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Highly Efficient Synthesis of (±)-Lamoxirene, the Gamete-Releasing and Gamete-Attracting Pheromone of the Laminariales (Phaeophyta)

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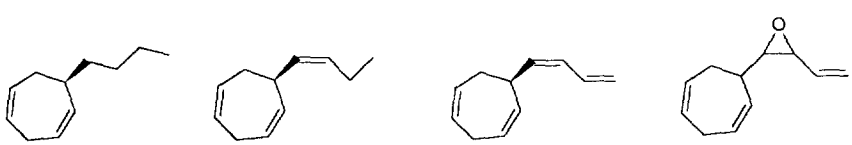
Abstract: An efficient and highly diastereoselective synthesis of lamoxirene (*cis*-2-cyclohepta-2,5-dienyl-3-vinyloxirane, **4**), the gamete releasing and -attracting pheromone of the Laminariales (Phaeophyceae), is reported. Ethyl cyclohepta-2,5-diene carboxylate (**7**) is effectively alkylated to provide the *syn*-α-chlorohydrin **8** *via* reductive chloroallylboration with DIBAL-H and (*Z*)-γ-chloroallyl-BBN. Cyclisation of the chlorohydrin **8** is readily achieved with DBU yielding the pheromone in 25% overall yield from the cyclopropyl ester **5**. © 1997 Elsevier Science Ltd.

The sexual reproduction of many marine brown algae is controlled by environmental and chemical factors.[1,2] In the highly evolved orders Laminariales, Desmarestiales, and Sporochnales chemical signals released from fertile eggs effectively synchronise the events of the reproductive cycle by first inducing spermatozoid release from the antheridia and secondly by attracting the liberated male gametes to the calling female.[3,4] The active principle was first isolated from exudes of fertile eggs of *Laminaria digitata*[3] and finally identified as *cis*-2-cyclohepta-2,5-dienyl-3-vinyloxirane (**4**). It was called lamoxirene according to its structure, function and origin.[5] Subsequent studies with other members of the Laminariales established lamoxirene as a general trait of the genus which typically triggers the gamete-release and gamete-attraction at threshold concentrations as low as 10 pM.[6]



dictyotene **1** ectocarpene **2** desmarestene **3** lamoxirene **4**

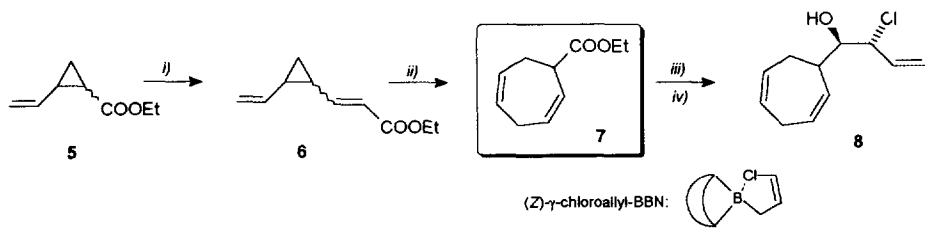
Scheme 1

Detailed chemical analyses of the female-derived signal blends revealed, besides lamoxirene, the presence of several other structurally related C_{11} hydrocarbons like for example dictyotene (**1**), ectocarpene (**2**) and desmarestene (**3**).[7] All of them are known as pheromones of other brown algae species, but, since none of the hydrocarbons had a significant biological effect (Scheme 1) on the Laminaria males, **1**, **2**, and **3** apparently represent only by-products of a common biosynthetic pathway. Recent work on the absolute configuration of the chemical messenger evidenced that lamoxirene is released from eggs of *L. digitata* as a mixture of enantiomers.[8] Considering that all of the hitherto examined Laminariales utilise the same signal compound, it appears reasonable to assume that the secretion of enantiomeric mixtures may serve as a means for the individualisation of the signal blends of plants sharing the same habitat. Similar strategies are well established for the insect kingdom.[9]

To gain more insight into structure-activity aspects of the signalling process of marine brown algae, the individual diastereoisomers of lamoxirene and related compounds are required for biological studies. The first, and, as yet, only synthesis of lamoxirene was achieved by random epoxidation of desmarestene with *m*-CPBA

and yielded **4** and the regioisomeric epoxides in low yield (≈ 2%) together with ca. 20 by-products, all of which had to be separated by tedious chromatographic operations.[5] Here we describe the first diastereoselective synthesis of **4** using the readily available vinylcyclopropyl ester (±)-**5** as the starting material.[10] The key step of the sequence is based on a novel „reductive chloroallylboration" of the ester **7** which by-passes the preparation of the corresponding unstable aldehyde intermediate. The method is of generally applicability for the conversion of esters into *syn*-chlorohydrins and (*Z*)-vinyloxiranes.

The cyclohepta-2,5-diene ester **7**, which represents a useful starting material for the preparation of all the 6-substituted cyclohepta-2,4-diene pheromones from brown algae, is most conveniently prepared from *cis/trans* ethyl 2-vinylcyclopropyl carboxylate (**5**). The latter is readily available in bulk quantities from butadiene and ethyl diazoacetate by rhodium(II) acetate catalysis[11] without the need for high pressure[10] equipment (76 % yield, *cis/trans*-**5**: 43/57). Reductive olefination[12] of the ester by successive treatment of **5** with DIBAL-H and the anion of triethylphosphonoacetate in a „one pot" procedure furnished *cis/trans* **6** in 54% overall yield. While the *cis*-isomer suffered from a spontaneous [3.3]-sigmatropic rearrangement at rt., brief heating of the crude mixture (xylene, 130°) was required for a quantitative conversion of all isomers into **7**.



i) 1.0 eq. DIBAL-H, -78 °C, 1.5 eq. $(EtO)_2POCH_2COOEt$, *n*-BuLi; *ii)* reflux (xylene), (54 %);
iii) 1.0 eq. DIBAL-H, -78 °C, 1.5 eq. (*Z*)-γ-chloroallyl-BBN, -95 °C; *iv)* 8-hydroxyquinoline (57 %)

Scheme 2

For the transformation of the ester **7** into lamoxirene (**4**), the *syn*-selective chloroallylboration of a corresponding cyclohepta-2,4-diene aldehyde according to the protocol of Oehlschlager[13,14] promised to be a very attractive method. However, owing to the facile isomerisation of the β,γ-unsaturated aldehyde intermediate required for alkylation, we decided to generate this carbonyl compound *in situ* by reduction of the ester **7** at low temperature (-78°) with DIBAL-H. Addition of the resulting organoaluminum intermediate to a preformed solution of (*Z*)-γ-chloro-BBN in Et_2O at -95° was expected to trap the β,γ-unsaturated aldehyde after decomposition of the organo aluminum compound.[12,15] In fact, the *syn*-chlorohydrin was obtained in high configurational purity (97:3, *erythro:threo*)[16] and without competing rearrangement of the β,γ-unsaturated aldehyde. Work-up and stirring with 8-hydroxyquinoline[17] cleaved the rather stable oxygen-boron bond under mild conditions and provided the *syn*-chlorohydrin **8** in 57% overall yield from **7**.

Scheme 3

Owing to the intrinsic lability of the pheromone **4**,[5] the transformation of the *syn*-chlorohydrin into lamoxirene failed with the commonly employed bases like, for example, K_2CO_3/MeOH, sodium ethoxide or potassium *t*-butoxide. Instead, treatment of **8** with non-nucleophilic bases (Hünig's base, BEMP, DBU)[18] was more

successful. Best results were obtained by stirring of **8** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane at 0 °C, and lamoxirene was obtained in high yield (81 %) and high configurational purity (*cis:trans* = 97:3).[16] DBU, immobilised on polystyrene, proved to be unsuccesful.[19]

In summary, we have developed a straightforward and highly effective synthesis of lamoxirene **(4)**, the gamete-releasing and -attracting pheromone of the industrially important kelps *via* reductive chloroallylboration of the cyclohepta-2,4-diene ester **7** (25 % overall yield from **5**). Exploratory experiments with a number of aliphatic and aromatic esters promise the reductive chloroallylboration to be a general method for the preparation of *cis*-vinyloxiranes from esters via *syn*-chlorohydrin intermediates. Moreover, the method is compatible with chiral organoboron reagents and, thus, provides a convenient access to chiral vinyloxiranes from stable ester precursors. As a first application the synthesis of the four optically active lamoxirene isomers will be reported soon.

EXPERIMENTAL

General: Reactions were performed under argon; solvents were dried according to standard methods. Dicyclohexylamine was distilled from CaH_2, allyl chloride from P_4O_{10} prior to use. IR: Perkin-Elmer Series 1600 FTIR Spectrophotometer. ^1H and ^{13}C NMR: Bruker AC 250 or Bruker AC 400 Spectrometer; $CDCl_3$ as solvent. Chemical shifts are given in ppm (δ) downfield relative to TMS. GC-MS (70 eV): Finnigan ITD 800 coupled with a Carlo Erba GC 6000 gas chromatograph, Model Vega, equipped with a WCOT fused silica column, 15m x 0.32mm, CP-SIL 5, Chrompack, Middelburg, The Netherlands. HR-MS: Kratos MS 50. Chromatography: silica gel, Si 60 (70-230 mesh, E. Merck, Darmstadt, Germany) and Florisil® (100-200 mesh, Aldrich Co.).

syn-2-Chloro-1-cyclohepta-2,5-dienyl-but-3-en-1-ol (8)

Reduction of the ester **7**: A solution of freshly distilled ethyl cyclohepta-2,5-diene carboxylate **(7)** (2.49 g, 15.0 mmol) in a mixture of dry toluene/pentane (50.0 ml, *v:v* = 1:1) was cooled to -78 °C. DIBAL-H (15.0 ml 1.0 M soln. in hexanes, 15.0 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 **7**. Stirring was continued (ca. 45 min) until GLC indicated >95 % reduction of the starting material.

Preparation of chloroallylborane: A solution of allyl chloride (2.44 ml, 30.0 mmol) and 9-MeO-9-BBN (22.5 ml 1.0 M soln. in hexanes) in ether (100.0 ml) was gradually treated with stirring at -95 °C with a solution of $LiN(^cHex)_2$ {prepared in THF (50.0 ml) from dicyclohexylamine (5.97 ml, 30.0 mmol) by deprotonation with *n*-BuLi (18.75 ml 1.6 M soln. in hexane, 30.0 mmol) and stirring at 0 °C for 0.5 h}. The mixture was stirred at -95 °C for 1 h, and $BF_3{\cdot}OEt_2$ (6.28 ml, 50.0 mmol) was added slowly.

In situ alkylation: The organoboron reagent was stirred for further 30 min at -95 °C and, then, the above solution of the reduced ester was carefully added by cannulation. The resulting mixture was stirred at -95 °C for an additional 6 h, and it was then allowed to come to rt. Following removal of the solvents *i.v.* at rt., the crude residue was treated with dry pentane, filtered through a small pad of Celite under argon and rinsed with dry pentane (2 x 40.0 ml). The combined filtrates were evaporated *i.v.* at rt.. 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 *i.v.* at rt., and the resulting crude oil was purified on silica gel using a pentane/ether gradient. Colourless oil. Yield: 1.69 g (57 %). ^1H NMR ($CDCl_3$, 250 MHz): δ 2.25-3.08 (5H, m), 3.71 (1H, pseudo dt, *J*=8, 3.5 Hz), 4.63 (1H, dd, *J*=8, 3.5 Hz), 5.22 (1H, dd, *J*=10, 1 Hz), 5.49 (1H, dd, *J*=17, 1 Hz), 5.64-5.86 (4H, m), 6.05 (1H, ddd, *J*=17, 10, 8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 27.8, 29.6, 41.7, 67.0, 76.1, 118.5, 127.9, 129.1, 130.1, 131.0, 136.1. IR (KBr,

film) 3442*br.*, 3015, 2927, 1683, 1646, 1420, 1381, 1079, 989, 909, 733 cm^{-1}. MS, *m/z* 163 ($M^{+\bullet}$, -35)(4), 145(13), 123(13), 105(39), 95 (20), 94(49), 93(82), 92(49), 91(100), 79(94), 77(67), 70(22), 67(17), 66(10), 65(11). HR-MS, *m/z* calcd for $C_{11}H_{15}O$ ($M^{+\bullet}$-Cl): 163.1122, found: 163.1119.

cis-2-Cyclohepta-2,5-dienyl-3-vinyloxirane (4, Lamoxirene)

A well-stirred and chilled solution of **8** (0.99 g, 5.0 mmol) in dry dichloromethane (40.0 ml) was gradually treated with a solution of DBU (2.24 ml, 15.0 mmol) in the same solvent (10.0 ml). Stirring was continued for 7 h at 0 °C. Then, the mixture was poured into a cold aqueous solution of $Cu(OAc)_2$ (20.0 ml, 5 %), the organic layer was separated, and the aqueous phase was extracted with ether (3 x 20.0 ml). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *i.v.* at rt. The crude product was purified by flash chromatography on Florisil® using a pentane/ether gradient for elution. Lamoxirene was obtained as an intensively fruity smelling, colourless liquid. Yield: 0.65 g (81 %). ^1H NMR ($CDCl_3$, 250 MHz): δ 2.19-2.61 (3H-C(1', 7'), m), 2.81-2.92 (2H-C(4'), m), 3.03 (1H-C(2), dd, *J*=9, 4.3 Hz), 3.48 (1H-C(3), dd, *J*=8.5, 4.3 Hz), 5.36 (1H-(HC=C$\underline{H}_2$), dd, *J*=10, 1 Hz), 5.49 (1H-(HC=C$\underline{H}_2$), dd, *J*=17, 1 Hz), 5.61-5.89 (5H-(C=C), ($\underline{H}$C=CH_2), m). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 29.3 (C(4')), 30.4 (C(7')), 36.7 (C(1')), 57.5 (C(3)), 61.4 (C(2)), 120.9 (HC=$\underline{C}H_2$), 128.6 (C=C), 129.0 (C=C), 129.2 (C=C), 129.5 (C=C), 132.5 ($H\underline{C}$=CH_2)). IR (KBr, film) 3014, 2963, 2905, 2846, 1654, 1447, 1406, 1338, 1257, 985, 925, 827, 683 cm^{-1}. MS, *m/z* 162 ($M^{+\bullet}$)(0.5), 147(0.6), 143(0.5), 131(3), 129(5), 106(9), 105(23), 103(6), 93(27), 92(33), 91(100), 79(28), 78(47), 77(30), 71(18), 67(9), 66(6), 65(10), 57(39), 56(42). HR-MS, *m/z* calcd for $C_{11}H_{14}O$ ($M^{+\bullet}$): 162.1044, found: 162.1010.

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