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Enantioselective Synthesis of R-(-)-Ligularenolide and the Progesterone Receptor Ligand R-(-)-PF1092C Starting from S-(+)-Carvone

Louis H.D. Jenniskens and Aede de Groot*

Laboratory of Organic Chemistry, Wageningen Agricultural University, Dreijenplein 8, 6703 HB Wageningen, The Netherlands

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Abstract: A new enantioselective synthesis of eremophilane sesquiterpenes was developed starting from S-(+)-carvone **3**, using a conjugate addition-annelation sequence. The synthesis of R-(-)-ligularenolide **1** was accomplished in a staightforward manner with the annelation of the lactone as the last step. For the synthesis of the progesterone receptor ligand R-(-)-PF1092C **2** a different strategy was followed in which first the lactone was annelated. The concommitant isomerization of the double bond of the isopropenyl group into the conjugate position then offered an alternative way to remove the side chain and simultanuously provide for an ideal functionality for the introduction of the *cis* β-diol function at the C2,C3 position.

INTRODUCTION

Both enantiomers of carvone have been widely used as starting material in enantioselective syntheses of natural products.[1-4] A conjugate addition-annelation procedure has been developed[2] that opens up an alternative route to drimanes and enables a direct access toward eremophilane sesquiterpenes.[5]

The eremophilane sesquiterpene R-(-)-ligularenolide **1** has been isolated from 'San-Shion', a Chinese herb drug prepared from the root of a *Ligularia* species.[6] Furthermore, R-(-)-ligularenolide **1** is the parent compound of the microbial metabolites R-(-)-PF1092A, B, and C (**2**), containing a *cis* β-diol function at the C2,C3 position of ligularenolide. These compounds are interesting new nonsteroidal progesterone receptor ligands, recently isolated from the culture broth of *Penicillium oblatum* by the Meiji Seika group.[7] Herein we report the first enantioselective synthesis of R-(-)-ligularenolide **1**[5] and of the diol R-(-)-PF1092C **2**. Starting from S-(+)-carvone **3**, short, straightforward, and efficient routes toward these eremophilane sesquiterpenes were developed.

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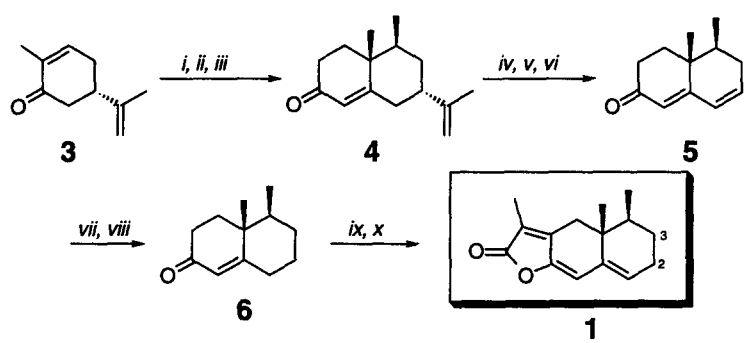
RESULTS AND DISCUSSION

S-(+)-Carvone **3** was first transformed into the Wieland-Miescher ketone **4** *via* a conjugate addition annelation sequence that was described previously (Scheme 1).[4] Next, the isopropenyl group was removed by a Criegee rearrangement. Thus, ozonolysis of **4** in $MeOH/CH_2Cl_2$, followed by addition of acetic anhydride, Et_3N, and DMAP resulted in a δ-acetoxy enone, which gave, upon treatment with sodium methoxide,[3] the dienone **5** in 61% yield. Conjugate reduction of **5** with L-Selectride®[4] in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), followed by treatment with NaOMe then gave the enone **6** in 58% yield. Finally, the lactone moiety was introduced *via* an α'-deprotonation of **6** with LDA at -78°C and a subsequent condensation with ethyl pyruvate in the presence of $ZnCl_2$. A treatment of the adduct with *p*-TsOH in refluxing toluene[8] gave dehydration and ringclosure to the lactone. The so-obtained R-(-)-ligularenolide **1** [70%, $[\alpha]_D$ -307 (c 2.3 $CHCl_3$)][5] was identical in all respects with the natural product.[6]

Scheme 1



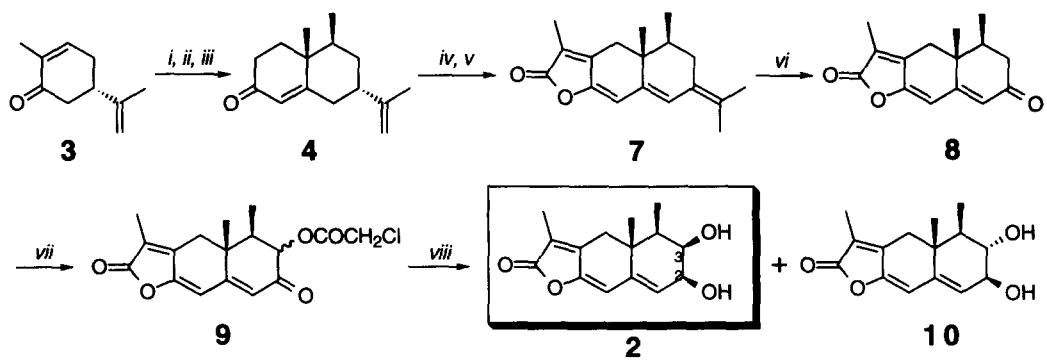
i. MeMgI, CuBr•DMS, HMPA; TMSCl; *ii.* MVK, BF_3•Et_2O; *iii.* NaOMe; *iv.* O_3, MeOH; *v.* Ac_2O, Et_3N, DMAP; *vi.* NaOMe; *vii.* L-Selectride®, DMPU; *viii.* NaOMe; *ix.* LDA, $ZnCl_2$, ethyl pyruvate; *x.* *p*TsOH, $PhCH_3$, Δ.

For the synthesis of the diol R-(-)-PF1092C **2**, a different strategy was followed. In preliminary experiments in which first the lactone moiety was annelated to compound **4**, we had found that the ringclosure of the lactone with *p*TsOH was accompanied by isomerization of the double bond of the isopropenyl group to the conjugate position. This gave the opportunity for a different removal of the sidechain in which simultaneously a strategically important carbonyl group at C2 could be introduced. This C2 carbonyl could offer good possibilities for the final introduction of the *cis* β-diol at the C2,C3 position (Scheme 2).

Thus, first S-(+)-carvone **3** was again transformed into the annelated product **4**.[4] Then, the lactone moiety was introduced in the same way as described above, *via* an α'-deprotonation of **4** with LDA at -78°C followed by a condensation of the enolate with methyl pyruvate in the presence of $ZnCl_2$.[8] Treatment of the intermediate with *p*-TsOH in refluxing toluene for 2h gave the formation of the lactone ring, together with an isomerization of the isopropenyl double bond to the isopropylidene position, to give compound **7** in 72% yield. Attempts to ozonolyze this exocyclic double bond selectively failed in our hands but after treatment of **7** with 3 - 9 equiv of $NaIO_4$ with 6% of RuO_2 in a mixture of CCl_4, MeCN, and H_2O,[9] the keto compound **8** could be obtained in 47% yield. Subsequent α'-oxidation[10] with $Mn(OAc)_3/ClCH_2COOH$ resulted in an inseparable 1:1 mixture of the

chloroacetates **9**. Direct reduction of this mixture of the chloroacetates **9** with $NaBH_4$ then gave a mixture of the *cis* β-diol, the progesterone receptor ligand R-(-)-PF1092C **2**, and the *trans* 2β,3α-diol **10**, which could be separated easily by column chromatography on silicagel to give **2** and **10** in 50% and 31% yield, respectively.

Scheme 2



i. MeMgI, CuBr•DMS, HMPA; TMSCl; *ii.* MVK, BF_3•Et_2O; *iii.* NaOMe; *iv.* LDA, $ZnCl_2$, methyl pyruvate; *v.* *p*TsOH, $PhCH_3$, Δ; *vi.* RuO_2, $NaIO_4$, MeCN, CCl_4, H_2O, 40°C; *vii.* $Mn(OAc)_3$, $ClCH_2COOH$, $PhCH_3$, Δ; *viii.* $NaBH_4$, EtOH.

EXPERIMENTAL

General. Melting points are uncorrected. NMR experiments were conducted with a Bruker AC-E 200 instrument; signals are reported in parts per million (δ), referenced to $CHCl_3$. HRMS data were obtained with a Finnigan MAT 95 spectrometer. Optical rotations were measured for chloroform or methanol solutions as specified with a Perkin-Elmer 241 polarimeter. Solvents were dried and freshly distilled by common practice. Product solutions were dried over $MgSO_4$ prior to evaporation of the solvent under reduced pressure by using a rotary evaporator. Reactions were monitored by TLC on silica gel plates and visualisation of the compounds was accomplished by UV detection and by spraying with basic $KMnO_4$ solution.

(4aR,5S)-4,4a,5,6-Tetrahydro-4a,5-dimethyl-2(3*H*)-naphthadienone (5). A solution of 2.16 g (9.91 mmol) of isopropenyl enone **4**[4] in 90 mL of a 5:1 mixture of CH_2Cl_2/MeOH was cooled to -80°C and O_3 was bubbled through until a pale blue colour appeared. The excess of O_3 was removed by a stream of N_2 and then 25 mL of acetic anhydride, 25 mL of Et_3N, and 2 mL of DMAP were added. The cooling bath was removed and the mixture was stirred for 1h at rt. Then the reaction mixture was poured into 1N HCl. After separation, the waterlayer was extracted with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine. After drying and evaporation of the solvent, the formed δ-acetoxy enone was dissolved in 50 mL of MeOH and 23 mL of 1M NaOMe in MeOH were added. After stirring for 20 min, the solvent was partly evaporated and the residue was taken into EtOAc. The organic layer was washed with 1N HCl, saturated aqueous $NaHCO_3$, and brine, and then dried and evaporated. The remaining residue was flash chromatographed on silica gel (10:1 petroleum ether (bp 40–60°C)/EtOAc) to give 1.06 g (61%) of the dienone **5**: ^1H NMR ($CDCl_3$, 200

MHz) δ 0.94 (d, *J*=6.9 Hz, 3H), 1.02 (s, 3H), 1.58-1.80 (m, 2H), 1.94-2.67 (m, 5H), 5.66 (s, 1H), 6.05-6.28 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.32 (q), 14.98 (q), 32.48 (t), 33.91 (t), 34.06 (t), 36.13 (s), 38.04 (d), 123.57 (d), 128.13 (d), 138.19 (d), 163.51 (s), 199.65 (s); MS *m/e* (rel intensity) 176 (M^+, 100), 161 (30), 148 (33), 133 (63), 119 (28), 105 (31), 91 (18); calcd for $C_{12}H_{16}O$ *m/e* 176.1201 , found *m/e* 176.1200 ; $[\alpha]_D$ +483 (c 3.2 in $CHCl_3$).

(4aR,5S)-4,4a,5,6,7,8-Hexahydro-4a,5-dimethyl-2(3*H*)-naphthalenone (6). To a mixture of 10 mL of 10 mL of 1M of L-Selectride® and 6 mL of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) in 40 mL of dry THF was added dropwise a solution of 1.47 g (8.35 mmol) of dienone **5** in 25 mL of dry THF at 0°C. After stirring for 1.5h an additional 1.5 mL of 1M of L-Selectride® was added and stirring was continued for 1 h. Then 0.1N HCl was added and the reaction mixture was taken into water. After extraction with EtOAc, the combined organic layers were washed with brine, dried and evaporated. The residue was taken into 30 mL of MeOH and 3 mL of 1M NaOMe was added. The mixture was stirred for 5 min and then taken into EtOAc, washed with brine, dried, evaporated, and flash chromatographed on silica gel (10:1 petroleum ether (bp 40–60°C)/EtOAc) to give 858 mg (58%) of the enone **6**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.89 (d, *J*=5.9Hz, 3H), 1.08 (s, 3H), 1.30-2.08 (m, 8H), 2.14-2.51 (m, 4H), 5.71 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.18 (q), 15.96 (q), 26.48 (t), 30.42 (t), 33.32 (t), 33.97 (t), 35.47 (t), 38.94 (s), 43.10 (d), 124.00 (d), 171.42 (s), 199.74 (s); $[\alpha]_D$ +210 (c 2.8 in $CHCl_3$).

R-(-)-Ligularenolide (1). A solution of 658 mg (3.70 mmol) of enone **6** in 10 mL of dry THF was added to 14 mL of 2M LDA in THF/ethylbenzene/hexane at -80°C. The reaction mixture was stirred for 1h after which time the temperature was raised to -30°C. Then 5.2 mL of a saturated etheral $ZnCl_2$ solution was added, followed by 3 mL of ethyl pyruvate and the mixture was stirred for 1h at rt. Then the reaction mixture was poured into a mixture of aqueous saturated NH_4Cl and water. After extraction with EtOAc, the combined organic layers were dried and evaporated. The residue was dissolved in 50 mL of toluene, 0.25 g of *p*TsOH was added and the reaction was boiled for 17h under Dean Stark conditions. The reaction mixture was cooled, poured into saturated aqueous $NaHCO_3$, and EtOAc was added. The water layer was extracted EtOAc and the combined organic layers were dried, evaporated and flash chromatographed on silica gel (10:1 petroleum ether (bp 40–60°C)/EtOAc) to give 610 mg (70%) of R-(-)-ligularenolide **1**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.95 (s, 3H), 0.98 (d, *J*=6.6 Hz, 3H), 1.45-1.85 (m, 4H), 1.90 (d, *J*=1.8 Hz, 3H), 2.15-2.32 (m, 3H), 5.78 (t, *J*=4.2 Hz, 1H), 5.93 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 8.51 (q), 15.68 (q), 19.57 (q), 26.16 (t), 26.47 (t), 34.80 (t), 37.70 (s), 38.82 (d), 109.68 (d), 120.43 (s), 131.31 (d), 139.21 (s), 147.32 (s), 147.33 (s), 170,25 (s); MS *m/e* (rel int) 230 (M^+, 92), 215 (100), 201 (8), 187 (13), 174 (25), 159 (23), 145 (18), 128 (22), 115 (29), 107 (25), 91 (39), 77 (25); $[\alpha]_D$ -307 (c 2.3 in $CHCl_3$).

(4aR,5S)-4a,5-Dihydro-3,4a,5-trimethyl-7-(1-methyl)ethylidene-4,6*H*-naphtho<2,3-b> furan-2-one (7). Introduction of the lactone moiety in 1.00 g (4.59 mmol) of the isopropenyl enone **4** was performed as described above for **6**, but methyl pyruvate was used instead of ethyl pyruvate and the reaction with *p*TsOH in refluxing toluene was completed within 2h. Flash chromatography on silicagel (5:1 to 3:1 petroleum ether (bp 40–60°C)/EtOAc) gave 902 mg (72%) of the isopropylidene lactone **7**: ^{1}H NMR ($CDCl_3$, 200MHz) δ 0.9-1.25 (m, 1H), 0.94 (s, 3H), 1.02 (d, *J*=6.7Hz, 3H), 1.78 (bs, 3H), 1.84 (bs, 3H), 1.91 (bs, 3H), 1.8-2.2

(m, 1H), 2.27 (bd, *J*=16.5Hz, 1H), 2.42 (dd, *J*=3.9, 15.8Hz, 1H), 2.81 (d, *J*=16.5Hz, 1H), 6.02 (bs, 1H), 6.50 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50MHz) δ 8.56 (q), 15.35 (q), 18.75 (q), 20.00 (q), 21.23 (q), 32.09 (t), 34.49 (t) 37.55 (s), 38.64 (d), 110.40 (d), 120.11 (s), 127.89 (s), 128.81 (d), 131.16 (s), 138.37 (s), 146.89 (s), 147.85 (s), 171.47 (s); MS *m/e* (rel int) 270 (M^+, 100), 255 (36), 213 (7), 199 (3); calcd for $C_{18}H_{22}O_2$ *m/e* 270.1620, found 270.1621; $[\alpha]_D$ -615 (c 2.2 in $CHCl_3$); mp 106°C.

(4aR,5S)-4a,5-Dihydro-3,4a,5-trimethyl-4,6*H*-naphtho<2,3-b>furane-2,7-dione (8). To a solution of 902 mg (3.34 mmol) of the isopropylidene lactone **7** in 20 mL of CCl_4, 20 mL of MeCN, and 30 mL of water were added 27 mg of RuO_2 and 1.57 g (2.2 equiv) of $NaIO_4$. The reaction was stirred at 50°C for 1.5 h, after which time another 2.2 equiv of $NaIO_4$ were added. Stirring was continued for 1h and then again 4.4 equiv of $NaIO_4$ were added. After a total time of 4.5h stirring at 50°C the reaction mixture was filtered over hyflo, separated, and the waterlayer was extracted with CH_2Cl_2. The combined organic layers dried, evaporated, and flash chromatographed on silica gel (2:1 petroleum ether (bp 40–60°C)/EtOAc) to give 381 mg (47%) of ketone **8**: ^{1}H NMR ($CDCl_3$, 200MHz) δ 0.95-1.25 (m, 1H), 1.07 (d, *J*=6.3Hz, 3H), 1.11 (s, 3H), 1.97 (d, *J*=2.1Hz, 3H), 2.1-2.4 (m, 4H), 2.93 (d, *J*=16.8Hz, 1H), 5.96 (bs, 1H), 6.06 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50MHz) δ 8.92 (q), 15.02 (q), 19.09 (q), 33.86 (t), 38.76 (s) 38.87 (d), 42.24 (t), 106.69 (d), 124.51 (s), 128.05 (d), 145.51 (s), 152.89 (s), 160.64 (s), 169.89 (s), 197.80 (s); MS *m/e* (rel int) 244 (M^+, 100), 202 (72), 187 (45), 174 (33), 160 (4), 146 (7), 115 (4), 91 (5); calcd for $C_{15}H_{16}O_3$ *m/e* 244.1099, found 244.1106; $[\alpha]_D$ -564 (c 1.8 in $CHCl_3$); mp 147°C.

Chloro-acetic acid (4aR,5S)-4a,5-dihydro-3,4a,5-trimethyl-2,7-dioxo-4,6*H*-naphtho <2,3-b>furan-7-yl ester (9). To a suspension of 1.81 g (6.76 mmol) of $Mn(OAc)_3 \cdot H_2O$ in 50 mL of toluene was added 1.27 mL (13.5 mmol) of Ac_2O. The mixture was stirred at 45°C for 50 min, and refluxed for 80 min under Dean Stark conditions. Then 1.92 g (20.3 mmol) of $ClCH_2COOH$ was added and refluxing was continued for another 30 min after which time 275 mg of the ketone **8** was added with the aid of a few mL's of toluene and reaction was refluxed overnight. The reaction mixture was poured into EtOAc and washed with 1N HCl, water, saturated aqueous $NaHCO_3$, and brine and subsequently dried, evaporated and flash chromatographed on silica gel (4:1 petroleum ether (bp 40–60°C)/EtOAc) to give 245 mg (65%) of a, according to NMR, 1:1 mixtureof the chloroacetates **9**: ^{1}H NMR ($CDCl_3$, 200MHz, characteristic peaks) α-OAcCl: δ 4.17 (s, 2H), 5.31 (d, *J*=12.9Hz, 1H); β-OAcCl: δ 4.04 (s, 2H), 5.44 (d, *J*=4.4Hz, 1H).

R-(-)-PF1092C (2) and (4aR,5S,6S,7S)-4a,5,6,7-tetrahydro-6,7-dihydroxy-3,4a,5-trimethyl-4*H*-naphtho<2,3-b>furan-2-one (10). To a solution of 225 mg of a 1:1 mixture of the chloroacatates **9** in 60 mL of absolute EtOH was added 88.5 mg (2.34 mmol) of $NaBH_4$. The mixture was stirred for 45 min at rt after which time it was poured into 1N HCl and extracted with EtOAc. The combined organic layers were washed with water, saturated aqueous Na_2HCO_3, and brine and subsequently dried, evaporated, and flash chromatographed on silicagel (1:1 petroleum ether (bp 40–60°C)/EtOAc) to give 87.5 mg (50%) of the progesterone receptor ligand R-(-)-PF1092C **2** and 54 mg (31%) of the *trans* diol **10**. Spectral data follow.
2: ^{1}H NMR ($CDCl_3$, 200MHz) δ 1.19 (s, 3H), 1.21 (d, *J*=5.4Hz, 3H), 1.77 (dq, *J*=1.6, 7.1Hz, 1H), 1.89 (d, *J*=1.6Hz, 3H), 2.16 (bd, *J*=16.3Hz, 1H), 2.83 (d, *J*=16.3Hz, 1H), 3.91 (bd, *J*=4.8Hz, 1H), 4.36 (bs, 1H), 5.64 (bs, 1H), 5.95 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50MHz) δ 8.56 (q), 12.99 (q), 2145 (q), 35.75 (t), 37.79 (s),

41.14 (d), 68.96 (d), 72.27 (d), 108.05 (d), 122.36 (s), 129.31 (d), 140.81 (s), 146.52 (s), 149.17 (s), 171.05 (s); MS *m/e* (rel int) 262 (M^+, 41), 244 (59), 229 (26), 215 (22), 204 (28), 188 (100), 175 (71), 161 (59), 147 (15); calcd for $C_{15}H_{18}O_4$ (M^+) *m/e* 262.1205, found 262.1195; $[\alpha]_D$ -70 (c 0.7 in $CHCl_3$); mp 168°C (dec).
10: ^1H NMR ($CDCl_3$, 200MHz) δ 0.99 (s, 3H), 1.12 (d, *J*=6.8Hz, 3H), 1.65-1.9 (m, 1H), 1.88 (bs, 3H), 2.23 (d, *J*=16.4Hz, 1H), 2.81 (d, *J*=16.4Hz, 1H), 3.51 (dd, *J*=7.8, 11.3Hz, 1H), 4.13 (dd, *J*=2.2, 7.8Hz, 1H), 5.62 (d, *J*=2.2Hz, 1H), 5.92 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50MHz) δ 8.47 (q), 10.20 (q), 20.62 (q), 34.63 (t), 39.74 (s), 43.28 (d), 74.09 (d), 74.21 (d), 107.85 (d), 121.87 (s), 129.52 (d), 140.34 (s), 146.22 (s), 148.99 (s), 171.18 (s); MS *m/e* (rel int) 262 (M^+, 25), 244 (26), 229 (13), 215 (6), 204 (8), 188 (21), 175 (22), 161 (25), 149 (14), 119 (100); calcd for $C_{15}H_{18}O_4$ (M^+) *m/e* 262.1205, found 262.1190; $[\alpha]_D$ -104 (c 0.8 in MeOH); mp 155°C (dec).

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