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SYNTHESIS OF THE HEXAHYDRONAPHTHALENE MOIETY OF (+)-MEVINOLIN

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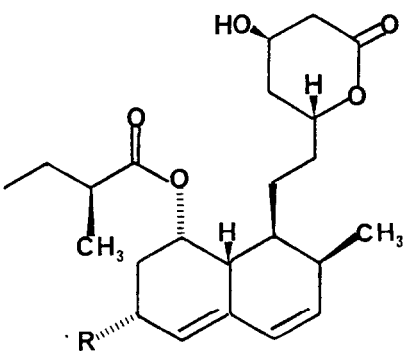
Summary: The synthesis of the hexahydronaphthalene moiety (6b) of (+)-mevinolin (1) has been achieved in 10 steps using an intramolecular Diels-Alder reaction of an alkenylallene to set up four of the chiral centers and the diene unit of (6b).

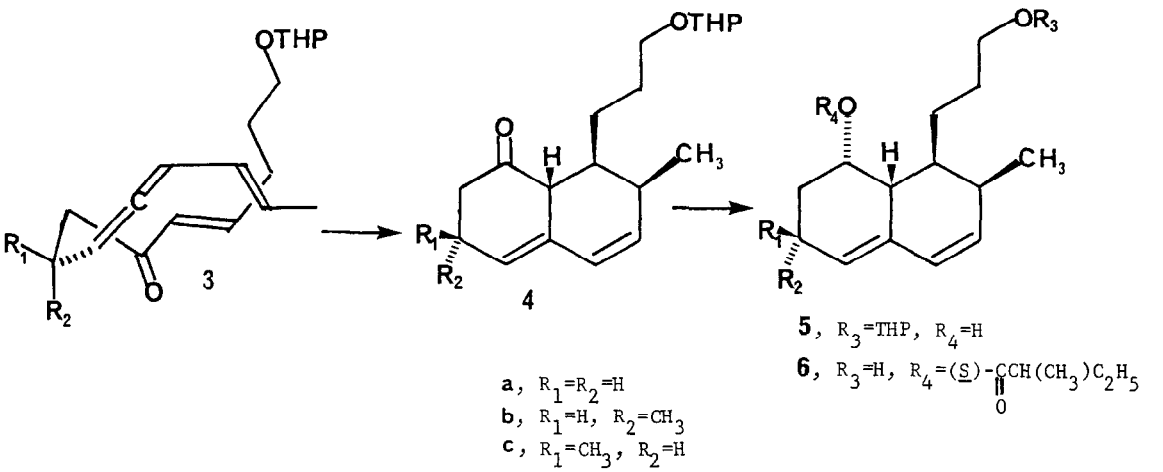
Mevinolin (1)[1] and monacolin K[2] are identical fungal metabolites isolated from Aspergillus terreus and Monascus ruber, respectively. Both mevinolin and the less active analog compactin (2) are potent inhibitors of HMG-CoA reductase and are therefore effective hypocholesterolemic agents.[1,2,3] Their biological activity and structural novelty have prompted extensive synthetic efforts which have led to the total synthesis of (+)-compactin,[4] the hexahydronaphthalene moiety of compactin (e.g. 6a),[5] and the more complex target, mevinolin.[6]



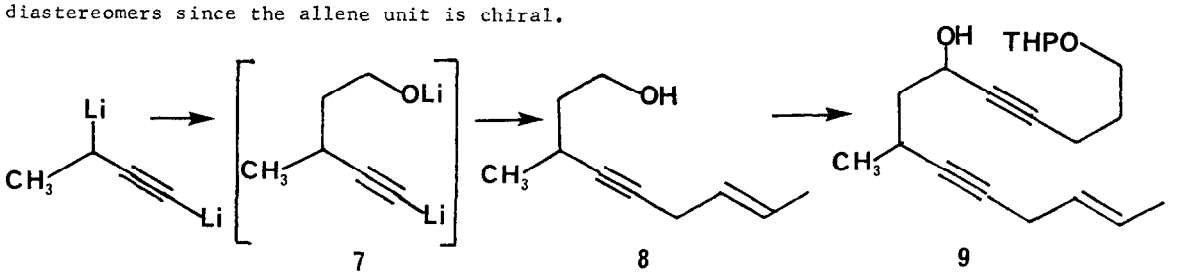
1, R = CH_3
2, R = H

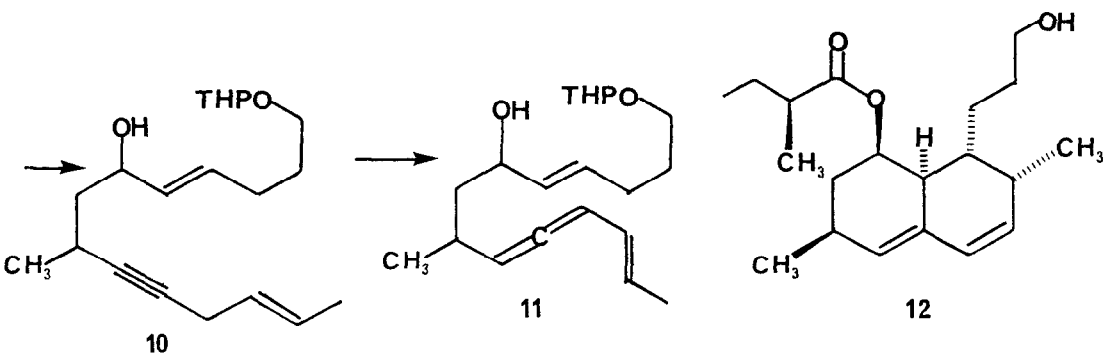
We recently reported an efficient synthesis of 6a[5b] and formal synthesis of 2[7] in which the key step is the intramolecular Diels-Alder reaction of 3a, with an alkenylallene as the diene component, to give 4a containing three of the chiral centers and the diene unit of compactin. We report here the extension of this approach to the synthesis of the mevinolin precursor 6b.

The preparation of 3b proceeded analogously to that of 3a. Enyne 8 was prepared in one-pot in 55% yield by treating the dianion of 1-butyne[8] (2.5 equiv of n-BuLi, THF-hexane, -30°C to 25°C, 4 h) with 1 equiv of ethylene oxide to give 7[8] which was coupled with crotyl bromide[9] (2 equiv, 7 mol % CuCl, 60°, 30 min). Oxidation of 8 with PCC-NaOAc[10] (CH_2Cl_2, 25°, 3h) gave the corresponding aldehyde, which was reacted with the acetylide prepared from the THP ether of 4-pentyn-1-ol[11] (n-BuLi, THF, 0°) to give 9 in 50% yield from 8 after chromatography. Reduction of 9 with 2:1 NaOMe-$LiAlH_4$[12] (THF, 70°, 1.5 h) gave a 90% yield of a mixture of 10 and the desired alkenylallene 11. Base catalyzed isomerization[13] of this mixture (0.2 M, 1 M



KO$\underline{t}$-Bu in $\underline{t}$-BuOH, 40°C, 12 h) gave a mixture containing $\underline{ca}$ 50% of $\underline{11}$ along with conjugated enynes and unreacted $\underline{10}$ which was used without purification. Oxidation of crude $\underline{11}$ with PCC-NaOAc[10] (CH_2Cl_2, 25°, 25 h) gave the crude enones $\underline{3b}$ and $\underline{3c}$ in 80% yield as a 1:1 mixture of diastereomers since the allene unit is chiral.





Intramolecular Diels-Alder reaction to give $\underline{4b}$ and $\underline{4c}$ was effected by heating $\underline{3b}$ and $\underline{3c}$, and 0.5% BHT in benzene for 3 h at 150°C in a sealed tube. Due to the anticipated instability

of the β,γ-unsaturated ketone 4, the crude mixture was immediately reduced with L-Selectride (THF, 0-12°, 3.5 h) to give 5b and 5c. Medium pressure liquid chromatography of the crude mixture on silica gel (2:1 hexane-ether) gave pure 5b[14] (5% from 9, ca. 56% from 3b) followed by a mixture of more polar acyclic alcohols and 5c. Further purification of this mixture by reverse-phase HPLC[15] gave pure 5c[14] (5% from 9, ca 56% from 3c). The relative stereochemistry of 5b and 5c was established by their polarity on silica gel. The hydroxyl group of 5b is hindered by the axial methyl group and binds weakly to silica gel. Alcohol 5b therefore elutes much more rapidly than 5c.[14] In addition,the more hindered alcohol of 5b is less easily esterified and the NMR absorption of the methyl group of 6b, but not 6c, corresponds closely to that of mevinolin (vide infra).

Esterification of 5c with (S)-2-methylbutyric anhydride[4a] (pyr, DMAP, 25°C, 20 h) followed by deprotection (pyridinium tosylate, EtOH, 50°, 20 h)[16] gave optically active 6c[17] and its diastereomer epimeric at the 5 ring centers in 44% yield. Esterification of 5b carried out similarly at 50°C (20 h),followed by deprotection gave a 1:1 mixture of optically active 6b[17] and 12[17] in 46% yield. These were easily separated using reverse-phase HPLC conditions developed at Merck[4d,18] for the separation of 6a from its diastereomer.

The stereochemistry of 6b and 12 was determined from their chiroptical properties. The CD spectrum of mevinolin and 6b were qualitatively identical showing a large positive Cotton effect with maxima at 231, 239 and 247 nm which results from the helical sense of the diene moiety.[19] The CD spectrum of the diastereomer 12 is the mirror image of that of 6b and mevinolin. In addition, 6b eluted first under these reverse-phase HPLC conditions as do 6a[4d] and 1[20] as compared to the diastereomers epimeric on the ester side chain. The differences between the NMR spectra of 6b and 12 correspond closely to those between the spectra of mevinolin and its epimer on the ester side chain.[20,21]

These results indicate the utility of the intramolecular Diels-Alder reaction of 3b for the construction of 6b. We are presently attempting to develop efficient methods for the synthesis of 3b, and analogs containing a preformed pyranoid side chain, with control of the relative and absolute stereochemistry.

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7. The diastereomeric mixture reported in ref 5b has been separated as reported by Girotra and Wendler[4d] to give pure (+)-6a mp 59-61°, lit. mp 66-67°C,[4a] which has been converted to 2 by Sih.[4a]

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11. We previously reported the use of the ethoxyethyl ether in the synthesis of 6a,[5b] but have since found that the THP ether gives more reproducible results, since it is more stable to hydrolysis in subsequent steps.

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14. R_f 5b = 0.30, 5c = 0.22 (1:1 hexane-ether); 5b NMR (CCl_4) δ 5.86 (d, 1, J=10 Hz), 5.68 (dd, 1, J=10,5 Hz), 5.40 (m, 1), 1.14 (d, 3, J=7 Hz), 0.85 (d, 3, J=7 Hz); 5c NMR (CCl_4) δ 5.90 (d, 1, J=10 Hz), 5.68 (dd, 1, J=10, 5 Hz), 5.32 (m, 1), 1.05 (d, 3, J=7 Hz), 0.87 (d, 3, J=7 Hz).

15. Ultrasphere ODS 5μ, 1 x 25 cm, 70:30 CH_3CN-H_2O, 4 mL/min, t_R = 34 min.

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17. 6b: NMR ($CDCl_3$) δ 1.13 (d, 3, J=7 Hz), 1.09 (d, 3, J=7 Hz), 0.90 (d, 3, J=7 Hz), 0.90 (t, 3, J=7 Hz); mp 80.5-81.5. 12: NMR ($CDCl_3$) 1.14 (d, 3, J=7 Hz), 1.09 (d, 3, J=7 Hz), 0.92 (t, 3, J=7 Hz), 0.90 (d, 3, J=7 Hz); mp 57-58°C. The downfield region of the NMR spectra of 6b and 12 are identical: 6.00 (d, 1, J=10 Hz), 5.80 (dd, 1, J=10,6 Hz), 5.54 (br, 1, $W_{1/2}$ = 9 Hz). 6c and diastereomer: 5.97 (d, 1, J=10 Hz), 5.77 (dd, 1, J=10,6 Hz), 5.41 (br, 1, $W_{1/2}$ = 3.75 Hz), 1.122 and 1.118 (2d, 3, J=7 Hz), 1.01 (d, 3, J=7 Hz), 0.89 (t, J=7 Hz), 0.90 (d, J=7 Hz).

18. Ultrasphere ODS 5μ, 1 x 25 cm, 40:60 CH_3CN-H_2O, 5 mL/min, 6b t_R=104.5 min; 12, t_R=112 min.

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21. We thank Dr. Smith for providing us with 360 MHz NMR spectra of 1 and its ester side chain epimer.[20]

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