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Article

A Short and Efficient Enantioselective Synthesis of (+) and (-)-(*Z*)-7,15-hexadecadien-4-olide. The Sex Pheromone of the Yellowish Elongate Chafer, *Heptophylla picea*

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Os enantiômeros (*R*) e (*S*) da *Z*-7,15-hexadecadien-4-olida (**4**), o feromônio sexual da *Heptophylla picea* foram sintetizados. Na etapa chave foi utilizada uma enantiolactonização já conhecida, intermediada por uma lipase, levando a um precursor comum de ambos enantiômeros do feromônio em 92% de e.e.

The (*R*) and the (*S*) enantiomers of the *Z*-7,15-hexadecadien-4-olide (**4**), the sex pheromone of *Heptophylla picea*, were synthesized. A known lipase-catalysed enantiolactonization in the key step afforded a common precursor for both enantiomers of the pheromone in 92% e.e.

Keywords: pheromone, *Heptophylla picea*, lipase

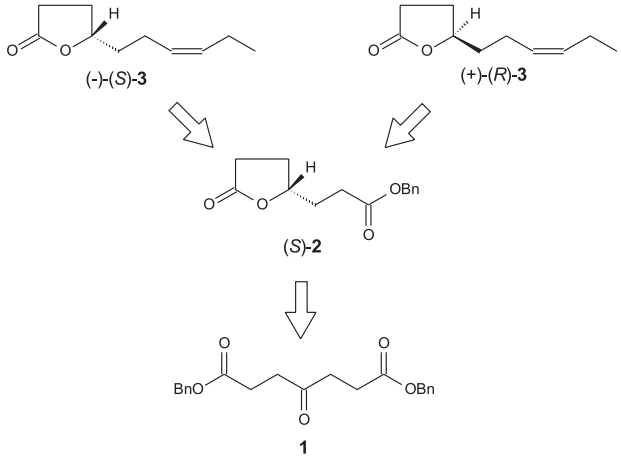
Introduction

Several classes of compounds such as pheromones,[1] aromas[2,3] and plant growth regulators[4] exhibit a γ-butyrolactone unity in their structures. Since the biological activity of such compounds often dependes on their absolut configuration, much work has been done to develop enantioselective routes to γ-butyrolactones.[5]

Recently we initiated a program aiming at the synthesis of enantiomericaly pure naturally occurring lactones using enzymes in a deracemization step.[6-8] A versatile protocol introduced by us consists in the application of a methodology developed by Gutmam and coworkers, which transforms the commercially available 4-ketopimelic acid (**1**) into the chiral lactone (*S*)-(-)-**2**, which was transformed in our laboratory into both (*S*)[7] and (*R*)[8] isomers of jasmolactone **3**, a compound with organoleptic properties, described as fruity, flowery, green, creamy, sweet and juicy[3] (Scheme 1).

This strategy is interesting since the common intermediate **2** can lead to both enantiomers of a naturaly occurring γ-butyrolactone. The female sex pheromone of the Yellowish Elongate Chafer (*Heptophylla picea*) (**4**)[9] would be a good candidate to demonstrate the versatility of our methodology.

Compound (*R*)-**4** was prepared by Leal and coworkers in 14 steps starting from L-malic acid.[9,10] Mori and Nakayama obtained (*R*)-**4** and (*S*)-**4** in respectively 95% and 94% e.e. through an enzymatic resolution of racemic **4** using different enzymes in more than one enzymatic step.[10,11]



Scheme 1.

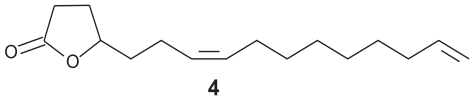


Figure 1. (Z)-7,15-hexadecadien-4-olide.

Results and Discussion

Scheme 2 shows the retrosynthetic analysis for (*R*)- and (*S*)-(*Z*)-7-15-hexadecadien-4-olide (**4**) using our approach.

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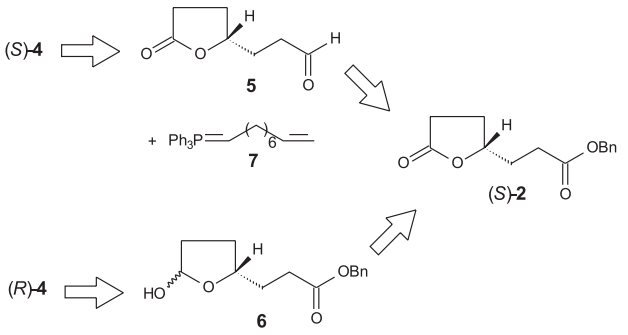
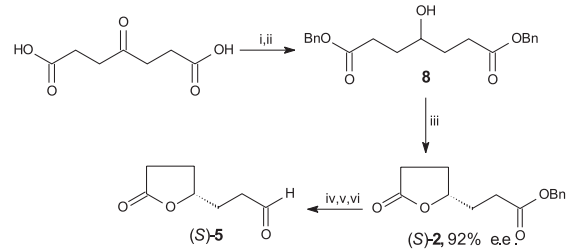


Scheme 2.

Compound (*S*)-**2** would be transformed into aldehyde **5** or into lactol **6**, which upon reaction with the *Wittig* reagent **7** would give (*S*)-**4** and (*R*)-**4**.

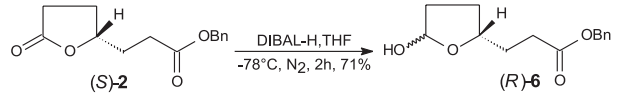
The synthesis of (*S*)-**4** started with the reduction of 4-ketopimelic benzyl ester as described previously (Scheme 3).[7,12] The obtained alcohol **8** was submitted to enantioselective lactonization by PPL leading to (*S*)-**2** in 92% e.e.[12] The (*S*) configuration of the lactone **2** was attributed by comparision of its specific rotation, $[\alpha]_D^{20}$ = -32,7 (c = 1.04; CH_2Cl_2), with the literature value, $[\alpha]_D^{25}$ = -40,86 (c = 0.74; CH_2Cl_2),[12] and its enantiomeric excess was determined by means of chiral HPLC.[7] Transformation of the ester function of (*S*)-**2** into an aldehyde was achieved by deprotection of the benzyl group followed by reduction with borane-methyl sulfide complex (BMS) and oxidation with pyridinium chlorochromate (PCC).[7,12] Using this procedure, the integrity of the stereogenic center was preserved and (*S*)-**5** was the product (Scheme 3).



Reagents and conditions:
(i) CrCO3, DMF / MeOH, pH 7.0, BnBr, r. t., 17h (84%); (ii) NaBH4, Et2O / MeOH, -20°C, 2h (95%); (iii) PPL, Et2O, 30°C, 24h (74%); (iv) Pd / C 10%, H2, 1 atm, 3h (95%); (v) BMS, THF, r. t., 2h (90%); (vi) PCC, CH2Cl2, r. t., 2h (90%).

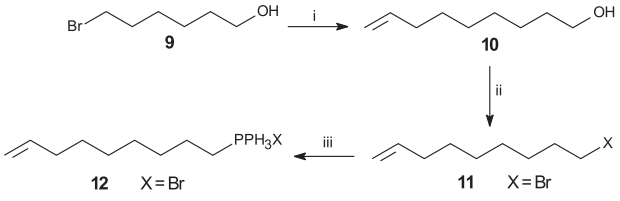
Scheme 3.

The lactol **6** was prepared by reduction of (*S*)-**2** with a slight excess of DIBAL-H in THF at –78 °C as previously reported[8] (Scheme 4).



Scheme 4.

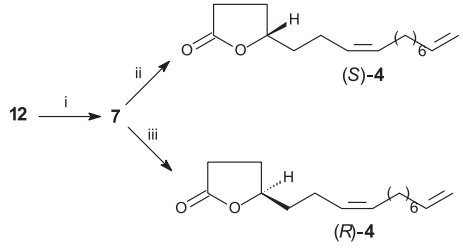
The phosphonium salt **12**, precursor of the *Wittig* reagent **7**, was obtained starting from the commercially available 6-bromo-1-hexanol **9**, which upon treatment with allylmagnesium bromide in THF in the presence of dilithium tetrachlorocuprate gave 8-nonenol **10** (Scheme 5). The bromide **11** was prepared by treating **10** with triphenylphosphine bromine complex in acetonitrile. The phosphonium salt **12** was prepared by refluxing triphenylphosphine and **11** in acetonitrile.[10]



Reagents and conditions:
(i) allylmagnesium bromide, Li2CuCl4, THF, 0°C to r. t.,18h (83%);
(ii) Ph3P-Br2, MeCN, -10°C to r. t., 1h (11b, 93%); (iii) PPh3, MeCN, reflux, 48h (12, 96%).

Scheme 5.

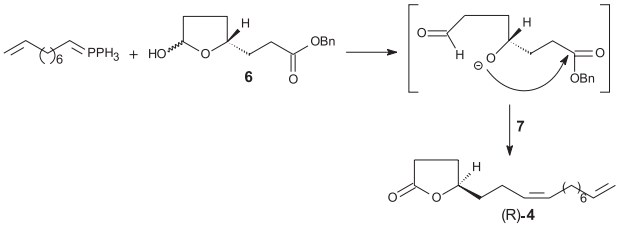
The *Wittig* reagent **7** was obtained by treatment of the phosphonium bromide **12** with sodium hexamethyldisilazide in THF at –40 °C and then reacted with **5** or **6** to give (*S*)-**4** and (*R*)-**4**, respectively, in 92% e.e. (Scheme 6).



Reagents and conditions:
(i) NaHMDS, THF, -40°C; (ii) (S)-5, THF, -100°C,1.5h (60%, Z/E = 96:4, 92% e.e.);
(iii) (R)-6, THF, -100°C, 1.5h (55%, Z/E = 96:4,92% e.e.)

Scheme 6.

For preparation of compound (*R*)-**4**, two equivalents of **7** were used. The first equivalent deprotonates the OH group opening the lactol ring and the second transforms the aldehyde into an olefine. The alkoxy oxygen at C_4 promotes a transesterification reaction of the benzyl ester group generating the lactone ring of (*R*)-**4** (Scheme 7).



Scheme 7.

Compounds (*S*)-**4** and (*R*)-**4** were obtained as *Z/E* mixtures (96 : 04), which were purified by column chromatography on silica gel impregnated with $AgNO_3$ to afford the desired products in pure form. The absolute configuration of both enantiomers was attributed by comparing the $[\alpha]^D$ values of our products with those reported in the literature.[10] Attempts to determine the enantiomeric excess of (*S*)-**4** and (*R*)-**4** by chiral gas chromatography were unsuccessful. In view of this failure compounds (*S*)-**4** and (*R*)-**4** were hydrogenated using Pd/C as catalyst and the products were analysed by chiral GC using a β-cyclodextrine as a chiral phase on a capillary column. This analysis showed that both (*S*)-**4** and (*R*)-**4** were obtained with 92% e.e. (Figure 2).

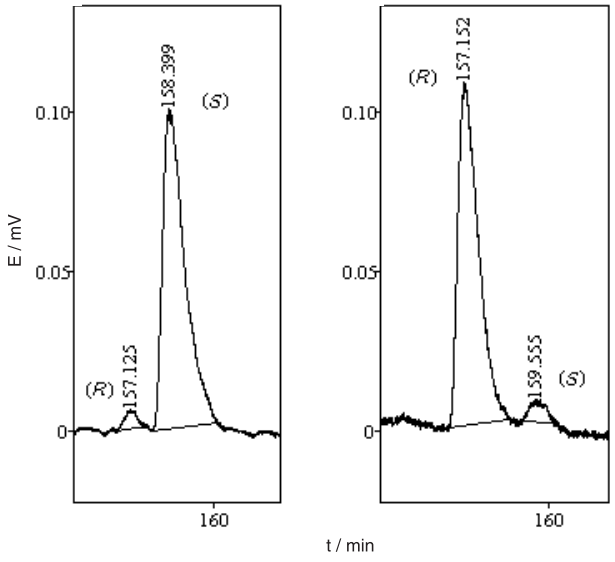


Figure 2. Chiral chromatograms of hydrogenated (S)-**4** and (R)-**4**.

In conclusion, (*S*) and (*R*)-(*Z*)-7,15-hexadecadien-4-olide (**4**) were obtained in high enantiomeric excess in 4 and 3 steps respectively, starting from the easily prepared common intermediate (*S*)-**2**. With the completion of this synthesis we showed that (*S*)-**2** is a versatile precursor of both enantiomers of naturally occurring γ-butyrolactones.

Experimental

General experimental procedures

The NMR spectra were recorded on Brucker DRX-500, Varian Inova (300 MHz) and Brucker AC-200 spectrometers using TMS (^{1}H NMR) and the central peak of the $CDCl_3$ signal (^{13}C NMR) as internal reference. IR spectra were obtained with a FTIR Bomem MB100 grating infrared spectrophotometer. The GC analysis were performed on a Hewlett-Packard 5890(II) instrument with a capillary crosslinked 5% Ph-Me silicone column (25 m x 0.20 mm x 0.33 μm) and on a Shimadzu GC-17A instrument equipped with a Chirasil-DEX CD (Crompack) chiral phase capillary column (30 m x 0.25 mm x 0.25 μm). The mass spectra were performed on a Shimadzu GC-17A/QP5050A spectrometer. Optical rotations were measured on a Jasco, DIP 370 digital polarimeter. The enzymatic reactions were monitored in a Shimadzu LC10AD HPLC. 8-Nonen-1-ol (**10**) and 9-bromo-1-nonene (**11**) were prepared as described in the literature.[10]

*Triphenyl-(8-noneyl)-phosphonium bromide, (**12**)*

A solution of 9-bromo-1-nonene, (**11**) (0.97 g, 4.72 mmol) and triphenylphosphine (1.78 g, 6.80 mmol) in acetonitrile (12 mL) was refluxed for 24 h under Ar. The acetonitrile was concentrated *in vacuo*, and the excess of PPh_3 was removed by chromatography on silica gel eluting with ethyl acetate / methanol (80 : 20) to give 2.12g (96%) of the phosphonium salt **12** as a gum. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.25 (br. s, 6H), 1.63 (m, 4H), 1.92-1.95 (m, 2H), 3.71 (br. s, 2H), 4.86-5.0 (m, 2H), 5.73 (ddt, *J* 16.7 Hz, 10.1 Hz and 6.58 Hz, 1H), 7.60-7.90 (m, 15H); IR (KBr) ν_{max}/cm^{-1}: 2932, 1431, 1104, 996, 733, 687, 521.

*(S)-7,15-Hexadecadien-4-olide, [(S)-**4**]*

To a solution of the dry phosphonium salt **12** (0.25 g, 0.53 mmol) in dry THF (4 mL) NaHDMS (0.58 mL, 0.58 mmol, 1 M THF solution) was added at –40 °C under Ar. After 10 min of stirring at the same temperature, the resulting orange solution was transferred via canula to a solution of the aldehyde **5** (0.071 g, 0.5 mmol) in dry THF (4 mL) at –78 °C under Ar. After stirring for 90 min at the same temperature, the reaction mixture was quenched with saturated NH_4Cl solution. The organic layer was separated, and the aqueous layer was extracted with diethyl ether. The organic layer was washed with water and brine, dried with $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by chromatography in silica gel impregnated with $AgNO_3$ eluting with pentane/diethyl ether (2 : 1) to give 0.074 g (60%) of the (*S*)-7,15-hexadecadien-4-olide [(*S*)-**4**]. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.21-1.4 (m, 8H), 1.5-1.7 (m, 1H), 1.75-1.91 (m, 2H), 2.00-2.08 (m, 4H), 2.16-2.22 (m, 2H), 2.33 (ddt, *J* 13.3 HZ, 6.8 HZ and 6.4 Hz, 1H), 2.53 (m, 2H), 4.50 (ddt, *J* 7.9 Hz, 6.7 Hz and 5.3 Hz, 1H), 4.9 (ddt, *J* 10.2 Hz, 3.3 Hz and 1.2 Hz, 1H), 4.98 (ddt, *J* 17.2 Hz, 13.6 Hz and 1.6 Hz, 1H), 5.35 (ddt, *J* 12.3 Hz, 7.2 Hz and 1.4 Hz, 1H), 5.45 (ddt, *J* 12.3 Hz, 7.2 Hz and 1.4 Hz,

1H), 5.8 (ddt, *J* 17.4 Hz, 10.3 Hz and 5.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.4, 27.4, 28.2, 29.0, 29.1, 29.3, 29.4, 29.8, 34.0, 35.9, 80.6, 114.4, 127.9, 131.7, 139.4, 177.4; IR (KBr) ν_{max}/cm^{-1}: 3104, 1775, 1667, 1452, 1362, 1177, 906; MS (m/z) (%rel): 41 (100), 55 (83.3), 67 (99.5), 79 (72.7), 93 (44.8), 107 (24.7), 121 (27.9), 135 (19), 150 (30.8), 166 (4), 177 (2.3), 190 (1.3), 207 (1.3); $[a]_D^{25}$: - 34.8 (c = 0.5, $CHCl_3$).

*(R)-7,15-Hexadecadien-4-olide, [(R)-**4**]*

To a solution of the dry phosphonium salt **12** (0.568 g, 1.06 mmol) in dry THF (8 mL) NaHDMS (1.16 mL, 1.16 mmol, 1 mol L^{-1} THF solution) was added at –40 °C under Ar. After 10 min of stirring the same temperature, the resulting orange solution was transferred via canula to a solution of lactol **6** (0.125 g, 0.5 mmol) in dry THF (4 mL) at –78 °C under Ar. After stirring for 90 min at the same temperature, the reaction mixture was quenched with a saturated NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with diethyl ether. The organic layer was washed with water and brine, dried with $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by chromatoghraphy in silica gel impregnated with $AgNO_3$ eluting with pentane / diethyl ether (2 : 1) to give 0.067 g (55%) of the (*R*)-7,15-hexadecadien-4-olide, [(*R*)-**4**]. The spectroscopic data agree with those of (*S*)-**4**. $[\alpha]_D^{25}$: + 35.1 (c = 0.5, $CHCl_3$).

*Enantiomeric purity of (S)-**4** and (R)-**4***

Compound (*S*)-**4** and (*R*)-**4** were hydrogenated to the corresponding 4-hexadecanolide by stirring in CH_3OH for 1 h under hydrogen atmosphere in the presence of catalytic amount of Pd/C. The solution was filtered through a short silica gel pad and directly injected in a gas chromatograph equipped with a Chirasil-DEX CD (Crompack) chiral phase capillary column. Separation of enantiomers was performed using the following gradient temperature program 145 °C (130 min) to 155 °C (30 min) at 1° C min^{-1} gradient. Carrier gas pressure (H_2) was 60 kPa. The injector and detector temperatures were maintained at 220 °C. The hydrogenated (*S*)-**4** and (*R*)-**4** were identified by their mass spectra. MS (*m/z*) (%rel): 28 (100), 29 (53), 41 (47), 43 (47), 55 (48), 57 (33), 69 (30), 83 (24), 85 (83) 254 (1).

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