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SYNTHETIC STUDIES RELATED TO COMPACTIN AND MEVINOLIN: A NEW SYNTHESIS OF THE HEXAHYDRONAPHTHALENE PORTION OF COMPACTIN.

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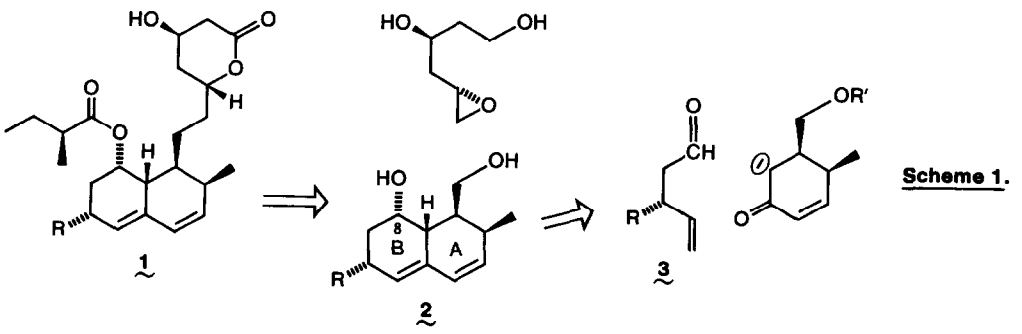
SUMMARY: The hexahydronaphthalene portion of the hypocholesterolemic agent, Compactin, has been synthesized by a process based on aldol metholodogy and titanium-induced intramolecular carbonyl coupling.

The fungal metabolites, Mevinolin[1] (1, R = Me) and Compactin[2] (1, R = H) have a wide range of biological properties and are the subject of a substantial patent and journal literature.[3-7] The interest in these compounds is due largely to the fact that they may provide useful information for the treatment of atherosclerosis: Both substances reduce blood cholesterol levels[8,9] and are relevant to medical research: A high level of cholesterol is a significant risk factor[10] for atherosclerosis and its associated coronary artery diseases, and, therefore, structure—activity studies for mevinolin or compactin may help in the design of valuable drugs. While certain analogues are accessible by modification of the natural materials[11] or by fermentation,[12] a more general approach would be one based on a flexible synthesis.[13]

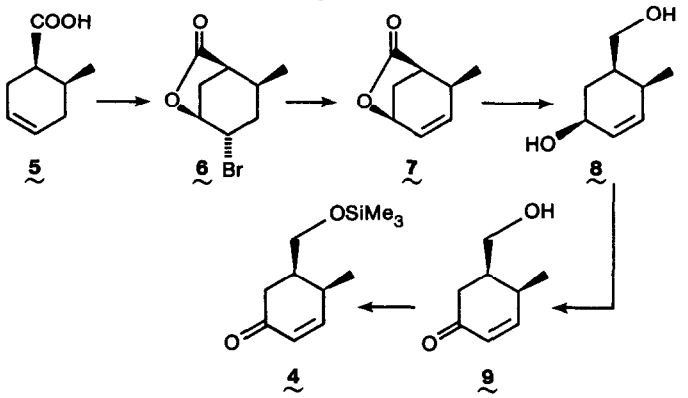
We report here a convergent route to compound 2 (R = H, Scheme 1) and its C(8) epimer, substances that represent the reduced naphthalene portion of compactin. The synthesis of 2 is a flexible one and, in principle, it could serve (see retrosynthetic Scheme 1) for making a naturally occurring member of this compound class.



Scheme 1.

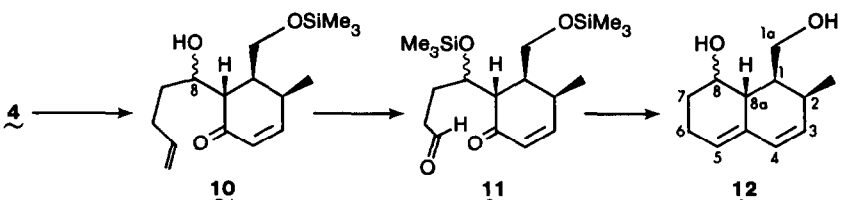
Our route, which is different from the approaches used so far,[14] requires starting materials 3 (R = H) and 4. The aldehyde 3 (R = H) is a known substance, preparable on a large scale by Claisen rearrangement of allyl vinyl ether[15] and the racemic enone 4 was synthesized by the method summarized in Scheme 2.

Bromolactonization [Br_2 (1.4 equiv.), DMF, room temp., 1.5 h, in the dark] of the silver salt of acid 5[16] afforded 6 (76% from 5) and treatment with DBN (3 equiv., refluxing toluene, 8 h) gave the olefinic lactone 7 (89%). Reduction (91%) [$LiAlH_4$ (8 equiv.), refluxing THF, 4 h] and oxidation (85%) (active MnO_2, $CHCl_3$, 3 h) effected the conversions 7 → 8 → 9. Finally, trimethylsilylation [Me_3SiCl (1.2 equiv.), Et_3N (1.2 equiv.), DMAP (0.1 equiv.), Et_2O, room temp., 3 h] produced the ring A synthon 4 (98%).



5 6 7 8 4 9 **Scheme 2.**

Kinetic deprotonation of 4 [LDA (1.1 equiv.), Et_2O, -78°] and condensation (5 min.) with the aldehyde 3 (R = H) produced (ca. 80%) (see Scheme 3) a mixture of diastereoisomers 10.[17] Protection (89%) of the C(8) hydroxyl [Me_3SiCl (1.7 equiv.), Et_3N (1.65 equiv.), DMAP (0.1 equiv.), room temp., 15 h] and ozonolysis



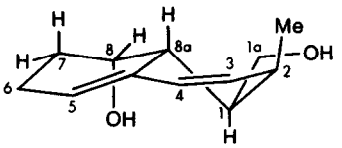
4 10 11 12 **Scheme 3.**

(76%) [O_3 (1 equiv.), CH_2Cl_2, -78°C; Ph_3P (2 equiv.), room temp., 24 h] gave the target keto-aldehyde 11 which, on treatment with low valent titanium[18] [from $TiCl_3$ and Zn/Cu] in refluxing DME, produced the desired hexahydronapthalene 12 (72%) as a 1.3 : 1 mixture of isomers, epimeric at C(8). In this ring closure the trimethylsilyl protecting groups can be removed or retained at will, depending on the method of workup.[19] For purposes of characterization the diols 12 were separated by preparative layer chromatography[20] but it is likely that the 8α and 8β isomers can both serve for elaboration into compactin-like compounds because close precedent exists[14a,c] for selective reduction of the corresponding C(8)

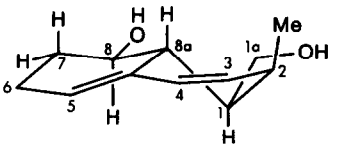
ketone from the β-face.

In principle, a sequence of the type 3 + 4 → 12 should be adaptable to the preparation of analogues with different substituents around the periphery of the reduced naphthalene unit and this possibility is under investigation.[21]

Each new compound was properly characterized [^{1}H and ^{13}C NMR, IR, mass measurement and/or combustion analysis (±0.30%)] and, in particular, the detailed NMR data for the individual isomers 12 established unambigously the structure and stereochemistry:



12 (8α − OH)



12 (8β − OH)

12 (8α hydroxyl, major isomer, ^{1}H NMR 400 MHz)[22]; 5.96 [H(4), d, $J_{3,4}$ = 9.5 Hz]; 5.68 [H(3), d of d, $J_{3,4}$ = 9.7, $J_{2,3}$ = 6.0 Hz]; 5.61 [H(5), br, s]; 4.25 [H(8), br s]; 3.84 [H(1a), d of d, J = 8.5, 10.0 Hz]; 3.72 [H(1a), br d, J = 10.0 Hz]; 2.88 [OH, br s]; 2.47 [OH and H(2), m]; 2.34 [H(8a) and H(6ax), m], 2.14 [H(6eq), d of br t, J = 17.7, 5.3 Hz]; 2.00 [H(1) and H(7eq), m]; 1.73 [H(7ax), m]; 0.88 [CH_3, d, J = 6.5 Hz]. Proton H(8) is equatorial as it shows no large coupling and the attached carbon has a chemical shift characteristic[23] of a cyclohexane carbon bearing an axial OH. Measurements made in the presence of $Cl_3CCONCO$ changed certain chemical shifts so that $J_{1,8a}$ (ca. 12 Hz) could be measured. This value establishes the trans diaxial relationship of H(8a) and H(1). Together with the observed value (<7 Hz, from decoupled spectra) for $J_{1,2}$, the above data establish the stereochemistry shown. δ ^{13}C (100.6 MHz; $CDCl_3$): 133.61 (s); 132.47 (d), 128.59 (d), 123.93 (d); 65.45 (t); 65.27 [d, C(8)], 40.55 (d); 38.60 (d); 33.26 (d); 28.62 (t); 20.38 (t); 14.75 (q). 12 (8β hydroxyl, minor isomer, ^{1}H NMR, 400 MHz)[22,24]: 5.94 [H(4), d, $J_{3,4}$ = 9.8 Hz]; 5.65 (H(3), d of d, $J_{3,4}$ = 9.5, $J_{2,3}$ = 5.8 Hz]; 5.51 [H(5), br s]; 4.11 [OH, br s]; 4.02 [OH, br s]; 3.88—3.71 [both H(1a), H(8)]; 2.33 [H(2) and H(8a), m]; 2.24 [both H(6), m]; 2.01 [H(7eq), d of q, J = 11.8, 3.3 Hz]; 1.78—1.63 [H(1) and H(7ax), m]; 0.94 [CH_3, d, J = 7.0 Hz]. Proton H(8) is axial as it shows two large couplings [J = 10 Hz],[24] and C(8) has the expected[23] chemical shift for an attached equatorial hydroxyl. The values of $J_{8a,1}$ (~11 Hz),[24] $J_{8a,8}$ (~12 Hz),[24] and $J_{2,3}$ (~5 Hz)[24] serve to define the stereochemistry. δ ^{13}C (100.6 MHz, $CDCl_3$): 135.27 (s); 132.76 (d); 127.93 (d); 124.56 (d); 71.32 [d, C(8)]; 66.11 (t); 45.14 (d); 41.91 (d); 34.82 (d); 32.31 (t), 25.03 (t); 15.33 (q).

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