Formal Preparation of Semisynthetic Analogues of the Cholesterol-lowering Agent Mevinolin

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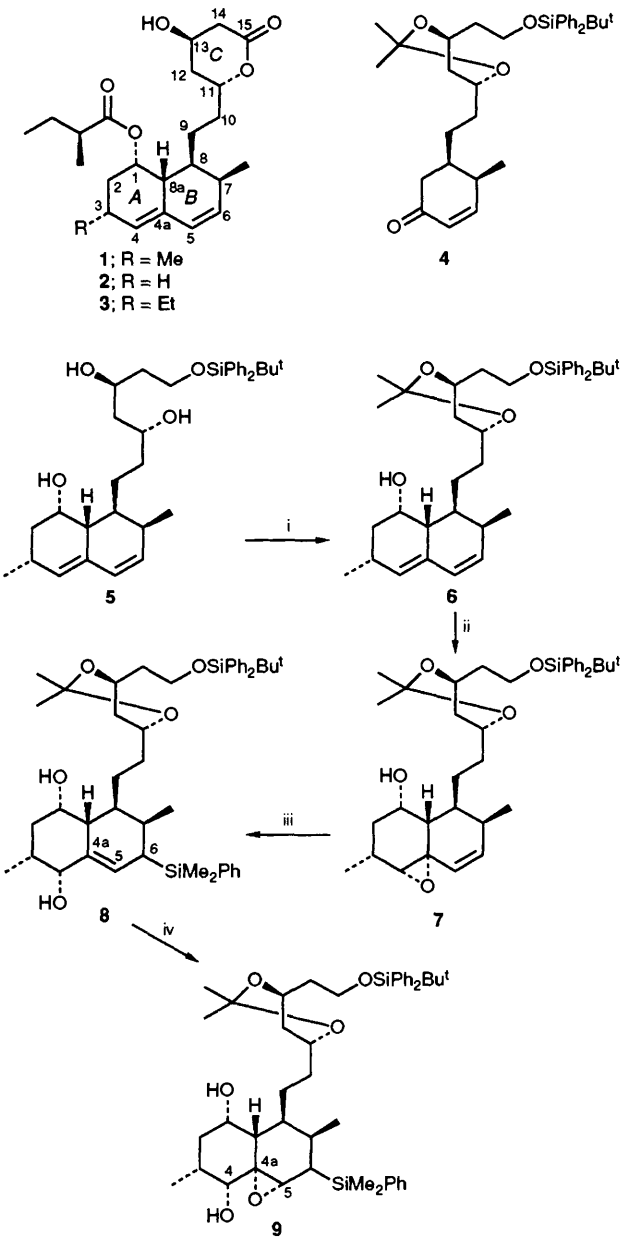
The cholesterol-lowering agent mevinolin **1** has been degraded to the enone **4**, which had previously been synthesized and converted into mevinolin **1**, compactin **2** and 3-ethylcompactin **3**.

Mevinolin **1**[1] and compactin **2**[2] are prominent and commercially important members of a group of related substances that lower blood levels of cholesterol, especially low density lipoprotein cholesterol—the form of the steroid believed to be most involved in the development of atherosclerosis.[3] Compounds **1** and **2** are lead substances for the design of other cholesterol-lowering drugs.[3] As **1** is significantly (three- to five-fold) more powerful than **2**[1a], it is clear that the level of biological activity† can be altered by changes to ring *A* and, in this context, a total synthesis of **1**–**3** was developed[4] *via* the common intermediate **4**. During the synthetic work it was realized that compound **4** might be accessible by degradation of natural **1** or **2**; attachment of different ring *A* units (by the

† Organ specificity may also be changed by structural modifications.

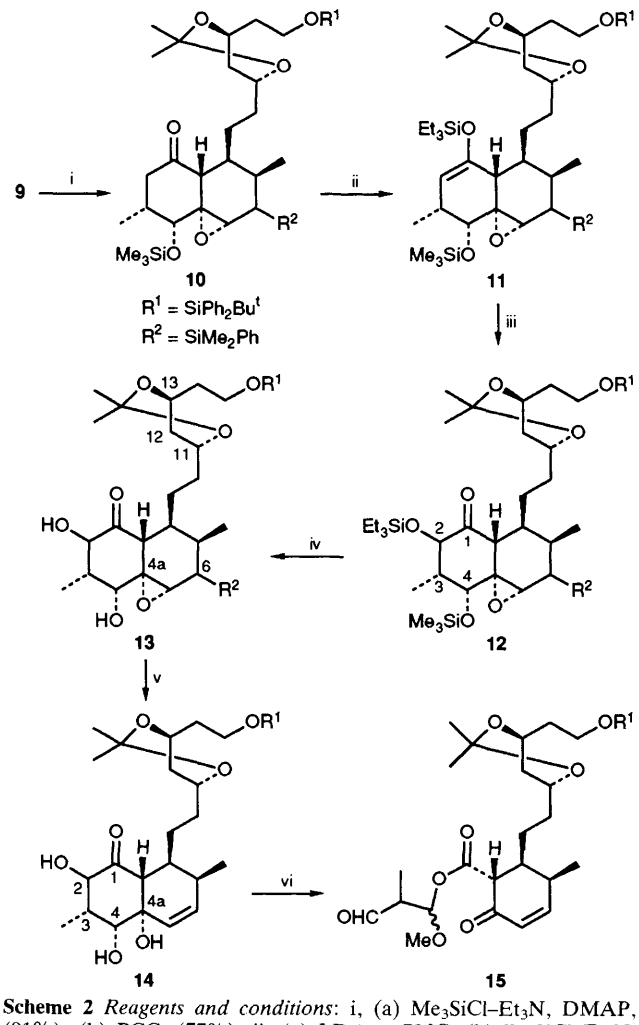


Scheme 1 *Reagents and conditions*: i, acetone, $TsOH{\cdot}H_2O$ (Ts = *p*-$MeC_6H_4SO_2$), (82%); ii, Bu^tOOH, $VO(acac)_2$ (Hacac = pentane-2,4-dione), PhH, 6–25 °C, (82%); iii, $Me_2PhSiLi$, −20 °C, (80–91%); iv, Bu^tOOH, $VO(acac)_2$, PhH, 25 °C, (85%)

method used to make **1–3**) would then afford semisynthetic analogues. We now report how this degradation may be done, starting with natural mevinolin. The route involves two sequences: in the first (Scheme 1) the diene chromophore of **1** is oxygenated and in the second (Scheme 2) the oxygen substituents are modified in such a way that the C(1)–C(2) and C(4)–C(4a) bonds can be broken by glycol- and α-ketol-cleaving agents.

Treatment of **1** with lithium aluminium hydride (84%) and selective silylation (Bu^tPh_2SiCl, dimethylformamide; 100%) of the resulting tetraol gave **5** (Scheme 1), which was then protected as a ketal (**5** → **6**; 82%). It was now possible to discriminate between the two double bonds by hydroxy-directed epoxidation.[5] Conjugate addition of $Me_2PhSiLi$[6,7] (**7** → **8**;‡ 80–91%) and a second hydroxy-directed epoxidation (85%), done in the presence of sodium hydrogen carbonate to

‡ Stereochemistry at C(6) in **8** was not established.



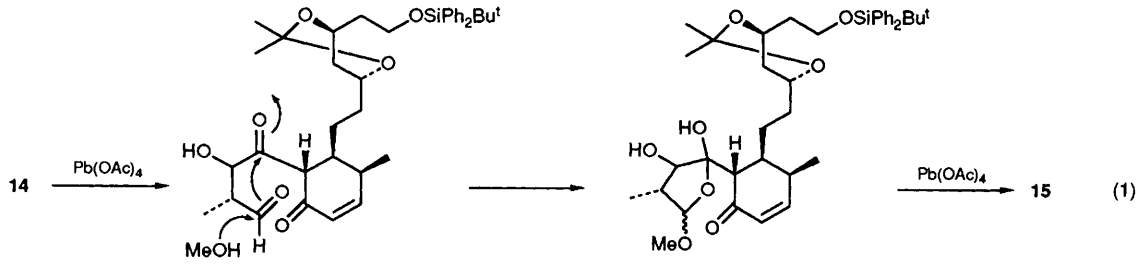
Scheme 2 *Reagents and conditions*: i, (a) Me_3SiCl–Et_3N, DMAP, (91%), (b) PCC, (77%); ii, (a) LDA, −78 °C, (b) Et_3SiCl–Et_3N, (100%); iii, MCPBA, EtOAc, (98%); iv, HOAc–Bu_4NF, THF, (85%); v, (a) PPTS, EtOH, (b) PPTS, acetone, (57%); vi, $Pb(OAc)_4$, PhH–MeOH, (67%)

ensure preservation of the Me_2PhSi-unit, took the sequence as far as **9**.§ This compound is a key intermediate in the degradation as it contains the oxygen substituents essential for cleavage of the C(4)–C(4a) bond.

The equatorial hydroxy at C(4) in **9** was silylated selectively [Me_3SiCl, Et_3N, 4-dimethylaminopyridine (DMAP); 91%] (Scheme 2) and oxidation of the C(1) hydroxy [pyridinium chlorochromate (PCC); 77%] gave ketone **10**. This was converted [lithium diisopropylamide (LDA), tetrahydrofuran (THF), Et_3SiCl, −78 °C; 100%] into the triethylsilyl enol ether **11** and epoxidation [*m*-chloroperbenzoic acid (MCPBA), EtOAc; 98%] then afforded the C(2)-oxygenated ketone **12**.¶ Exposure to tetrabutylammonium fluoride in acetic acid–THF served to deprotect the C(2) and C(4) oxygens (**12** → **13**; 85%), and then treatment with pyridinium toluene *p*-sulfonate (PPTS) in ethanol converted the C(4a)–C(6) epoxysilane unit into an allylic alcohol. During this experiment there is some hydrolysis of the C(11)–C(13) ketal, and so the crude product is treated with PPTS in acetone to restore the ketal function (**13** → **14**; 57%). Treatment of **14** with lead tetraacetate in 1 : 1 benzene–methanol resulted in cleavage of the C(4)–C(4a) and C(1)–C(2) bonds to produce

§ Stereochemistry at C(4a) and C(5) assigned on the basis of the normal mechanism of the Bu^tOOH–$VO(acac)_2$ process.

¶ Stereochemistry at C(2) was not established.



(67%) a mixture of esters to which we tentatively assign structure **15**. Formation of **15** is understandable in the terms shown by eqn. (1).

Finally, when **15** was heated in dioxane in the presence of a trace of acid (use of a chromic acid-washed flask), the desired enone **4** was obtained (80%). This compound, previously available only by total synthesis, can be used[4] to make a variety of mevinolin analogues.

All new compounds were fully characterized by spectroscopic methods, elemental composition being established by mass measurement and/or combustion analysis.

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