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A NEW ROUTE IN THE SEQUENTIAL TOTAL SYNTHESIS OF COMPACTIN

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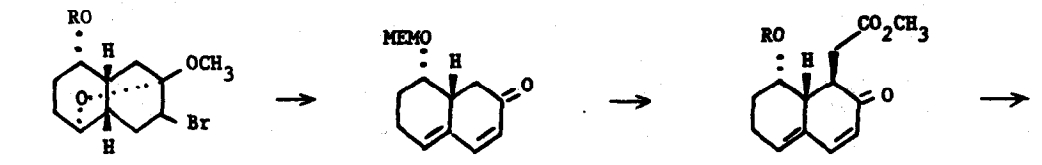
Summary: The synthesis and regioselective hydrogenation of 1,2,6,7,8, 8aβ-hexahydro-8α-hydroxy-2-methylene-1β-naphthaleneacetic acid methyl ester 4a, has provided a novel synthetic pathway to the hypocholesterolemic agent, compactin 9.

Earlier we reported[1] a total synthesis of the HMG-CoA reductase inhibitor, compactin, in both the racemic and optically active forms by a sequence originating from butadiene and p-benzoquinone. This route as originally projected had encountered difficulties necessitating at the time the alternative pathway reported.[2] These obstacles have since been surmounted in good measure, thereby providing a new synthetic route to compactin whereby the dienic chromophore of this substance is uniquely constructed via regioselective hydrogenation of a conjugated trienic intermediate.

The bromoketal 1 (derived in six steps from the butadiene-p-benzoquinone adduct)[1] in the form of its MEM ether (MEMCl, CH_2Cl_2,N,N-Diisopropylethylamine) was successively dehydrobrominated ($KOBu^t$,DMSO,25°;H_3O^+) and dehydrated (CH_3SO_2Cl,py,0°;py,80°) to give the dienone 2 in 65% overall yield (purified on silica gel with 10% acetone-CH_2Cl_2);λ^{max}_{MeOH} 289 nm E,14500. NMR ($CDCl_3$,60 MHz) δ3.38 (OCH_3,s), 4.00 (H_8, broad s), 5.83 (H_3,d,J = ca 10), 6.18 (H_5, broad s) and 6.97 (H_4,d,J = ca 10). M^+252. Carbomethoxymethylation of 2 (LDA, THF,-78; $BrCH_2CO_2CH_3$, -78° to -35°) proceeded stereoselectively β to the ring system to yield 3 (65%) (purified on silica gel with 15% acetone - CH_2Cl_2). NMR ($CDCl_3$,60 MHz) δ3.35 (OCH_3,s), 3.65 (CO_2CH_3,s), 4.12 (H_8, broad s) 5.85 (H_3,d,J = ca 10), 6.18 (H_5, broad s) and 6.93 (H_4,d,J = ca 10). M^+324. Hydrolysis of 3 (aqHCl, THF, 60°) afforded the hydroxy acid 3a mp 144-146° which was methylated (CH_2N_2) to hydroxy ester 3b mp 86-88°. M^+236. 3b was in turn converted (98%) to the silyl ether 3c [$(CH_3)_3SiCl$,THF,py,25°)] and the latter transformed by Wittig olefination ($Ph_3P{=}CH_2$,THF, 0°) to the conjugated triene 4 (80%). Desilylation of 4 (aqHCl, THF,0°) provided 4a (82%) NMR (C_6D_6, 60 MHz) δ3.33 (OCH_3,s) 4.05 (H_8 broad s) 4.97 (=CH_2,m), 5.50 (H_5,m) and 6.03 (H_3,H_4,s). M^+234

Hydrogenation of crude 4a [$(Ph_3P)_3RhCl$,tol.,25°] afforded 60% of a 1:1 mixture of 2βCH_3 5 [Rf 0.5; NMR (C_6D_6,60 MHz) δ0.83 (CH_3,d,J = ca 7), 3.33 (OCH_3,s), 3.80 (H_8, broad s) and 5.97 (H_4d,J = ca 9)] and 2αCH_3 5a [Rf 0.6; NMR (C_6D_6,60 MHz) δ0.92 (CH_3,d,J = ca 7) 3.27 (OCH_3,s), 4.13 (H_8, broad s) and 6.03 (H_4,dd, J = ca 9 and J_2 = ca 2)] together with a minor amount (~5%) of tetrahydro product (separated on silica gel 5% acetone - CH_2Cl_2).[3] Saponification of 5 (1N aqNaOH-CH_3OH, 25°) and ring closure of the intermediate acid (10% aqHCl-CH_2Cl_2,25°) yielded (75%) crystalline lactone 6 mp 99-101°. M^+204. The lactone 6 in turn was reduced (DIBAL, tol., -78°) to the corresponding lactol 6a followed by Wittig olefination ($Ph_3P{=}CH_2$,THF,25°) to give

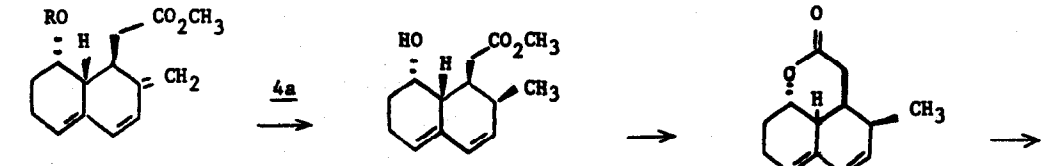
crystalline triene 7 mp 100-102° (35% not optimized). Acylation of 7 to 7a ($\pm C_4H_9CO)_2O$, py, DMAP, 25°) with ensuing hydroboration-oxidation (9BBN,H_2O_2) yielded (90%) the known carbinol 8. The latter has previously been converted to (±) compactin 9.[1]



1 R = H
1a R = MEM = $CH_3OCH_2CH_2OCH_2$

2

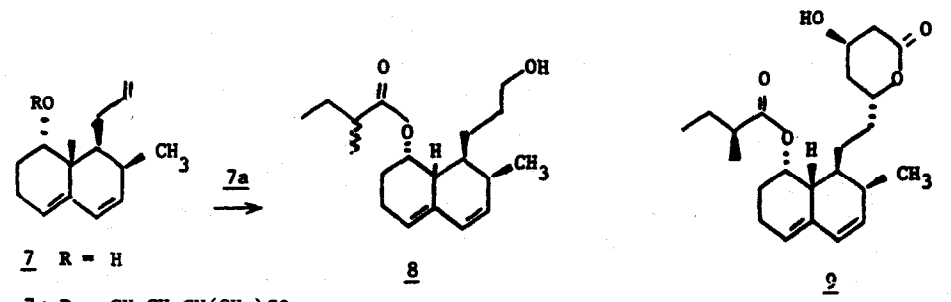
3 R = MEM
3a R = H; CH_3 = H
3b R = H
3c R = $(CH_3)_3Si$



4 R = $(CH_3)_3Si$
4a R = H

5 2βCH_3
5a 2αCH_3

6
6a CO = CHOH



7 R = H
7a R = $CH_3CH_2CH(CH_3)CO$

8

9

References and Notes

1. N.N. Girotra and N.L. Wendler, Tetrahedron Letters, 5501 (1982). For other syntheses see P.A. Grieco, R.E. Zelle, R. Lis and J. Finn, J. Am. Chem. Soc. 105, 1403 (1983) and ref. therein.
2. Difficulties were encountered in controlling the stereochemical course of hydrogenation of the trienic system for which eventually a partial but nonetheless workable solution was found. In this regard the triene derived from 2 ($Ph_3P{=}CH_2$) had been found earlier to undergo hydrogenation in good yield to give the corresponding 2β-methyl derivative. The corresponding acetic ester derivative 4 (R=MEM), by contrast, afforded to a major extent the undesired 2α-methyl diene. Furthermore, except in the case of the hydroxy ester 4a, the directional course of hydrogenation of systems involving other alterations of -OR and CO_2R substituents were found to yield primarily 2α-methyl species in all instances investigated.
3. The trienic systems 4 and 4a are very unstable, rapidly deteriorating to more polar species; consequently the conversion 3b → 5 was effected without purification of intermediates.

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