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Alcohol Dehydrogenase-Catalyzed Synthesis of Enantiomerically Pure δ-Lactones as Versatile Intermediates for Natural Product Synthesis

Thomas Fischer[a] and Jörg Pietruszka[a,*]

[a] Institut für Bioorganische Chemie der Heinrich-Heine-Universität Düsseldorf im Forschungszentrum Jülich, Stetternicher Forst Geb. 15.8, 52426 Jülich, Germany
Fax: (+49)-2461-616196; e-mail: j.pietruszka@fz-juelich.de

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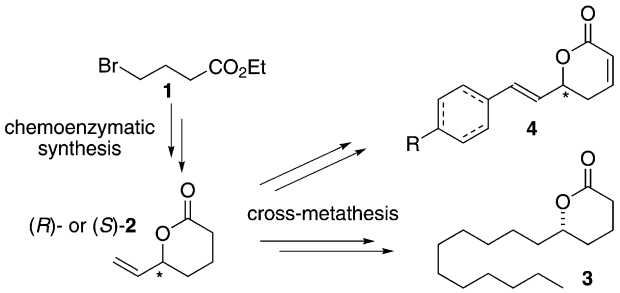
Abstract: Starting from ethyl 4-bromobutyrate, the chemoenzymatic synthesis of 6-vinyl-*tetrahydro*-pyran-2-one has been accomplished. A screening of a number of available alcohol dehydrogenases and intense optimization of reaction parameters enabled us to establish an efficient synthesis of either enantiomer of the vinyllactone with excellent enantiomeric excess (>99%). The scope of possible applications of enantiopure vinyllactones has been verified by subjection to cross-metathesis resulting in the total synthesis of the insect pheromone (*S*)-5-hexadecanolide and the cytotoxic styryllactone goniothalamine as well as derivatives thereof.

Keywords: alcohol dehydrogenases; asymmetric synthesis; cross-metathesis; enzymes; natural product synthesis

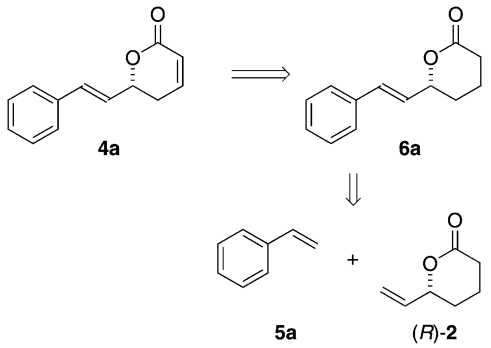
Introduction

The synergy of chemical and biotechnological methods has been recognized by academia and industry as a solution for many unsolved problems as well as to alternative approaches. In the last years, special emphasis has been placed on the principles of *Green Chemistry*[1] and consequently several efficient syntheses of important building blocks also for natural product synthesis have been established.[2] In organic synthesis mainly hydrolases, especially lipases,[3] were applied intensively. Further examples for the formation of valuable building blocks by lyases[4] and oxidoreductases[5] can be found in literature. In continuation of our ongoing efforts to establish novel chemoenzymatic approaches in natural product synthesis,[6] we focus in the present paper on the enzymatic reduction of prochiral ketones derived from a simple precursor **1** by ketoreductases;[7] as the ultimate goal, enantiomerically pure δ-lactones **2** as common structural motifs in physiologically interesting natural products were envisaged (Scheme 1).[8] For instance, the lactone moieties are frequently found in a number of insect pheromones,[9] including (*S*)-5-hexadecanolide (**3**), a pheromone of the queen of the oriental hornet *Vespa orientalis*,[10] whose syntheses have been reported.[11] Noteworthy is a three-step procedure by Li et al. giving a good example for the application of proline-catalyzed aldol reactions.[12]

The value of enantiomerically pure vinyllactones is emphasized by the retrosynthetic analysis of goniothalamine (**4a**) (R = H), a styryllactone isolated from a number of Asian trees and bushes of the genus *Goniothalamus*.[13] We decided to use the approach of a cross-metathesis between vinyllactone (*R*)-**2** and the corresponding olefins **5** to intermediates **6** in order to achieve the total synthesis of naturally occurring (*R*)-goniothalamine (**4a**), its (*S*)-enantiomer (*S*)-**4a** and some selected derivatives thereof with high flexibility in the choice of the second olefin, introducing



Scheme 1. Natural products **3**+**4** derived from a common enantiomerically pure precursor **2**.



Scheme 2. Retrosynthetic analysis of goniothalamine (**4a**).

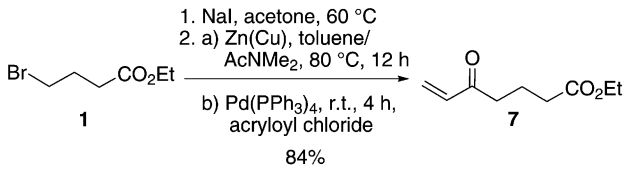
a common access to a manifold of structurally related substances (Scheme 2).

Extracts from the leafs and roots of *Goniothalamus* sp. have already been used in traditional Asian medicine.[14] Recent evaluations of the physiological activity of goniothalamine have revealed antifungal and antimicrobial properties.[15] With great interest, an inhibitory effect on the growth of several human cancer cell lines was observed.[16] While IC_{50} values of naturally occurring goniothalamine were moderate, the (*S*)-enantiomer (*S*)-**4a** and derivatives **4b** and **4c** disclosed high activity with IC_{50} values of 4–5 nM on kidney and breast cancer cells. The mechanism of inhibition has been widely studied, based on the activation of caspases and thus induction of apoptosis. The configuration of the stereogenic center in the lactone and the Michael system were identified as crucial for the biological activity. Due to these interesting properties, goniothalamine and derivatives have been model target molecules for evaluation of several chemical and chemoenzymatic methods.[11b,17]

Results and Discussion

Starting form commercially available ethyl 4-bromobutyrate (**1**) we achieved the synthesis of prochiral ketone **7** as substrate for the enzymatic reduction with alcohol dehydrogenases by applying a well-established sequence of Finkelstein reaction followed by a Pd-catalyzed cross-coupling to acryloyl chloride (84% yield over 2 steps, Scheme 3).[7,8e]

The reduction of ketone **7** by CBS-reduction (Corey–Bakshi–Shibata)[18] method failed to deliver



Scheme 3. Synthesis of ethyl 5-oxohept-6-enoate (**7**).

high yield and selectivity (see Experimental Section). Thus ω-stannylated or ω-silylated derivatives were used instead in the past, leading to additional steps.[8e] Hence, we tried to establish an alternative enzymatic approach using ketoreductases. Activity tests for various enzymes were performed by the photometric measurement of the NAD(P)H consumption in different buffers leading to alcohol dehydrogenases from *Thermoanaerobacter* sp. (ADH-T)[19] and from *Lactobacillus* sp. (ADH-LB or ADH-LK)[20] as the most promising candidates for the enzymatic reduction of **7**. A statistical approach by DoE studies (Design of Experiment performed with DesignExpert®; for details on DoE and enzyme activities see the Supporting Information) led to the optimized reaction conditions for the enzymatic reduction. We looked for the highest possible conversion at maximized substrate concentrations with a minimal enzyme concentration. For example, with respect to enzyme stability at different pH values and temperatures we found the biotransformation in phosphate buffer pH 6 as most desirable for the enzymatic reduction of ketone **7** with ADH from *Lactobacillus kefir* (Figure 1). As a compromise of temperature stability and enzyme activity, reactions were performed in Eppendorf® tubes at 30 °C.

ADH-T and ADH-LB were used for further experiments and kinetic parameters for the reduction of ketone **7** were determined. A strong substrate surplus inhibition could especially be observed for ADH-T (Figure 2), but the high reaction rate as indicated by the outstanding values calculated for K_M (68.3 μM) and V_{max} (24.0 U/mg) in the Michaelis–Menten kinetics allowed us to perform the biotransformation on a gram-scale with full conversion regardless of the substrate inhibition. Kinetic parameters for the enantioselective reduction with ADH-LB were determined as $K_M = 9.5 \pm 0.9$ mM and $V_{max} = 177.5 \pm 8.7$ U/mg.

Nevertheless, the encountered problems in up-scaling the reaction to higher substrate concentrations led us to a more detailed examination concerning the reasons for the inhibition or deactivation of all alcohol dehydrogenases by ketone **7**. We suspected the Michael system in the substrate to be responsible for enzyme deactivation by interacting with nucleophilic side chains readily available for Michael addition in the enzyme. We were able to prove our rational by measuring the deactivation constants of ketone **7** on the employed alcohol dehydrogenases and comparing these and half-lives toward the respective saturated substrate **8** (Figure 3 and Figure 4). Conversion of enone **7** to ketone **8** was achieved by hydrogenation with H_2 over Pd/C in almost quantitative yield (98%, Scheme 4). After incubation of the enzymes in buffer in presence of 10 mM ethyl 5-oxohept-6-enoate (**7**) a rapid loss of activity could be observed for ADH-LB with a half-life of $t_{1/2} = 84.5$ min ($k_{deactivation} = 8.2 \times 10^{-3}$ min^{-1}) and even more striking for ADH-T with

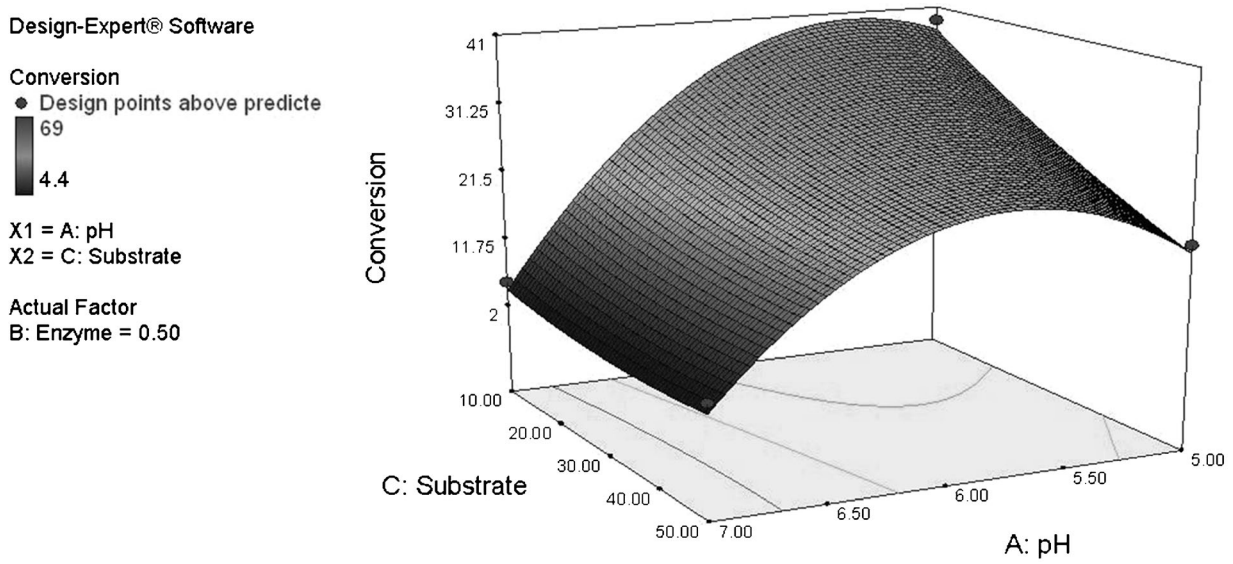


Figure 1. Design-of-experiment study on enzymatic reduction of ketone **7** with ADH-LK.

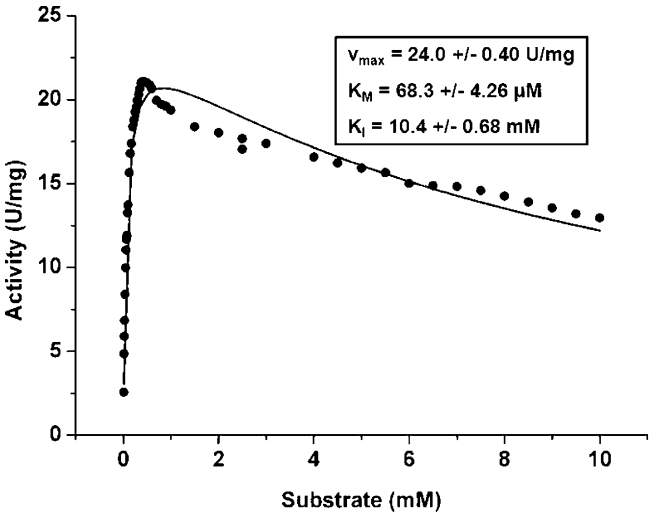


Figure 2. Michaelis–Menten kinetics for ADH-T.[25]

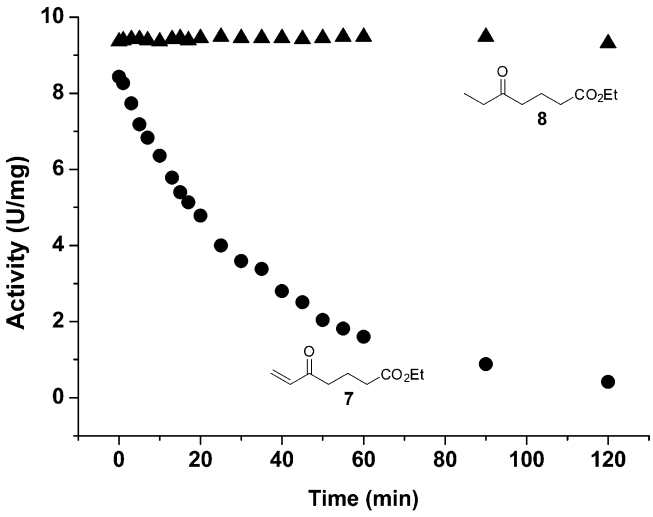


Figure 3. Deactivation of ADH-T by substrate **7**.[25]

a half-life of $t_{1/2} = 27.2$ min ($k_{deactivation} = 25.5 \times 10^{-3}$ min^{-1}). In contrast, no effect on enzyme activity could be detected with the saturated substrate **8**. The inhibitory effects of the corresponding products **9** were also examined, but turned out to be negligible up to concentrations of 10 mM.

The information about the kinetic parameters of the enzymes and the intense optimization of the reaction parameters enabled us to synthesize both enantiomers of ethyl 5-hydroxyhept-6-enoate (**9**) with outstanding enantioselectivities (as proven by GLC analysis; synthesis of racemic reference compounds: see Experimental Section) in high yields. Reduction of 1.0 g of enone **7** catalyzed by ADH-T in TEA buffer (50 mM, pH 7) and extraction of the reaction mixture with MTBE led to the (*R*)-enantiomer (*R*)-**9** (0.93 g, 92%, >99% *ee*) and usage of ADH-LB in phosphate buffer (100 mM, pH 6, 1 mM $MgCl_2$) delivered the corresponding (*S*)-configured alcohol (*S*)-**9** (0.88 g, 87%, >99% *ee*). The cofactor NADPH was in both cases regenerated by addition of 2-propanol as a co-substrate being oxidized to acetone.

The obtained enantiomerically pure allylic alcohols **9** could then be converted into the corresponding vinyllactones **2** by saponification of the ester functionality with LiOH followed by lactonization using DMAP and EDC hydrochloride with good yields.[8e] A purification step after the enzyme reaction was shown not to be essential for the success of the lactonization, so that the crude material was used after extraction with

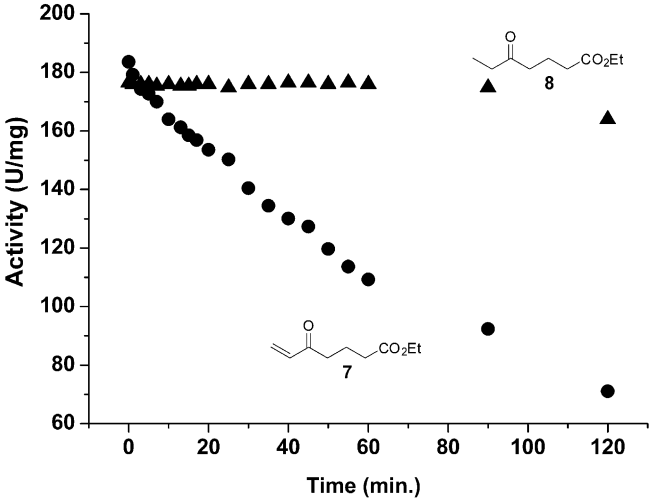
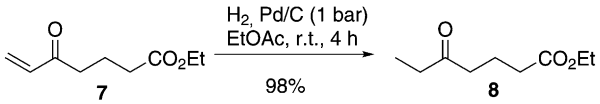


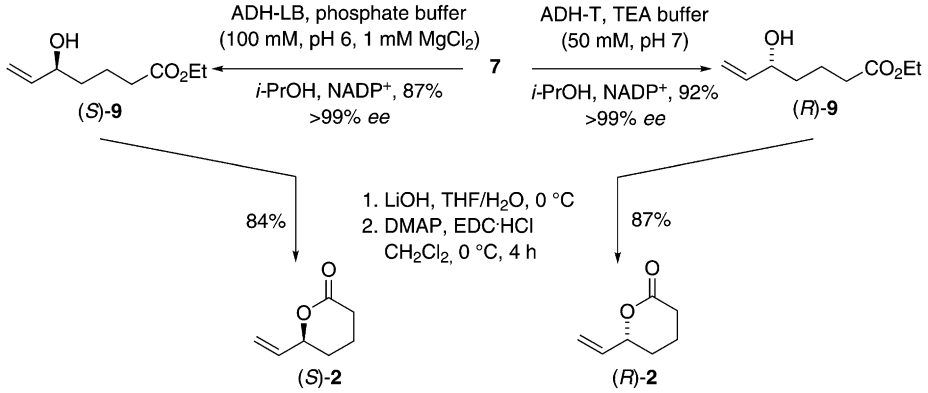
Figure 4. Deactivation of ADH-LB by substrate **7**.[25]



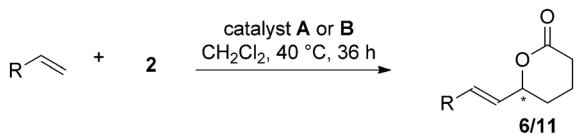
Scheme 4. Synthesis of ketone **8**.

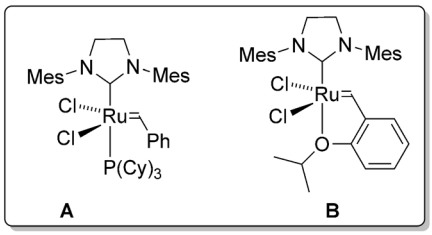
MTBE. Overall, we were able to provide both enantiomers of vinyllactone **2** in a total yield of 73% starting from ethyl 4-bromobutyrate (**1**) as a versatile building block for the envisaged natural product synthesis (Scheme 5).

Next, the modification of the olefin moiety was examined (Scheme 6): Cross-metathesis of lactone (*R*)-**2** with undec-1-ene (**10**) using second generation Grubbs catalyst **A**[21] yielded olefin **11** (85%, entry 1) while Hoveyda–Blechert catalyst **B**[22] did not increase the yield (72%). The observed *E*/*Z*-selectivity of 8:1 (and 1:1, respectively) was of no consequence for the completion of the total synthesis of the natural product since the double bond is not found in the final product. Hydrogenation of olefin **11** with H_2 over Pd/C delivered (*S*)-5-hexadecanolide (**3**) in quantitative yield (overall 62% over 7 steps, Scheme 7). For the synthesis of the target compounds from the goniothalamine family, cross-metathesis with the respective olefins **5a–c** and a subsequent oxidative generation of the Michael system, being essential for physiological activity, had to be established. The metatheses were carried out under standard conditions in dichloromethane. Again, Grubbs catalyst **A** and Hoveyda–Ble-



Scheme 5. Chemoenzymatic synthesis of enantiomerically pure vinyllactones **2**.

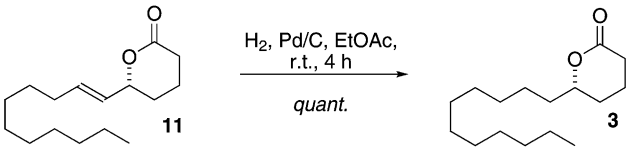




Entry	Olefin	Catalyst	Product	Yield[a]	*E*/*Z*
1	C_9H_{19} **10**	A	**11**	85% (*R*)	8:1
		B		72% (*R*)	1:1
2	**5a**	A	**6a**	46% (*S*)	
		B		90% (*S*)	>20:1
		B		87% (*R*)	
3	**5b**	A	**6b**	88% (*S*)	
		B		93% (*S*)	>20:1
		B		89% (*R*)	
4	MeO **5c**	A	**6c**	48% (*S*)	
		B		54% (*S*)	>20:1
		B		31% (*R*)	

[a] Configuration of product in parenthesis.

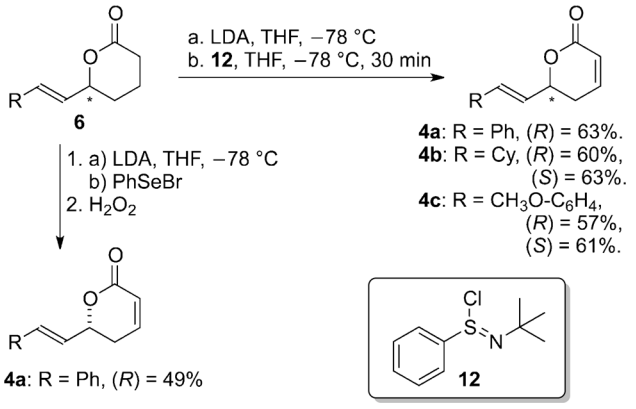
Scheme 6. Cross-metathesis with vinyllactones **2**.



Scheme 7. Synthesis of (*S*)-5-hexadecanolide (**3**).

chert catalyst of the 2nd generation **B** were used. In comparison, the Hoveyda–Blechert catalyst **B** was superior in performance in all cases and yields of 87–93% could be achieved for the synthesis of **6a** and **6b**; however, the cross-metathesis between vinyllactone **2** and 4-methoxystyrene (**5c**) to form intermediate **6c** caused problems and yields were remarkably lower (up to 54%). Under the chosen reaction conditions, *E*/*Z*-selectivity on the formed double bond was excellent (>20:1) in favor of the desired *E*-isomer.

Several methods for the generation of α,β-unsaturated carbonyl compounds, as needed in the lactone moiety with regard to the goniothalamine derivatives **4a–c**, have been reported. Our first choice was the use of organoselenium compounds for α-selenation and consecutive oxidative elimination, leading to the desired Michael system.[17d,23] Although the reaction was carried out successfully, the obtained product could not be completely separated from undesired by-products by means of flash chromatography or MPLC, so that goniothalamine (**4a**) was isolated in 49% yield containing some impurities. Finally, we took advantage of a protocol by Matsuo and Aizawa,[24] using *N-tert*-butylbenzenesulfinimidoyl chloride (**12**) as reagent for the one-pot dehydrogenation of carboxylic acid derivatives to α,β-unsaturated carbonyl compounds. By this method, intermediates **6a–c** could readily be converted into the target compounds **4a–c** after generation of the corresponding lithium enolates by treatment with LDA in THF at −78 °C giving highly reproducible yields of 57–63%; all by-products were removable by flash chromatography (Scheme 8). The purity of the natural product **4a**, its derivatives **4b** and **4c** and the intermediates **6a–c** was verified by several analytical methods including optical rotation.



Scheme 8. Synthesis of goniothalamine (derivatives) **4a–c**.

Conclusions

In summary, we have reported the enantioselective synthesis of vinyllactone **2** in a short and efficient chemoenzymatic procedure in which we were able to drive the enzymatic reaction to either enantiomer as desired by choice of the respective alcohol dehydrogenase. Furthermore, we were able to emphasize the value of vinyllactone **2** as a chiral building block in natural product synthesis and described the successful application in a number of cross-metatheses. The total synthesis of insect pheromone (*S*)-5-hexadecanolide (**3**) as well as cytotoxic compounds such as goniothalamine (**4a**) and its derivatives **4b** and **4c** were completed by just one additional step. We thus demonstrated that the cross-metathesis between vinyllactone **2** and aliphatic, cyclic and aromatic olefins is possible, enabling the synthesis of diverse target compounds.

Experimental Section

General Experimental Condtions

Unless otherwise specified the reactions were carried out using standard Schlenk techniques under dry N_2 with magnetic stirring. Glassware was oven-dried at 120 °C overnight. Solvents were dried and purified by conventional methods prior to use. All the reagents were used as purchased from commercial suppliers without further purification. Enzymes were kindly provided by Julich Chiral Solutions (Codexis), evocatal and the Institute for Molecular Enzyme Technology (Heinrich-Heine University Düsseldorf) and used as received as crude extracts or freeze dried. Common solvents for chromatography (petroleum ether 40–60 °C, ethyl acetate) were distilled prior to use. Flash column chromatography was performed on silica gel 60, 0.040–0.063 mm (230–400 mesh). TLC (monitoring the course of the reactions) was performed on pre-coated plastic sheets with detection by UV (254 nm) and/or by coloration with cerium molybdenum solution [phosphomolybdic acid (25 g), $Ce(SO_4)_2{\cdot}H_2O$ (10 g), concentrated H_2SO_4 (60 mL), H_2O (940 mL)]. Preparative medium-pressure liquid chromatography (MPLC) was performed using a packed column (25×300 mm or 40×475 mm; Si 60–15–25 μm) and a UV detector (254 nm). HPLC was performed on standard devices equipped with a Chiralcel OB or Chiralcel IA column. ^1H and ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$ on a spectrometer at 600 and 151 MHz, respectively. The chemical shifts are given in ppm relative to internal standard TMS (^1H: $\delta[Si(CH_3)_4]=0.00$ ppm) or relative to the resonance of the solvent (^{13}C: $\delta(CDCl_3)=77.0$ ppm). Coupling constants *J* are given in Hz. Higher order δ and *J* values are not corrected. ^{13}C NMR signals were assigned by means of C, H, COSY and HSQC or HMBC spectroscopy. Optical ro-

tations were measured at 20 °C using a quartz cell with 1 mL capacity and a 10 cm path length. Alcohol dehydrogenase activity tests (U/mL) were performed by photometric measurement (340 nm) of the NAD(P)H consumption. Modelling of Michaelis–Menten kinetics with substrate surplus inhibition and calculations for half-lives in the deactivation process were performed according to formulae given in the literature and in the Supporting Information.[25]

Ethyl 5-Oxohept-6-enoate (7)

Ethyl 4-bromobutyrate (35.3 g, 172 mmol) was dissolved in acetone (250 mL) and 77.3 g (516 mmol) sodium iodide were added. The reaction mixture was stirred overnight at 60 °C, cooled to room temperature and diluted with Et_2O. After washing with 2 M Na_2SO_3, the organic layer was separated, dried over $MgSO_4$, and the solvent was evaporated.

Without further purification, the residue was dissolved in 250 mL toluene and 120 mL *N,N*-dimethylacetamide and added slowly to a suspension of 35 g Zn/Cu[26] in 50 mL toluene. The mixture was stirred at room temperature for one hour and then at 80 °C overnight. The heating bath was removed and 1.20 g (1.04 mmol) tetrakis(triphenylphosphine)-palladium(0) in 50 mL toluene were added. After 5 min, 17.9 g (190 mmol) acryloyl chloride dissolved in 200 mL toluene were added slowly through a dropping funnel. After 4 h, the reaction was completed (as judged by TLC). The mixture was filtered through celite and washed subsequently with saturated aqueous NH_4Cl, saturated aqueous Na_2CO_3 and brine. The organic layer was dried over $MgSO_4$ and the solvents were removed under reduced pressure. The deep brown crude product was purified by vacuum distillation (0.1 mbar) to afford of the ketone **7** as a colorless oil; yield: 24.8 g (146 mmol, 84%). The spectroscopic data were in full agreement with previously published values.[7,8e] $R_f = 0.25$ (petroleum ether/EtOAc 85:15); bp 78–81 °C (0.1 mbar); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 1.26$ (t, $J = 7.1$ Hz, 3 H, 2′-H), 1,96 (tt, $J = 7.2$ Hz, 7.2 Hz, 2 H, 3-H), 2.36 (t, $J = 7.2$ Hz, 2 H, 2-H), 2.67 (t, $J = 7.2$ Hz, 2 H, 4-H), 4.13 (q, $J = 7.1$ Hz, 2 H, 1′-H), 5.84 (dd, $J = 10.6$ Hz, 1.5 Hz, 1 H, 7-H_Z), 6.24 (dd, $J = 17.7$ Hz, 1.5 Hz, 1 H, 7-H_E), 6.35 (dd, $J = 17.7$ Hz, 10.6 Hz, 1 H, 6-H); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 14.3$ (C-2′), 19.1 (C-3), 33.3 (C-2), 38.4 (C-4), 60.4 (C-1′), 128.3 (C-7), 136.5 (C-6), 173.2 (C-1), 200.0 (C-5); IR (film): ν_{max} = 2982, 2906, 2937, 1730, 1700, 1682, 1616, 1448, 1403, 1375, 1244, 1196, 1180, 1148, 1100, 1057, 1027, 967, 880, 857, 758 cm^{-1}; LC-MS (ESI): *m/z* (%) = 193.1 (100) [$(M+Na)^+$], 171.2 (23).

Ethyl 5-Oxoheptanoate (8)

Ketone **7** (1.0 g, 5.9 mmol) was dissolved in 25 mL EtOAc, 200 mg Pd/C (10% Pd) were added and the reaction flask was set under an H_2 atmosphere. The reaction mixture was stirred at room temperature for 4 h. Completion of the reaction was verified by NMR analysis; the reaction mixture was filtered over a silica gel pad and the solvent was evaporated to afford of the saturated ketone **8** as a colorless oil; yield: 990 mg (5.8 mmol, 98%). The spectroscopic data were in full agreement with previously published values.[27] R_f = 0.25 (petroleum ether/EtOAc 85:15); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 1.05$ (t, $J = 7.3$ Hz, 3 H, 7-H), 1.25 (t, $J = 7.1$ Hz, 3 H, 2′-H), 1.90 (tt, $J = 7.2$, 7.2 Hz, 2 H, 3-H), 2.33 (t, $J =$ 7.2 Hz, 2 H, 2-H), 2.42 (q, $J = 7.3$ Hz, 2 H, 6-H), 2.48 (t, $J =$ 7.2 Hz, 2 H, 4-H), 4.13 (q, $J = 7.1$ Hz, 2 H, 1′-H); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 7.8$ (C-7), 14.2 (C-2′), 19.0 (C-3), 33.3 (C-6), 35.9 (C-4), 41.1 (C-2), 60.3 (C-1′), 173.2 (C-1), 210.7 (C-5); IR (film): ν_{max} = 2972, 2932, 2901, 1732, 1714, 1449, 1413, 1373, 1249, 1182, 1158, 1112, 1092, 1080, 1032 cm^{-1}; GC-MS: *m/z* (%) = 172 (6), 143 (87), 127 (86), 115 (95), 99 (59), 87 (86), 57 (100).

Synthesis of Racemic Allylic Alcohol *rac*-9

$CeCl_3$ (400 mg, 1.62 mmol) was vacuum-dried at 100 °C for 4 h and dissolved in 2.5 mL anhydrous EtOH. To this solution, ketone **7** (90 mg, 0.53 mmol, dissolved in 2.5 mL anhydrous EtOH) was added through a syringe and the resulting mixture was stirred at room temperature for 30 min. The mixture was cooled to −78 °C and $NaBH_4$ (40 mg, 1.06 mmol) was added in three portions. After 3 h the reaction was completed (as judged by TLC) and could be hydrolyzed by addition of 2 M aqueous HCl. The clear solution was extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (petroleum ether/EtOAc 70:30) to afford the racemic allylic alcohol **9** as a colorless oil; yield: (69 mg, 0.40 mmol, 76%). The analytical data were in agreement to those reported for the enantiomerically pure compound (*vide infra*).

Synthesis of Enantiomerically Enriched Allylic Alcohol 9 by CBS Reduction

Ketone **7** (500 mg, 2.94 mmol) was dissolved in 10 mL anhydrous toluene, 250 mg molecular sieves (4 Å) and (*R*)-methyloxazaborolidin (1 M solution in toluene, 5.8 mL, 5.8 mmol) were added and the reaction mixture was cooled to −78 °C. After addition of catecholborane (2 M solution in toluene, 3.0 mL, 6.0 mmol), the mixture was stirred for 6 h while the temperature was kept below −50 °C. When reaction was completed (as judged by TLC), the mixture was cooled to −78 °C and hydrolyzed by addition of 2.0 mL MeOH. Subsequently, 50 mL Et_2O and then 50 mL of a 2:1-mixture of 1 M NaOH and saturated $NaHCO_3$-solution were added. The organic layer was separated and the aqueous phase was extracted with Et_2O. The combined organic layer was washed with 1 M HCl and saturated NaCl solution, dried over $MgSO_4$ and the solvents were removed under reduced pressure. Flash column chromatography (petroleum ether/EtOAc 70:30) of the crude product afforded allylic alcohol **9** with an enantiomeric excess of 82% in favor of the (*S*)-enantiomer; yield: 199 mg (1.16 mmol, 39%). The analytical data were in agreement to those reported for the enantiomerically pure compound (*vide infra*).

(*R*)-Ethyl 5-Hydroxyhept-6-enoate [(*R*)-9]

Ketone **7** (1.0 g, 5.9 mmol) was dissolved in 90 mL buffer (50 mM TEA, pH 7, 1 mM $MgCl_2$) and 10 mL 2-propanol. To this solution 47 mg (60 μmol) $NADP^+$ and 100 μL ADH-T (in 50% glycerol, 17.14 mg mL^{-1}, 320 U/mL) were added. The flask with the reaction mixture was shaken at room temperature for 20 h with 250 rpm. Complete conversion was verified by GLC before the aqueous solution was ex-

tracted with MTBE (3×). The organic phase was dried over $MgSO_4$ and the solvents were removed under reduced pressure. The crude product was purified by flash column chromatography (petroleum ether/EtOAc 70:30) to afford the desired alcohol (*R*)-**9** as a colorless oil; yield: 930 mg (5.4 mmol, 92%). The spectroscopic data were in full agreement with previously published values.[7,8c] R_f = 0.26 (petroleum ether/EtOAc 70:30); $[\alpha]_D^{20}$: −71.2 (*c* 1.10 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.1 Hz, 3H, 2′-H), 1.57 (m_c, 2H, 4-H), 1.67–1.79 (m, 3H, 3-H, O*H*), 2.34 (t, *J* = 7.0 Hz, 2H, 2-H), 4.11 (m_c, 1H, 5-H), 4.13 (q, *J* = 7.1 Hz, 2H, 1′-H), 5.12 (ddd, *J* = 10.4, 1.4, 1.2 Hz, 1H, 7-H_Z), 5.24 (ddd, ^3J = 17.4, 1.4, 1.4 Hz, 1H, 7-H_E), 5.87 (ddd, *J* = 17.4, 10.4, 6.2 Hz, 1H, 6-H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 14.3 (C-2′), 20.8 (C-3), 34.1 (C-2), 36.4 (C-4), 60.4 (C-1′), 72.7 (C-5), 114.9 (C-7), 140.9 (C-6), 173.6 (*C*=O); IR (film): ν_{max} = 3426 (br), 2987, 2930, 2860, 1732, 1714, 1421, 1373, 1305, 1239, 1162, 1119, 1065, 1030, 991, 921, 858 cm^{-1}; MS (70 eV): *m/z* = (%) 127 (29), 57 (91); >99% *ee* as determined by GLC [Lipodex G, H_2 (0.6 bar), 90 °C iso]: t_R = 39.4 min.

(*S*)-Ethyl 5-Hydroxyhept-6-enoate [(*S*)-9]

Ketone **7** (1.0 g, 5.9 mmol) was dissolved in 90 mL buffer (100 mM KP_i, pH 6, 1 mM $MgCl_2$) and 10 mL 2-propanol. To this solution 47 mg (60 μmol) $NADP^+$ and 100 μL ADH-LB (crude extract, 18.3 mg mL^{-1}, 160 U/mL) were added. The flask with the reaction mixture was shaken at 30 °C for 20 h with 250 rpm. Complete conversion was verified by GLC before the aqueous solution was extracted with MTBE (3×). The organic phase was dried over $MgSO_4$ and the solvents were removed under reduced pressure. The crude product was purified by flash column chromatography (petroleum ether/EtOAc 70:30) to afford the desired alcohol (*S*)-**9** as a colorless oil; yield: 880 mg (5.1 mmol, 87%); $[\alpha]_D^{20}$: +69.5 (*c* 1.10 in $CHCl_3$); >99% *ee* as determined by GC [Lipodex G, H_2 (0.6 bar), 90 °C iso]: t_R = 40.6 min.

6-Vinyltetrahydropyran-2-one (2)

The enantiopure alcohol **9** (1.0 mg, 5.81 mmol) was dissolved in 90 mL THF and cooled to 0 °C. At this temperature, 0.2 M aqueous LiOH solution was added over a period of 1 h (3 portions of 30 mL, 18.0 mmol total). The solution was stirred for 1 h before it was transferred into an emulsion of 100 mL 1 M hydrochloric acid in 100 mL ethyl acetate. The acidic aqueous layer was extracted three times with EtOAc, the combined organic extracts were dried over $MgSO_4$ and the solvents were removed under reduced pressure. A solution of the residue in 150 mL CH_2Cl_2 at 0 °C was treated with 4-(dimethylamino)pyridine (355 mg, 2.9 mmol) followed by 1-[(3-dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.34 g, 7.0 mmol). The mixture was stirred for three hours at room temperature, diluted with diethyl ether (200 mL) and subjected to a filtration over silica gel. The filtrate was concentrated under reduced pressure, and the residue purified by flash column chromatography (petroleum ether/EtOAc 70:30) affording lactone **2** as a colorless oil (yield: 636 mg, 5.04 mmol, 87%). The spectroscopic data were in full agreement with previously published values.[8e] R_f = 0.43 (petroleum ether/EtOAc 50:50); (*R*)-**2**: $[\alpha]_D^{20}$: −67.4 (*c* 1.05 in $CHCl_3$), (*S*)-**2**: $[\alpha]_D^{20}$: +67.7 (*c* 1.10 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.68 (m_c, 1H, 5-H), 1.87–1.94 (m, 2H, 4-H), 2.00 (m_c, 1H, 5-H), 2.50 (ddd, *J* = 17.8, 8.1, 7.0 Hz, 1H, 3-H), 2.60 (ddd, *J* = 17.8, 6.8, 6.1 Hz, 1H, 3-H), 4.83 (m_c, 1H, 6-H), 5.25 (ddd, *J* = 10.6, 1.3, 1.1 Hz, 1H, 2′-H_Z), 5.35 (ddd, *J* = 17.2, 1.5, 1.2 Hz, 1H, 2′-H_E), 5.88 (ddd, *J* = 17.2, 10.6, 5.4 Hz, 1H, 1′-H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 18.1 (C-4), 28.0 (C-5), 29.6 (C-3), 80.3 (C-6), 116.9 (C-2′), 136.1 (C-1′), 171.1 (C-2); IR (film): ν_{max} = 2952, 2916, 2881, 1727, 1646, 1464, 1441, 1426, 1408, 1360, 1340, 1234, 1191, 1163, 1108, 1036, 984, 929, 855, 771 cm^{-1}; MS (EI, positive ion,70 eV): *m/z* (%) = 126 (1), 98 (100), 55 (34); >99% *ee* as determined by GC [Hydrodex-β-TBDAc, H_2 (0.6 bar), 130 °C iso]: (*R*)-**2**: t_R = 20.5 min, (*S*)-**2**: t_R = 21.1 min.

General Procedure for Cross-Metathesis

Under an atmosphere of dry argon, 3 mol% metathesis catalyst were added to a solution of vinyllactone **2** (100 mg, 0.79 mmol) in 5 mL anhydrous CH_2Cl_2. Then 7.5 equivalents of the respective second olefin were added. After stirring for 36 h, the reaction mixture was filtered through a pad of celite and the solvent was removed under reduced pressure. The crude product was subjected to flash column chromatography for purification.

(*R*,*E*)-6-(Undec-1-en-1yl)tetrahydro-2*H*-pyran-2-one (11)

According to the general procedure for cross-metathesis with 2nd generation Grubbs catalyst, **11** could be isolated as a colorless oil; yield:170 mg (0.67 mmol, 85%). The spectroscopic data were in full agreement with previously published.[11] R_f = 0.15 (petroleum ether/EtOAc 90:10); $[\alpha]_D^{20}$: −31.1 (*c* 0.09 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$; data for *E*-isomer): δ = 0.88 (t, *J* = 7.0 Hz, 3H, 11′-H), 1.23 −1.30 (m, 12H, 5′-H, 6′-H, 7′-H, 8′-H, 9′-H, 10′-H), 1.37 (m, 2H, 4′-H), 1.65 (m, 1H, 5-H), 1.85 (m, 1H, 4-H), 1.94 (m, 2H, 4-H, 5-H), 2.05 (m, 2H, 3′-H, 4-H), 2.47 (ddd, *J* = 17.8, 8.4, 6.9 Hz, 1H, 3-H), 2.58 (ddd, *J* = 17.8, 6.9, 5.5, 1H, 3-H), 4.76 (m_c, 1H, 6-H), 5.49 (ddt, *J* = 15.4, 6.7, 1.5 Hz, 1H, 1′-H), 5.77 (dtd, *J* = 15.4, 6.8, 1.1, 1H, 2′-H); ^{13}C NMR (151 MHz, $CDCl_3$; data for *E*-isomer): δ = 14.1 (C-11′), 18.3 (C-4), 22.7, 28.4 (C-5), 28.9 (C-4′), 29.1, 29.3, 29.5 (C-3), 29.5, 29.6, 31.9, 32.2 (C-3′), 80.7 (C-6), 127.9 (C-1′), 134.7 (C-2′), 171.4 (C-2); IR (film): ν_{max} = 2922, 2851, 1733, 1461, 1444, 1376, 1340, 1238, 1168, 1118, 1075, 1044, 1034, 928, 718 cm^{-1}; GC-MS: *m/z* (%) = 252 (26), 192 (15), 154 (19), 136 (31), 125 (88), 112 (48), 97 (100), 81 (64), 67 (55), 55 (76).

(*S*)-5-Hexadecanolide (3)

157 mg (0.62 mmol) of olefin **11** were dissolved in 4 mL EtOAc, 65 mg Pd/C (5% Pd) were added and the reaction flask was set under an H_2 atmosphere. The reaction mixture was stirred at room temperature for 4 h. Completion of the reaction was verified by NMR analysis and the reaction mixture was filtered through a pad of celite and the solvent was evaporated to afford (*S*)-5-hexadecanolide (**3**) as a white solid; yield: 155 mg (0.61 mmol, 98%). The spectroscopic data were in full agreement with previously published values.[9] R_f = 0.3 (petroleum ether/EtOAc 85:15); mp 34.5–35.5 °C; $[\alpha]_D^{25}$: −30.7 (*c* 1.1 in $CHCl_3$); ^{1}H NMR (600 MHz,

$CDCl_3$): $\delta = 0.88$ (t, $J = 7.0$ Hz, 3H, 11′-H), 1.24 –1.32 (m, 16H, 3′-H, 4′-H, 5′-H, 6′-H, 7′-H, 8′-H, 9′-H, 10′-H), 1.36 (m_c, 1H, 2′-H), 1.45–1.55 (m, 2H, 2′-H, 5-H), 1.57 (ddt, $J =$ 10.2, 7.1, 3.2 Hz, 1H, 1′-H), 1.71 (ddt, $J = 10.2$, 7.3, 5.0 Hz, 1H, 1′-H), 1.84 (m, 1H, 4-H), 1.87–1.92 (m, 2H, 4-H, 5-H), 2.44 (ddd, $J = 17.5$, 8.8, 7.0 Hz, 1H, 3-H), 2.59 (ddd, $J = 17.5$, 6.5, 4.3, 1H, 3-H), 4.28 (dddd, $J = 10.6$, 7.8, 5.0, 3.2 Hz, 1H, 6-H); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 14.1$ (C-11′), 18.5 (C-4), 22.7, 24.7, 24.9 (C-2′), 27.8 (C-5), 29.1, 29.3, 29.3, 29.4 (C-3), 29.4, 29.5, 29.5, 29.6, 29.6, 29.6, 31.9, 35.9 (C-1′), 80.6 (C-6), 172.0 (C-2); IR (film): $\nu_{max} = 2923$, 2853, 1735, 1465, 1441, 1376, 1341, 1238, 1171, 1123, 1075, 1048, 931, 721 cm^{-1}; GC-MS: m/z (%) = 254 (1), 192 (12), 114 (19), 99 (100), 83 (20), 71 (36), 55 (35).

(*E*)-6-Styryltetrahydropyran-2-one (6a)

According to the general procedure for cross-metathesis with 2nd generation Hoveyda–Blechert catalyst, **6a** could be isolated as a white solid; yield: 144 mg (0.71 mmol, 90%). The spectroscopic data were in full agreement with previously published values.[16] $R_f = 0.25$ (petroleum ether/EtOAc 70:30); mp 70.5–71 °C; (*R*)-**6a**: $[\alpha]_D^{25}$: +6.4 (*c* 1.05 in $CHCl_3$), (*S*)-**6a**: $[\alpha]_D^{25}$: −6.5 (*c* 1.2 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 1.77$ (dddd, $J = 14.0$, 9.8, 5.2, 5.1 Hz, 1H, 5-H), 1.92 (m, 1H, 4-H), 2.00 (ddddd, $J = 14.2$, 7.0, 6.9, 5.2, 4.9 Hz, 1H, 4-H), 2.08 (ddddd, $J = 14.0$, 5.1, 4.9, 3.9, 0.9 Hz, 1H, 5-H), 2.54 (ddd, $J = 17.8$, 8.3, 7.0 Hz, 1H, 3-H), 2.65 (dddd, $J =$ 17.8, 6.9, 5.7, 0.9 Hz, 1H, 3-H), 5.01 (dddd, $J = 9.8$, 5.9, 3.9, 1.2 Hz, 1H, 6-H), 6.21 (dd, $J = 15.9$, 5.9 Hz, 1H, 1′-H), 6.67 (dd, $J = 15.9$, 1.2 Hz, 1H, 2′-H), 7.26–7.41 (m, 5H, Ar-H); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 18.3$ (C-4), 28.5 (C-5), 29.6 (C-3), 80.3 (C-6), 126.6 (2C, Ar), 127.0 (C-1′), 128.2 (Ar), 128.7 (2C, Ar), 132.1 (C-2′), 136.0 (Ar), 171.1 (C-2); IR (film): $\nu_{max} = 3025$, 2953, 2881, 1711, 1655, 1598, 1678, 1494, 1461, 1450, 1388, 1355, 1331, 1234, 1187, 1156, 1131, 1074, 1023, 998, 973, 943, 928, 865, 833, 750, 694, 667 cm^{-1}; GC-MS: m/z (%) = 202 (68), 142 (54), 129 (100), 115 (46), 104 (20), 91 (33), 77 (16), 51 (9).

(*E*)-6-(2-Cyclohexylvinyl)tetrahydro-2*H*-pyran-2-one (6b)

According to the general procedure for cross-metathesis with the Hoveyda–Blechert catalyst, product **6b** could be isolated as a colorless oil; yield: 154 mg (0.74 mmol, 93%). $R_f = 0.30$ (petroleum ether/EtOAc 70:30); mp 35.6–36.0 °C; (*R*)-**6b**: $[\alpha]_D^{20}$: −41.2 (*c* 1.10 in $CHCl_3$), (*S*)-**6b**: $[\alpha]_D^{20}$: +42.5 (*c* 1.09 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 1.02$–1.12 (m, 2H, Cy), 1.16 (m_c, 1H, 4″-H), 1.22–1.32 (m, 2H, Cy), 1.61–1.68 (m, 2H, 4″-H, 5-H), 1.69–1.75 (m, 4H, Cy), 1.81–1.90 (m, 1H, 4-H), 1.90–2.01 (m, 3H, 1″-H, 4-H, 5-H), 2.47 (ddd, $J = 17.7$, 8.3, 6.9 Hz, 1H, 3-H), 2.58 (dddd, $J = 17.7$, 6.9, 5.4, 1.1 Hz, 1H, 3-H), 4.75 (dddd, $J = 9.9$, 6.5, 3.1, 1.0 Hz, 1H, 6-H), 5.44 (ddd, $J = 15.6$, 6.5, 1.4 Hz, 1H, 1′-H) 5.71 (ddd, $J = 15.6$, 6.6, 1.0 Hz, 1H, 2′-H); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 18.3$ (C-4), 25.9 (2C, Cy), 26.1 (Cy), 28.5 (C-5), 29.5 (C-3), 32.5 (Cy), 32.6 (Cy), 40.2 (C-1″), 80.9 (C-6), 125.5 (C-1′), 140.1 (C-2′), 171.5 (C-2); IR (film): $\nu_{max} = 2970$, 1923, 2851, 1737, 1448, 1366, 1350, 1232, 1217, 1204, 1161, 1091, 1036, 969, 928 cm^{-1}; HR-MS (ESI, positive ion): $m/z = 209.15353$, calcd. for $C_{13}H_{21}O_2$ $[M + H]^+$: 209.15361; anal. calcd. for $C_{13}H_{20}O_2$ (208.1): C 74.96, H 9.68; found: C 74.66, H 9.70.

(*E*)-6-(4-Methoxystyryl)-tetrahydro-2*H*-pyran-2-one (6c)

According to the general procedure for cross-metathesis with the Hoveyda–Blechert catalyst, product **6c** could be isolated as a colorless solid; yield: 99 mg (0.43 mmol, 54%). $R_f = 0.14$ (petroleum ether/EtOAc 70:30); mp 71.8–72.1 °C; (*R*)-**6c**: $[\alpha]_D^{20}$: +0.9 (*c* 0.90 in $CHCl_3$), (*S*)-**6c**: $[\alpha]_D^{20}$: −1.8 (*c* 1.09 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 1.76$ (dddd, $J = 13.8$, 10.0, 9.9, 5.2 Hz, 1H, 5-H), 1.91 (m, 13.5, 10.2, 8.4, 6.9, 5.0 Hz, 1H, 4-H), 1.99 (ddddd, $J = 13.5$, 7.1, 5.5, 5.3, 5.0 Hz, 1H, 4-H), 2.06 (ddddd, $J = 13.8$, 5.0, 5.0, 3.6, 1.0 Hz, 1H, 5-H), 2.52 (ddd, $J = 17.8$, 8.4, 7.1 Hz, 1H, 3-H), 2.63 (dddd, $J = 17.8$, 6.9, 5.5, 1.0 Hz, 1H, 3-H), 3.81 (s, 3H, OCH_3), 4.97 (dddd, $J = 9.9$, 6.3, 3.6, 1.2 Hz, 1H, 6-H), 6.07 (dd, $J = 15.9$, 6.3 Hz, 1H, 1′-H), 6.61 (dd, $J = 15.9$, 1.2 Hz, 1H, 2′-H), 6.85–6.88 (m, 2H, Ar-H), 7.31–7.34 (m, 2H, Ar-H); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 18.3$ (C-4), 28.6 (C-5), 29.6 (C-3), 55.3 (Me), 80.7 (C-6), 114.1 (2C, Ar), 124.8 (C-1′), 127.9 (2C, Ar), 128.7 (Ar), 131.8 (C-2′), 159.7 (Ar), 171.2 (C-2); IR (film): $\nu_{max} = 3035$, 2992, 2970, 2839, 1721, 1650, 1604, 1576, 1511, 1463, 1443, 1421, 1392, 1353, 1309, 1272, 1239, 1190, 1175, 1110, 1028, 972, 969, 933, 930, 918, 848, 822, 806 cm^{-1}; HR-MS (ESI, positive ion): $m/z =$ 233.11733, calcd. for $C_{14}H_{17}O_3$ $[M + H]^+$: 233.11722; anal. calcd. for $C_{14}H_{16}O_3$ (232.3): C 72.39, H 6.94; found: C 72.02, H 6.94.

General Procedure for the Synthesis of α,β-Unsaturated Lactones

N-Butyllithium (1.4 M in hexane, 267 μL, 0.37 mmol) was added to a solution of 52.5 μL diisopropylamine in 3 mL THF at −78 °C and stirred for 5 min. A solution of lactone **6a–c** (0.25 mmol) in 2 mL THF was added slowly followed by 80 mg (0.37 mmol) *N*-*tert*-butylbenzenesulfinimidoyl chloride (**12**) in 2 mL THF. After 30 min, the reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture was extracted with EtOAc (3×). The combined organic layer was washed with brine, dried over $MgSO_4$ and the solvent was evaporated. The obtained crude products were purified by flash column chromatography.

Goniothalamins (4a)

According to the general procedure for the synthesis of α,β-unsaturated lactones, 50 mg (0.25 mmol) of lactone **6a** were converted into goniothalamin (**4a**); yield: 31 mg (0.15 mmol, 63%). The spectroscopic data were in full agreement with previously published values.[16] $R_f = 0.25$ (petroleum ether/EtOAc 70:30); mp 83.8–85.0 °C; (*R*)-**4a**: $[\alpha]_D^{25}$: +172.5 (*c* 1.10 in $CHCl_3$), (*S*)-**4a**: $[\alpha]_D^{20}$: −174.2 (*c* 1.15 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 2.53$–2.56 (m, 2H, 5-H), 5.11 (dddd, $J = 9.1$, 6.3, 3.7, 1.2 Hz, 1H, 6-H), 6.09 (ddd, $J = 9.8$, 2.0, 1.6 Hz, 1H, 3-H), 6.28 (dd, $J = 16.0$, 6.3 Hz, 1H, 1′-H), 6.73 (dd, $J = 16.0$, 1.2 Hz, 1H, 2′-H), 6.93 (ddd, $J = 9.8$, 4.7, 3.7 Hz, 1H, 4-H), 7.27–7.42 (m, 5H, Ar-H); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 29.9$ (C-5), 78.0 (C-6), 121.7 (C-3), 125.6 (C-1′), 126.7 (Ar), 128.4 (C-2′), 128.7 (2 C, Ar), 133.1 (Ar), 135.8 (Ar), 144.6 (C-4), 163.9 (C-2); IR (film): $\nu_{max} =$

3058, 3027, 2937, 2896, 1718, 1653, , 1595, 1578, 1494, 1449, 1420, 1382, 1299, 1242, 1211, 1150, 1085, 1057, 1020, 966, 920,877, 830, 812, 749, 693, 662 cm^{-1}; GC-MS: *m/z* (%) = 200 (73), 172 (23), 155 (24), 131 (24), 115 (26), 104 (97), 91 (50), 77 (15), 68 (100), 51 (12).

(*E*)-6-(2-Cyclohexylvinyl)-5,6-dihydro-2*H*-pyran-2-one (4b)

According to the general procedure for the synthesis of α,β-unsaturated lactones, 50 mg (0.24 mmol) of lactone **6b** were converted into compound **4b** as a white solid; yield: 31 mg (0.15 mmol, 63%). The spectroscopic data were in full agreement with previously published values.[16] R_f 0.35 (petroleum ether/EtOAc 70:30); mp 43.5–44.0 °C; (*R*)-**4b**: $[\alpha]_D^{25}$: + 55.5 (*c* 0.95 in $CHCl_3$), (*S*)-**4b**: $[\alpha]_D^{20}$: −56.1 (*c* 1.05 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.03–1.12 (m, 2H, Cy), 1.12–1.20 (m, 1H, 4″-H), 1.26 (m, 3H, Cy), 1.60–1.68 (m, 1H, 4″-H), 1.73 (m, 3H, Cy), 1.99 (m_c, 1H, 1″-H), 2.42 (m, 2H, 5-H), 4.86 (m_c, 1H, 6-H), 5.53 (ddd, *J* = 15.6, 6.8, 1.4 Hz, 1H, 1′-H), 5.78 (ddd, *J* = 15.6, 6.6, 1.1 Hz 1H, 2′-H), 6.04 (ddd, *J* = 9.8, 1.8, 1.8 Hz 1H, 3-H), 6.87 (ddd, *J* = 9.8, 4.5, 3.8 Hz, 1H, 4-H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 25.9 (2 C, Cy), 26.1 (C-4″), 30.0 (C-5), 32.4 (Cy), 32.5 (Cy), 40.3 (C-1″), 78.5 (C-6), 121.6 (C-3), 124.3 (C-1′), 141.3 (C-2′), 144.7 (C-4), 164.2 (C-2); IR (film): ν_{max} = 2923, 2851, 1718, 1671, 1449, 1421, 1382, 1282, 1243, 1149, 1056, 1020, 967, 916, 870, 818 cm^{-1}; GC-MS: *m/z* (%) = 206 (12), 161 (15), 138 (11), 121 (84), 109 (13), 97 (34), 79 (53), 68 (100), 55 (20).

(*E*)-6-(4-Methoxystyryl)-5,6-dihydro-2*H*-pyran-2-one (4c)

According to the general procedure for the synthesis of α,β-unsaturated lactones, 35 mg (0.15 mmol) of lactone **6c** were converted into compound **4c** as a white solid; yield: 21 mg (0.09 mmol, 61%). The spectroscopic data were in full agreement with previously published values.[16] R_f = 0.13 (petroleum ether/EtOAc 70:30); mp 100.4–102.1 °C; (*R*)-**4c**: $[\alpha]_D^{20}$: +128.0 (*c* 1.10 in $CHCl_3$), (*S*)-**4c**: $[\alpha]_D^{20}$: −131.2 (*c* 0.90 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.52–2.55 (m, 2H, 5-H) , 3.82 (s, 3H, OCH_3), 5.08 (m, 1H, 6-H), 6.09 (dt, *J* = 9.8, 1.8 Hz, 1H, 3-H), 6.14 (dd, *J* = 15.9, 6.6 Hz, 1H, 1′-H), 6.67 (dd, *J* = 15.9, 1.1 Hz, 1H, 2′-H), 6.86–6.88 (m, 2H, Ar-H), 6.92 (ddd, *J* = 9.8, 4.5, 3.8 Hz, 1H, 4-H), 7.32–7.35 (m, 2H, Ar-H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 30.0 (C-5), 55.3 (Me), 78.3 (C-6), 114.1 (2 C, Ar), 121.7 (C-3), 123.4 (C-1′), 128.0 (2C, Ar), 128.5 (Ar), 132.9 (C-2′), 144.6 (C-4), 159.8 (Ar), 164.0 (C-2); IR (film): ν_{max} = 2972, 2932, 2835, 1708, 1676, 1649, 1606, 1575, 1514, 1456, 1441, 1422, 1379, 1343, 1272, 1255, 1179, 1147, 1120, 1108, 1055, 1027, 969, 936, 914, 872, 849, 810, 771 cm^{-1}; GC-MS: *m/z* (%) = 230 (100), 207 (31), 185 (91), 134 (82), 121 (59), 91 (21), 77 (22), 65 (13), 51 (11).

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