# A FORMAL SYNTHESIS OF DIHYDROCOMPACTIN†

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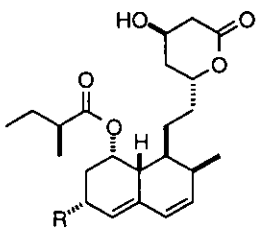
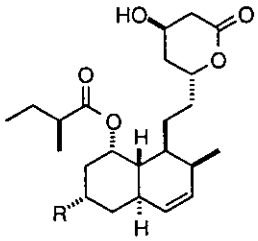
**Abstract** - A formal synthesis of dihydrocompactin is reported. A key intermediate, tricyclic lactone (**1b**), was prepared by an efficient method of lactone synthesis, based on an intramolecular cycloaddition reaction of allenyl ether.

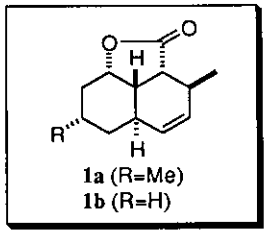
The mevinic acids compactin, mevinolin, and their dihydro-analogues have attracted considerable synthetic attention because of their biological activity as inhibitors of HMG CoA reductase, the rate-limiting enzyme in cholesterogenesis in man. Most plausible and intriguing strategy depends on the coupling of a decaline portion with a δ-lactone moiety.[1] Recently, Hanessian's group[2] and Hagiwara's group[3] have reported the total synthesis of mevinic acids, which have been proceeding through the tricyclic lactones (**1**) for the construction of the decaline system present in mevinic acids. These recent reports from other laboratories have prompt us to describe herein our synthetic studies of mevinic acids, based on the allenyl ether intramolecular Diels-Alder strategy.[4]



**mevinolin** (R=Me)
**compactin** (R=H)



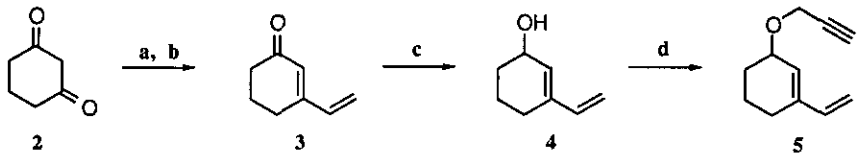
**dihyromevinolin** (R=Me)
**dihyrocompactin** (R=H)



**1a** (R=Me)
**1b** (R=H)

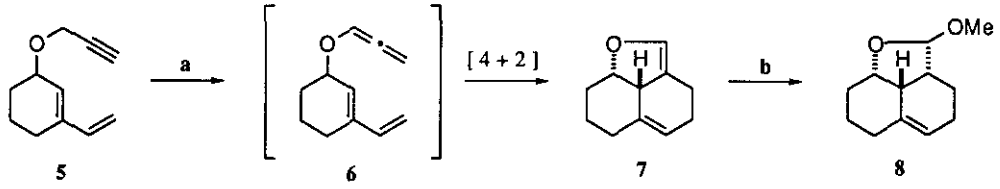
† Dedicated to Dr. Arnord Brossi, Scientist Emeritus NIH, on the occasion of his 70th birthday.

We prepared the desired substrate (**5**)[5] from the commercial 1,3-cyclohexanedione (**2**) in four steps (Scheme I): (i) treatment of the dione (**2**) with *i*-BuOH in the presence of a catalytic amount of *p*-TsOH; (ii) treatment of the resulting enol ether with vinylmagnesium bromide in tetrahydrofuran, then with aqueous $H_2SO_4$; (iii) reduction of the dienone (**3**) with $LiAlH_4$ in tetrahydrofuran; (iv) etherfication of the alcohol (**4**) with propargyl bromide [65% overall yield].




**Scheme I. Reagents and conditions** ; (a) *p*-TsOH (cat.), *i*-BuOH, benzene, reflux. (b) vinylmagnesium bromide, THF, 0°C; aq. $H_2SO_4$ (c) $LiAlH_4$, THF, 0°C (d) propargyl bromide, 50% NaOH-$Et_2O$, $Bu_4NI$ (cat.), 25°C

When the ether (**5**) was heated in *t*-BuOH in the presence of *t*-BuOK (excess) for 1 h, the adduct (**7**) was obtained as the sole product *via* intramolecular Diels-Alder reaction of the allenyl ether intermediate (**6**) (Scheme II). Due to the lability of the resultant enol ether (**7**), the crude adduct was directly treated with 5% solution of 10-camphorsulphonic acid (CSA) in methanol to give the methyl acetal (**8**) in 79% overall yield from the propargyl ether (**5**).

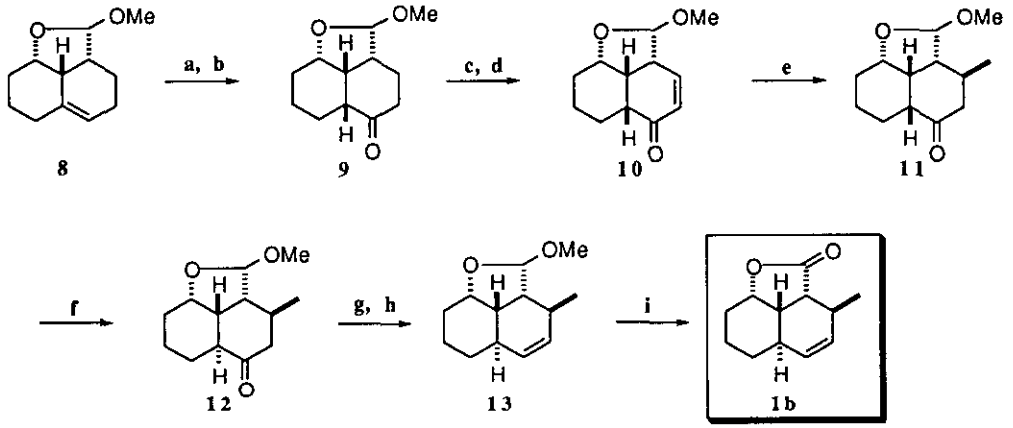



**Scheme II. Reagents and conditions** ; (a) *t*-BuOK, *t*-BuOH, reflux. (b) 5% CSA in MeOH, 0°C

Hydroboration of the alkene (**8**) occurred from the less-hindered β-face (79% yield), and subsequent oxidation furnished the *cis*-fused ketone (**9**) in 78% yield (Scheme III). The ketone was converted into the enone (**10**) in 65% yield by Saegusa's method,[6] and stereoselective conjugate methylation was accomplished using lithium dimethyl cuprate to give the product (**11**) in 88% yield. After epimerization of the

methylated ketone (**11**) (97% yield), the resulting *trans*-fused ketone (**12**) was converted into the less-substituted olefin (**13**) by Bamford-Stevens reaction.[7] Finally, Jones oxidation of the methyl acetal afforded the desired fused tricyclic lactone (**1b**) in 52% overall yield from the ketone (**12**), whose physical properties agreed with the data kindly provided by Dr. Hagiwara.[3] Since the lactone (**1b**) has previously been converted into dihydrocompactin,[3] our work reported herein constitutes its formal synthesis.

Although these experiments were performed with racemic compounds, the ready resolution of the alcohol (**4**) into its antipodes makes this strategy potentially enantioselective. Studies are currently in progress to synthesize key intermediates for other mevinic acids, as well as to prepare the intermediates in optically pure form.




**Scheme III. Reagents and conditions** ; (a) $BH_3$•THF, THF, 0°C; 10% NaOH, 30% $H_2O_2$, 0°C to room temperature (b) PCC, Celite, $CH_2Cl_2$, 0°C (c) LDA, THF, -78°C; TMSCl, -78°C to room temperature (d) $Pd(OAc)_2$, MeCN, 35°C (e) $Me_2CuLi$, $Et_2O$, 0°C (f) $K_2CO_3$, MeOH, reflux. (g) *p*-$TsNHNH_2$, MeOH, reflux. (h) BuLi, THF, 0°C (i) Jones reagent, acetone, 0°C

## ACKNOWLEDGEMENT

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