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A Stereocontrolled Total Synthesis of Methyl (±)-*O*-methylpisiferate

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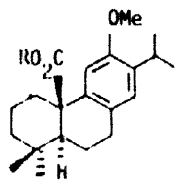
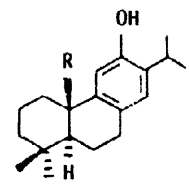
Abstract : A stereocontrolled total synthesis of methyl (±)-*O*-methylpisiferate 2 has been successfully accomplished using aryl participated intramolecular cyclisation of the diazomethyl ketone **16** as a key step.

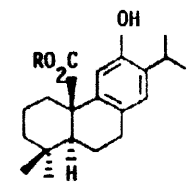
(+)-*O*-Methylpisiferic acid **1** and a few related diterpenes, (+)-pisiferol **3**, (+)-pisiferal **4**, (+)-pisiferic acid **5**, and methyl (+)-pisiferate **6** were isolated from the leaves of *Chamaecyparis pisifera* by Yatagai *et al.*[1,2] Earlier methodologies for the synthesis of the diterpenes 3-6 by Matsumoto and co-workers[3,4] most commonly employed transannular oxidation of the angular methyl group as a key reaction. We report here for the first time an aryl participated diazoketone cyclisation strategy for a stereocontrolled total synthesis of methyl (±)-*O*-methylpisiferate **2**. Since **2** is easily converted[3] into **5** and **6**, the present work constitutes formal total synthesis



1, R=H
2, R=Me



3, R=CH_2OH
4, R=CHO



5, R=H
6, R=Me

of (±)-pisiferic acid **5** and methyl (±)-pisiferate **6**. The salient features of our synthesis are (i) facile conversion of the easily accessible tetralone **7** into the diazomethyl ketone **16**, (ii) aryl participated intramolecular cyclisation[5] of **16** to provide the tricyclic ene-dione **17** as a key intermediate, and (iii) stereoselective transformation of **17** into methyl *O*-methylpisiferate **2** in high yield.

Reformatsky reaction of the tetralone **7** with methyl 4-bromocrotonate[6] followed by catalytic hydrogenation of the resulting product furnished the ester **8**.[7] Oxidation of **8** with CrO_3 gave the keto-ester **9**. Bromination of **9** in ether[8] furnished the bromoketone **10** which on dehydrobromination followed by methylation afforded the ester **11**. Treatment of **11** with MeMgI followed by intramolecular cyclisation of the resulting carbinol provided **12** which on oxidation with pyridinium chlorochromate furnished the tricyclic ketone **13** (Scheme 1). The hydroxymethylene derivative of **13** was treated[9] with alkaline H_2O_2 followed by CH_2N_2 to afford the diester **14**, m.p. 85-86 °C. Partial hydrolysis of **14** under controlled conditions (aq. KOH, THF, 25 °C)

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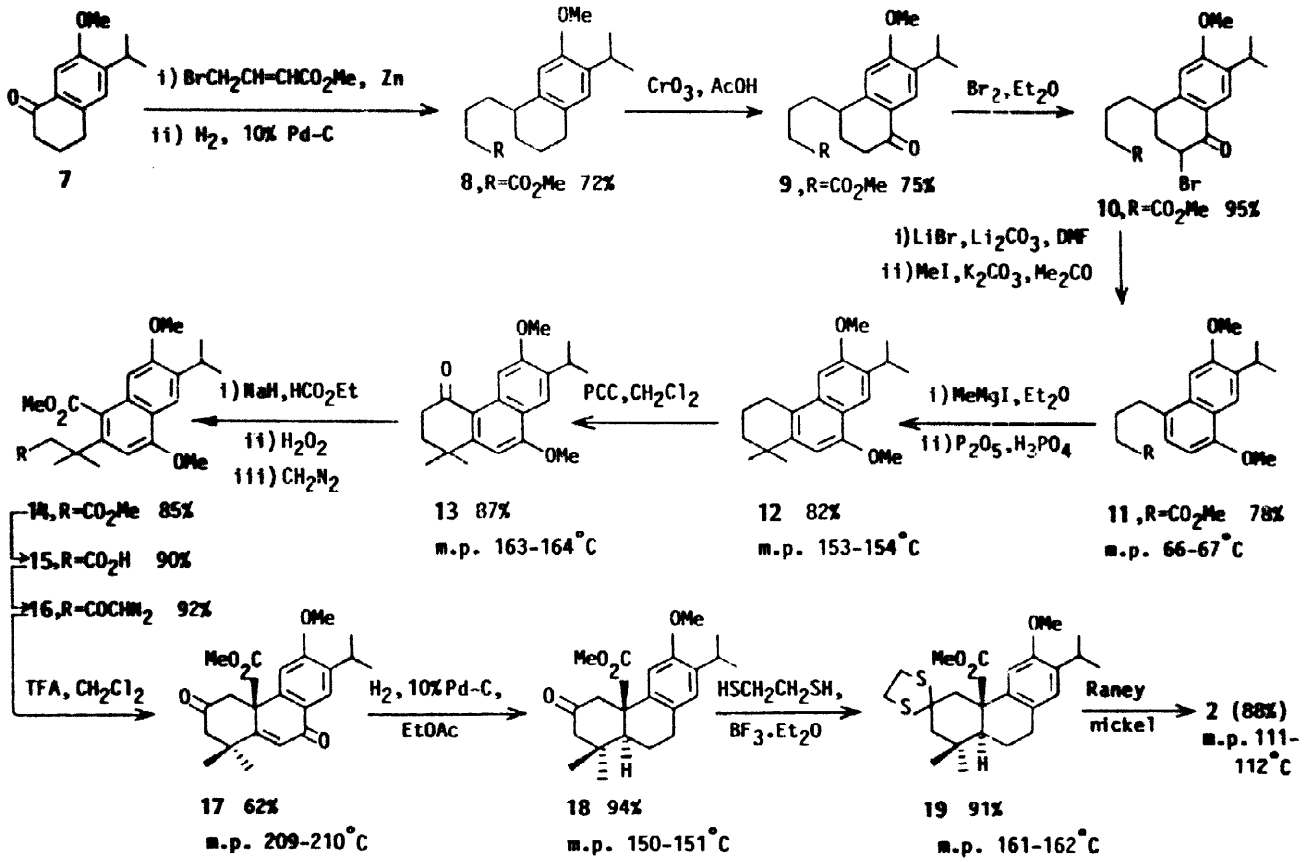

Scheme 1

furnished the half acid-ester **15**, m.p. 158-159°C. Reaction of **15** with ethyl chloroformate in the presence of Et_3N followed by treatment of the resulting mixed anhydride with CH_2N_2 provided the diazomethyl ketone **16**. Intramolecular cyclisation of **16** was effected[5] with trifluoroacetic acid in CH_2Cl_2 at -20°C to afford the ene-dione **17**.

Catalytic hydrogenation of **17** proceeded stereoselectively with uptake of 3 moles of H_2 to furnish the keto-ester **18** which was converted into the thioacetal **19**. *Trans*-stereochemistry has been assigned to **18** since catalytic hydrogenation of closely related enones had generated[4,10] exclusively *trans*-stereochemistry at A/B ring junctures. Desulfurisation of **19** with Raney nickel furnished methyl (±)-*O*-methylpisiferate **2**. The spectral data of **2** agreed very well with those reported in the literature.[3]

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