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THERMOSTABLE ENZYMES IN ORGANIC SYNTHESIS, 5.# TOTAL SYNTHESIS OF S-(+)-Z-DODEC-3-EN-11-OLIDE (FERRULACTONE II) USING A TBADH-GENERATED BIFUNCTIONAL CHIRON.

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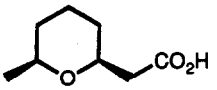
Abstract: The total synthesis of (S)-(+)-ferrulactone (**2**), one of several synergistic aggregation pheromones produced by male flat grain beetles, *Cryptolestes ferrugineus* (Stephens) was achieved in a five-step synthesis in very high optical purity (>99% ee) and 17.5% chemical yield, starting from (S)-(+)-methyl-8-hydroxynonanoate (**5**) and a three-carbon Wittig reagent **11**. The nine-carbon bifunctional chiron **5** was obtained from methyl 8-oxononanoate via enantioselective reduction with *Thermoanaerobium brockii* alcohol dehydrogenase (TBADH).

A reliable and widely applied approach to the total synthesis of optically active biochemicals and pharmaceuticals involves the use of readily available chiral starting materials (chirons).[1] One time-tested method for producing novel chiral building blocks, particularly those not easily derived from common natural products, is enzymatic synthesis.[2] In preceding papers,[3,4,5] we have introduced a wide variety of chiral mono- and bifunctional aliphatic secondary alcohols that were efficiently produced by reduction of the corresponding ketones with the aid of *Thermoanaerobium brockii* alcohol dehydrogenase (TBADH). Besides the remarkably broad range of substrates reduced by this enzyme, excellent enantioselectivities were achieved in most cases.

These bifunctional, chiral alcohols are excellent building blocks that may be conveniently employed for syntheses of natural products containing chiral carbinol centers. We exemplified this approach by the employment of S-(+)-5-chloropentan-2-ol in the total synthesis of (+)-(S,S)-(cis-6-methyltetrahydropyran-2-yl)acetic acid, **1**, a natural constituent of the perfume material civet.[4,6]



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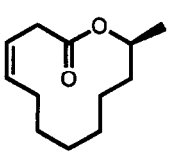

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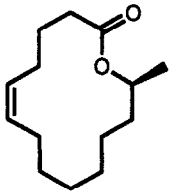


3

Of particular interest are the naturally occurring macrolides,[7] many of which contain a methyl carbinol moiety, frequently characterized by an S configuration (e.g. zearalenone, curvularin, brefeldin A, etc.). We

decided to demonstrate this advantage by the total synthesis of two insect pheromones, (S)-(+)-Z-dodec-3-en-11-olide (ferrulactone II) (**2**) and (S)-(+)-Z-tetradec-5-en-13-olide (**3**). Ferrulactone II is one of several synergistic aggregation pheromones produced by male rusty grain beetles, *Cryptolestes ferrugineus* (Stephens), a widely distributed pest that primarily infests stored grains.[8] The 14-membered macrolide **3** is a corresponding pheromone of the flat grain beetle, *Cryptolestes pusillus* (Schonherr),[9] another major world-wide pest of stored grains.[10] These pheromones stimulated synthetic efforts[9b,11] due to the possibility that these macrolides could be utilized to increase the efficiency of detection traps for *C. ferrugineus* and *C. pusillus* in grain storage facilities.[12]

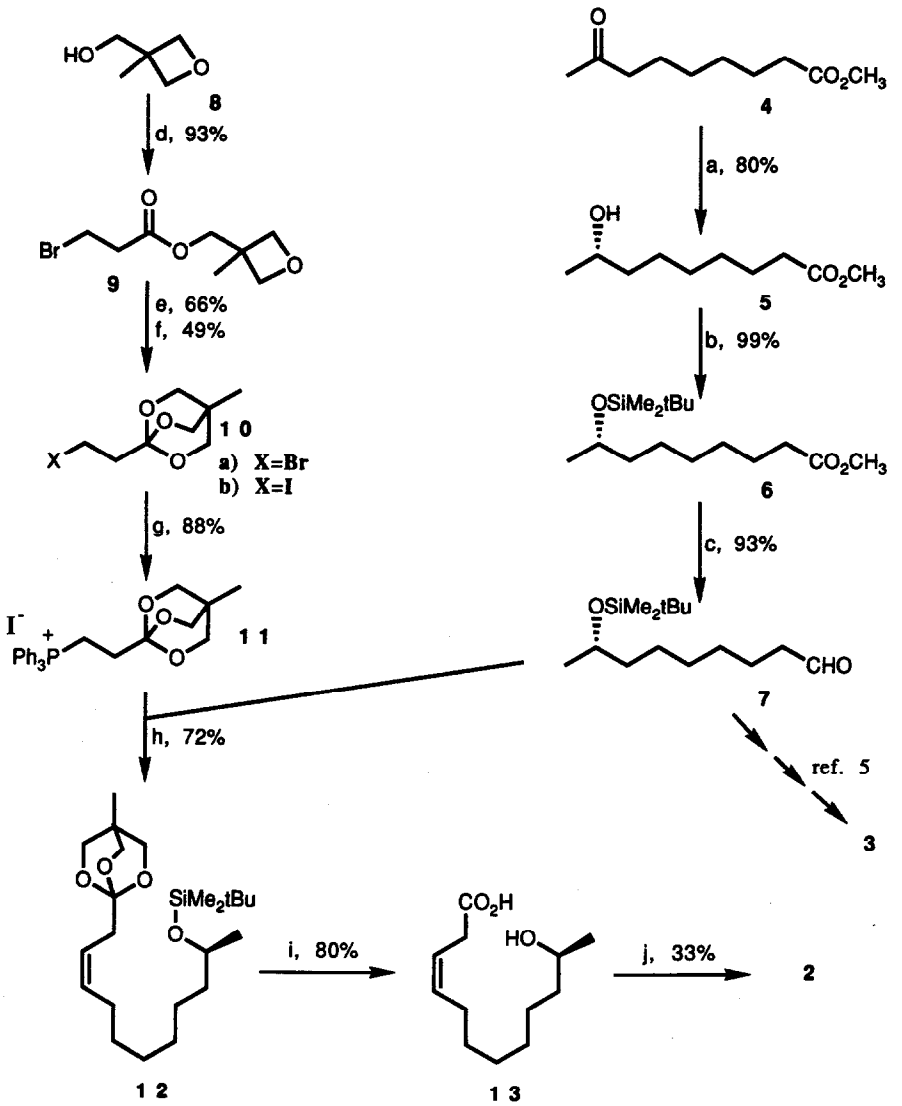
We have recently completed the total synthesis of **3** in a six-step synthesis, starting from (S)-(+)-methyl-8-hydroxynonanoate, **5**, with optical purity that exceeds 99%.[5] In this paper we demonstrate once again the synthetic usefulness of **5** by its employment as a starting material in the total synthesis of ferrulactone II (**2**).

The nine-carbon bifunctional chiron **5** was obtained in very high optical purity (>99% ee) from methyl 8-oxononanoate (**4**) via enantioselective reduction with TBADH.[5] Protection of this alcohol as a *t*-butyldimethylsilyl ether **6** (see Scheme) followed by reduction of the ester function with lithium aluminum hydride and oxidation with pyridinium chlorochromate in dichloromethane yielded the corresponding aldehyde **7** in 92% overall yield.[5]

The three-carbon phosphonium salt **11**[13] was prepared in four steps from 3-Methyl-3-hydroxymethyloxetane, **8**.[14] Esterification with 3-bromopropionyl chloride in dry THF afforded oxetane **9** which, upon treatment with Lewis acid, was rearranged to the bridged carboxylic ortho ester **10a**. Substitution of the bromide by iodide gave **10b** which was reacted with triphenylphosphine to give the desired phosphonium iodide salt **11**.[13]

Condensation of aldehyde **7** with the Wittig reagent prepared from **11** was initially carried out with dimsyl sodium in DMSO.[13] This procedure, however, afforded the protected seco-acid **12** as a 90:10 mixture of the Z and E isomers of the newly formed double bond at position 3. Better stereoselectivity (Z:E = >98:<2) was achieved with sodio-hexamethyldisilazane in THF/HMPA at low temperatures.[15] Both protecting groups, the *t*-butyldimethylsilyl ether and the bridged ortho ester were cleaved under mild acidic conditions followed by treatment with methanolic KOH. The resultant seco-acid, 11-hydroxytetradec-3-enoic acid (**13**) was finally macrolactonized using Corey's double activation method,[16] which has already been employed by Oehlschlager[11a] and Mori[11e] in their syntheses of this pheromone.

Synthesis was carried out with both racemic and optically active forms of **5**, resulting in racemic and optically active samples of **2**. Physical properties of the latter (NMR, IR, MS) were identical to those reported by Oehlschlager for the naturally occurring pheromone.[11a] Optical purity was determined by optical rotation measurement. It was found to be higher than that reported earlier: $[\alpha]_D$ +97.8° (c=0.57, $CHCl_3$), [Lit: +70.5° (c=0.96, $CHCl_3$);[11a] +92.2° (c=0.415, $CHCl_3$)[11e]]. An alternative, more reliable determination of optical purity was carried out by NMR, using europium chiral shift reagent, tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]-europium(III) ($Eu(tfc)_3$, Figure I). Comparison of the NMR spectra of racemic and chiral compounds shows that optical purity of the latter exceeds 99%.



Scheme: Total synthesis of ferrulactone II: a) TBADH, NADP+, iPrOH/H_2O, pH 8, 37°C. b) $ClSiMe_2tBu$, imidazole, DMF, 55°C. c) $LiAlH_4$, ether; then PCC, CH_2Cl_2. d) $BrCH_2CH_2COCl$, pyridine/THF, 0°C, 1h. e) BF_3-Et_2O, CH_2Cl_2, 0°C, 3h, then Et_3N. f) NaI, $NaHCO_3$, DMF, 100°C, 2h. g) PPh_3, $NaHCO_3$, CH_3CN, reflux, 20 hrs. h) $NaN(SiMe_3)_2$, THF, HMPA, -78°C to room temp. i) H_2SO_4 (0.3N), 5 min, then NaOH (1N), 15 h. j) Py_2S_2, PPh_3, CH_3CN, 25°C, then $AgClO_4$, xylene, reflux.

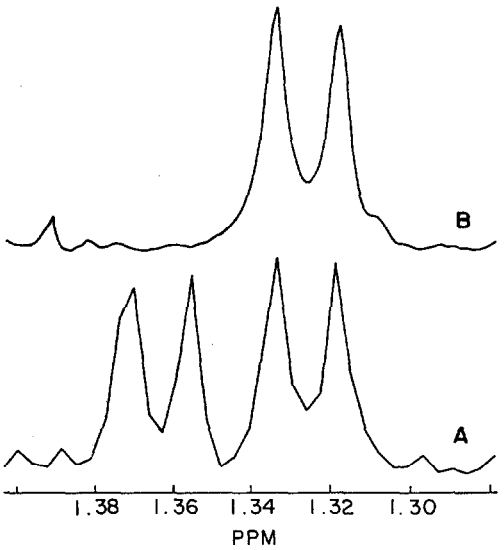


Figure I: Determination of optical purity of 2 by ^1H NMR: A. Partial NMR spectrum of the racemic sample in $CDCl_3$ with the presence of 25 mol % $Eu(tfc)_3$. **B.** Spectrum of the optically active compound taken under the same conditions.

In conclusion, in this paper we have shown once again that chiral alcohols produced by TBADH-catalyzed asymmetric reduction of bifunctional ketones are useful building blocks for natural products synthesis. In particular, this has been demonstrated by the total synthesis of (S)-(+)-Z-dodec-3-en-11-olide (**2**). A five-step synthesis, starting from (S)-(+)-methyl-8-hydroxynonanoate and a three-carbon Wittig reagent **11**, afforded **2** with optical purity that exceeds 99%. The total synthesis of (S)-(-)-zearalenone, curvularin as well as other naturally occurring macrolides is currently carried out in our laboratories.

EXPERIMENTAL SECTION

General Methods

Infrared spectra were measured in chloroform solutions with either a Perkin-Elmer 467 grating spectrometer or an FT infrared Nicolet MX-1 spectrometer, and are given in cm^{-1}. NMR spectra were measured in deuteriochloroform on a Bruker ACE-200 or Bruker AM-400 NMR spectrometers. All chemical shifts are reported in δ units downfield from Me_4Si, and the J values are given in Hertz. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Optical rotations were measured by a JASCO DIP 370 polarimeter, using a one decimeter (1 ml) cell. High-resolution mass spectra were determined on a Varian 711 spectrometer. Thin-layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel (Merck, Kieselgel 60, F254, Art. 5549). Column chromatographic separations were performed on silica gel (Merck, Kieselgel 60, 230-400 mesh, Art. 9385) under pressure of 0.4 atm (flash chromatography). Preparative TLC was performed on glass plates precoated with silica gel (Merck, Kieselgel 60 F-254, Art. 5717). Distillations were usually performed with a Büchi kugelrohr

apparatus, with the temperatures noted being pot temperatures. Tetrahydrofuran was dried by distillation over sodium benzophenone ketyl. Methylene chloride was dried by distillation over phosphorus pentoxide, dimethyl formamide by distillation from barium oxide, and dimethyl sulfoxide by distillation over calcium hydride under reduced pressures. Tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]-europium(III), $Eu(tfc)_3$ was purchased from Aldrich Chemical Co.

3-Bromopropionate ester of 3-methyl-3-hydroxy methyl oxetane 9 :

3-Methyl-3-hydroxymethyloxetane, **8**,[14] (10.2 g, 0.1 mole) was dissolved in dry THF (200 ml) and pyridine (9.7 ml, 0.12 mole). The solution was cooled to 0°C and 3-bromopropionyl chloride (18.9 g, 0.11 mol) was added. The mixture was stirred for 1 hr at the same temperature and then worked up with water and CH_2Cl_2 to give ester **9** in the form of a colorless oil (22 g, 93%) which was found to be essentially pure by ^1H and ^{13}C NMR. Because this compound suffers HBr elimination to produce the corresponding acrylic ester upon column chromatography, it was taken to the next step without further purification. It is important to note that dry THF is the solvent of choice for this esterification reaction, as reactions in CH_2Cl_2 proceed more sluggishly, producing significant amounts of side products. **^1H NMR** ($CDCl_3$): 4.46 (d, J=6.0 Hz, 2H); 4.32 (d, J=6.0 Hz, 2H); 4.16 (s, 2H); 3.53 (t, J=6.6 Hz, 2H); 2.91 (t, J=6.6 Hz, 2H), 1.28 (s, 3H). **^{13}C NMR** ($CDCl_3$): 179.5, 79.2, 68.9, 38.9, 37.4, 25.8, 20.9. **HRMS**: Calcd for C_3H_4OBr ($M-C_5H_9O_2$): 134.9401/136.9397, Found: 134.9423/136.9411.

1-(2-Bromoethyl)-4-methyl-2,6,7-trioxabicyclo[2,2,2] octane, 10a:

Crude **9** (22 g, 92.8 mmol) was dissolved in CH_2Cl_2 (100 ml), cooled to 0°C and treated with BF_3-Et_2O (3.2 ml, 26 mmol) for 3 h at the same temperature. The mixture was quenched with triethylamine (14.5 ml, 104 mmol), ether (100 ml) was added, the solid precipitate was removed by filtration and the solvent was removed under reduced pressure. The resultant crude **10a** was found to be quite pure by NMR. It was further purified by washing it with hexane through a short silica gel column (pretreated with 5% triethylamine in hexane) affording **10a** in the form of white crystals (14.5 g, 61% from **8**). **M.P.** 72°C. **^1H NMR** ($CDCl_3$): 3.84 (s, 6H); 3.38 (dd, J=8.8, 8.2 Hz, 2H); 2.22 (dd, J=8.8, 8.2 Hz, 2H); 0.76 (s, 3H). **^{13}C NMR** ($CDCl_3$): 118.6, 72.5, 40.4, 30.2, 26.0, 14.4. **MS** (rel intensity): 237/235 (M-1, 1), 209/207 (4), 208/206 (55), 137/135 (36), 109/107 (38), 84 (3), 83 (4), 82 (3), 81 (4), 73 (14), 72 (100), 71 (26), 70 (11), 69 (9). **HRMS**: Calcd for $C_8H_{12}O_3Br$ (M-1): 234.9950/237.0004, Found: 234.9960/236.9977.

1-(2-Iodoethyl)-4-methyl-2,6,7-trioxabicyclo[2,2,2]-octane, 10b:[13]

Compound **10a** (7.11 g, 30 mmol) was dissolved in dry DMF (100 ml) together with NaI (150 g, 300 mmol) and $NaHCO_3$ (12.6 g, 150 mmol) and heated to 100°C for 2 h. The mixture was cooled to room temperature and worked up with ether and water, followed by washing through a silica gel column, as described above for the bromide **10a**, affording **10b** (4.21 g, 49%) in the form of a white crystalline solid that was found to be pure by NMR.[13] **^1H NMR** ($CDCl_3$): 3.81 (s, 6H); 3.10 (dd, J=9.3, 7.9 Hz, 2H); 2.22 (dd, J=9.3, 7.9 Hz, 2H); 0.73 (s, 3H).

1-(2-Triphenylphosphoniumethyl)-4-methyl-2,6,7-trioxa-bicyclo-[2,2,2]-oxetane iodide, 11:[13]

The iodoorthoester **10b** (4.21 g, 14.8 mmol) was dissolved in dry acetonitrile (45 ml) together with triphenylphosphine (19.44 g, 74 mmol) and sodium bicarbonate (1.37 g, 16.3 mmol). The mixture was refluxed for 20 hrs, cooled to room temperature and filtered through celite using CH_2Cl_2 in order to remove the inorganic salts. Removal of the solvent under reduced pressure afforded a white gummy solid. Trituration with ether gave pure **11** in the form of a white powder which was dried over P_2O_5 under vacuum (7.07 g, 88%). **M.P.** 204°C. **^{1}H NMR** ($CDCl_3$): 7.83-7.56 (m, 15 H); 3.80 (s, 6H); 3.27 (m, 2H); 1.92 (m, 2H); 0.74 (s, 3H). **^{13}C NMR** ($CDCl_3$): 135.0, 132.7 (d, J=10.6 Hz), 130.3 (d, J=12.6 Hz), 116.8 (d, J=87.0 Hz), 106.8 (d, J=15.0 Hz), 72.2, 29.8, 29.1 (br s), 17.5 (d, J=52.9 Hz), 13.8.

1-[Z-10-(Dimethyl-*t*-butylsiloxy)undec-2-enyl)-4-methyl-2,6,7-trioxabicyclo[2,2,2] Octane, 12:

Phosphonium salt **11** (600 mg, 1.1 mmol) was dissolved in dry THF (10 ml) at room temperature. Sodio-hexamethyldisilazane (1 ml of 1M THF solution) was added and the mixture was refluxed for 2 hrs. The resulting Wittig reagent was cooled to -78°C, HMPA (1 ml) was added and the mixture was stirred for 1 h during which the temperature was allowed to warm up to -30°C. The mixture was cooled back to -78°C and solution of aldehyde **7**[5] (150 mg, 0.55 mmol) in THF (1 ml) was slowly added to the reaction mixture over 10 min. The mixture was stirred at -78°C for 2h, then at room temperature for 16 h and then worked up with ether and water. Removal of the solvent under reduced pressure and column chromatography (using hexane:ethyl acetate 9:1) afforded pure **12** (165 mg, 72%) in the form of a colorless oil. **^{1}H NMR** ($CDCl_3$): 5.59-5.37 (m, 2H); 3.88 (s, 6H); 2.42 (d, J=5.9 Hz, 2H); 1.98 (q, J=6.3 Hz, 2H); 1.15-1.40 (br m, 10H); 1.08 (d, J=6 Hz, 3H), 0.86 (s, 9H); 0.77 (s, 3H); 0.02 (s, 6H).

11-hydroxydodec-3-enoic acid 13:

Compound **12** (160 mg, 0.39 mmol) was treated with methanolic solution of H_2SO_4 (0.3N, 10 ml) at room temperature for 5 min. The mixture was then cooled to 0°C, methanolic KOH (1N, 10 ml) was added and the mixture was stirred overnight at room temperature. Acidification with 0.3N H_2SO_4 and extraction with CH_2Cl_2 followed by removal of the solvent under reduced pressure afforded the hydroxy acid **13** (65 mg, 80%) in the form of a colorless oil. This product was found to be identical (by ^{1}H NMR and IR) with the seco-acid reported by Oehlschlager.[11] **^{1}H NMR** ($CDCl_3$): 5.53 (m, 2H); 3.77 (m, 1H); 3.08 (d, J=6.4 Hz, 2H); 2.00 (q, J=6.8 Hz, 2H); 1.43-1.22 (br m, 10H); 1.14 (d, J=6 Hz, 3H).

Ferrulactone II, 2:

Triphenylphosphine (147 mg, 0.56 mmol) was added to a solution of 2,2'-bipyridyldisulfide (124 mg, 0.56 mmol) and hydroxy acid **13** (60 mg, 0.28 mmol) in dry acetonitrile (5 ml) and the mixture was stirred at 23°C under argon atmosphere for 3 hrs. The resulting yellow solution was diluted with 25 ml dry xylene and added dropwise over 4 hrs to a refluxing solution of silver perchlorate (130 mg, 0.62 mmol) in xylene (50 ml) under argon. The reaction mixture was refluxed overnight, cooled to room temperature and placed on a short

silica gel column (30 g). Elution with hexane (200 ml) removed most of the xylene. Elution with hexane:ethyl acetate 95:5, afforded 35 mg of crude product. Kugelrohr distillation (60-70°C) yielded pure ferrulactone II (2) (18 mg, 33%). Spectroscopic data of the latter (^{1}H NMR, IR) were identical with those reported by Oehlschlager for the naturally occurring pheromone.[8] Optical rotation was found to be higher than reported: $[\alpha]_D$ +97.8° (c=0.57, $CHCl_3$), [Lit: +70.5° (c=0.96, $CHCl_3$);[11a] +92.2° (c=0.415, $CHCl_3$)[11e]].

Determination of optical purity of ferrulactone II, 2, by NMR.

Racemic **2** (5 mg) was dissolved in $CDCl_3$ in an NMR tube to which small portions (5 mol % each) of tris[3-(trifluoromethyl-hydroxymethylene)-(+)-camphorato]-europium(III) ($Eu(tfc)_3$) were added. Optimal separation of the methyl doublets was achieved with 25 mol % $Eu(tfc)_3$, as shown in Figure IA. The same experiment was repeated with optically active **2**, using 25 mol % $Eu(tfc)_3$. Only one doublet appeared in this experiment with no observable indication for the presence of the other enantiomer (Figure IB). In order to increase sensitivity, the signal corresponds to the methine proton was irradiated in both samples, leading to collapse of the doublets to singlets. Again, no trace of the non-natural enantiomer was observed.

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