Sequencing Pericyclic Reactions: The Ester Dienolate [2,3]-Wittig/Oxy-Cope Rearrangement/Carbonyl Ene Reaction, a New Access to Substituted Carbocycles

Martin Hiersemann[a]

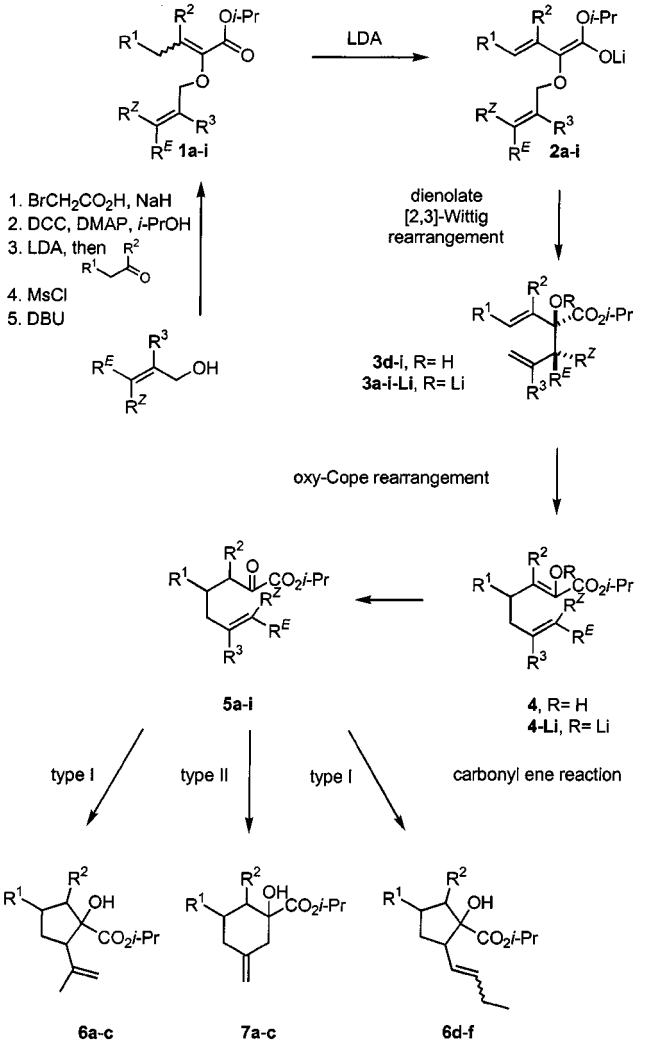
Keywords: Carbocycles / Domino reactions / Ene reactions / Ester dienolates / Pericyclic reactions / Rearrangements

The sequential ester dienolate [2,3]-Wittig/oxy-Cope rearrangement/carbonyl ene reaction has been investigated. Acyclic α,β-unsaturated α-allyloxy-substituted esters **1a–j** were transformed into cyclopentane- or cyclohexanecarboxylates **6a–f** and **7a–7d**. This study presents a domino ester dienolate [2,3]-Wittig/oxy-Cope rearrangement or a domino oxy-Cope rearrangement/carbonyl ene reaction, depending on the substrate structure. The thermal intramolecular type-I carbonyl ene reaction as the terminating ring-closing reaction proceeds with high simple diastereoselectivity, but low induced diastereoselectivity. The corresponding type-II ene reaction afforded the cyclohexanecarboxylates **7a–d** in high yield with complete simple and induced diastereoselectivity. Unfortunately, an attempted auxiliary-controlled enantioselective sequence was inefficient.

Introduction

The development of general and efficient synthetic methods for C−C bond formation remains a significant challenge for organic chemists. A general strategy to improve synthetic efficiency is to combine different C−C-connecting transformations in a domino reaction.[1] Given the importance of carbocyclic ring systems in natural product chemistry, we are interested in developing general procedures for the synthesis of carbocycles, based on sequences of catalyzed or uncatalyzed pericyclic domino reactions.[2] We utilize sigmatropic rearrangements of easily accessible starting materials to generate an appropriate substrate for a cyclizing pericyclic reaction (e.g. electrocyclic reaction or ene reaction). In this context, we set out to study a sequence of pericyclic reactions featuring the dienolate [2,3]-Wittig rearrangement followed by an oxy-Cope rearrangement and terminating in an intramolecular carbonyl ene reaction of an α-oxo ester (Scheme 1). This approach offers a number of interesting features with regard to synthetic efficiency and variability. The substrate synthesis would be highly convergent, allowing access to a broad spectrum of products. The pivotal C−C-connecting pericyclic reactions provide an inherent possibility of stereocontrol through well-defined cyclic transition states.

The utility of the ester dienolate [2,3]-Wittig rearrangement as an extension of the ester enolate [2,3]-Wittig rearrangement was recently demonstrated.[3] Furthermore, we reported the first examples of a domino ester dienolate [2,3]-Wittig/oxy-Cope rearrangement and of the thermal oxy-Cope rearrangement of a 3-alkoxycarbonyl-3-hydroxy-substituted 1,5-hexadiene.[4,5] Whereas Lewis acid pro-



Scheme 1. The sequential dienolate [2,3]-Wittig/oxy-Cope rearrangement/carbonyl ene reaction

[a] Institut für Organische Chemie der Technischen Universität Dresden,
01062 Dresden, Germany
Fax: (internat.) + 49-(0)351/463-7030
E-mail: martin.hiersemann@chemie.tu-dresden.de

  1434−193X/01/0203−0483 $ 17.50+.50/0

moted intramolecular carbonyl ene reactions of unsaturated aldehydes have been thoroughly investigated,[6,7] apparently no example exists of a Lewis acid mediated or a thermal intramolecular carbonyl ene reaction of an α-oxo ester. A number of synthetic studies have been reported in which the synthetic potential of the oxy-Cope rearrangement was combined with different types of, mostly anionic, transformations to give domino reactions.[8] In particular, a reported sequence of a ring-expanding oxy-Cope rearrangement followed by a transannular carbonyl ene reaction is related to our approach.[9]

Our initial objective was to control the ring size of the desired carbocycles by inducing ene reactions of different types. This task should be achievable by an appropriate setup of the substrate structure; this is an inherent strength of our convergent synthesis of the starting material. We preferred to utilize thermal reaction conditions in order to avoid the employment of large amounts of Lewis acids for the ene reaction, or of donor solvents for the oxy-Cope rearrangement.

Results and Discussion

The Sequential Ester Dienolate [2,3]-Wittig/Oxy-Cope Rearrangement/Type-I Carbonyl Ene Reaction

The substrates **1a**−**i** for the dienolate [2,3]-Wittig rearrangement were synthesized in multigram quantities using the previously reported aldol condensation strategy.[3,10] The domino dienolate [2,3]-Wittig rearrangement/oxy-Cope rearrangement was accomplished by treating the esters **1a**−**c** with lithium diisopropylamide (LDA) in THF at −78 °C, followed by warming the reaction mixture to room temperature. The oxy-Cope rearrangement proceeded at room temperature and product formation could conveniently be followed by TLC. After an aqueous workup procedure, the crude α-oxo esters **5a**−**c** were used for the thermal intramolecular type-I carbonyl ene reaction to afford the corresponding isopropyl cyclopentanecarboxylates **6a**−**c** as mixtures of diastereomers, along with the α-oxo esters **5a**−**c** (Scheme 2, Table 1).

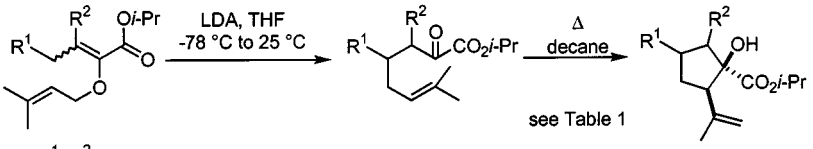
The ratio of products for the transformation depicted in Scheme 2 is apparently thermodynamically controlled.[11] Table 1 indicates that the amount of remaining α-oxo ester **5a**−**c** is independent of the reaction time and reaction temperature. Furthermore, heating different diastereomeric mixtures of the isopropyl cyclopentanecarboxylate **6c** to 180 °C affords the same ratio of products as was obtained from the ene reaction of the α-oxo ester **5c**.

Finally, it should be emphasized that, up to this point, the presence of a geminal dimethyl group in the 3-oxy-substituted 1,5-hexadiene ($R^E = R^Z$ = methyl in **4-Li**) is a prerequisite for the occurrence of a *domino* ester dienolate [2,3]-Wittig rearrangement/oxy-Cope rearrangement.

The Sequential Ester Dienolate [2,3]-Wittig Rearrangement/ Domino Oxy-Cope Rearrangement/Type-I Ene Reaction

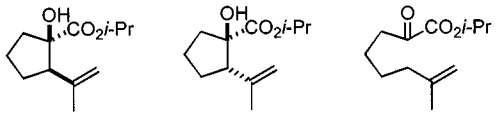
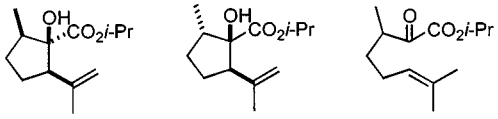
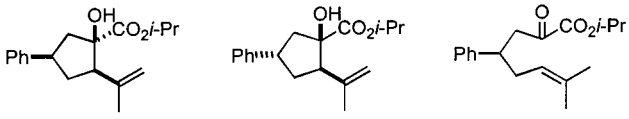
The ester dienolate [2,3]-Wittig rearrangement of the α-hex-2-enyloxy-substituted α,β-unsaturated esters **1d**−**f** afforded the 3-alkoxycarbonyl-3-hydroxy-substituted 1,5-hexadienes **3d**−**f** in high yields and with moderate to high diastereoselectivities (Scheme 3, Table 2, Entries 1−3).

Heating the 1,5-hexadienes **3d**−**f** in decane afforded the isopropyl cyclopentanecarboxylates **6d**−**f** as mixtures of diastereomers and double-bond isomers (Scheme 3, Table 3). In contrast to the type-I ene reaction of the α-oxo esters **5a**−**c** with trisubstituted double bonds, it was possible to transform the α-oxo esters **5d**−**f**, with disubstituted double bonds, completely into the type-I ene reaction products **6d**−**f**. As expected, the reaction temperatures and the reaction times were pivotal for the complete consumption of the intermediate α-oxo esters **5d**−**f** (Table 3). The necessary reaction times for completion of the ene reactions in turn depended on the substituent pattern on the α-oxo esters **5d**−**f** (Table 3). The relative configurations of the cyclic products were determined by NOESY experiments. Unfortunately, we were unable to assign the double-bond configurations because of overlapping ^{1}H NMR signals. In order to simplify the NMR spectra and to prove the existence of double-bond isomers unequivocally, the double bonds of the ene reaction products **6d**−**f** were hydrogenated to afford the corresponding saturated isopropyl cyclopentanecarboxylates **8d**−**f** (Table 3). We briefly investigated the thermal

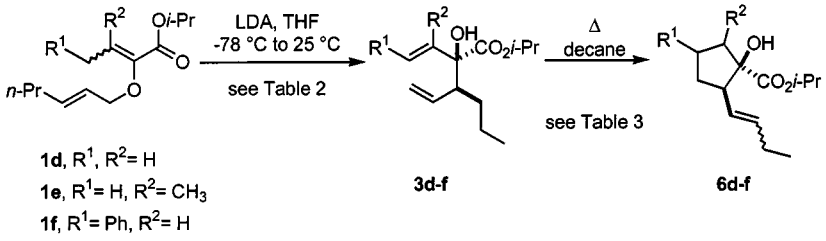


Scheme 2. The sequential ester dienolate [2,3]-Wittig/oxy-Cope rearrangement/type-I ene reaction

Table 1. Conditions and products for the dienolate [2,3]-Wittig/oxy-Cope rearrangement/type-I ene reaction

substrate	R^1	R^2	product	ene reaction conditions [a]	product structures [b] yield from **1** [%] (ratio) [c]
1a	H	H	**6a**		
				180 °C, 3 d	66 (62:2:36)
				180 °C, 7 d	68 (63:6:31)
1b	CH_3	H	**6b**		
				180 °C, 40 h	78 (74:13:13)
				180 °C, 5 d	78 (73:12:15)
1c	H	Ph	**6c**		
				180 °C, 21 h	83 (53:35:12)
				200 °C, 15 h	88 (53:35:12)

[a] Reactions performed in decane using a pressure tube with a threaded plug. – [b] Racemic products, relative configuration assigned on the basis of NOESY experiments. – [c] Isolated yield after column chromatography, α-oxo ester **5** can be separated.



Scheme 3. The sequential ester dienolate [2,3]-Wittig/oxy-Cope rearrangement/type-I ene reaction

Table 2. The dienolate [2,3]-Wittig rearrangement

Entry	Substrate	Substrate (*Z*)/(*E*)	R^1	R^2	Product	Yield[a] [%]	*dr*[b] *syn*/*anti*
1	**1d**	61:39	H	H	**3d**	87	91:9
2	**1e**	–[c]	H	CH_3	**3e**	88	98:2
3	**1f**	97:3	Ph	H	**3f**	91	79[d]:21[d]
4	**1g**	59:41	H	H	**3g**	82	–
5	**1h**	–[c]	H	CH_3	**3h**	72	–
6	**1i**	95:5	Ph	H	**3i**	89	–

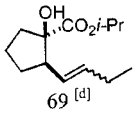
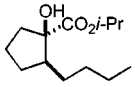
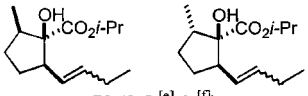
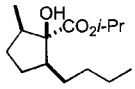
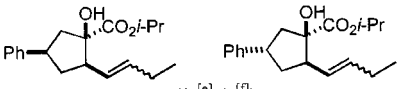
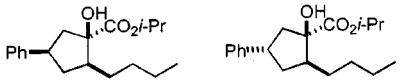
[a] Isolated yield after chromatographic purification. – [b] Determined from ^{1}H NMR spectra. – [c] Substrate used as a 3:1 mixture of the β,γ- and α,β-unsaturated esters. – [d] Exclusively (*E*)-configured.

epimerization of the isopropyl cyclopentanecarboxylates (1*R**,2*R**,5*R**)- and (1*R**,2*R**,5*S**)-**6e**. The (1*R**,2*R**,5*R**)-**6e** diastereomer did not isomerize or decompose when heated to 180 °C in decane for 4 d. On the other hand, heating the (1*R**,2*R**,5*S**)-**6e** diastereomer to 180 °C resulted in a slow epimerization at the C-5 carbon atom. These results, along with the observed ene reaction diastereoselectivities, indicate that the (1*R**,2*R**,5*R**)-**6e** diastereomer is the kinetically and thermodynamically favored product.

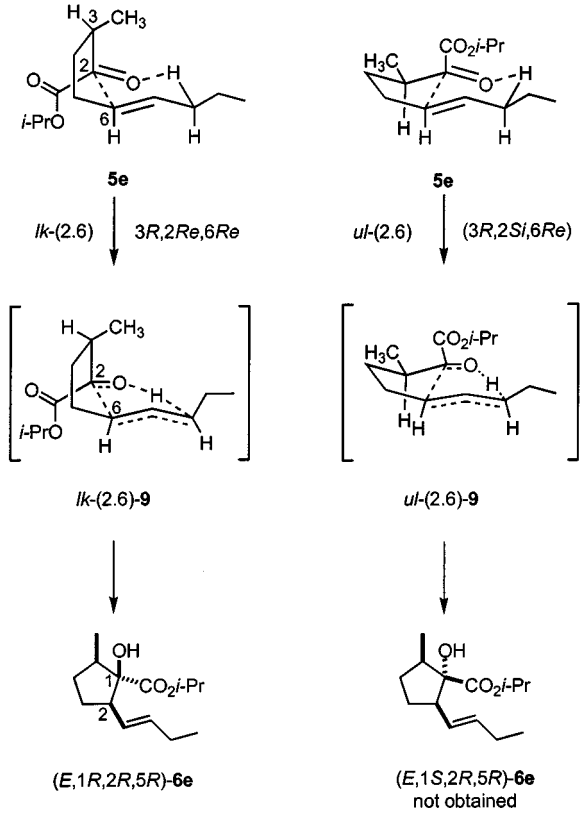
The type-I ene reactions of the α-oxo esters **5a**–**f** proceed with very high simple diastereoselectivities, but low induced diastereoselectivities. The most significant stereochemical feature is the complete simple diastereoselectivity for the formation of the 2,3-*cis*-substituted products. This result is in agreement with the general stereochemical trend for thermal and Lewis acid mediated intramolecular ene reactions of 1,6-hexadienes and 5,6-unsaturated aldehydes to form *cis*-configured products.[6,7h,7l] On the basis of the results of a theoretical study of the transition structures of ene reactions by Houk,[12] we propose the depicted transition structures *lk*-(2.6)-**9** and *ul*-(2.6)-**9** to explain the simple diastereoselectivity (Scheme 4).

Following Houk's argument, we believe that the three-carbon-atom tether between C-2 and C-6 destabilizes the *ul*-(2.6)-**9** transition structure, because of the distortion that results from the formal *trans* annulation of the cyclopentane and the "stretched cyclopentane" in the bicyclo[3.3.0]oct-

Table 3. Conditions and products for the dienolate [2,3]-Wittig/oxy-Cope rearrangement/type-I ene reaction and the subsequent hydrogenation

substrate	R^1	R^2	product	ene reaction conditions [a]	product structures [b] yield from **1** [%] (ratio) [c]	hydrogenation product	product structures yield [%] ratio
1d	H	H	**6d**	180 °C, 7 d	 69 [d]	**8d**	 86
				180 °C, 4 d	74, 9 % of α-keto ester **5d**		
1e	CH_3	H	**6e**	180 °C, 7 d	 78 (2.5 [e]:1 [f])	**8e**	 88 [g]
				170 °C, 7 d	80 (3:1), 10 % of α-keto ester **5e**		
1f	H	Ph	**6f**	180 °C, 3 d	 87 (3 [e]:1 [f])	**8f**	 92 (3:1)
				180 °C, 40 h	82 (3:1)		

[a] Reactions performed in decane using a pressure tube with a threaded plug. – [b] Racemic products, relative configuration assigned on the basis of NOESY experiments. – [c] Ratio determined from ^{1}H NMR spectra. Isolated yield after column chromatography. – [d] 7:3 mixture of double-bond isomers. – [e] 3:1 mixture of double-bond isomers. – [f] 2:1 mixture of double-bond isomers. – [g] The diastereomeric ene reaction products were separated by column chromatography but only the (1*R**,2*R**,5*R**) diastereomer was hydrogenated.



Scheme 4. Proposed transition structures for the type-I ene reaction of the α-oxo ester **5e**

ane-type transition structure *ul*-(2.6)-**9** (Scheme 4). The transition structure *lk*-(2.6)-**9** resembles a less strained *cis*-annulated bicyclo[3.3.0]octane and, consequently, leads to the exclusive formation of the 1,2-*cis*-configured product of the thermal ene reaction.

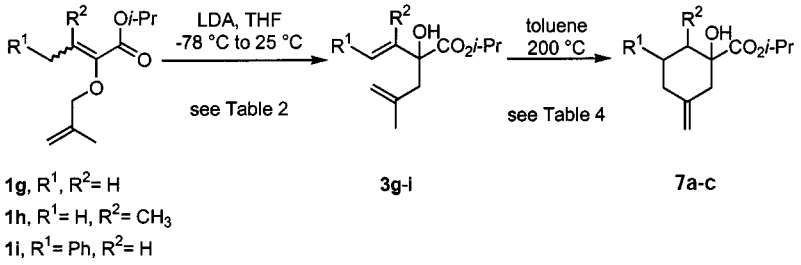
The Sequential Ester Dienolate [2,3]-Wittig Rearrangement/Domino Oxy-Cope Rearrangement/Type-II Ene Reaction

The 3-alkoxycarbonyl-3-hydroxy-5-methyl-substituted 1,5-hexadienes **3g–i** are accessible on a gram scale by means of the dienolate [2,3]-Wittig rearrangement of the esters **1g–i** (Scheme 5, Table 2, Entries 4–6).

The domino oxy-Cope rearrangement/ene reactions were performed by heating the 1,5-hexadienes **3g–i** in toluene, and afforded the substituted cyclohexanecarboxylates **7a–c** as single diastereomers (Table 4). No further attempts were made to optimize the procedure by changing the solvent or the reaction temperature.

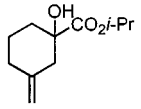
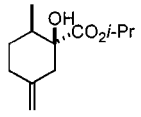
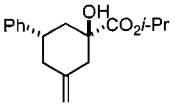
The high induced diastereoselectivities can be explained by a bicyclic transition state structure **10**, in which R^1 and R^2 are in equatorial positions (Scheme 6).

Nakai has shown that with (–)-8-phenylmenthol as a chiral auxiliary, the ester enolate [2,3]-Wittig rearrangement proceeds with high simple and auxiliary-induced diastereoselectivities.[13] It is also well known that the Lewis acid mediated *inter*molecular ene reaction of pyruvates and glyoxylates can be performed diastereoselectively if covalently bonded, cyclohexyl-based chiral auxiliaries are employed.[6] Therefore, we attempted to perform an asymmetric ester *di*enolate [2,3]-Wittig/oxy-Cope rearrangement/type-II ene reaction by using (–)-8-phenylmenthol as a chiral auxiliary. Unfortunately, and somewhat surprisingly, neither the dienolate [2,3]-Wittig rearrangement nor the thermal type-II ene reaction proceeded with any significant auxiliary-induced



Scheme 5. The sequential ester dienolate [2,3]-Wittig/oxy-Cope rearrangement/type-II ene reaction

Table 4. Conditions and products for the dienolate [2,3]-Wittig/oxy-Cope rearrangement/type-II ene reaction

sub-strate	R^1	R^2	product	ene reaction [a] conditions	product structures [b] yield from **1** [%] [c]
1g	H	H	**7a**	200 °C, 14.5 h	 59
1h	CH_3	H	**7b**	200 °C, 2 d	 51
1i	H	Ph	**7c**	200 °C, 19 h	 76

[a] Reaction performed in toluene using a pressure tube with threaded plug. Temperature refers to oil bath temperature. – [b] Racemic products, relative configuration assigned based on NOESY experiments. – [c] Non-optimized, isolated yield after column chromatography.

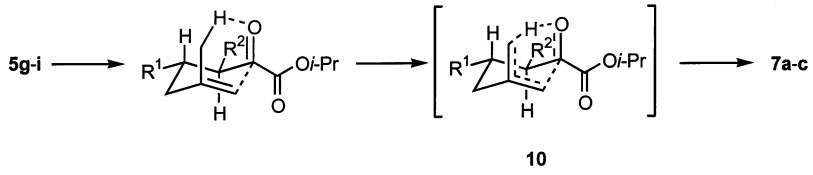
diastereoselectivity (Scheme 7). This result clearly indicates that alternative approaches toward an asymmetric reaction sequence have to be pursued.

Further work aimed at extending the method to the synthesis of bicyclic carbocycles and instituting an asymmetric reaction sequence is currently underway.

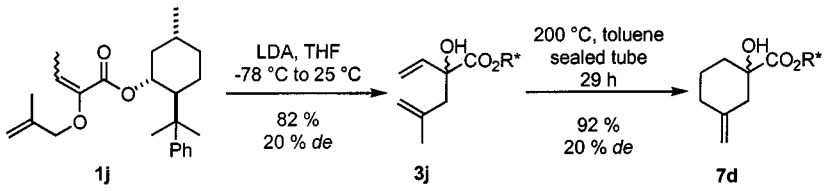
Experimental Section

General: All reactions were performed in septum-sealed, flame-dried flasks under argon. Solvents, reagents, and substrates were transferred by means of syringes. All solvents were dried by standard methods. Reagents were used as purchased unless otherwise noted. Commercial decane (99+%) was used as purchased without further purification. Commercial *n*BuLi solutions in hexanes were titrated following Kofron's procedure.[14] Crude products were purified by column chromatography using silica gel (0.040–0.063 mm) and mixtures of ethyl acetate and heptane. – ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AC 300 or a DRX 500 in $CDCl_3$. The terms H^{major} and H^{minor} are used to indicate separated proton resonance for major or minor diastereomers. The assignment of NMR resonance is based on COSY, HSQC, and NOESY experiments. – IR spectra were recorded with a Nicolet 205 FT-IR spectrometer. – Elemental analyses were obtained with a Carlo Erba CHN-S analyzer.

General Procedure I for the Domino Dienolate [2,3]-Wittig/Oxy-Cope Rearrangement: Lithium diisopropylamide was prepared by



Scheme 6. Proposed transition structures for the type-II ene reaction



Scheme 7. The attempted auxiliary-controlled domino oxy-Cope rearrangement/type-II ene reaction proved to be inefficient

the addition of *n*-butyllithium (1.1 equiv.) to a solution of diisopropylamine (1.2 equiv.) in THF (2 mL/mmol of ester) at −78 °C. After stirring for 30 min at −78 °C, a cooled (−78 °C) solution of the ester **1a**−**c** (1 equiv.) in THF (2 mL/mmol of ester) was added. After stirring for 30 min at −78 °C, the cooling bath was removed and the reaction mixture was allowed to warm to room temperature. The reaction mixture was then stirred at ambient temperature until TLC indicated the completion of product formation (2−4 h). The reaction was quenched by the addition of saturated aqueous NH_4Cl solution and then diluted with water and CH_2Cl_2. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 ×). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuum. The crude product oil was purified by column chromatography (ethyl acetate/heptane) or used without further purification.

General Procedure II for the Thermal Ene Reaction and for the Thermal Domino Oxy-Cope Rearrangement/Carbonyl Ene Reaction: The crude or purified α-oxo esters or 1,5-hexadienes were dissolved in toluene or decane (0.5 M) in a pressure tube with a threaded plug, equipped with a magnetic stirring bar. The sealed pressure tube was heated in an oil bath to the desired temperature for the appropriate time. The solvent was then removed in vacuum and the crude product oil was purified by column chromatography (ethyl acetate/heptane).

General Procedure III for the Dienolate [2,3]-Wittig Rearrangement: Lithium diisopropylamide was prepared by the addition of *n*-butyllithium (1.1 equiv.) to a solution of diisopropylamine (1.2 equiv.) in THF (2 mL/mmol of ester) at −78 °C. After stirring for 30 min at −78 °C, a cooled (−78 °C) solution of the ester **1d**−**j** (1 equiv.) in THF (2 mL/mmol of ester) was added. The reaction mixture was slowly warmed to ambient temperature overnight. Alternatively, the dry ice cooling bath was removed after 30 min and the reaction mixture was allowed to warm to ambient temperature. The reaction was then quenched by the addition of saturated aqueous NH_4Cl and then diluted with water and CH_2Cl_2. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 ×). The organic phase was dried ($MgSO_4$) and concentrated. The crude product could be purified by column chromatography (ethyl acetate/heptane).

(1*R,2*R**)-Isopropyl 1-Hydroxy-2-isopropenylcyclopentanecarboxylate (6a):** Following general procedure I, the ester **1a** (455 mg, 2.14 mmol) was treated with LDA [prepared in situ from diisopropylamine (2.57 mmol) and *n*BuLi (2.35 mmol)] to afford the crude isopropyl 7-methyl-2-oxooct-6-enecarboxylate **5a**. Following general procedure II, the crude α-oxo ester **5a** was dissolved in decane under argon, filtered into the reaction tube under argon and heated to 180 °C for 7 d to afford, after chromatographic purification, the cyclopentanecarboxylate (**6a**) (212 mg, 47%) as a 91:9 mixture with the (1*R**,2*S**) diastereomer and isopropyl 7-methyl-2-oxooct-6-enecarboxylate (**5a**) (101 mg, 22%) as slightly yellow oils. − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26 (d, *J* = 6.3 Hz, 3 H, O*i*Pr-CH_3), 1.27 (d, *J* = 6.3 Hz, 3 H, O*i*Pr-C*H*$_3$), 1.69 [s, 3 H, C(C*H*$_3$)=CH_2], 1.80−1.95 (m, 5 H) and 2.18−2.26 (m, 1 H, 3-, 4-, 5-CH_2), 2.80 (dd, J_1 = 11.4, J_2 = 6.9 Hz, 1 H, 2-CH), 2.88 (s, 1 H, OH), 4.79 [s, 1 H, C(CH_3)=C*H*$_2$], 4.91 [s, 1 H, C(CH_3)=C*H*$_2$], 5.06 (qq, J_1 = J_2 = 6.3 Hz, 1 H, O*i*Pr-C*H*). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.7 (O*i*Pr-CH_3), 23.0 [C(*C*H$_3$)=CH_2], 22.3, 28.7, 39.2 (3-, 4-, 5-CH_2), 69.3 (O*i*Pr−CH), 81.7 (C-1), 113.1 [C(CH_3)=C*H*$_2$], 142.8 [**C**(CH_3)=CH_2], 176.2 (C=O). − $C_{12}H_{20}O_3$ (212.3): calcd. C 67.81, H 9.50; found C 67.86, H 9.92.

Isopropyl (1*R,2*R**,5*R**)- and (1*R**,2*R**,5*S**)-1-Hydroxy-2-isopropenyl-5-methylcyclopentanecarboxylate (6b):** Following general procedure I, the ester **1b** (453 mg, 2 mmol) was treated with LDA [prepared in situ from diisopropylamine (2.4 mmol) and *n*BuLi (2.2 mmol)] to afford the crude isopropyl 3,7-dimethyl-2-oxooct-6-enecarboxylate (**5b**). Following general procedure II, the crude α-oxo ester **5b** was dissolved in decane under argon, filtered into the reaction tube under argon and heated to 180 °C for 40 h to afford, after chromatographic purification, the (1*R**,2*R**,5*R**)-cyclopentanecarboxylate **6b** (355 mg, 78%) as a 74:13:13 mixture with the (1*R**,2*R**,5*S**) diastereomer and isopropyl 7-methyl-2-oxooct-6-enecarboxylate (**5b**) as slightly yellow oils. The products were separated by column chromatography (ethyl acetate/heptane, 10:1) to afford 33 mg of the α-oxo ester **5b**, 213 mg of the (1*R**,2*R**,5*R**) diastereomer and 39 mg of the (1*R**,2*R**,5*S**) diastereomer. − **(1*R**,2*R**,5*R**) Diastereomer:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 6.8 Hz, 3 H, 5-CH_3), 1.27 (d, *J* = 6.2 Hz, 3 H, O*i*Pr-C*H*$_3$), 1.29 (d, *J* = 6.2 Hz, 3 H, O*i*Pr-C*H*$_3$), 1.41−1.59 (m, 1 H, 4-CH_2), 1.72 [s, 3 H, C(C*H*$_3$)=CH_2], 1.82−2.03 (m, 3 H, 4-CH_2 and 3-CH_2), 2.34−2.48 (m, 1 H, 5-CH), 2.88 (s, 1 H, OH), 3.02 (dd, J_1 = J_2 = 9.1 Hz, 1 H, 2-CH), 4.80 [s, 1 H, C(CH_3)=C*H*$_2$], 4.89 [s, 1 H, C(CH_3)=C*H*$_2$], 5.09 (qq, J_1 = J_2 = 6.2 Hz, 1 H, O*i*Pr-C*H*). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.7 (5-CH_3), 21.7 (O*i*Pr-*C*H$_3$), 22.7 [C(*C*H$_3$)=CH_2], 26.7 (3-CH_2), 29.9 (4-CH_2), 43.7 (5-CH), 54.7 (2-CH), 69.2 (O*i*Pr-*C*H), 83.7 (C-1), 112.6 [C(CH_3)=*C*H$_2$], 143.4 [*C*(CH_3)=CH_2], 175.7 O). − IR: ṽ = 3520, 3090−2875, 1720 cm^{-1}. − $C_{13}H_{22}O_3$ (226.3): calcd. C 68.99, H 9.80; found C 69.07, H 10.12. − **(1*R**,2*R**,5*S**) Diastereomer:** ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 6.9 Hz, 3 H, 5-CH_3), 1.29 (d, *J* = 6.3 Hz, 6 H, O*i*Pr-C*H*$_3$), 1.69 [s, 3 H, C(C*H*$_3$)=CH_2], 1.22−1.32 (m, partially covered, 1 H) and 1.92−1.99 (m, 1 H, 4-CH_2), 1.77−1.89 (m, 2 H, 3-CH_2), 2.14 (m, 1 H, 5-CH), 2.96 (dd, J_1 = 11.4, J_2 = 6.9 Hz, 1 H, 2-CH), 3.07 (s, 1 H), 4.75 [s, 1 H, C(CH_3)=C*H*$_2$], 4.87 [s, 1 H, C(CH_3)=C*H*$_2$], 5.11 (qq, J_1 = J_2 = 6.3 Hz, 1 H, O*i*Pr-C*H*). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.2 (5-CH_3), 21.9 (O*i*Pr-*C*H$_3$), 22.8 [C(*C*H$_3$)=CH_2], 28.5 (3-CH_2), 32.7 (4-CH_2), 48.1 (5-CH), 54.3 (2-CH), 69.5 (O*i*Pr-*C*H), 84.2 (C-1), 112.5 [C(CH_3)=*C*H$_2$], 144.0 [*C*(CH_3)=CH_2], 175.7 (C=O).

Isopropyl (1*R,2*R**,4*R**)- and (1*R**,2*R**,4*S**)-1-Hydroxy-2-isopropenyl-4-phenylcyclopentanecarboxylate (6c):** Following general procedure I, the ester **1c** (577 mg, 2 mmol) was treated with LDA [prepared in situ from diisopropylamine (2.4 mmol) and *n*BuLi (2.2 mmol)] to afford the crude isopropyl 7-methyl-2-oxo-4-phenyloct-6-enecarboxylate (**5c**). Following general procedure II, the crude α-oxo ester **5b** was dissolved in decane under argon, filtered into the reaction tube under argon and heated to 180 °C for 40 h to afford, after chromatographic purification, the cyclopentanecarboxylate **6c** (412 mg, 71%) and the α-oxo ester **5c** (68 mg, 12%) as slightly yellow oils. Spectral data reported for a mixture of diastereomers (1*R**,2*R**,4*R**)-**6c**/(1*R**,2*R**,4*S**)-**6c** = 60:40. − **(1*R**,2*R**,4*R**) Diastereomer:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (d, *J* = 6.2 Hz, 3 H, O*i*Pr-C*H*$_3$), 1.32 (d, *J* = 6.2 Hz, 3 H, O*i*Pr-C*H*$_3$), 1.74 [s, 3 H, C(C*H*$_3$)=CH_2], 2.01 (dd, J_1 = 14.3, J_2 = 8.4 Hz, 1 H, 5-CH_2), 2.11−2.21 (m, 2 H, 3-CH_2), 2.77 (dd, J_1 = 14.3, J_2 = 10.1 Hz, 1 H, 5-CH_2), 3.00 (dd, J_1 = 10.9, J_2 = 8.0 Hz, 1 H, 2-CH), 3.10 (s, 1 H, OH), 3.28 (m, 1 H, 4-CH), 4.83 [s, 1 H, C(CH_3)=C*H*$_2$], 4.97 [s, 1 H, C(CH_3)=C*H*$_2$], 5.11 (qq, J_1 = J_2 = 6.3, 1 H, O*i*Pr-C*H*), 7.15−7.38 (m, 5 H, aryl-H). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.6 (O*i*Pr-*C*H$_3$), 22.8 [C(*C*H$_3$)=CH_2], 38.7 (3-CH_2), 42.8 (4-CH), 47.7 (5-CH_2), 55.9 (2-CH), 69.6 (O*i*Pr-*C*H), 81.3 (1-C), 113.4 [C(CH_3)=*C*H$_2$], 126.0, 127.2, 128.3, 142.2, 144.9 [aryl-C and *C*(CH_3)=CH_2], 176.1 (C=O). − **(1*R**,2*R**,4*S**) Diastereomer:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (d, *J* = 6.2 Hz, 3 H, O*i*Pr-CH_3), 1.31 (d, *J* = 6.2 Hz, 3 H, O*i*Pr-C*H*$_3$), 1.76 [s, 3 H, C(C*H*$_3$)=CH_2], 1.94−2.06 (m, 1 H, 3-CH_2), 2.28−2.37 (m,

2 H, 5-CH_2), 2.50 (ddd, J_1 = 13.2, J_2 = J_3 = 10.5 Hz, 1 H, 3-CH_2), 3.08 (s, 1 H, OH), 3.28 (m, 1 H, 2-CH), 3.60 (m, 1 H, 4-CH), 4.87 [s, 1 H, C(CH_3)=CH_2], 4.97 [s, 1 H, C(CH_3)=CH_2], 5.17 (qq, J_1 = J_2 = 6.3 Hz, 1 H, O*i*Pr-C*H*), 7.15−7.38 (m, 5 H, aryl-H). − ^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.4 (O*i*Pr-*C*H_3), 22.9 [C(*C*H_3)=CH_2], 36.4 (3-CH_2), 41.6 (4-CH), 47.4 (5-CH_2), 54.2 (2-CH), 69.6 (O*i*Pr-*C*H), 82.8 (1-C), 113.3 [C(CH_3)=*C*H_2], 126.0, 126.9, 128.4, 142.7, 146.1 [aryl-C and *C*(CH_3)=CH_2), 175.3 (C=O). − IR: ṽ = 3485, 3085−2875, 1720 cm^{-1}. − $C_{18}H_{24}O_3$ (288.4): calcd. C 74.97, H 8.39; found C 75.14, H 8.77.

Isopropyl (1*R,2*R**)-2-[(*E*/*Z*)-But-1-enyl]-1-hydroxycyclopentanecarboxylate (6d):** Following general procedure III, the ester **1d** (453 mg, 2 mmol) was treated with LDA [prepared in situ from diisopropylamine (2.4 mmol) and *n*BuLi (2.2 mmol)] to afford isopropyl 2-hydroxy-3-propyl-2-vinylpent-4-enecarboxylate (**3d**) (395 mg, 87%) as a colorless oil after chromatographic purification [diastereomeric ratio (2*R**,3*S**)/(2*R**,3*R**) = 91:9]. Following general procedure II, the 1,5-hexadiene **3d** (395 mg, 1.75 mmol) was dissolved in decane and heated for 7 d at 180 °C (oil bath temperature). The solvent was then evaporated under reduced pressure and the crude product was purified by chromatography to afford isopropyl 2-[(*E*/*Z*)-but-1-enyl]-1-hydroxycyclopentanecarboxylate (**6d**) (313 mg, 79%) as a colorless oil. NMR-spectroscopic data determined from a 69:31 mixture of double-bond isomers. − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.92 (t, J = 7.6 Hz, 3 H^{minor}, 4′-CH_3), 0.94 (t, J = 7.6 Hz, 3 H^{major}, 4′-CH_3), 1.246 (d, J = 6.3 Hz, 6 H^{major}, O*i*Pr-CH_3), 1.253 (d, J = 6.3 Hz, 6 H^{minor}, O*i*Pr-CH_3), 1.63−2.07 (m, 7 H, 3-, 4-, 5-, 3′-CH_2), 2.14−2.26 (m, 1 H, 4-CH_2), 2.68 (ddd, J_1 = 10.6 Hz, J_2 = J_3 = 8.4 Hz, 1 H^{major}, 2-CH), 2.92 (s, 1 H^{major}, OH), 3.01−3.08 (m, partially covered, 1 H^{minor}, 2-CH), 3.03 (s, 1 H^{minor}, OH), 5.00−5.09 (m, 1 H, O*i*Pr-C*H*), 5.29−5.37 (m, 1 H, 2′-CH), 5.43−5.52 (m, 1 H, 3′-CH). − ^{13}C NMR (125 MHz, $CDCl_3$, major isomer) δ = 13.9 (4′-CH_3), 21.9 (O*i*Pr-*C*H_3), 22.6 (5-CH_2), 25.7 (3′-CH_2), 30.2 (3-CH_2), 37.9 (4-CH_2), 53.0 (2-CH), 69.2 (O*i*Pr-*C*H), 83.4 (C-1), 126.0 and 135.3 (1′-, 2′-CH), 175.9 (C=O). − ^{13}C NMR (125 MHz, $CDCl_3$, minor isomer) δ = 14.6 (4′-CH_3), 21.2 (3′-CH_2), 21.8 (O*i*Pr-CH_3), 23.0 (5-CH_2), 31.5 (3-CH_2), 38.6 (4-CH_2), 47.3 (2-CH), 69.5 (O*i*Pr-C*H*), 83.4 (C-1), 126.2 and 134.2 (1′-, 2′-CH), 176.1 (C=O). − IR: ṽ = 3530, 2980−2875, 1725 cm^{-1}. − $C_{13}H_{22}O_3$ (226.3): calcd. C 68.99, H 9.80; found C 69.14, H 10.19.

Isopropyl (1*R,2*R**)-2-Butyl-1-hydroxycyclopentanecarboxylate (8d):** Isopropyl (1*R**,2*R**)-2-[(*E*/*Z*)-but-1-enyl]-1-hydroxycyclopentanecarboxylate (**6d**) (257 mg, 1.14 mmol) was dissolved in 2-propanol (6 mL). 10% Pd/C (60.4 mg, 0.057 mmol Pd) was added and the reaction mixture was stirred under H_2 (balloon) for 2 d at ambient temperature. The solvent was then removed and the crude product was purified by column chromatography (ethyl acetate/heptane, 5:1) to afford the ester **8d** as a colorless oil (221 mg, 86%). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (t, J = 6.2 Hz, 3 H), 1.13−1.52 (m, partially covered, 5 H), 1.268 (d, J = 6.2 Hz, 3 H), 1.273 (d, J = 6.2 Hz, 3 H), 1.63−1.98 (m, 5 H), 2.04−2.21 (m, 2 H), 3.11 (s, 1 H), 5.08 (qq, J_1 = J_2 = 6.3 Hz, 1 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 21.6, 22.4, 22.8, 28.0, 30.4, 39.3, 48.9, 69.1, 82.3, 176.9. − IR: ṽ = 3525, 2960−2860, 1720 cm^{-1}. − $C_{13}H_{24}O_3$ (228.3): calcd. C 68.38, H 10.59; found C 68.18, H 10.86.

Isopropyl (1*R,2*R**,5*R**)- and (1*R**,2*R**,5*S**)-2-[(*E*/*Z*)-But-1-enyl]-1-hydroxy-5-methylcyclopentanecarboxylate (6e):** Following general procedure III, the ester **1e** (2.23 g, 9.3 mmol) was treated with LDA [prepared in situ from diisopropylamine (11.1 mmol) and *n*BuLi (10.2 mmol)] to afford isopropyl 2-hydroxy-2-isopropenyl-3-propylpent-4-enecarboxylate (**3e**) (1.96 g, 88%) as a colorless oil after chromatographic purification [diastereomeric ratio (2*S**,3*S**)/(2*S**,3*R**) = 98:2]. Following general procedure II, the 1,5-hexadiene **3e** (481 mg, 2 mmol) was dissolved in decane and heated for 7 d at 180 °C (oil bath temperature). The solvent was then evaporated under reduced pressure and the crude product was purified by chromatography to afford isopropyl (1*R**,2*R**,5*R**)-2-[(*E*/*Z*)-but-1-enyl]-1-hydroxy-5-methylcyclopentanecarboxylate (**6e**) (314 mg, 65%, 3:1 mixture of double-bond isomers) and the (1*R**,2*R**,5*S**) diastereomer (117 mg, 24%, 2:1 mixture of double-bond isomers) as colorless oils. NMR-spectroscopic data determined from a mixture of double bond isomers. − **(1*R**,2*R**,5*R**) Diastereomer:** ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87 (d, J = 6.9 Hz, 3 H, 5-CH_3), 0.92 (t, J = 7.6 Hz, 3 H, 4′-CH_3), 1.239 (d, J = 6.3 Hz, 6 H^{major}, O*i*Pr-CH_3) 1.241 (d, J = 6.3 Hz, 6 H^{minor}, O*i*Pr-CH_3), 1.42−1.50 (m, 1 H, 4-CH_2), 1.65−1.74 (m, 1 H, 3-CH_2), 1.82−2.07 (m, 4 H, 3-, 4-, 3′-CH_2), 2.32−2.43 (m, 1 H, 5-CH), 2.84 (td, J_1 = 9.3, J_2 = 9.0 Hz, 2-CH), 2.89 (s, 1 H^{major}, OH), 2.97 (s, 1 H^{minor}, OH), 3.21 (td, J_1 = 9.8, J_2 = 9.7 Hz, 1 H^{minor}, 2-CH), 5.04 (qq, J_1 = J_2 = 6.2 Hz, 1 H^{minor}, O*i*Pr-C*H*), 5.08 (qq, J_1 = J_2 = 6.3 Hz, 1 H^{major}, O*i*Pr-C*H*), 5.34−5.48 (m, 2 H, 2′-, 3′-CH). − IR: ṽ = 3530, 2960−2875, 1720 cm^{-1}. − $C_{14}H_{24}O_3$ (240.3): calcd. C 69.96, H 10.06; found C 69.64, H 10.36. − **(1*R**,2*R**,5*S**) Diastereomer:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91−1.01 (series of d and t, 6 H, 5-CH_3 and 4′CH_3), 1.26−1.32 (series of d, 6 H, O*i*Pr-CH_3), 1.57−1.73 (m, 1 H, 3-CH_2), 1.79−1.92 (m, 1 H, 3-CH_2), 1.95−2.10 (m, 4 H, 3′-, 4-CH_2), 2.10 −2.22 (m, 1 H, 5-CH), 2.89 (ddd, J_1 = 11, J_2 = J_3 = 7.5 Hz, 1 H^{major}, 2-CH), 2.98 (br s, 1 H, OH), 3.23 (ddd, J_1 = 10.7, J_2 = 9.1, J_3 = 7.5 Hz, 1H^{minor}, 2-CH), 5.10 (qq, J_1 = J_2 = 6.4 Hz, 1 H, O*i*Pr-C*H*), 5.33−5.55 (m, 2 H, 2′-, 3′CH). − ^{13}C NMR (125 MHz, $CDCl_3$, major isomer): δ = 13.8 and 17.2 (4′-CH_3 and 5-CH_3), 21.8 (O*i*Pr-*C*H_3), 25.7 (3′-CH_2), 30.1 (3-CH_2), 32.5 (4-CH_2), 46.7 (5-CH), 50.3 (2-CH), 69.2 (O*i*Pr-*C*H), 85.5 (C-1), 127.0 (1′-CH), 134.4 (2′-CH), 175.1 (C=O). − ^{13}C NMR (125 MHz, $CDCl_3$, minor isomer): δ = 14.6 and 16.5 (4′-CH_3 and 5-CH_3), 21.0 (3′-CH_2), 21.8 (O*i*Pr-*C*H_3), 31.5 (3-CH_2), 32.9 (4-CH_2), 45.0 (2-CH), 47.4 (5-CH), 69.5 (O*i*Pr-*C*H), 127.3 (1′-CH), 133.3 (2′-CH), 175.4 (C=O).

Isopropyl (1*R,2*R**,5*R**)-2-Butyl-1-hydroxy-5-methylcyclopentanecarboxylate (8e):** Isopropyl (1*R**,2*R**5*R**)-2-[(*E*/*Z*)-but-1-enyl]-1-hydroxy-5-methylcyclopentanecarboxylate (**6e**) (300 mg, 1.25 mmol) was dissolved in 2-propanol (7.5 mL). 10% Pd/C (66.5 mg, 0.063 mmol Pd) was added and the reaction mixture was stirred under H_2 (balloon) for 3 d at ambient temperature. The solvent was then removed and the crude product was purified by column chromatography (ethyl acetate/heptane, 10:1) to afford the ester **8e** as a colorless oil (264 mg, 88%). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.855 (t, J = 7.0 Hz, 3 H), 0.864 (d, J = 6.8 Hz, 3 H), 1.11−1.48 (m, partially covered, 6 H), 1.26 (d, J = 6.3 Hz, 3 H), 1.27 (d, J = 6.3 Hz, 3 H), 1.79−1.99 (m, 2 H), 2.23−2.37 (m, 2 H), 2.96 (s, 1 H), 5.10 (qq, J_1 = J_2 = 6.3 Hz, 1 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.5, 13.9, 21.6, 21.7, 22.8, 28.9, 29.0, 30.1, 30.3, 43.8, 48.4, 69.2, 83.8, 176.5. − IR: ṽ = 3530, 2960−2870, 1720 cm^{-1}. − $C_{14}H_{26}O_3$ (242.4) calcd. C 69.38, H 10.81; found C 69.35, H 11.13.

Isopropyl (1*R,2*R**,4*R**)- and (1*R**,2*R**,4*S**)-2-[(*E*/*Z*)-But-1-enyl]-1-hydroxy-4-phenylcyclopentanecarboxylate (6f):** Following general procedure III, the ester **1f** (605 mg, 2 mmol) was treated with LDA [prepared in situ from diisopropylamine (2.4 mmol) and *n*BuLi (2.2 mmol)] to afford isopropyl 2-hydroxy-2-[(*E*)-styryl]-3-vinylhexanoate **3f** (571 mg, 94%) as a colorless oil after chromatographic purification [diastereomeric ratio (2*S**,3*S**)/(2*S**,3*R**) = 79:21]. Following general procedure II, the 1,5-hexadiene **3f** (571 mg, 1.89 mmol) was dissolved in decane and heated for 40 h at 180

°C (oil bath temperature). The solvent was then evaporated under reduced pressure and the crude product was purified by chromatography to afford the pure (1*R**,2*R**,4*R**) diastereomer (269 mg, 47%, 3:1 mixture of double-bond isomers) and a mixture of diastereomers [237 mg, 42%, (1*R**,2*R**,4*S**)/(1*R**,2*R**,4*R**) = 3:2] as colorless oils. The (1*R**,2*R**,4*S**) diastereomer was isolated as a 2:1 mixture of double-bond isomers. NMR spectroscopic data determined from a mixture of double bond isomers. − **(1*R**,2*R**,5*R**) Diastereomer:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.5 Hz, 3 H^{minor}, 4′-CH_3), 0.96 (t, *J* = 7.5 Hz, 3 H^{major}, 4′-CH_3), 1.28 (d, *J* = 6.2 Hz, 6 H, O*i*Pr-C*H*$_3$), 1.92−2.22 (m, 5 H, 3-, 5-, 3′-CH_2), 2.75−2.90 (m, 2 H, 5-CH_2, 2-CH), 3.10−3.20 (m, 2 H, 4-CH, OH), 5.08 (qq, J_1 = J_2 = 6.3 Hz, 1 H^{minor}, O*i*Pr-C*H*), 5.09 (qq, J_1 = J_2 = 6.3 Hz, 1 H^{major}, O*i*Pr-C*H*), 5.37−5.60 (m, 2 H, 1′-, 2′-CH), 7.13−7.21 and 7.24−7.38 (m, 5 H, aryl-H).). − ^{13}C NMR (75 MHz, $CDCl_3$, major, minor double-bond isomer): δ = 13.7, 14.5 (4′-CH_3), 21.7, 21.8 (O*i*Pr-*C*H$_3$), 25.7, 21.2 (3′-CH_2), 40.5, 41.6 (3-CH_2), 43.4, 43.8 (4-CH), 46.4, 47.0 (5-CH_2), 53.7, 48.1 (2-CH), 69.3, 69.5 (O*i*Pr-*C*H), 82.74, 82.96 (C-1), 125.2, 125.4 (1′-CH), 126.0, 127.3, 128.3, 135.6, 134.5 (aryl-CH), 145.4, 145.2 (2′-CH), 175.5, 175.8 (C=O).

Isopropyl (1*R,2*R**,4*R**)- and (1*R**,2*R**,4*S**)-2-Butyl-1-hydroxy-4-phenylcyclopentanecarboxylate (8f):** Isopropyl 2-[(*E*/*Z*)-but-1-enyl]-1-hydroxy-4-phenylcyclopentanecarboxylate (**6f**) (526 mg, 1.74 mmol) was dissolved in 2-propanol (9 mL). 10% Pd/C (185 mg, 0.174 mmol Pd) was added and the reaction mixture was stirred under H_2 (balloon) for 3 d at ambient temperature. The solvent was then removed and the crude product was purified by column chromatography (ethyl acetate/heptane, 5:1) to afford the ester **8f** (483 mg, 92%) as a (4*R**)/(4*S**) = 3:1 mixture of diastereomers. The diastereomers could be separated by column chromatography. − **(1*R**,2*R**,4*R**) Diastereomer:** ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.0 Hz, 3 H, 4′-CH_3), 1.18−1.47 (m, partially covered, 6 H, 1′-, 2′-, 3′-CH_2), 1.29 (d, *J* = 6.2 Hz, 6 H, O*i*Pr-C*H*$_3$), 1.68 (ddd, J_1 = J_2 = 14.0, J_3 = 11.4 Hz, 1 H, 3-CH_2), 1.93 (dd, J_1 = 14.0, J_2 = 8.0 Hz, 1 H, 5-CH_2), 2.18−2.31 (m, 2 H, 3-CH_2 and 2-CH), 2.74 (dd, J_1 = 14.0, J_2 = 10.0 Hz, 1 H, 5-CH_2), 3.17−3.32 (m, partially covered, 1 H, 4-CH), 3.29 (s, 1 H, OH), 5.11 (qq, J_1 = J_2 = 6.3 Hz, 1 H, O*i*Pr-C*H*), 7.13−7.20 and 7.24−7.35 (m, 5 H, aryl-H). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9 (4′-CH_3), 21.6 and 21.7 (O*i*Pr-*C*H$_3$), 22.8 (3′-CH_2), 27.6 and 30.3 (1′-, 2′-CH_2), 39.3 (3-CH_2), 43.4 (4-CH), 47.9 (5-CH_2), 49.9 (5-CH), 69.5 (O*i*Pr-*C*H), 81.8 (C-1), 125.9, 127.3, 128.3 and 145.7 (aryl-C), 176.8 (C=O). − IR: ṽ = 3495, 2985−2860, 1710 cm^{-1}. − $C_{19}H_{28}O_3$ (304.4) calcd. C 74.96, H 9.27; found C 74.72, H 9.43. White solid. − **(1*R**,2*R**,4*S**) Diastereomer:** ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.3 Hz, 3 H, 4′-CH_3), 1.30 (d, *J* = 6.3 Hz, 3 H, O*i*Pr-*C*H$_3$), 1.31 (d, *J* = 6.3 Hz, 3 H, O*i*Pr-*C*H$_3$), 1.28−1.48 (m, partially covered, 6 H, 1′-, 2′-, 3′-CH_2), 1.98−2.10 (m, 1 H, 2-CH_2), 2.19−2.31 (m, 2 H, 5-CH_2), 2.55 (dddd, J_1 = J_2 = J_3 = 9.1, J_4 = 5.7 Hz, 1 H, 2-CH), 3.28 (s, 1 H, OH), 3.56 (m, 1 H, 4-CH), 5.13 (qq, J_1 = J_2 = 6.2 Hz, O*i*Pr-*C*H), 7.17−7.22 and 7.27−7.36 (m, 5 H, aryl-CH). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9 (4′-CH_3), 21.6 (O*i*Pr-*C*H$_3$), 22.8 (2′-CH_2), 28.7 and 30.3 (1′-, 3′-CH_2), 38.6 (3-CH_2), 41.9 (4-CH), 47.8 (5-CH_2), 47.9 (5-CH), 69.5 (O*i*Pr-*C*H), 82.9(C-1), 125.9, 126.9, 128.4 and 146.5 (aryl-CH), 176.1 (C=O).

Isopropyl 1-Hydroxy-3-methylenecyclohexanecarboxylate (7a): Following general procedure III, the ester **1g** (397 mg, 2 mmol) was treated with LDA [prepared in situ from diisopropylamine (2.4 mmol) and *n*BuLi (2.2 mmol)] to afford isopropyl 2-hydroxy-4-methyl-2-vinylpent-4-enecarboxylate (**3g**) (324 mg, 82%) as a colorless oil after chromatographic purification. Following general procedure II, the 1,5-hexadiene **3g** (310 mg, 1.56 mmol) was dissolved in toluene and heated for 14 h at 200 °C (oil bath temperature). The solvent was then evaporated under reduced pressure and the crude product was purified by chromatography to afford **7a** (242 mg, 78%) as a colorless oil. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (d, *J* = 6.5 Hz, 6 H), 1.66−1.95 (m, 4 H), 2.01−2.14 (m, 1 H), 2.23 (d, *J* = 13.6 Hz, 1 H), 2.27−2.38 (m, partially covered, 1 H), 2.57 (d, *J* = 13.6 Hz, 1 H), 2.95 (s, 1 H), 4.73 (d, *J* = 2 Hz, 1 H), 4.82 (d, *J* = 1.6 Hz, 1 H), 5.09 (qq, J_1 = J_2 = 6.3 Hz, 1 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7, 22.4, 33.9, 34.2, 43.6, 69.5, 110.8, 144.2, 175.7. − IR: ṽ = 3500, 1725 cm^{-1}. − $C_{11}H_{18}O_3$ (198.3): calcd. C 66.64, H 9.15; found C 66.90, H 9.36.

Isopropyl (1*S,2*R**)-1-Hydroxy-2-methyl-5-methylenecyclohexanecarboxylate (7b):** Following general procedure III, the ester **1h** (1 g, 4.71 mmol) was treated with LDA [prepared in situ from diisopropylamine (5.65 mmol) and *n*BuLi (5.18 mmol)] to afford isopropyl 2-hydroxy-4-methyl-2-isopropenylpent-4-enecarboxylate (**3h**) (721 mg, 72%) as a colorless oil after chromatographic purification. Following general procedure II, the 1,5-hexadiene **3h** (350 mg, 1.65 mmol) was dissolved in toluene and heated for 2 d at 200 °C (oil bath temperature). The solvent was then evaporated under reduced pressure and the crude product was purified by chromatography to afford **7b** (249 mg, 71%) as a colorless oil. − ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.79 (d, *J* = 6.8 Hz, 3 H, 2-CH_3), 1.29 (d, *J* = 6.2 Hz, 6 H, O*i*Pr-C*H*$_3$), 1.47 (ddd, J_1 = 26, J_2 = 13, J_3 = 4 Hz, 1 H, 3-H), 1.55−1.65 (m, 1 H, 3-H), 1.95−2.07 (m, 1 H, 2-H), 2.07−2.20 (m, 1 H, 4-H), 2.27 (dd, J_1 = 13.3, J_2 = 2 Hz, 1 H, 6-H), 2.35 (m, 1 H, 4-H), 2.54 (dd, J_1 = 13.3, J_2 = 2 Hz, 1 H, 6-H), 3.00 (s, 1 H, OH), 4.72 (dd, J_1 = 3, J_2 = 1 Hz, 1 H, C=CH_2), 4.81 (dd, J_1 = 4, J_2 = 2 Hz, 1 H, C=CH_2), 5.09 (qq, J_1 = J_2 = 6.3 Hz, 1 H, O*i*PrC*H*). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.1 (2-CH_3), 21.6 and 21.8 (O*i*Pr-*C*H$_3$), 30.4 (3-CH_2), 34.1 (4-CH_2), 36.9 (2-CH), 44.3 (6-CH_2), 69.6 (O*i*Pr-*C*H), 110.6 (C=*C*H$_2$) 143.6 (5-C), 175.7 (C=O). − IR: ṽ = 3525, 2900−2835, 1720 cm^{-1}. − $C_{11}H_{18}O_3$ (212.3): calcd. C 67.89, H 9.50; found C 68.55, H 10.08.

Isopropyl (1*R,3*S**)-1-Hydroxy-5-methylene-3-phenylcyclohexanecarboxylate (7c):** Following general procedure III, the ester **1i** (549 mg, 2 mmol) was treated with LDA [prepared in situ from diisopropylamine (2.4 mmol) and *n*BuLi (2.2 mmol)] to afford isopropyl 2-hydroxy-4-methyl-2-[(*E*)-styryl]pent-4-enecarboxylate (**3i**) (490 mg, 89%) as a colorless oil after chromatographic purification. Following general procedure II, the 1,5-hexadiene **3i** (330 mg, 1.2 mmol) was dissolved in toluene and heated for 19 h at 200 °C (oil bath temperature). The solvent was then evaporated under reduced pressure and the crude product was purified by chromatography to afford the diastereomerically pure **7c** (279 mg, 85%) as a colorless oil. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (d, *J* = 6.2 Hz, 3 H, O*i*PrC*H*$_3$), 1.29 (d, *J* = 6.2 Hz, 3 H, O*i*Pr-C*H*$_3$), 1.91 (m, 1 H, 2-H), 2.05 (dd, J_1 = J_2 = 12.8 Hz, 1 H, 2-H), 2.29 (dd, J_1 = J_2 = 12.5 Hz, 1 H, 4-H), 2.35 (td, J_1 = 13.2, J_2 = 1.5 Hz, 1 H, 6-H), 2.57 (m, 1 H, 4-H), 2.65 (dd, J_1 = 13.3, J_2 = 1.3 Hz, 1 H, 6-H), 3.13 (dddd, J_1 = J_2 = 12.7, J_3 = J_4 = 3.7 Hz, 1 H, 3-H), 4.89 (dd, J_1 = 2.9, J_2 = 1.3 Hz, 1 H, C=CH_2), 4.92 (dd, J_1 = 3.4, J_2 = 1.8 Hz, 1 H, C=CH_2), 5.09 (qq, J_1 = J_2 = 6.3 Hz, 1 H, O*i*Pr-C*H*$_3$), 7.19−7.36 (m, 5 H, aryl-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7 (O*i*Pr-**C**H$_3$), 39.9 (3-CH), 41.5, 41.7 (2-CH_2, 4-CH_2), 42.9 (6-CH_2), 69.9 (O*i*Pr-*C*H), 74.5 (1-C), 111.7 (C=*C*H$_2$), 126.5, 126.9, 128.5 (aryl-CH), 143.5, 145.2 (aryl-C, 5-C), 175.6 (C=O). − IR: ṽ = 3510, 3070−2835, 1725 cm^{-1}. − $C_{17}H_{22}O_3$ (274.4): calcd. C 74.42, H 8.08; found C 74.19, H 8.45.

Acknowledgments

Financial support from the state of Saxony (habilitation fellowship), the Fonds der Chemischen Industrie and the DFG is gratefully acknowledged. I thank Prof. H.-U. Reißig and Prof. P. Metz for their support and Dr. M. Gruner for numerous NMR measurements.

[1] [1a] L. F. Tietze, U. Beifuss, *Angew. Chem.* **1993**, *105*, 137−170; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131−312. − [1b] L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115−136. − [1c] L. F. Tietze, *Nachr. Chem. Tech. Lab.* **1997**, *12*, 1181−1187.

[2] For selected examples of sequential pericyclic transformations, see: [2a] S. Saito, K. Shimada, H. Yamamoto, *Synlett* **1996**, 720−722. − [2b] P. A. Jacobi, L. M. Armacost, H. L. Brielmann, R. O. Cann, J. I. Kravitz, M. J. Martinelli, *J. Org. Chem.* **1994**, *59*, 5292−5304. − [2c] K. Mikami, K. Takahashi, T. Nakai, *J. Am. Chem. Soc.* **1990**, *112*, 4035. − [2d] K. Mikami, N. Kishi, T. Nakai, Y. Fujita, *Tetrahedron* **1986**, *42*, 2911−2917. − [2e] F. E. Ziegler, J. J. Mencel, *Tetrahedron Lett.* **1984**, *25*, 123−126. − [2f] K. Mikami, S. Taya, T. Nakai, *J. Org. Chem.* **1981**, *46*, 5449−5450.

[3] [3a] M. Hiersemann, C. Lauterbach, A. Pollex, *Eur. J. Org. Chem.* **1999**, 2713−2724. − [3b] M. Hiersemann, *Tetrahedron* **1999**, *55*, 2625−2638.

[4] M. Hiersemann, *Synlett* **2000**, 415−417.

[5] For the domino [2,3]-Wittig/oxy-Cope rearrangement of diallylic ethers, see: [5a]N. Greeves, W. Lee, *Tetrahedron Lett.* **1997**, *36*, 6445−6448. − [5b] N. Greeves, W. Lee, *Tetrahedron Lett.* **1997**, *36*, 6449−6452. − [5c] N. Greeves, K. J. Vines, *J. Chem. Soc., Chem. Commun.* **1994**, 1469−1470. − [5d] N. Greeves, K. J. Vines, *Tetrahedron Lett.* **1994**, *35*, 7077−7080.

[6] For reviews, see [6a] K. Mikami, M. Shimizu, *Chem. Rev.* **1992**, *92*, 1021−1050. − [6b]J. K. Whitesell, *Methods Org. Chem. (Houben-Weyl)* **1995**, vol. E 21d, p. 3271−3297. − [6c]W. Oppolzer, V. Snieckus, *Angew. Chem.* **1978**, *90*, 506−516, *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 476−486.

[7] For selected leading references, see: [7a] P. Kocovský, G. Ahmed, J. Srogl, A. V. Malkov, J. Steele, *J. Org. Chem.* **1999**, *64*, 2765−2775. − [7b] K. Mikami, Y. Koizumi, A. Osawa, M. Terada, H. Takayama, K. Nakagawa, *Synlett* **1999**, 1899−1902. − [7c] H. Okamoto, H. Arita, N. Kato, H. Takeshita, *Chem. Lett.* **1994**, 2335−2338. − [7d] T. Ooi, K. Maruoka, H. Yamamoto, *Tetrahedron* **1994**, *50*, 6505−6522. − [7e] J. A. Marshall, M. W. Andersen, *J. Org. Chem.* **1993**, *58*, 3912−3918. − [7f] J. A. Marshall, M. W. Andersen, *J. Org. Chem.* **1992**, *57*, 5851−5856. − [7g] F. E. Ziegler, S. B. Sobolov, *J. Am. Chem. Soc.* **1990**, *112*, 2749−2758. − [7h] K. Maruoka, T. Ooi, H. Yamamoto, *J. Am. Chem. Soc.* **1990**, *112*, 9011−9012. − [7i] K. Takahashi, H. Sato, K. Mikami, T. Nakai, *Chem. Lett.* **1989**, 247−250. − [7j] M. I. Johnston, J. A. Kwass, R. B. Beal, B. B. Snider, *J. Org. Chem.* **1987**, *52*, 5419−5424. − [7k] B. B. Snider, E. Ron, *J. Am. Chem. Soc.* **1985**, *107*, 8160−8164. − [7l] N. H. Andersen, S. W. Hadley, J. D. Kelly, E. R. Bacon, *J. Org. Chem.* **1985**, *50*, 4144−4151. − [7m] F. E. Ziegler, T. Wang, *J. Am. Chem. Soc.* **1984**, *106*, 718−721. − [7n] B. B. Snider, M. Karras, R. T. Price, D. J. Rodini, *J. Org. Chem.* **1982**, *47*, 4538−4545.

[8] For a review, see L. A. Paquette, *Tetrahedron* **1997**, *41*, 13971−14020.

[9] [9a] L. Lorenc, M. Rajkovic, A. Milovanovic, M. L. Mihailovic, *J. Chem. Soc., Perkin Trans. 1* **1988**, 1495−1498. − [9b] S. Janardhanam, K. Rajagopalan, *J. Chem. Soc., Perkin Trans. 1* **1992**, 2727−2728. − [9c] S. Janardhanam, B. Devan, K. Rajagopalan, *Tetrahedron Lett.* **1993**, *34*, 6761−6764. − [9d] A. Balakumar, S. Janardhanam, K. Rajagopalan, *J. Org. Chem.* **1993**, *58*, 5482−5486. − [9e] P. Shanmugam, K. Rajagopalan, *Tetrahedron* **1996**, *52*, 7744. − [9f] J. M. Warrington, G. P. A. Yap, L. Barriault, *Org. Lett.* **2000**, *2*, 663−665.

[10] M. Hiersemann, *Synthesis* **2000**, *9*, 1279−1290.

[11] The retro ene reaction leading to an enone with a trisubstituted double bond is a significant side reaction when divinylcyclohexanols are heated, see: J. M. Warrington, G. P. A. Yap, L. Barriault, *Org. Lett.* **2000**, *2*, 663−665.

[12] R. J. Loncharich, K. N. Houk, *J. Am. Chem. Soc.* **1987**, *109*, 6947−6952.

[13] O. Takahashi, K. Mikami, T. Nakai, *Chem. Lett.* **1987**, 69−72.

[14] W. G. Kofron, L. M. Baclawski, *J. Org. Chem.* **1976**, *41*, 1879−1880.

Received May 18, 2000
[O00247]