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Total Synthesis of a Monocyclic Analogue of Compactin

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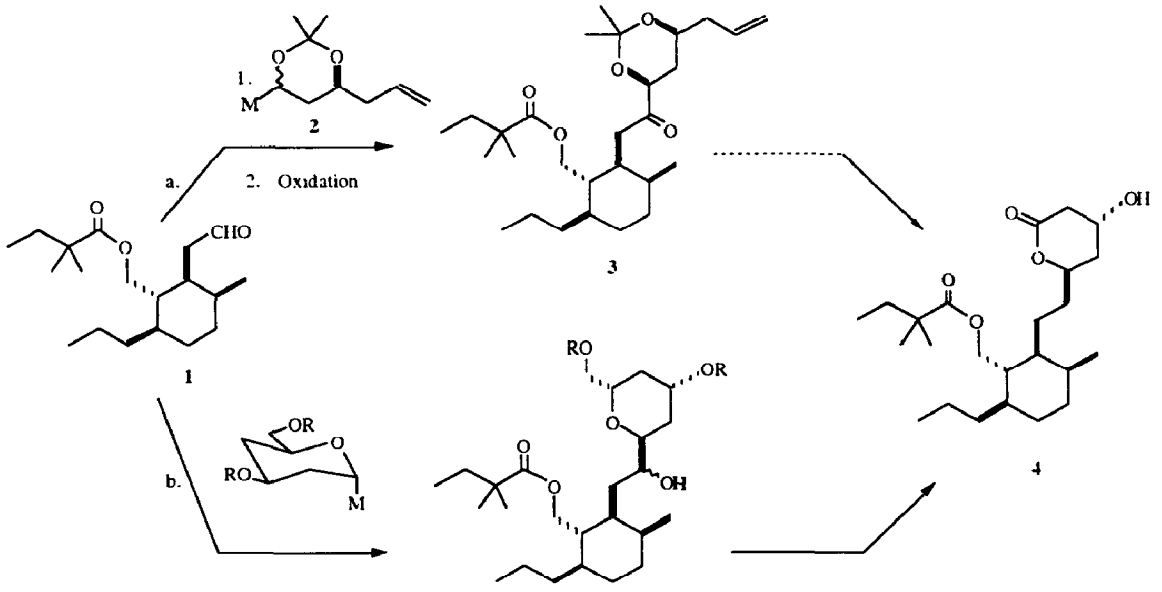
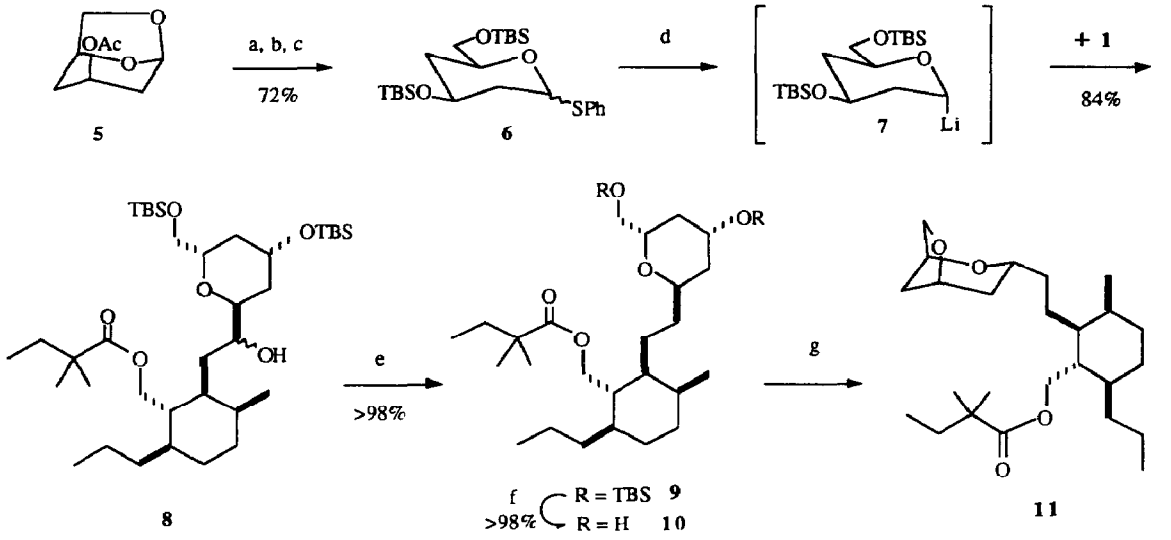
Abstract: *Total synthesis of Karanewsky's monocyclic Compactin analogue* **4** *has been accomplished.*

In the preceeding Letter[1], we have described the stereoselective synthesis of the aldehyde **1**, the cyclohexane core of a new semi-synthetic HMG-CoA reductase inhibitor **4**[2]. Since related aldehydes have already been used in the synthesis of mevinic acids[3], the synthesis of **4** might be considered as formally completed. However, the acetaldehyde type spacer chain in **1** offers other possibilities for the construction of the lactone portion of **4**. One of these (route a), although devoided of stereochemical restrictions at the C-C bond forming step[4], had some inherent disadvantages: the reagent **2** (M = SnBu3) required a multistep synthesis and the overall yield was modest. However, the C-glycosidation method (route b) afforded the lactone **4** in a straightforward manner (Scheme 1).



Scheme 1

Acetate **5**, readily available from levoglucosan in 60-65% yield[5], was converted into the thioglycoside **6**, isolated as a 5 : 2 α/β anomeric mixture. Upon treatment with lithium 4,4'-di-tert-butylbiphenyl (LiDBB)[6] in THF at -78°C, **6** underwent fast reductive metallation to give the kinetic α-glycosyllithium reagent **7**[7]. Addition of **1** to 1.1 equiv. of **7** at -78°C afforded two products in a ca. 7 : 1 ratio. They were separated, deoxygenated via the derived xanthates[8], to give the same C-glycoside **9**, thus confirming their structure as epimers of **8** at their carbinol centre. Desilylation of **9** gave rise to **10**, considered to be a suitable intermediate towards lactone **4** via elaboration of its hydroxymethyl group into an exo-methylene enol ether followed by ozonolysis. To this end, **10** was treated with the CBr_4-Ph_3P/Py mixture, known to be selective for primary hydroxyl group substitution[9]. At room temperature the reaction proceeded slowly leading to the formation of the 3,6-anhydro product **11**[10] instead of the desired bromomethylene derivative, probably as a result of cyclisation of the intermediate alkoxyphosphonium species (Scheme 2).

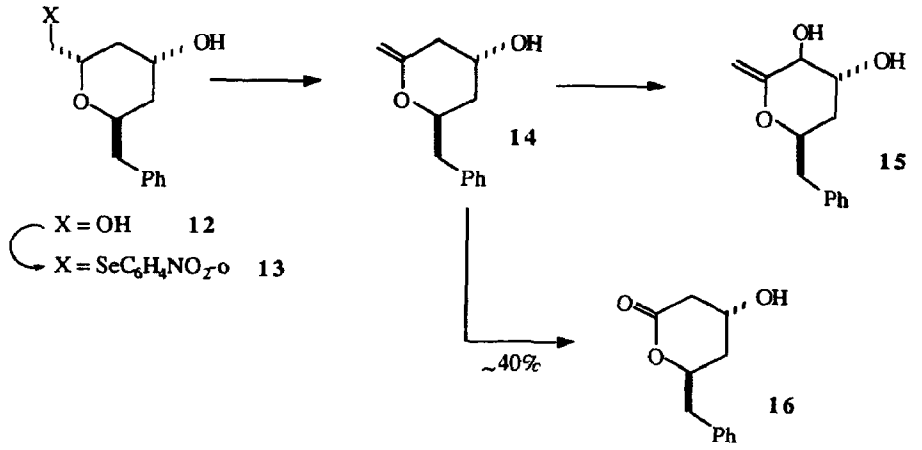


5 6 7 8 11

a. PhSH, $BF_3.Et_2O$: b. MeONa: c. TBSCl, ImH/DMF; d. LiDBB/THF, -78°C: e. NaH, CS_2, MeI/THF, then Bu_3SnH, AIBN/$PhCH_3$, Δ: f. HF aq./CH_3CN; g. CBr_4-Ph_3P/Py.

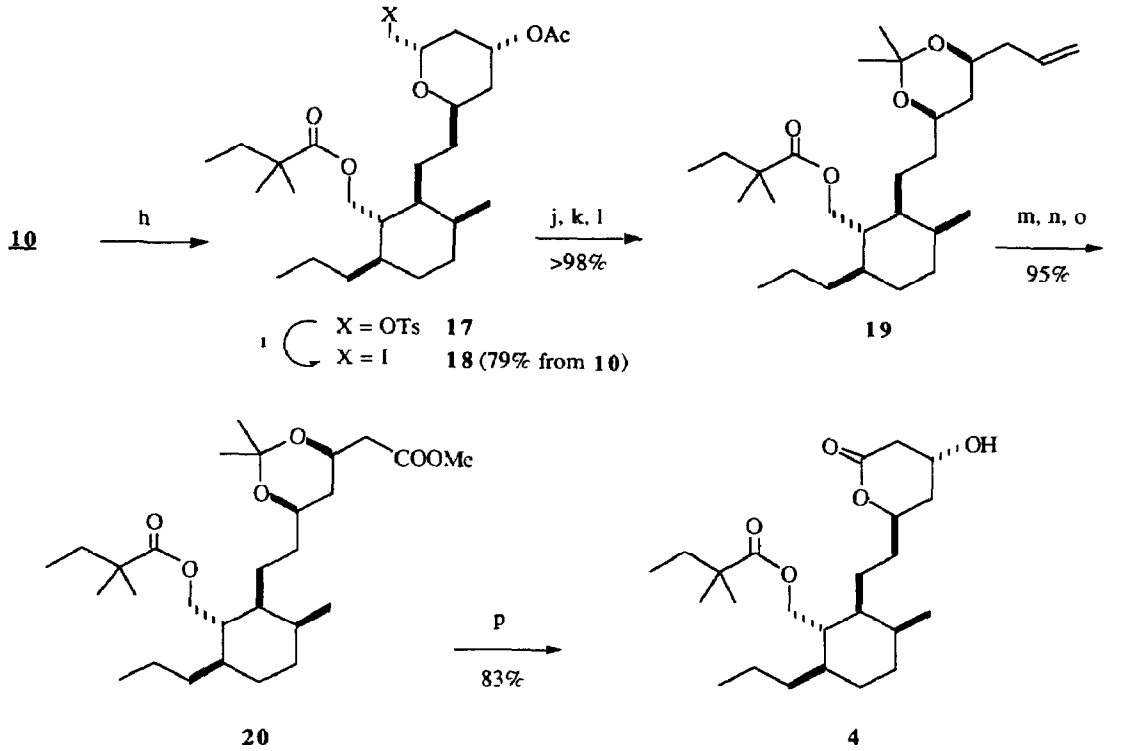
Scheme 2

In model studies on C-glycoside **12**, prepared from **7** and benzaldehyde, the primary hydroxyl could be selectively substituted by the ArSe group. However, oxidation of **13** by sodium periodate at 22°C followed by thermolysis gave the desired enol ether **14** in only moderate yield. The main by-product **15** resulted from allylic oxidation, even in the presence of a seleninic acid trap (Et_2NH; $i\text{-}Pr_2NH$)[11]. Moreover, as ozonolysis of **14** (CH_2Cl_2-Py, -78°C, followed by Me_2S) provided model lactone **16** in only low yield, this approach had to be abandoned (Scheme 3).



Scheme 3

An appropriate solution to the lactone synthesis was eventually found as shown in Scheme 4. Diol **10** was selectively tosylated at the primary position and then acetylated in one pot to give **17**, together with the diacetate (15%) of **10** which could be recycled.



h. TsCl/Py., 2 days at 4°C, then Ac_2O; i. LiI-HMPA/$PhCH_3$, Δ; j. Zn/MeOH, Δ; k. K_2CO_3/MeOH, rt; l. Me_2CO-DMP, CSA(cat.); m. O_3/CH_2Cl_2, then Ph_3P; n. $KMnO_4$/t-BuOH, NaH_2PO_4 aq.; o. CH_2N_2; p. HF aq./CH_3CN.

Scheme 4

The tosyloxy group in **17** was substituted by iodide[12] to give **18** which was reductively split with Zn dust in boiling MeOH to furnish after deacetylation an acyclic 1,3-*syn*-diol. The structure of the latter was proved by the ^{13}C NMR spectrum of its isopropylidene derivative **19**[13]. Ozonolysis of **19** followed by oxidation of the resulting aldehyde with $KMnO_4$ in buffered t-BuOH[14] gave the protected seco-mevinic acid, isolated as its methyl ester **20**. Deprotection with simultaneous lactone ring closure was effected, as described[2], by treatment of **20** with 48% aqueous HF in MeCN to give the targeted highly crystalline **4**[15], {mp 128-130°C (from heptane), $[\alpha]_D$ + 34.7° (c 0.59, $CHCl_3$)}, identical in all respects with a sample {[Lit.[2] mp 128-129.5°C, $[\alpha]_D$ + 34.9° (c 0.54, $CHCl_3$)]} derived from naturally occurring Pravastatin. The 300 MHz ^1H NMR spectrum of our synthetic sample is identical to the 270 MHz ^1H NMR spectrum of **4** kindly provided by Dr. Karanewsky, Bristol-Myers Squibb, USA.

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References and Notes

1 The preceeding Letter in this Issue.
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13. ^{13}C-NMR resonances of carbons within isopropylidene moiety of **19**, diagnostic for 1,3- syn-diol arrangement, are 20.0, 30.4 and 98.4 ppm; cf. (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945-948; (b) Evans, D. A.; Reiger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099-7100; (c) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511-3515.
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15. All new compounds gave spectral and analytical data consistent with the assigned structure. Specific rotations were measured in $CHCl_3$ solution, using c = 1.0, whenever not specified. Selected data: **9** : +23°; **10** : +30°; **18** : +37°; **19** : +10°; **20** : +16.1° (c = 1.09).

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