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TOTAL SYNTHESIS OF (+)-MONACOLIN K (MEVINOLIN)

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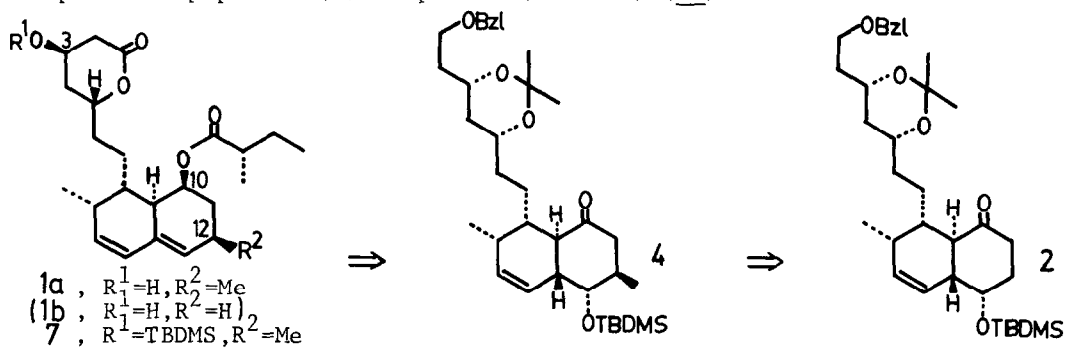
Abstract: (+)-Monacolin K (mevinolin) (1a), an extremely potent inhibitor of HMG-CoA reductase, has been stereospecifically synthesized from intermediate 2 employed in the synthesis of (+)-compactin (ML-236B) (1b).

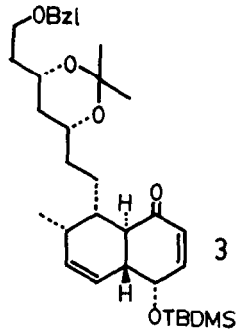
Monacolin K (1a), a fungal metabolite isolated in 1979 from cultures of Monuscus ruber,[1] is identical to mevinolin from Aspergillus terreus.[2] This substance has proven to be a more potent competitive inhibitor of HMG-CoA reductase than compactin (ML-236B) (1b) and highly hypocholesterolemic agent as well.[1,2,3] We herein report the first enantio- and stereo-selective synthesis of 1a from trans-octalone 2, which is the synthetic intermediate described in our previous paper on (+)-compactin (ML-236B) (1b).[4a]



1a , R^1=H, R^2=Me
(1b , R^1=H, R^2=H)
7 , R^1=TBDMS, R^2=Me

There exists an additional chiral center (C12) on the functionalized hexahydronaphthalene moiety of 1a as compared with 1b. This chiral center was stereospecifically introduced by Michael addition of lithium dimethyl cuprate (ether/0 °C, 91%) to the enone 3[5] [$[\alpha]_D^{24}$ +123.5°; δ($CDCl_3$) 6.59(dd, J=10.0, 5.0 Hz, H12), 5.86(d, J=10.0, H11), 4.23(dd, J=5.0, 2.9, H13), 2.99(t, J=11.4, H9)] which was synthesized from 2[4a] via enol silyl ether formation (LDA/-78 °C; TMSCl/NEt_3/-78 °C → r.t.) followed by oxidation [$Pd(OAc)_2$/p-benzoquinone/r.t.][6] in 57% overall yield. This cuprate addition proceeded exclusively from the β-side as expected in view of both the steric hindrance of the bulky t-butyldimethylsilyl ether group and the stereoelectronic preference of axial addition. Ketone 4[5] [$[\alpha]_D^{23}$ +78°; δ($CDCl_3$) 3.64(br s, H13)] thus obtained was converted to the 10S-acyloxy primary alcohol 5[5], $[\alpha]_D^{24}$ +65°, in four steps: (1) K-Selectride/r.t.,89%; (2) Li/NH_3/-78 °C/2 min, 90%; (3) S-2-methylbutyric anhydride/pyridine/DMAP/r.t.,

76%[7]; (4) 1N-NaOH/EtOH/r.t., 90%. The subsequent transformation of 5 to δ-lactone and the introduction of diene system were achieved in an analogous manner to the synthesis of 1b.[4a] Oxidation (Collins and then PDC/DMF)[8] and acid treatment (aq.HF/CH_3CN) gave the dihydroxy lactone 6[5], $[\alpha]_D^{24}$ +94°, in 56% overall yield. The C3-OH of 6 was selectively protected as t-butyldimethylsilyl ether (TBDMSCl/imidazole/DMF, 88%) and then the C13-OH was dehydrated with $SOCl_2$-pyridine (0 °C → r.t.) to afford in 49% yield monacolin K silyl ether 7[5] ($[\alpha]_D^{26}$ +197°) which was identical in all respects with an authentic specimen ($[\alpha]_D^{21}$ +218°) prepared from natural 1a. Desilylation (aq.HF/CH_3CN/0 °C/5 h) of 7 provided 1a in 77% yield.



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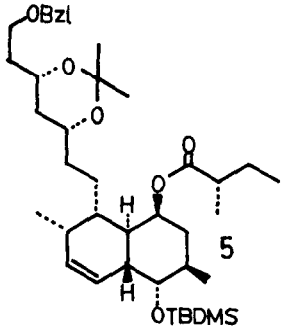

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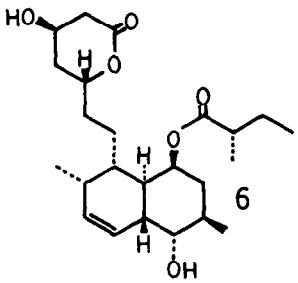

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References and Footnotes

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5) These compounds exhibited satisfactory spectral properties and exact mass data. The specific rotation $[\alpha]_D$ was measured in $CHCl_3$.
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7) This acylation must be performed after deprotection of C1-benzyl ether group. Otherwise, Li/NH_3 reduction caused debenzylation with inavoidable concomitant deacylation of C10-ester group, that was avoided in the case of the synthesis of 1b[4a].
8) Direct oxidation of primary alcohol 5 to the acid by PDC/DMF gave an unsatisfactory yield.

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