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AN APPROACH TO THE SYNTHESIS OF THE HEXAHYDRONAPHTHALENE UNIT OF PRAVASTATIN†

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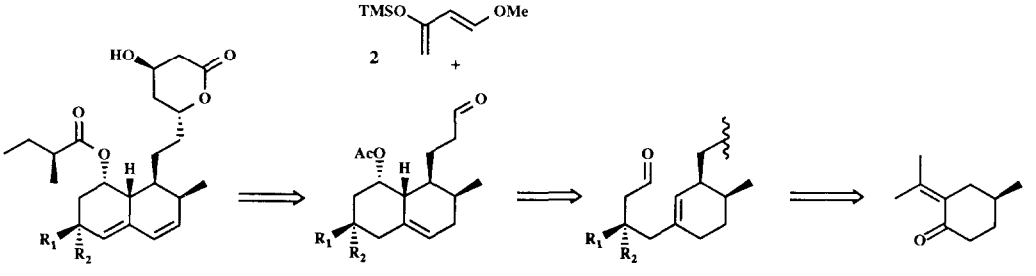
Summary: The aldehyde **3b** is prepared from (S)-pulegone (**5**) by a series of highly effective transformations, including a stereospecific [2,3]-Wittig rearrangement of the allyl ether of **6**, stereoselective selenolactonization of **8c**, SN2' addition to **10** and a stereospecific intramolecular *ene* reaction of **11b**.

In a recent report from this laboratory, Wovkulich, et al.[2] described a novel strategy for the synthesis of lovastatin (**1a**) in which the lactone chirality is generated via the diastereoselective cycloaddition of **2** to the decalin aldehyde **3a**. Chiral **3a**, in turn, was prepared from (S)-pulegone, **5**, by a series of highly stereoselective transformations, the key one being the intramolecular *ene* reaction of **4a**. In the present paper, we describe an approach to the decalin aldehyde **3b** required for the synthesis of the clinically effective HMG-CoA reductase inhibitor pravastatin, **1b**[3].



1a R_1 = H, R_2 = Me Lovastsatin
b R_1 = OH, R_2 = H Pravastatin

3a R_1 = H, R_2 = Me
b R_1 = OH, R_2 = H

4a R_1 = H, R_2 = Me
b R_1 = OH, R_2 = H

5

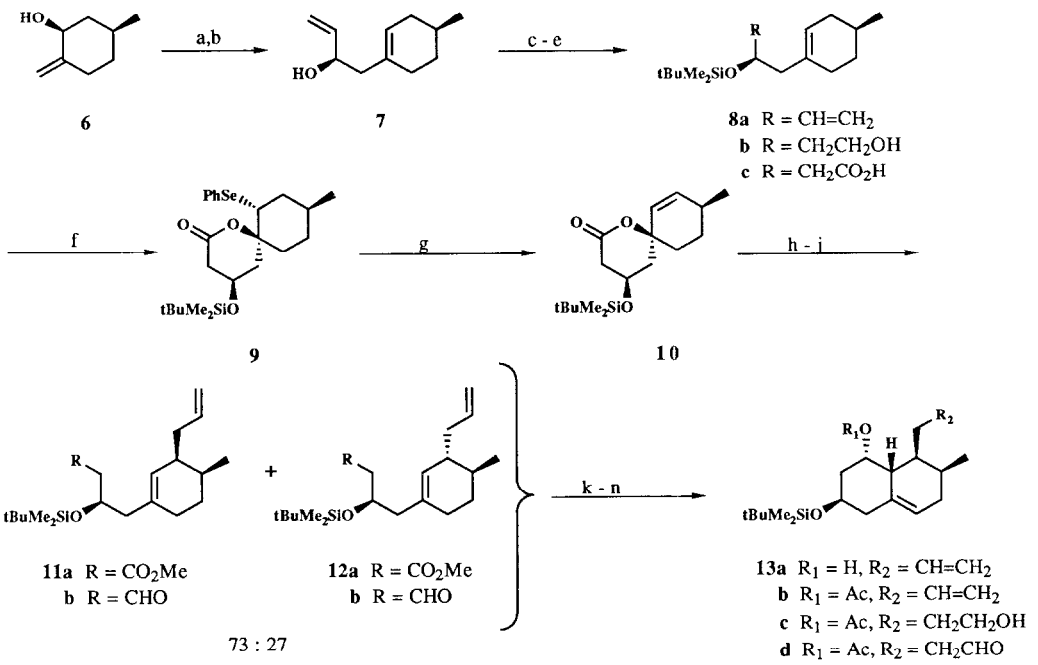
The alcohol **6**[2] (Scheme) was converted to its allylic ether which underwent Wittig rearrangement upon treatment with n-BuLi[4] to give a single diastereomer **7**[5,6]. The alcohol was protected as its *t*-butyldimethysilyl ether **8a** and the terminal olefin selectively hydroborated with 9-BBN. Oxidation of the resulting alkylborane gave a primary alcohol **8b** which was oxidized to the carboxylic acid **8c**.

Although the iodolactonization of **8c** ($NaHCO_3/I_2$) was stereospecific, in analogy to the lovastatin case,[2] the elimination of the iodide to the olefin could not be accomplished without concomitant elimination of the silyloxy group. Mild oxidative elimination of the corresponding selenolactone proved to be more fruitful. Selenolactonization of crude **8c** with phenylselenenyl chloride[7,8] using $NaHCO_3$ as base gave **9** in 50% isolated yield along with 7% of its diastereomer which was removed by flash chromatography. The lower selectivity of phenylselenolactonizations as compared to iodolactonizations has been seen previously.[9] Oxidation with H_2O_2

† This paper is dedicated to the memory of our good friend and co-worker Milton Jones.

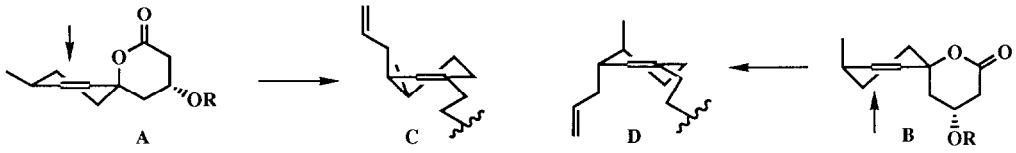
gave the selenoxide which underwent smooth elimination at room temperature to give **10** in 85% yield.

Scheme



CONDITIONS: a) NaH, CH_2=$CHCH_2Br$; b) BuLi, THF, -78°C (58%); c) TBDMS-Cl; d) 9-BBN then NaOH, H_2O_2, e) PDC, DMF (66%); f) PhSeCl, $NaHCO_3$, CH_3CN (50%); g) 30% H_2O_2 (85%); h) allyl-TMS, $SnCl_4$, -90°C; i) CH_2N_2 (74%); j) DIBAL, $PhCH_3$ (97%); k) Me_2AlCl, CH_2Cl_2 (68%); l) Ac_2O; m) Disiamylborane then H_2O_2 (85%); n) $(COCl)_2$, DMSO (64%).

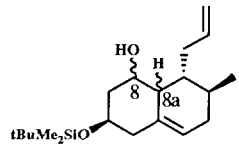
Addition of trimethylallylsilane to a CH_2Cl_2 solution of **10** and one equivalent of $SnCl_4$ at -90°C gave predominantly axial, syn attack (see **A** below) by the allyl group resulting in, after esterification, a 73:27 mixture of **11a**:**12a**.[10,11] To our knowledge, stereoselective SN2' addition of an allyl group to an unsaturated lactone is unprecedented.[12] In the case of a glycal acetate, the reaction is known to be biased towards axial attack of the allyl moiety even if the acetate group is anti.[13] The minor isomer, **12a**, may be derived from axial attack on



the half-chair conformation **B**. The energy differences(MM2) between the starting material conformers (**A** vs. **B**, 1 Kcal/mol) and the product initial conformers (**C** vs **D**, 0.3 Kcal/mol) suggests that a more product-like transition

state is responsible for the observed stereoselection. The diastereomers **11a** and **12a** could not be separated at this point and were carried on as a mixture.

Reduction with DIBAL-H gave the aldehydes (**11b, 12b**) which underwent a smooth *ene* reaction on treatment with Me_2AlCl. Three products (**13a, 14,** and **15**) were isolated by flash chromatography in yields of 68, 12 and 12% respectively.[14] From the product distribution (74:13:13), it may be deduced that the major aldehyde **11b** underwent a stereospecific intramolecular *ene* reaction to form **13b**, while the minor aldehyde **12b** reacted nonselectively. The stereochemistry at C_8 and C_{8a} for both **14** and **15** was not determined.



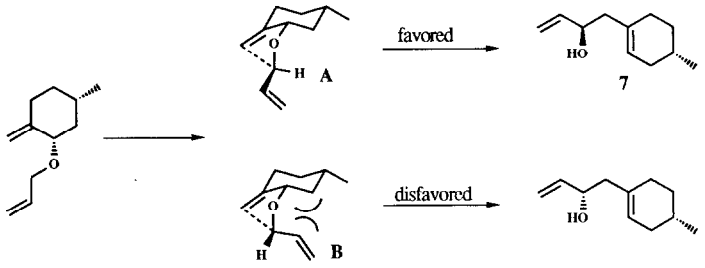
14,15

The secondary alcohol was protected as the acetate as required for the later stereocontrolled cycloaddition. Regioselective hydroboration with disiamylborane gave the primary alcohol. The relative stereochemistry of a derivative of **13c** was confirmed by an X-ray crystallographic analysis.[15] Finally, Swern oxidation of **13c** gave the aldehyde **3b**. Completion of the synthesis of **1b** will be reported in due course.

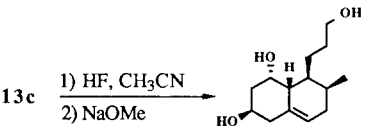
Acknowledgement: We would like to thank the members of the Physical Chemistry Department of Hoffmann-La Roche, Inc. for determination of spectral and analytical data, and especially L. J. Todaro and A. M. Chiu for the X-ray crystallographic analysis. We also thank Dr. D. Kronenthal for reading this manuscript.

References

1. Current Address: Squibb Institute for Medical Research, P.O. Box 4000, Princeton, NJ 08543.
2. P. M. Wovkulich, P. C. Tang, N. K. Chada, A. D. Batcho, J. C. Barrish, M. R. Uskoković, *J. Am.Chem. Soc.* **1989**, *111*, 2596.
3. (a) Isolation: N. Serizawa, K. Nakagawa, K. Hamano, Y. Tsujita, A. Terahara, H. Kuwano, *J. Antibiotics* **1983**, *36*, 604; N. Serizawa, S. Serizawa, K. Nakagawa, K. Furuya, T. Okazaki, A. Terahara, *J. Antibiotics* **1983**, *36*, 887. (b) Structure: H. Haruyama, H. Kuwano, T. Kinoshita, A. Terahara, T. Nishgaki, C. Tamura, *Chem. Pharm. Bull.* **1986**, *34*, 1459. (c) *in vivo* activity : Y. Tsujita, M. Kuroda, Y. Shimada, K. Tanazawa, M. Arai, I. Kaneko, M. Tanaka, H. Masuda, C. Tarumi, Y. Watanabe, S. Fujii, *Biochim. Biophys. Acta* **1986**, *877*, 50; N. Nakaya, Y. Homma, H. Tamachi, Y. Goto, *Atherosclerosis* **1986**, *61*, 125. The synthesis of pravastatin or an advanced intermediate has not yet been reported.
4. This sterechemistry is predicted by the model of Nakai. T. Nakai, K. Mikami, S. Taya, *J. Am. Chem. Soc.* **1981**, *103*, 6492; K. Mikami, Y. Kimura, N. Kishi, T. Nakai, *J. Org. Chem.* **1983**, *48*, 279; T. Nakai, K. Mikami, *Chem. Rev.* **1986**, *86*, 885.
5. All new compounds had satisfactory ^1H NMR, ^{13}C NMR, infrared, mass spectrum, and elemental analysis. Selected NMR data are given in the references below.
6. Transition state **B** (see below) leading to the diastereomer of **7** is disfavored compared to transition state **A** due to a severe steric interaction between the allyl olefin and the indicated methylene group on the cyclohexyl ring.



7. K. C. Nicolaou, Z. Lysenko, *J. Am. Chem. Soc.* **1977**, *99*, 3185; K. C. Nicolaou, S. P. Seitz, W. J. Sipio, J. F. Blount, *J. Am. Chem. Soc.* **1979**, *101*, 3884.
8. **9**: ^{1}H NMR ($CDCl_3$): δ 0.03 (s, 3H), 0.04 (s, 3H), 0.88 (s, 9H), 0.93 (d, J=6 Hz, 3H), 3.38 (brs, 1H), 4.18 (m, 1H); ^{13}C NMR ($CDCl_3$): (C) 169.7, 129.5,83.4, 17.8; (CH) 133.9, 129.3, 127.8, 62.4, 51.5, 27.0; (CH_2) 41.3, 39.8, 35.7, 35.2, 28.7; (CH_3) 25.6, 21.2, -4.5.
   Diastereomer: ^{1}H NMR ($CDCl_3$): δ 0.09 (s, 6H), 0.90 (s, 9H), 0.91 (d, J=6 Hz, 3H), 2.50 (dd, J=11,16 Hz, 1 H), 2.85 (dd, J=5,16 Hz, 1H), 3.34 (dd, J=4,12 Hz, 1 H), 4.08 (m, 1H); ^{13}C NMR ($CDCl_3$): (C) 169.7, 129.1, 84.7, 17.9; (CH) 134.9, 129.0, 127.7, 62.8, 56.6, 33.4; (CH_2) 40.9, 40.8, 37.3, 35.3, 31.5,; (CH_3) 25.6, 21.2, -4.5.
9. P. A. Bartlett, D. P. Richardson, J. Myerson, *Tetrahedron* **1984**, *40*, 2317.
10. **11a [12a]**: ^{1}H NMR ($CDCl_3$): δ [0.03 (s, 3H)], 0.04 9s, 3H), [0.05 (s, 3H)], 0.07 (s, 3H), 0.84 (d, J=7 Hz, 3H), [0.85 (s, 9H)], 0.86 (s, 9H), [0.95 (d, J=6 Hz, 3H)], 2.32 (dd, J=8,13 Hz, 1H), 2.46 (dd, J=4,13 Hz, 1H), 3.65 (3, 3H), [3.66 (s, 3H)], 4.27 (m, 1H), 5.01 (m, 2H), 5.27 (brs, 1H), [5.32 (brs, 1H)], 5.80 (m, 1H); ^{13}C NMR ($CDCl_3$): (C) 174.2, (133.9), 133.5, 17.8; (CH) 137.6, (136.7), (128.3), 127.6, 68.5, (68.2), (42.2), 38.9, (32.0), 29.8; (CH_2), (115.8), 115.4, (46.7), 46.2, 41.9, (38.0), 36.3, (30.5), 28.4, (28.2), 26.8; (CH_3) 51.2, 25.6, (19.7), 14.5, -4.5.
11. Other Lewis acids were tried including $TiCl_4$, BF_3•Et_2O, $ZnBr_2$, $MgBr_2$, $Ti(OiPr)_4$, Me_2AlCl, CF_3CO_2H and $MgBr_2$ + *n*-Bu_4NF, but all resulted in either no reaction or lower selectivities. The use of tributylallyl stannane and *t*-butyldimethylallyl silane also did not improve the selectivity.
12. We have also seen similar selectivity (4:1) in the addition of allyltrimethylsilane to an intermediate for the synthesis of lovastatin (see Reference 1, footnote 11): For a general example of Lewis acid promoted SN2' addition of trimethylallylsilane to an unsaturated lactone, see: T. Fujisawa, M. Kawashima, S. Ando, *Tetrahedron Lett.* **1984**, *25*, 3213.
13. S. Danishefsky, J. F. Kerwin, *J. Org. Chem.* **1982**, *47*, 3803.
14. **13a**: ^{1}H NMR ($CDCl_3$): δ 0.05 (s, 6H), 0.81 (d, J=7 Hz, 3H), 0.87 (s, 9H), 3.90 (m, 1H), 4.08 (brs, 1H), 4.99 (d, J=10 Hz, 1H), 5.02 (d, J=16 Hz, 1H), 5.59 (brs, 1H), 5.78 (m, 1H); ^{13}C ($CDCl_3$): (C) 132.7, 18.1 ; (CH) 137.8, 124.0, 69.4, 67.2, 44.2, 38.1, 28.1; (CH_2) 115.7, 44.9, 43.4, 34.3, 31.9; (CH_3) 25.8, 13.9, -4.5.
   14 (lower R_f isomer): ^{1}H NMR ($CDCl_3$): δ 0.07 (s, 6H), 0.87 (s, 9H), 0.98 (d, J=7 Hz, 3H), 4.00 (m, 1H), 4.20 (brs, 1H), 5.01 (d, J=10 Hz, 1H), 5.03 (d, J=16 Hz, 1H), 5.59 (m, 1H), 5.83 (m, 1H).
   15 (higher R_f isomer): ^{1}H NMR ($CDCl_3$): δ 0.04 (s, 6H), 0.86 (s, 9H), 0.89 (d, J=7 Hz, 3H), 3.84 (m, 1H), 4.22 (m, 1H), 5.01 (d, J=10 Hz, 1H), 5.08 (d, J=16 Hz, 1H), 5.70 (m, 1H), 5.80 (m, 1H).
15. The X-ray crystal structure of (**i**) will be published elsewhere.



(**i**)

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