4.2 Hz, 1 H, CH), 3.75 (s, 3 H, OCH_3), 3.57 (dd, $^2J_{H,H}$ = 17.8, $^3J_{H,H}$ = 6.5 Hz, 1 H, CH_2), 3.49 (dd, $^2J_{H,H}$ = 17.8, $^3J_{H,H}$ = 7.1 Hz, 1 H, CH_2), 3.05 ppm (d, $^3J_{H,H}$ = 5.9 Hz, 1 H, OH). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 198.1, 174.3, 141.1, 136.7, 133.0, 128.4 (4C), 127.9 (4C), 127.0, 74.1, 52.5, 44.2, 39.1 ppm. Elemental analysis for $C_{18}H_{18}O_4$ (298.3): calcd. C 72.47, H 6.08; found: C 72.59, H 6.20.

Methyl (2*R*,3*R*)-2-Hydroxy-5-oxo-5-phenyl-3-(thien-2-yl)pentanoate (10e) and Methyl (2*R*,3*R*)-5-Hydroxy-5-methyl-3-(thien-2-yl)tetrahydrofuran-2-carboxylate (11): Yield 70% based on the converted (74%) starting material (0.10 mmol, 25 mg), mixture of isomers **10e**:**11** = 60:40, oil. Compound 10e: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.20–7.12 (m, 1 H, CH), 7.0–6.89 (m, 2 H, CH), 4.33 (dd, $^3J_{H,H}$ = 6.0 and 3.7 Hz, 1 H, CH), 4.0 (ddd, $^3J_{H,H}$ = 7.4, 6.5 and 3.7 Hz, 1 H, CH), 3.77 (s, 3 H, OCH_3), 3.07 (d, $^3J_{H,H}$ = 6.0 Hz, 1 H, OH), 2.97 (dd, $^2J_{H,H}$ = 17.8, $^3J_{H,H}$ = 6.5 Hz, 1 H, CH_2), 2.91 (dd, $^2J_{H,H}$ = 17.8, $^3J_{H,H}$ = 7.4 Hz, 1 H, CH_2), 2.10 ppm (s, 3 H, CH_3CO). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 206.3, 173.7, 143.1, 126.9, 126.6, 125.3, 73.8, 52.7, 45.0, 39.7, 30.4 ppm. Elemental analysis for $C_{11}H_{14}O_4S$ (242.3): calcd. C 54.53, H 5.82; found: C 54.69, H 5.71. Compound **11** (*dr,* 81:19), major isomer: ^{1}H NMR: δ = 7.20–7.12 (m, 1 H, CH), 7.0–6.89 (m, 2 H, CH), 4.58 (d, $^3J_{H,H}$ = 7.5 Hz, 1 H, CH), 4.15 (dt, $^3J_{H,H}$ = 14.9 and 7.5 Hz, 1 H, CH), 3.79 (s, 3 H, OCH_3), 3.41 (br.s, 1 H, OH), 2.57 (dd, $^2J_{H,H}$ = 12.5, $^3J_{H,H}$ = 7.5 Hz, 1 H, CH_2), 2.13 (dd, $^2J_{H,H}$ = 12.5, $^3J_{H,H}$ = 14.9 Hz, 1 H, CH_2), 1.62 ppm (s, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 173.8, 143.9, 124.6, 124.3, 124.0, 106.8, 83.7, 52.5, 47.5, 43.8, 26.2 ppm. Minor isomer (distinct signals): ^{1}H NMR: δ = 4.70 (d, $^3J_{H,H}$ = 7.9 Hz, 1 H, CH), 1.65 (s, 3 H, CH_3).

Methyl (2*R*,3*R*)-2-Hydroxy-3-methyl-5-oxo-5-phenylpentanoate (10f): Yield 71% based on the converted (68%) starting material (0.10 mmol, 23 mg), oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.92–7.87 (m, 2 H, CH), 7.54–7.48 (m, 1 H, CH), 7.43–7.38 (m, 2 H, CH), 4.12 (dd, $^3J_{H,H}$ = 5.6 and 3.8 Hz, 1 H, CH), 3.75 (s, 3 H, OCH_3), 2.99 (dd, $^2J_{H,H}$ = 17.2, $^3J_{H,H}$ = 5.1 Hz, 1 H, CH_2), 2.94 (d, $^3J_{H,H}$ = 5.6 Hz, 1 H, OH), 2.88 (dd, $^2J_{H,H}$ = 17.2, $^3J_{H,H}$ = 7.8 Hz, 1 H, CH_2), 2.73–2.63 (m, 1 H, CH), 1.06 ppm (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 199.1, 175.0, 136.9, 133.1, 128.6 (2C), 128.0 (2C), 74.4, 52.6, 39.9, 33.2, 17.2 ppm. Elemental analysis for $C_{13}H_{16}O_4$ (236.3): calcd. C 66.09, H 6.83; found: C 66.19, H 6.49.

The *syn* diastereoisomer was also present in 8% (distinct signals): ^{1}H NMR: δ = 7.95–7.92 (m, 2 H, CH), 4.26 (dd, $^3J_{H,H}$ = 5.4 and 2.8 Hz, 1 H, CH), 3.77 (s, 3 H, OCH_3), 3.22 (dd, $^2J_{H,H}$ = 17.5, $^3J_{H,H}$ = 7.0 Hz, 1 H, CH_2), 2.90 (dd, $^2J_{H,H}$ = 17.5, $^3J_{H,H}$ = 6.4 Hz, 1 H, CH_2), 2.75–2.67 (m, 1 H, CH), 0.86 (d, $^3J_{H,H}$ = 6.9 Hz, 1 H, CH_3).

General Procedures for the Radical Reductions and Allylation: To a solution of **3** or **4** (0.3 mmol) in dry benzene (3 mL) at reflux, were added Ph_3SnH (0.9 mmol) or allyltributylstannane (2.7 mmol) and a catalytic amount of AIBN in three portions over a period of 3h and the reactions were stirred for 1h. The crude mixtures obtained after evaporation of the solvent under reduced pressure were purified by chromatography on a silica gel column using mixtures of light petroleum and ethyl ether as eluents.

The absolute configurations of the reduction products derived from **3c**, **3d**, **3f**, **4f**, **4c** and **5** were assigned by comparing their optical rotations with those of the products reported in the literature.[13] The substitution product **12** was present as an 85:15 mixture of the two enantiomerically pure *syn* and *anti* products. Spectroscopic data are in agreement with those reported for a similar racemic mixture of *syn* and *anti* diastereoisomers.[17]

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[1] a) *Top. Curr Chem.* (Ed.: T. Wirth), Springer-Verlag Berlin, **2000**; b) *Organoselenium Chemistry – A Practical Approach*. (Ed.:T. G. Back), Oxford University Press Inc., New York, **2000**; c) C. Paulmier, "*Selenium Reagents and Intermediates in Organic Synthesis*", Pergamon, Oxford, **1986**.

[2] M. Tiecco, *Electrophilic Selenium, Selenocyclizations* in *Top. Curr. Chem.* (Ed.:T. Wirth), Springer, Berlin, **2000**, 7–54.

[3] M Tiecco, L. Testaferri, C. Santi, C. Tomassini, F. Marini, L. Bagnoli, A. Temperini, *Angew. Chem. Int. Ed.* **2003**, *42*, 3131–3133.

[4] a) M. Tiecco, L. Testaferri, F. Marini, S. Sternativo, L. Bagnoli, C. Santi, A. Temperini, *Tetrahedron: Asymmetry* **2001**, *12*, 1493–1502; b) M. Tiecco, L. Testaferri, F. Marini, S. Sternativo, C. Santi, L. Bagnoli, A. Temperini, *Tetrahedron: Asymmetry* **2001**, *12*, 3053–3059; c) M. Tiecco, L. Testaferri, L. Bagnoli, V. Purgatorio, A. Temperini, F. Marini, C. Santi, *Tetrahedron: Asymmetry* **2001**, *12*, 3297–3304.

[5] a) Z. Li, R. Wu, R. Michalczyk, R. B. Dunlap, J. D. Odom, L. A. J. Silks, *J Am. Chem. Soc.* **2000**, *122*, 386–387; b) M. Iwaoka, S. Tomoda, *Nucleophilic Selenium* in *Top. Curr. Chem.* (Ed.:T. Wirth), Springer, Berlin, **2000**, 55–80.

[6] M. Tiecco, L. Testaferri, F. Marini, S. Sternativo, C. Santi, L. Bagnoli, A. Temperini, *Tetrahedron: Asymmetry* **2004**, *15*, 783–791.

[7] a) J. Leonard, E. Diez-Barra, S. Merino, *Eur. J. Org. Chem.* **1998**, 2051–2061; b) J. Christoffers, A. Baro, *Angew. Chem. Int. Ed.* **2003**, *42*, 1688–1690; c) V. A. Soloshonok, C. Cai, V. J. Hruby, *Org. Lett.* **2000**, *2*, 747–750; d) D. P. Jang, J. W. Chang, B. J. Uang, *Org. Lett.* **2001**, *3*, 983–985; e) J. H. Smitrovich, G. N. Boice, C. Qu, L. Di Michele, T. D. Nelson, M. A. Huffman, J. Murry, J. McNamara, P. J. Reider, *Org. Lett.* **2002**, *4*, 1963–1966; f) M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc.* **2003**, *125*, 11204–11205; g) H. Ito, T. Nagahara, K. Ishihara, S. Saito, H. Yamamoto, *Angew. Chem. Int. Ed.* **2004**, *43*, 994–997.

[8] L. Lebarillier, F. Outurquin, C. Paulmier, *Tetrahedron* **2000**, *56*, 7483–7493.

[9] G Deng, X. Tian, Z. Qu, J. Wang, *Angew. Chem. Int. Ed.* **2002**, *41*, 2773–2776.
[10] M. Tiecco, L. Testaferri, L. Bagnoli, F. Marini, A. Temperini, C. Tomassini, C. Santi, *Tetrahedron Lett.* **2000**, *41*, 3241–3245.
[11] T. G. Back, B. P. Dyck, M. Parvez, *J. Org. Chem.* **1995**, *60*, 703–710.
[12] The stereochemistries of the 1,4 adducts **3a**–**3e** and **4a**–**4c** could be assigned using the chemical shifts of the methoxy group which is shielded in the *anti* adducts by the *gauche* positioned aryl group. This has already been observed by Heathcock (D. A. Oare, C. H. Heathcock, *J. Org. Chem.* **1990**, *55*, 157–172). The assignment of **3f** was made by analogy with the results observed with the other (*E*)-enones. The conversion described below in Scheme 5 starting from the mixture of **3f** and **4f** afforded two diastereomeric hydroxy esters. This indicates that compound **4f** has the *anti* configuration indicated in Table 2.
[13] a) A. Diaz-Ortiz, E. Diez-Barra, A. De la Hoz, P. Prieto, A. Moreno, *J. Chem. Soc. Perkin Trans. 1* **1996**, 259–263; b) E. Dieters, K. Papadopoulos, *Tetrahedron Lett.* **1983**, *24*, 4967–4970; c) Y. Shi, W. D. Wulff, G. P. A. Yap, A. L. Rheingold, *Chem. Commun.* **1996**, 2601–2602; d) G. H. Posner, M. Weitzberg, T. G. Hamill, E. Asirvatham, H. Cun-Heng, J. Clardy, *Tetrahedron* **1986**, *42*, 2919–2929.
[14] The (*Z*) geometry was assigned by analogy with the enolate **2a**.
[15] a) T. Kataoka, S. Watanabe, K. Yamamoto, M. Yoshimatsu, G. Tanabe, O. Muraoka, *J. Org. Chem.* **1998**, *63*, 6382–6386; b) S. Watanabe, K. Yamamoto, Y. Itagaki, T. Iwamura, T. Iwama, T. Kataoka, G. Tanabe, O. Muraoka, *J. Chem. Soc. Perkin Trans. 1* **2001**, 239–247; S. Watanabe, T. Ikedo, T. Kataoka, G. Tanabe, O. Muraoka, *Org. Lett.* **2003**, *5*, 565–567.
[16] a) S. Ponthieux, F. Outurquin, C. Paulmier, *Tetrahedron Lett.* **1998**, *39*, 4017–4020; b) S. Boivin, F. Outurquin, C. Paulmier, *Tetrahedron Lett.* **2000**, *41*, 663–666; c) C. Betancor, E. I. Leon, T. Prange, J. A. Salazar, E. Suarez, *J. Chem. Soc., Chem. Commun.* **1989**, 450–454; d) A. Krief, *Tetrahedron* **1980**, *36*, 2531–2640.
[17] U. Jahn, *Chem. Commun.* **2001**, 1600–1601.
[18] D. A. Oare, M. A. Henderson, M. A. Sanner, C. H. Heathcock, *J. Org. Chem.* **1990**, *55*, 132–157.
[19] G. P. Mullen, R. B. Dunlap, J. D. Odom, *Biochemistry* **1986**, *25*, 5625–5632.
[20] A. Bernardi, C. Marchionni, B. Novo, K. Karamfilova, D. Potenza, C. Scolastico, P. Roversi, *Tetrahedron* **1996**, *52*, 3497–3508.
[21] 30% of the diastereomeric alcohol (2*S*,3*S*,5*R*) was also separated by column chromatography.
[22] 7% of the diastereomeric alcohol (2*S*,3*S*,5*S*) was also separated by column chromatography.

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