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# COMPACTIN FROM HAJÓS (-)-ENEDIONE

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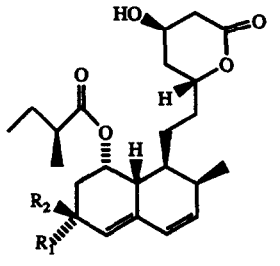
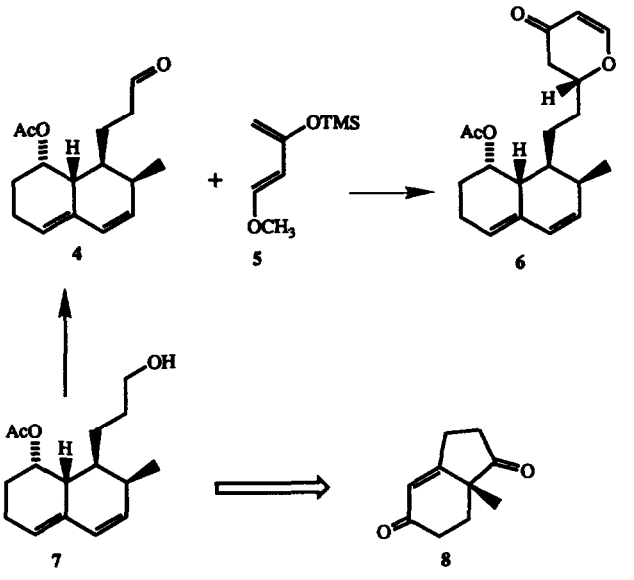
*Summary*: Starting from easily accessible (-)-enedione **8** , the hexahydronaphthalene part of compactin **1** was synthesized. The most important steps of this synthesis are: reductive alkylation of **8**, cyclization of iodide **12** with $SmI_2$ and Zn, and regiospecific dehydrations of **19** and **21** using Martin reagent.

Fungal metabolites compactin[1] (**1**), the methyl analog mevinolin[1] (**2**), and the hydroxy analog pravastatin[2] (**3**) are inhibitors of HMG-CoA reductase, the enzyme involved in the rate controlling step of cholesterol biosynthesis. Mevinolin is being used in medicine as a drug for control of blood cholesterol and triglycerides levels.



**1** $R_1 = R_2 = H$ (compactin)
**2** $R_1 = CH_3$, $R_2 = H$ (mevinolin)
**3** $R_1 = H$, $R_2 = OH$ (pravastatin)

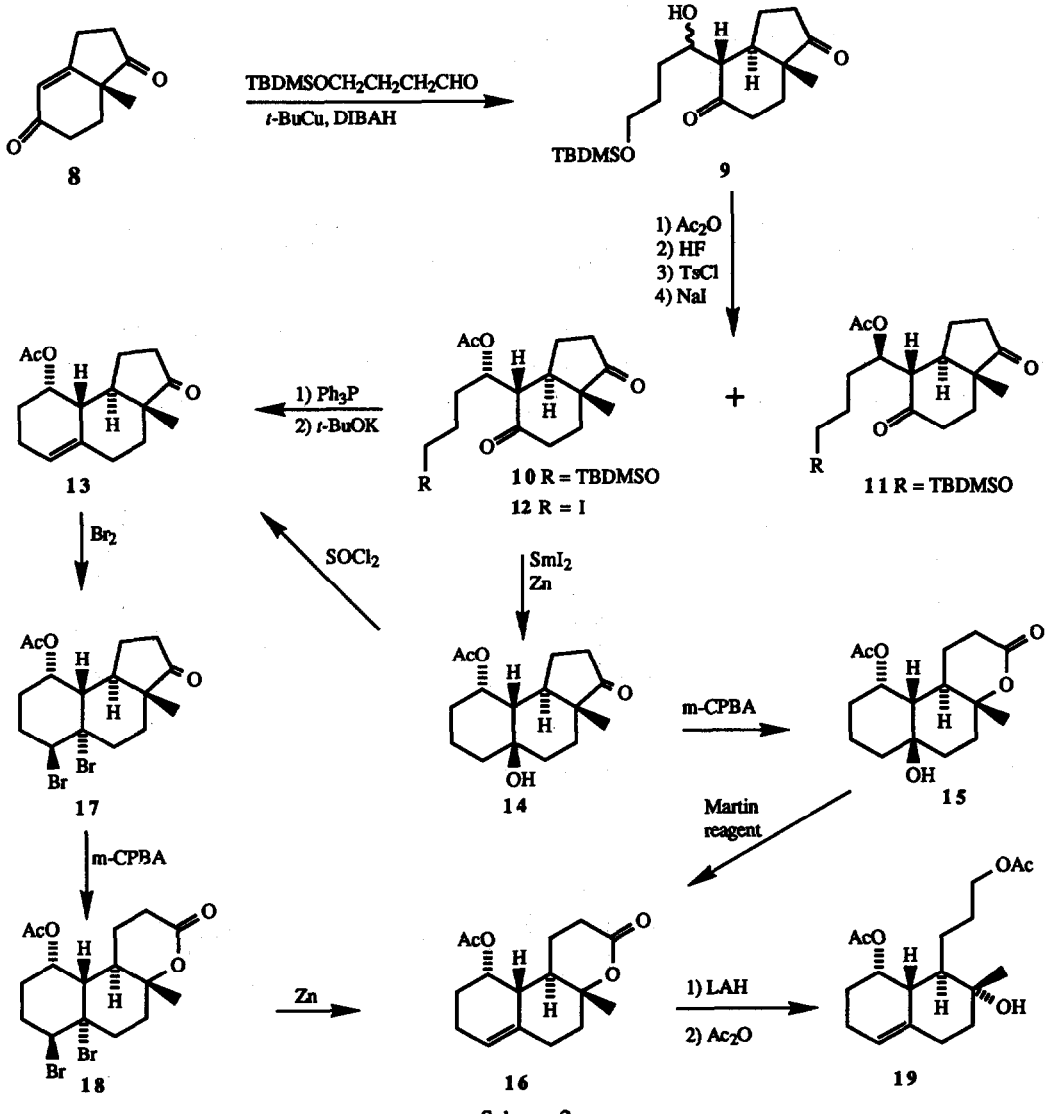


Scheme 1

Following an original observation in this laboratory[3], Danishefsky has synthesized compactin by employing cycloaddition reaction of the aldehyde **4** and the diene **5** thus affording pyranone **6** with good stereoselection[4]. The latter compound has been converted to **1** in few easy steps.

We would like to report the synthesis of the alcohol **7**, a precursor of the Danishefsky aldehyde **4**, starting from the Hajós[5] (-)-enedione **8**, (Scheme 2). Compound **8** was reductively alkylated[6] using as a reducing agent the hydride obtained *in situ* from *tert*-butyl copper and diisobutylaluminum hydride and 4-(*tert*-butyldimetylsilyloxy)-butanal as the alkylating agent. This one pot procedure has produced a mixture (2:1) of

diastereoisomers **9** (70%) which were separated after acetylation by column chromatography. The structure of the minor **11** was confirmed by x-ray. The isomer **10** was converted to the iodide **12**, *via* the tosylate, in high overall yield.

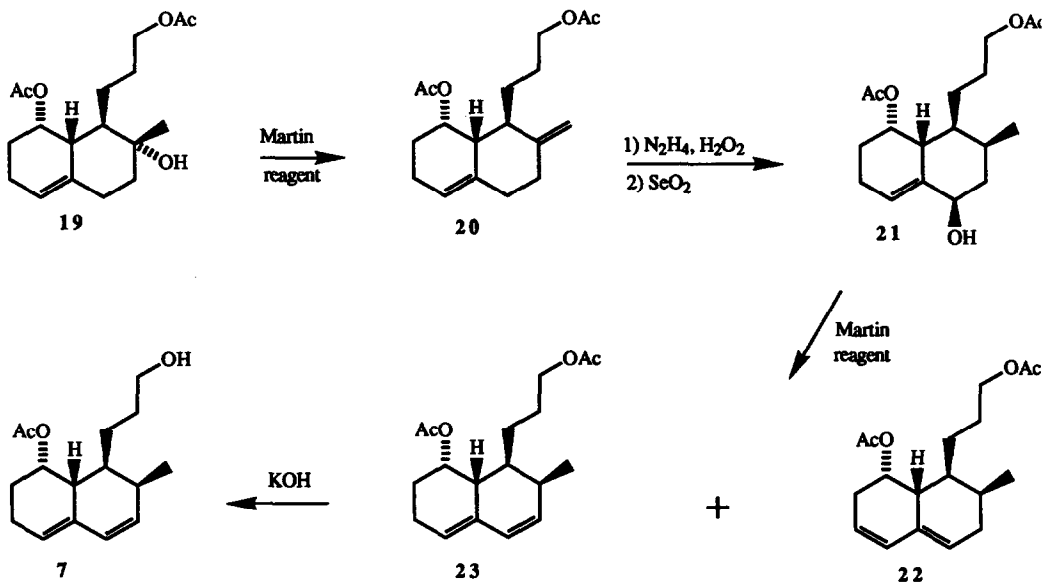



Scheme 2

Two methods for cyclization of ring A were investigated. First the iodide **12** was transformed into phosphonium iodide and the cyclization was carried out by treatment with potassium *tert*-butoxide. The cyclic

olefin **13** was obtained in about 40% yield. The low yield of the intramolecular Wittig reaction was attributed to the elimination of the acetoxy group. The second method of cyclization was based on treatment of the iodide **12** with $SmI_2$ in the presence of zinc. This led stereospecifically to the tertiary alcohol **14** with *cis* ring junction in 65% yield. The same cyclization of **12** using two moles of $SmI_2$ according to conditions described by Molander[7] led to a mixture of cyclic compounds in 34% yield with *cis:trans* ring junction in a ratio of 4:1. Stereochemistry at the ring junction in **14** was confirmed by NMR. The signal of the proton (axial) adjacent to the acetoxy group (equatorial) appeared as a two triplets with J = 12.4 and 4.4 Hz. The *cis* ring junction was an important structural feature of **14** since allowed for clean $E_2$ elimination to the desired $C_{4-5}$ double bond. Compound **14** was transformed into **13** with thionyl chloride in pyridine.

The three carbon hydroxy side chain of the target molecule was obtained by scission of the cyclopentanone ring. The Baeyer-Villiger ring expansion of **14** produced the lactone **15** which underwent regioselective elimination (90%) to form $C_{4-5}$ olefin **16** on treatment with Martin reagent. Compound **16** was also obtained starting from **13** thus confirming the position of the double bond. The bromination of **13** afforded dibromide **17**, which was oxidized with m-CPBA yielding dibromo lactone **18**, the structure of which was confirmed by x-ray. Deprotection of the double bond in **18** with Zn in methanol produced **16** in almost quantitative yield. Finally, the reductive lactone opening and acetylation gave in high yield the desired hydroxy diacetate **19**.




Scheme 3

Completion of the synthesis required then elimination of the tertiary hydroxy group with retention of the β–methyl configuration and the introduction of the $C_{6-7}$ double bond. Dehydration of the tertiary hydroxy group in **19** using Martin reagent afforded the exo-methylene compound **20** (Scheme 3) in 90% yield. The

selective hydrogenation with hydrazine and hydrogen peroxide produced a difficult to separate mixture in which the desired compound predominated to an extent of 65% as estimated by NMR. Fortunately after allylic hydroxylation of this mixture using selenium dioxide in dioxane, the pure allylic alcohol **21** was easy to isolate with chromatography in 60% yield based on diene **20**. The dehydration of the allylic alcohol **21** was carefully studied. It was found that mesyl chloride and triethyl amine yield mixture of **22** and **23** in a ratio 4:1. Copper(II) triflate in THF converted **21** into the same two compounds but in a ratio 1:1, whereas the Martin reagent produced a 1:4 mixture of **22** and **23** in which the desired diene **23** predominated. In all cases mentioned above, the conversion of **21** took place in high yield. The selective hydrolysis of the primary acetoxy group and crystallization from hexane-ethyl acetate furnished the desired alcohol **7** [ mp 114-114.5°C, $[\alpha]^{25}_D$= + 357.5], the NMR of which was in good agreement with that of the same racemic compound obtained by Danishefsky.

In summary, four stereogenic centers of the hexahydronaphthalene moiety (i.e. **7**) of compactin have been installed by intramolecular asymmetric induction from the single stereogenic center of the starting Hajós (-)-enedione **8**.

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