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Enantioselective Synthesis of R-(-)-Ligularenolide Starting from S-(+)-Carvone

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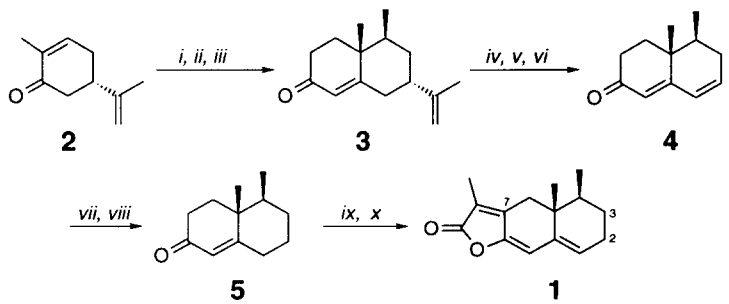
Abstract: The first enantioselective synthesis of R-(-)-ligularenolide **1** starting from S-(+)-carvone **2** is described. © 1997 Elsevier Science Ltd.

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

S-(+)-Carvone **2** was first transformed into ketone **3** as described previously.[3] Next, the isopropenyl group was removed *via* a Criegee rearrangement. Thus, ozonolysis of **3** in MeOH/CH_2Cl_2, followed by addition of acetic anhydride, Et_3N, and DMAP resulted in a δ-acetoxy enone, which gave, upontreatment with



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.

sodium methoxide,[4] the dienone **4**[5] in 61% yield. Conjugate reduction of **4** with L-Selectride®[6] in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), followed by treatment with NaOMe gave the enone **5**[7] in 58% yield.

Finally, the lactone moiety was introduced *via* an α'-deprotonation of **4** with LDA at -78°C and condensation of the enolate with ethyl pyruvate in the presence of $ZnCl_2$, followed by treatment with *p*-TsOH in refluxing toluene.[8] The so-obtained R-(-)-ligularenolide **1** (70%, $[\alpha]_D$ -307 (c 2.3 $CHCl_3$)) was identical in all respects with the natural product.[1]

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5 **4**: ^1H NMR ($CDCl_3$, 200 MHz) δ 0.94 (d, *J* = 6.9 Hz, 3 H), 1.02 (s, 3 H), 1.58-1.80 (m, 2 H), 1.94-2.67 (m, 5 H), 5.66 (s, 1 H), 6.05-6.28 (m, 2 H); ^{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 (d), 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 ; [α]D +483 (c 3.2 in $CHCl_3$).

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