Tandem Reduction−Chloroallylboration of Esters: Asymmetric Synthesis of Lamoxirene, the Spermatozoid Releasing and Attracting Pheromone of the Laminariales (Phaeophyceae)

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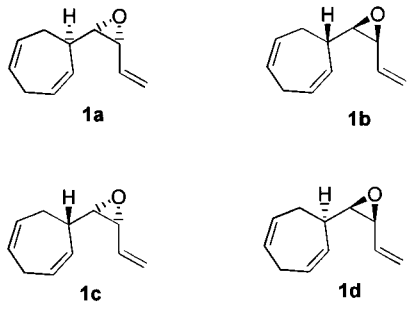
The asymmetric synthesis of all four stereoisomers of lamoxirene (*cis*-2-cyclohepta-2,5-dienyl-3-vinyloxirane), the spermatozoid-releasing and -attracting pheromone of the Laminariales (Phaeophyceae), is reported. Chiral ethyl cyclohepta-2,5-diene carboxylates, prepared by a divinylcyclopropane Cope rearrangement, were effectively alkylated by means of a novel tandem DIBAL-H reduction/asymmetric α-chloroallylboration using (*Z*)-γ-chloroallyldiisopinocampheylboranes. The ensuing *syn*-α-chlorohydrins were transformed into the corresponding vinyloxiranes with DBU, providing all four isomers of the pheromone in good chemical and excellent optical yield (90−97% ee). Spermatozoid-release assays were conducted with the sympatrically growing species *L. digitata*, *L. hyperborea*, and *L. saccharina* and established (1′*S*,2*R*,3*S*)-**1c** as the most active isomer in all cases.

Introduction

During the sexual reproduction of many marine brown algae, a highly specific and complex signaling occurs between the mating organisms.[1,2] Especially in the highly evolved orders Laminariales, Desmarestiales, and Sporochnales, chemical signals released from mature eggs synchronize the events of the reproductive cycle by first inducing spermatozoid release from the male reproductive organs (antheridia) and second by attracting the liberated male spermatozoids to the calling female.[3,4] The active principle was first isolated from extracts of fertile eggs of *Laminaria digitata*[5] and finally identified as *cis*-2-cyclohepta-2,5-dienyl-3-vinyloxirane (**1**).[6] Subsequent studies with other members of the Laminariales established lamoxirene (**1**) as a general trait of the genus that typically triggers the spermatozoid release and attraction at threshold concentrations as low as 30 pmol.[2,7] Detailed chemical analyses of the female-derived signal blends revealed, besides lamoxirene (**1**), the presence of several other structurally related C_{11} hydrocarbons, byproducts of a common biosynthetic pathway.[1,2] However, these compounds have no significant effect on the *Laminaria* males. Recent work on the absolute configuration of lamoxirene (**1**) proved that the chemical messenger is released from eggs of *L. digitata* as a mixture of diastereomers (71% **1a**, 29% **1c**; Scheme 1),[8] while the sympatric species *Undaria pinnatifida* sequests one single isomer (**1a**, >97% ee).[9] Considering that all of the hitherto examined Laminariales utilize the same signal compound, with these findings it appears reasonable to assume that the secretion of enantiomeric mixtures may serve as a means for the individualization of the signal blends of plants sharing the same habitat. While similar strategies are known for many insects, at present, there is no precedent for the plant kingdom.[10]

Scheme 1



To gain more insight into structure−activity aspects of the signaling process of marine brown algae, the individual diastereoisomers of lamoxirene (**1**) were required for biological studies. Here, we report the first enantioselective synthesis of all four possible lamoxirene isomers **1a**−**d** by means of asymmetric tandem reduction−chloroallylboration of the cycloheptadiene esters **3a** and **3b**. This methodology is a promising implement for the preparation of enantiomerically enriched vinyloxiranes from stable carboxylic esters.

Results and Discussion

Stereodivergent Synthesis of the Lamoxirene Isomers. Owing to the intrinsic frailness of lamoxirene (**1**), it appeared rational to introduce the oxirane moiety at the last step of the synthesis. For the preparation of chiral *cis*-vinyloxiranes, Oehlschlager and co-workers

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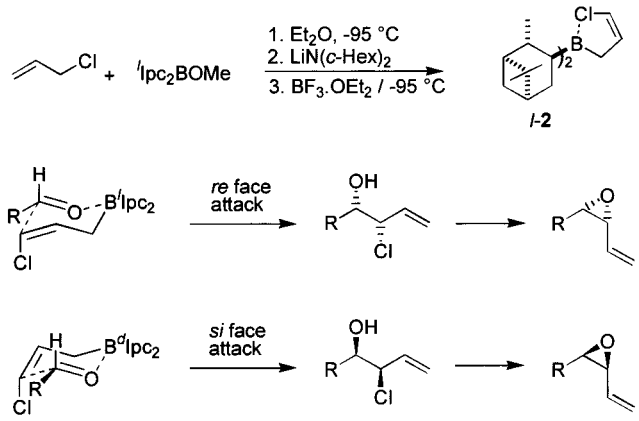
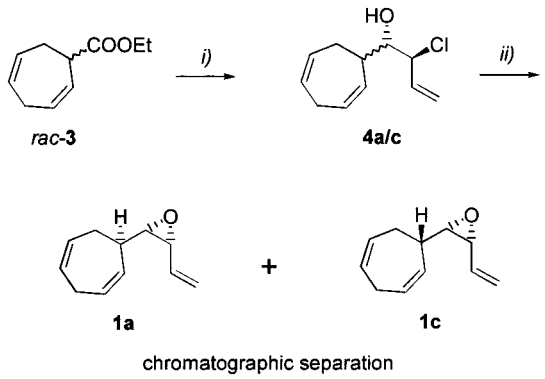
Scheme 2



recently introduced the asymmetric α-chloroallylboration of aldehydes and subsequent base-mediated ring closure of the ensuing *syn*-chlorohydrins as an excellent novel synthetic method[11−13] that appeared to be ideal for this purpose.[14] Chiral γ-(*Z*)-chloroallylboranes,[11,12] *d*-**2** and *l*-**2**, can be prepared in situ from readily available $^{l}Ipc_2BOMe$ or $^{d}Ipc_2BOMe$,[15] allyl chloride and lithium dicyclohexylamide at −95 °C (Scheme 2). With achiral model aldehydes, *syn*-halohydrins and *cis*-vinyloxiranes are obtained with remarkably high diastereoselectivity and enantiomeric excess,[12] and, as a capital advantage of the diisopinocampheyl auxiliaries, the configuration of the newly generated sp^3-center of the allylboration products is predictable. On the basis of reliable mechanistic models, *l*-**2** preferentially performs a *re* facial attack of the carbonyl, while with *d*-**2**, the *si* face is selectively allylated (Scheme 2).[15b]

Unfortunately, the β,γ-unsaturated cyclohepta-2,5-diene carbaldehyde required for allylation proved to be subject to facile isomerization and epimerization. For this reason, we decided to generate this carbonyl compound in situ by reduction of the corresponding ester **3** at low temperature (−78 °C) with DIBAL-H[16] prior to allylation. This strategy has already been established, among others, for the synthesis of racemic *cis*- and *trans*-lamoxirene.[17,18] In general, addition of the resulting organoaluminum intermediate to a preformed solution of the allylation agent in Et_2O at −95 °C was expected to trap the β,γ-unsaturated aldehyde after decomposition of the aluminoacetal. Initial experiments using aromatic and aliphatic carboxylic esters for asymmetric in situ reduction−chloroallylboration showed that neither diastereomeric nor enantiomeric excess of the ensuing vinyloxiranes was altered in comparison with those reported by Oehlschlager and co-workers.

Scheme 3. Stereodivergent Synthesis of the Lamoxirene Isomers[a]



[a] The transformation of *rac*-**3** is demonstrated only for **1a** and **1c**. (i) (1) DIBAL-H, −78 °C, (2) *l*-**2**, −95 °C, (3) 8-HQ (8-hydroxyquinoline), rt; (ii) DBU, 0 °C (one pot).

Table 1. Results of Stereodivergent and Double Diastereoselective Synthesis of the Lamoxirene Isomers 1a−d

			% ee[a]			
entry	substrate	reagent	**1a**	**1b**	**1c**	**1d**
1	*rac*-**3**	*l*-**2**	88		95	
2	*rac*-**3**	*d*-**2**		77		90
3	**3a**	*l*-**2**	97			
4	**3a**	*d*-**2**				96
5	**3b**	*d*-**2**		90		
6	**3b**	*l*-**2**			>97	

[a] The ee of individual isomers was determined by chiral GLC (see the Experimental Section).

The most convenient and straightforward approach to all four isomers of lamoxirene **1a−d** would be a stereodivergent synthesis starting from readily available *rac*-**3** (Scheme 3). Tandem reduction−chloroallylboration of *rac*-**3** with asymmetric allylation agents *l*-**2** or *d*-**2** and subsequent cyclization of the halohydrins was expected to give a pair of separable diastereomers. In fact, sequential low-temperature reduction of *rac*-**3** with DIBAL-H and in situ α-chloroallylboration with *l*-**2** in Et_2O at −95 °C resulted in a successful trapping of the sensitive β,γ-unsaturated aldehyde without competing rearrangement. Workup and stirring with 8-hydroxyquinoline[19] cleaved the rather stable oxygen−boron bond under mild conditions and provided a pair of *syn*-chlorohydrins in high configurational purity (97:3, syn/anti, according to GLC) and good overall yields (55−62%) from *rac*-**3**. Since the corresponding pair of diastereoisomeric vinyloxiranes proved to be easily separable by chromatography, the crude mixture of halohydrins was cyclized by treatment with DBU prior to separation.

For both *d*-**2** and *l*-**2**, sequential reduction with DIBAL-H and asymmetric chloroallylboration of racemic ester finally provided pairs of diastereoisomeric vinyloxiranes **1a/c** and **1b/d** with very good syn/anti ratio (98:2) and good enantiomeric excess (77−95% ee, see Table 1). This stereodivergent route, thus, represents a highly effective short-step approach (three isolated steps start-

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(13) Hu, S. J.; Jayaraman, S.; Oehlschlager, A. C. *J. Org. Chem.* **1998**, *63*, 3, 8843.
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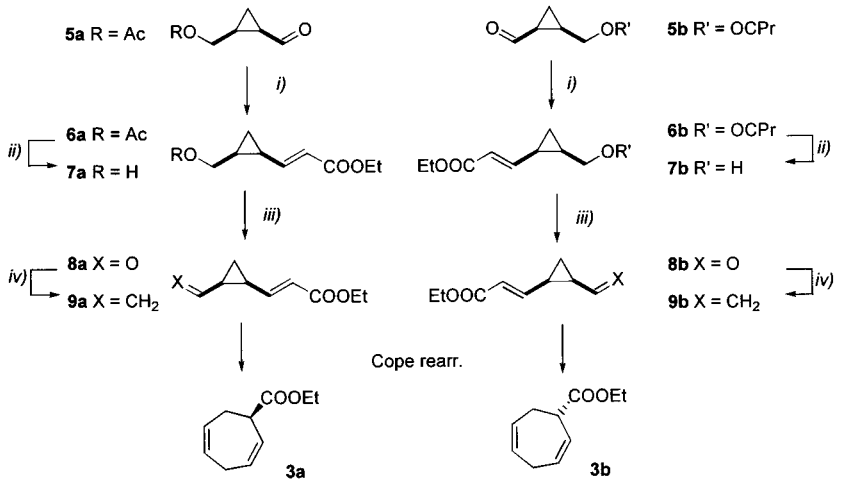
Scheme 4. Synthesis of Chiral Ethyl Cyclohepta-2,5-dienecarboxylates[a]



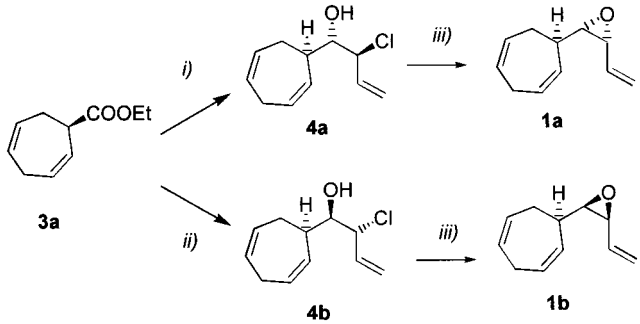
[a] Key: (i) $(EtO)_2P(O)CH_2COOEt$, DBU, LiCl, CH_3CN, rt; (ii) $Ti(O\text{-}i\text{-}Pr)_4$, C_2H_5OH; (iii) Swern oxidation; (iv) $CH_2{=}P(C_6H_5)_3$.

ing from butadiene, 21−23% overall yield)[17] to enantiomerically enriched lamoxirene isomers. However, for a reliable comparative bioassay synthetic samples with ee ≫ 90% are required, and hence, another course applying double diastereoselection had to be followed.

Double Diastereoselective Synthesis. The stereodivergent tandem reduction−chloroallylboration of racemic ester *rac*-**3** indicated a limited enantiotopos discrimination of the asymmetric allylation agents *d*-**2** and *l*-**2**. This obstruction was meant to be overcome by double diastereoselection using chiral substrates **3a** and **3b** and asymmetric allylation agents *d*-**2** and *l*-**2**. Consequently, the *re*- and *si*-faces of the carbonyl become diastereotopes, and the resulting diastereomers were separable to give enantiopure samples.[20] For this purpose, optically pure cyclohepta-1,5-diene esters were required as substrates.

Synthesis of Chiral Ethyl Cyclohepta-1,5-dienecarboxylates. For the preparation of enantiomerically enriched cyclohepta-2,5-diene carboxylates, enzymatic and chemical resolution of *rac*-**3** have already been described.[21] However, the enzymatic approach with *Rhodotorula minuta* var. did not provide products with acceptable optical purity (<78% ee), and the chemical separation of the racemate (up to 95% ee) using quinine proved to be unsatisfactory due to low yields (<6%).[21] Moreover, the absolute configuration and the optical purity of the products have not been rigorously addressed. Alternatively, chiral functionalized cyclohepta-2,5-dienes are easily accessible via a stereocontrolled Cope rearrangement of substituted divinylcyclopropanes[22] as has been demonstrated previously en route to other brown algae pheromones.[23] As a result of the strictly attended boat conformation of the divinylcyclopropane moiety during the [3,3]-sigmatropic rearrangement, the absolute configuration of the seven-membered ring is unambiguously predictable, and a defined (*E*)- or

Scheme 5. Double Diastereoselective Tandem Reduction and Chloroallylboration of 3a[a]



[a] Key: (i) (1) DIBAL-H, (2) *l*-**2**, (3) 8-HQ; (ii) (1) DIBAL-H, (2) *d*-**2**, (3) 8-HQ; (iii) DBU (one pot) (43−51%).

(*Z*)-geometry of the double bond cleanly translates to the absolute configuration. As starting materials were used the enantiomeric cyclopropyl aldehydes **5a** (97% ee) and **5b** (99% ee),[24−26] both readily available on a multigram scale from meso compounds such as *cis*-1,2-cyclopropyldimethanol by enzyme catalyzed esterification[26] and the corresponding bis-butyrate by enzymatic saponification[25] using porcine pancreatic lipase (PPL)[27,28] as the biocatalyst (Scheme 4). Swern oxidation[25] and subsequent Horner−Emmons olefination[29] of the aldehydes **5a** and **5b**

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(27) For a review on the use of PPL in organic synthesis, see: Hertweck, C.; Boland, W. *J. Prakt. Chem.* **1997**, *339*, 200.

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using DBU/LiCl as base provided α,β-unsaturated esters **6a** and **6b** quantitatively and free from (*Z*)-isomers.[29] To improve the optical purity, acetate **6a** was recrystallized from ether/pentane at − 78 °C to give enantiopure (99% ee) material. Transesterification of **6a** and **6b** with titanium tetraisopropoxide in ethanol[30] afforded 84−90% of the deprotected alcohols **7a** and **7b**. No isomerizations or intramolecular cyclizations to ethers were observed along the entire sequence. Finally, sequential Swern oxidation and Wittig olefination with methylidenetriphenylphosphorane established the vinyl side chain. To avoid undesired 1,4-attack of the ylide onto the acrylate moiety, the Wittig reagent was slowly added at −78 °C to the aldehyde until GC monitoring indicated complete consumption of **8a** and **8b**. Upon warming to ambient temperature, the thermolabile divinylcyclopropanes **9a** and **9b** rearranged spontaneously to give the cyclohepta-2,5-dienes **3a** and **3b** in 85−88% yield. Gas chromatographic analysis of the purified esters on chiral stationary phase indicated optical purity (>98% ee) for both antipodes.

Double Asymmetric Allylation. Chiral ethyl cyclohepta-2,5-diene carboxylates **3a** and **3b** were individually subjected to reduction−chloroallylboration with *d*-**2** and *l*-**2**, as described for the stereodivergent route (Scheme 5). The corresponding vinyloxiranes were readily available in good overall yield (43−51%). After careful chromatographic purification, highly pure samples of lamoxirene isomers (90−97% ee, >97% de) were obtained.[31] In contrast to recently published results on excellent diastereoselectivities in the matched case, and moderate to good diastereoselectivity in the mismatched case,[13] the chloroallylboration of **3a** and **3b** proceeded apparently reagent controlled. Yields and enantiomeric excess of the individual isomers are within the same range (except of the combination *rac*-**3**/*d*-**2**) and thus do not give evidence for matched or mismatched cases (Table 1).

Biological Activity of Lamoxirenes 1a−d. The tandem reduction and double diastereoselective α-chloroallylboration of chiral cycloheptadiene esters provides a feasible and highly selective approach to all four possible isomers of lamoxirene (**1**), the spermatozoid releasing and attracting pheromone of the industrially important large kelps. Isomerically pure samples of 90−97% ee were sufficiently pure for first comparative bioassays with different species of the sympatrically growing Laminariales *L. digitata, L. hyperborea,* and *L. saccharina*.

The biological activity of **1a−d** for gamete mass release was assessed by adding defined solutions of the lamoxirene isomers **1a−d** in seawater to fertile male gametophytes in seawater. Mass release of spermatozoids occurred within seconds after addition of solutions with the bioactive compounds.[32] Interestingly, all three species (Table 2) showed the lowest threshold concentration for the same lamoxirene isomer (1′*S*,2*S*,3*R*)-**1c**. Data concerning the enantiomeric composition of the natural secretions and bioassays with defined enantiomeric mixtures of lamoxirene (**1**) to study potential synergistic or antagonistic effects along with results for other species from the two taxa Laminariales and Alariaceae will be presented elsewhere.[9]

Table 2. Biological Activity (nM) of Lamoxirenes 1a−d

	lamoxirenes			
algal species	**1a**	**1b**	**1c**	**1d**
Laminaria digitata	1	1	0.1	10
Laminaria hyperborea	0.1	0.1	0.01	2
Laminaria saccharina	1	2	1	20

The biological activity of **1a−d** for gamete mass release was determined using the three sympatrically growing species *L. digitata, L. hyperborea,* and *L. saccharina*.[32] The threshold concentrations represent concentrations of the pheromone in seawater.

Exploratory experiments with a number of aliphatic and aromatic esters promise the asymmetric reductive chloroallylboration to be a general method for the preparation of enantiomerically enriched *cis*-vinyloxiranes from generally more stable esters precursors. The approach bypasses the isolation of labile aldehyde intermediates, such as α-hydroxy or α-amino aldehydes, and hence, the novel protocol will give access to wide range of biologically relevant as well as synthetically useful vinyloxiranes that are difficult to prepare using other methods.[33]

Experimental Section

General Methods. All reactions were carried out under argon in flame-dried glassware using standard gastight syringes, cannulas, and septa. Solvents and reagents were dried prior to use according to standard procedures. Thin-layer chromatography was performed with silica gel plates. Column chromatographic separations were performed with silica gel (Merck) and Florisil (>200 mesh, Aldrich). ^{d}Ipc$_2$BOMe, ^{l}Ipc$_2$BOMe, and B-MeO-9BBN were purchased from Aldrich Co. ^{1}H and ^{13}C NMR: Chemical shifts of ^{1}H (400/500 MHz) and ^{13}C NMR (100/125 MHz) are given in ppm (δ) downfield relative to TMS as internal standard. Enantiomeric excess (ee) was determined by chiral GC using a FS-Lipodex E capillary column, 25 m × 0.25 mm (Macherey-Nagel, Düren, Germany) using a racemic reference to optimize separation.[17] Elemental analyses were performed by the Microanalytical Laboratory of the Kekulé-Institute of Organic Chemistry, University Bonn, Germany.

(1*S*,2*S*)-3-(2-Acetoxymethylcyclopropyl)acrylic Acid Ethyl Ester (6a). To a suspension of lithium chloride (4.4 g, 82 mmol) in dry acetonitrile (100 mL) at room temperature were added triethyl phosphonoacetate (18.38 g, 82 mmol), 1,8-diazabicyclo-[5.4.0]-undec-7-ene (10.2 g, 67 mmol), and finally, aldehyde **5a** (9.5 g, 67 mmol). After the mixture was stirred for 10 min at room temperature, water (30 mL) was added, and the pH was immediately adjusted to 7.0 by quick titration with dilute HCl. The aqueous phase was extracted with ether, and the combined organic phases were washed with brine and dried over $MgSO_4$. After evaporation of the solvent in vacuo, the residue was purified by FC on silica with 1:1 pentane/diethyl ether. Yield: 13.2 g (93%). The light yellow oil could be crystallized from pentane at −30 °C and yielded a colorless semisolid material: $[\alpha]^{23}_D = +2.71$ (*c* 1.15, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.68 (q, *J* = 5.5 Hz, 1H), 1.14 (dt, *J* = 8.4, 5.5 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.55 (m, 1H); 1.73 (m, 1H), 2.0 (s, 3H), 3.88 (dd, *J* = 11.8, 8.4 Hz, 1H), 4.12 (q, 2H), 4.22 (dd, *J* = 11.8, 7.0 Hz, 1H), 5.88 (d, *J* = 15.2 Hz, 1H), 6.60 (dd, *J* = 15.2, 10.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.1, 14.3, 19.1, 19.2, 20.9, 60.2, 64.4, 121.4, 148.0, 166.2, 171.0; IR (KBr, film) ν 2983, 2904, 1739, 1717, 1646, 1266, 1190 cm^{-1}; EIMS, [IP 70 eV; *m*/*z* (rel int)] 212 ($M^{\bullet+}$, 1), 152 (5), 124 (8),

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(31) A slight degree of epimerization (1−3%) could not be excluded.

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95 (4), 79 (27), 59 (20), 53 (5), 43 (100). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.13; H, 7.68.

(1*R*,2*R*)-3-(2-Butyryloxymethylcyclopropyl)acrylic Acid Ethyl Ester (6b). Prepared from **5b** (13.1 g, 71 mmol) by analogy to **6a**: yield 15.5 g, 91%; colorless oil; $[\alpha]^{25}_D = +3.65$ (*c* 1.48, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.67 (q, $J = 5.5$ Hz, 1H), 0.87 (t, $J = 7.6$ Hz, 3H), 1.13 (dt, $J = 8.5, 5.5$ Hz, 1H), 1.21 (t, $J = 7.5$ Hz, 3H), 1.51−1.61 (m, 3H), 1.67−1.76 (m, 1H), 2.21 (t, $J = 7.3$ Hz, 2 H), 3.88 (dd, $J = 11.7, 8.4$ Hz, 1H), 4.10 (q, $J = 7.5$ Hz, 2H), 4.22 (dd, $J = 11.9, 6.6$ Hz, 1H), 5.88 (d, $J = 15.5$ Hz, 1H), 6.59 (dd, $J = 15.5, 10.0$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.1, 13.5, 14.2, 18.4, 19.2, 20.4, 36.1, 60.1, 64.0, 121.3, 147.9, 166.1, 173.5; IR (KBr, film) ν 2966, 2939, 2876, 2811, 1734, 1717, 1647, 1266, 1189, 982 cm^{-1}; EIMS, [IP 70 eV; *m*/*z* (rel int)] 241 ($M^{\bullet+} + 1$, 2), 170 (16), 152 (9), 124 (8), 96 (15), 71 (82), 43 (100). Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.51; H, 8.28.

(1*S*,2*S*)-3-(2-Hydroxymethylcyclopropyl)acrylic Acid Ethyl Ester (7a). A solution of ester **6a** (6.36 g, 30 mmol) and titanium tetraisopropoxide (0.85 g, 3.5 mmol) in ethanol (150 mL) was heated to reflux for 6 h under an argon. After being cooled to 40 °C, the solution was poured into 1.0 M HCl (30 mL) and extracted with ether. The organic phase was washed with saturated aqueous $NaHCO_3$ and dried over $MgSO_4$. After removal of the solvent in vacuo, the crude oil was purified by FC on silica with 1:4 pentane/ether: yield 4.6 g (90%); colorless, viscous oil; $[\alpha]^{23}_D = +17.1$ (*c* 1.47, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.64 (q, $J = 5.5$ Hz, 1H), 1.12 (dt, $J = 8.2, 5.5$ Hz, 1H), 1.22 (t, $J = 7.2$ Hz, 3H), 1.53 (m, 1H), 1.70 (m, 1H), 2.4 (s, 1H), 3.50 (dd, $J = 11.8, 8.5$ Hz, 1H), 3.76 (dd, $J = 11.8, 6.9$ Hz, 1H), 4.10 (q, 2H), 5.90 (d, $J = 15.2$ Hz, 1H), 6.65 (dd, $J = 15.2, 10.2$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.1, 14.3, 19.1, 23.4, 60.2, 62.5, 120.9, 149.1, 166.7; IR (KBr, film) ν 3413, 2983, 2938, 2877, 1712, 1643, 1267, 1042, 733 cm^{-1}; EIMS, [IP 70 eV; *m*/*z* (rel int)] 170 ($M^{\bullet+}$, 13), 152 (31), 138 (15), 124 (27), 112 (30), 97 (47), 81 (100), 67 (65), 53 (76). Anal. Calcd for $C_9H_{14}O_3$: C, 63.50; H, 8.29. Found: C, 63.55; H, 8.26.

(1*R*,2*R*)-3-(2-Hydroxymethylcyclopropyl)acrylic Acid Ethyl Ester (7b). Prepared from (1*R*,2*R*)-3-(2-butyryloxymethylcyclopropyl)acrylic acid ethyl ester (**6b**) (7.2 g, 30 mmol) by analogy to **7a**: yield 4.28 g (84%); colorless oil; $[\alpha]^{25}_D = -16.95$ (*c* 1.51, CH_2Cl_2). Spectroscopic data identical with **7a**.

(1*S*,2*S*)-3-(2-Formylcyclopropyl)acrylic Acid Ethyl Ester (8a). A solution of oxalyl chloride (1.1 mL, 13 mmol) in dichloromethane (50 mL) was cooled to −78 °C, and DMSO (1.7 mL, 23.5 mmol) in dichloromethane (20 mL) was added dropwise. After being stirred for 10 min at −78 °C, a solution of the alcohol **7a** (2.0 g, 11.8 mmol) in dichloromethane (20 mL) was slowly added and stirring was continued for 20 min prior to the addition of triethylamine (8.2 mL, 59 mmol). The solution was allowed to warm to room temperature, and following hydrolysis with water (100 mL), the aqueous phase was extracted with ether. The combined organic layers were successively washed with 1% HCl, H_2O, a saturated aqueous solution of $NaHCO_3$, and brine and dried over Na_2SO_4. After removal of the solvents, the crude product (1.85 g, 93%) was used without purification for olefination: yellow oil; $[\alpha]^{22}_D = +4.96$ (*c* 1.27, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, $J = 7.2$ Hz, 3H), 1.50 (dt, $J = 5.9, 8.0$ Hz, 1H), 1.59 (q, $J = 5.2$ Hz, 1H), 2.20 (m, 1H), 2.30 (m, 1H), 4.11 (q, 2H), 5.90 (d, $J = 15.6$ Hz, 1H), 6.75 (dd, $J = 15.6, 9.9$ Hz, 1H), 9.40 (d, $J = 4.5$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 15.6, 25.7, 30.9, 60.4, 123.1, 144.7, 165.8, 199.2; IR (KBr, film) ν 2983, 2843, 2737, 1714, 1649, 1266 cm^{-1}; EIMS, [IP 70 eV; *m*/*z* (rel int)] 168 ($M^{\bullet+}$, 31), 123 (100), 112 (18), 95 (27), 55 (31). Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.36; H, 7.15.

(1*R*,2*R*)-3-(2-Formylcyclopropyl)acrylic Acid Ethyl Ester (8b). Prepared from (1*R*,2*R*)-3-(2-hydroxymethylcyclopropyl)acrylic acid ethyl ester **(7b)** (2.0 g, 11.8 mmol) by analogy to **8a**: yield 1.92 g, 97%); colorless oil; $[\alpha]^{25}_D = -5.0$ (*c* 1.44, CH_2Cl_2). Spectroscopic data identical with **8a**.

(1*R*)-Ethyl 2,5-Cycloheptadienecarboxylate (3a). A solution of aldehyde **8a** (0.84 g, 5.0 mmol) in THF (30 mL) was cooled to −78 °C and slowly titrated with a preformed solution of methylidenetriphenylphosphorane [prepared from methyltriphenylphosphonium bromide (2.14 g, 6.0 mmol) and *n*-BuLi (3.1 mL 1.6 M soln. in hexanes, 5 mmol) in THF (20 mL) at −78 °C] by cannulation until GC control indicated complete consumption of the starting material. Then, the reaction mixture was warmed and poured into a saturated aqueous solution of NH_4SO_4 (20 mL). Extractive workup with ether followed FC on silica with 1:2 pentane/ether: colorless, fruity smelling liquid; yield 0.71 g (85%); $[\alpha]^{24}_D = -13.09$ (*c* 1.10, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.3 (t, 3H), 2.5 (m, 2H), 2.6−3.0 (m, 2H), 3.5 (m, 1H), 4.1 (q, 2H), 5.9 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 28.1, 29.6, 43.5, 60.7, 128.6, 128.7, 129.1, 129.5, 174.1. All spectroscopic data were in agreement with those reported.[21]

(1*S*)-Ethyl 2,5-Cycloheptadienecarboxylate (3b). Prepared from aldehyde **8b** (0.84 g, 5.0 mmol) in analogy to **3a**: yield 0.73 g, 88%; fruity smelling, colorless liquid; $[\alpha]^{24}_D = +13.21$ (*c* 1.12, CH_2Cl_2). Spectroscopic data were identical with those reported.[21]

Asymmetric Tandem Reduction and Chloroallylboration: General Procedure. (1′*R*,2*S*,3*R*)-2-Cyclohepta-2,5-dienyl-3-vinyloxirane, (1′*R*,2*S*,3*R*)-Lamoxirene, 1a. Reduction of the Ester 3a. A solution of ethyl cyclohepta-2,5-dienecarboxylate **3a** (0.50 g, 3.0 mmol) in a mixture of dry toluene/pentane (10.0 mL, v/v = 1:1) was cooled to −78 °C. DIBAL-H (3.0 mL 1.0 M solution in hexanes, 3.0 mmol) was added slowly through a precooled cannula by a syringe pump at a rate of 0.2 mL/min to the well-stirred solution of **3a**. Stirring was continued (ca. 45 min) until GLC indicated >95% reduction of the starting material.

Preparation of Chloroallylborane *l*-2.[12] A cold (−95 °C) and well-stirred solution of allyl chloride (0.49 mL, 6.0 mmol) and ^{l}Ipc$_2$BOMe (1.42 g, 4.5 mmol) in ether (20.0 mL) was gradually treated with a solution of LiN(*c*-Hex)$_2$ [prepared in THF (10.0 mL) from dicyclohexylamine (1.2 mL, 6.0 mmol) by deprotonation with *n*-BuLi (3.75 mL 1.6 M solution in hexane, 6.0 mmol) and stirring at 0 °C for 0.5 h]. The mixture was stirred at −95 °C for 1 h, and BF_3·OEt_2 (1.26 mL, 10.0 mmol) was added slowly.

In Situ Alkylation. The organoboron reagent was stirred for another 30 min at −95 °C, and then the solution of the reduced ester was carefully added by cannulation. The mixture was stirred at −95 °C for an additional 6 h and allowed to come to room temperature. Following removal of the solvents in vacuo at room temperature, the crude residue was treated with dry pentane, filtered under argon through a small pad of Celite, and rinsed with dry pentane (2 × 40 mL). The combined filtrates were evaporated in vacuo at room temperature. The residual semisolid was dissolved in chilled ether (50.0 mL), and a solution of 8-hydroxyquinoline (2.9 g, 20.0 mmol) in ether (30.0 mL) was added slowly with concomitant formation of a heavy fluorescent suspension. Stirring was continued for 6 h at 0 °C, the precipitate was filtered off, and the organic layer was extracted with water to remove inorganic and polar compounds. After drying (Na_2SO_4), the solvent was evaporated in vacuo at room temperature.

Base-Mediated Cyclization. The resulting crude oil was dissolved in dichloromethane (25.0 mL) and gradually treated with a solution of DBU (1.5 mL, 10.0 mmol) in the same solvent (5.0 mL) at 0 °C. Stirring was continued at 0 °C until TLC showed quantitative conversion of the halohydrin (ca. 8 h). The mixture was poured into 10% $NaHCO_3$ solution (20 mL), the organic layer was separated, and the aqueous phase was extracted with ether (4 × 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo at room temperature. The crude product was purified by flash chromatography on Florisil (>200 mesh) using a pentane/ether gradient for elution. Lamoxirene was obtained as an intensively fruity smelling, colorless liquid: yield 43−51% (from **3a**); $[\alpha]^{25}_D = +45.0$ (*c* 0.42, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.19−2.61 (m, 3H), 2.81−2.92 (m, 2H), 3.03 (dd, $J = 9, 4.3$ Hz, 1H), 3.48 (dd, $J = 8.5, 4.3$ Hz, 1H), 5.36 (dd, $J = 10, 1$ Hz, 1H), 5.49 (dd, $J = 17, 1$ Hz, 1H), 5.61−5.89 (m, 5H); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 29.3, 30.4, 36.7,

57.5, 61.4, 120.9, 128.6, 129.0, 129.2, 129.5, 132.5. Spectroscopic data were identical with those reported.[17]

(1′*S*,2*R*,3*S*)-2-Cyclohepta-2,5-dienyl-3-vinyloxirane, (1′*S*,-2*R*,3*S*)-Lamoxirene, 1b. Prepared from **3b** and *d*-**2** by analogy to **1a**. Spectroscopic data are identical with those for **1a**: $[\alpha]^{25}_D = -40.3$ (*c* 0.79, CH_2Cl_2).[17]

(1′*S*,2*S*,3*R*)-2-Cyclohepta-2,5-dienyl-3-vinyloxirane, (1′*S*,-2*S*,3*R*)-Lamoxirene, 1c. Prepared from **3b** and *l*-**2** by analogy to **1a**. Spectroscopic data are identical with those for **1a**: $[\alpha]^{26}_D = -61.7$ (*c* 0.47, CH_2Cl_2).[17]

(1′*R*,2*R*,3*S*)-2-Cyclohepta-2,5-dienyl-3-vinyloxirane,(1′*R*,-2*R*,3*S*)-Lamoxirene, 1d. Prepared from **3a** and *d*-**2** by analogy to **1a**. Spectroscopic data are identical with **1a**: $[\alpha]^{24}_D = +66.3$ (*c* 0.49, CH_2Cl_2).[17]

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