Tetrahedron Letters,Vol.28,No.13,pp 1385-1388,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

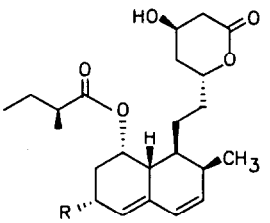
SYNTHESIS OF AN HMG-COA REDUCTASE INHIBITOR; A DIASTEREOSELECTIVE ALDOL APPROACH

J. E. Lynch*, R. P. Volante, R. V. Wattley, I. Shinkai
Merck Sharp and Dohme Research Laboratories
P.O. Box 2000, Rahway, New Jersey 07065

ABSTRACT

The synthesis of the β-hydroxy-δ-lactone moiety of an HMG-CoA reductase inhibitor in its correct absolute configuration (94% ee) has been accomplished via a diastereoselective aldol reaction between aldehyde 4 and the magnesium enolate of S(+)1,2,2-triphenylethylacetate, Claisen condensation, and hydroxyl directed reduction of the resulting δ-hydroxy-β-keto ester.

The discovery of mevinolin 1a[1] and compactin 1b[2] as potent inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase has resulted in an intensive effort to develop efficient laboratory syntheses of these[3] and other related hypocholesterolemic agents.[4] The key structural feature common to these HMG-CoA inhibitors is the β-hydroxy-δ-lactone moiety.[5] Furthermore, it appears that this unit in its correct absolute configuration (that which corresponds to 1a and 1b) is essential for enzyme inhibition.[5] Thus, we[6],

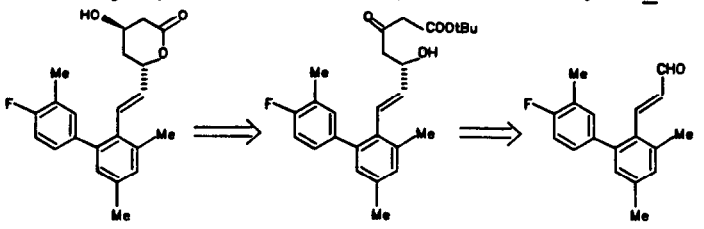


1a R=CH_3
1b R=H

as well as others[7],have been interested in the development of an efficient method for the synthesis of such a structural unit.

Prior syntheses of β-hydroxyl-δ-lactone HMG-CoA reductase inhibitors have been accomplished by initial generation of an appropriate, non-racemic lactone "synthon" followed by the coupling of this unit to the remaining portion of the molecule at a site removed from the asymmetric centers.[6] These routes have typically suffered from either inefficient generation of the asymmetric synthon and/or inefficient coupling reactions.

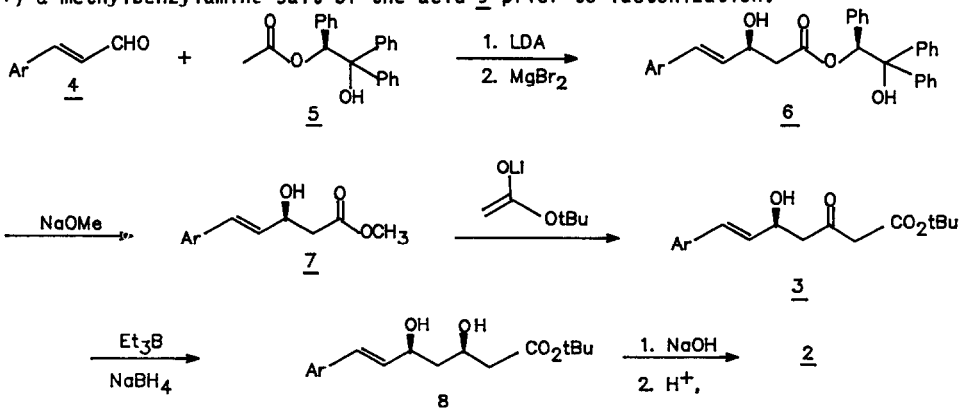
Our strategy is based on the use of a diastereoselective aldol reaction followed by a Claisen condensation for the generation of the 5(S) stereocenter of keto-alcohol 3 from aldehyde 4. The 5(S)hydroxyl function of 3 would then be expected to direct the reduction of the 3-keto group to the desired 3(R) stereochemistry of 2.



2 3 4

A long standing problem in the preparation of simple (α-unsubstituted) β-hydroxy esters (acids) has been the lack of aldehyde facial selectivity in the aldol reaction with chiral acetate enolates.[8] However, several solutions to this problem have recently appeared.[9] We wish to report here the use of one of these methods for the diastereoselective synthesis of the biphenyl HMG-CoA inhibitor 2.[10]

The magnesium (II) enolate of S(+)-2-acetoxy-1,1,2-triphenylethanol (5) (1.1 equiv) was condensed with aldehyde 4 in tetrahydrofuran at -78° via the procedure of Braun and Devant[9] to produce the diastereomers 6 in 93% yield (SS:SR=97:3, as determined by PMR and HPLC analysis.[13] Transesterification of 6 with 1.05 equivalent of sodium methoxide in methanol gave methyl ester 7 (S/R = 97:3) in 95% yield.[14] Treatment of ester 7 with 3 equivalents of lithio-t-butyl acetate in tetrahydrofuran at -30 to -40°C for 1 hr. resulted in the formation of β-keto-δ-hydroxy ester 3 in 90% yield.[15] Highly stereospecific reduction of the β-keto functionality was effected using sodium borohydride-triethylborane in tetrahydrofuran-methanol (4:1) at -78° giving diol 8 in 93% yield.[6,11,12] The diol ester was saponified with sodium hydroxide in aqueous methanol, acidified to pH 3.8, and the resulting acid 9, was lactonized by heating in toluene at 90° for 8 hr to afford lactone 2 in 85% yield (3R5S:3S5R = 97:3 as determined by HPLC analysis of the corresponding R(+)-α-methylbenzylamide derivatives).[13] The enantiomeric purity of 2 could be enhanced to >99% ee by recrystallization of the R(+)-α-methylbenzylamine salt of the acid 9 prior to lactonization.[14]



Acknowledgement: We wish to thank Mr. R. Reamer and Ms. L. DiMichele for NMR measurements and Mr. K. Ryan and Mr. E. Corley for chemical assistance, and Ms. Lee Dolan for manuscript preparation.

1. Alberts, A.O.W., Chen, J.; Kuron, G.; Hunt, V.; Huff, J.; Hoffman, C.; Rothrock, J.; Lopez, M.; Joshua, H.; Harris, E.; Patchett, A.; Monaghan, R.; Currie, S.; Stapley, E.; Albers-Schonberg, G.; Hensens, O.; Hirshfield, J.; Hoogsteen, K.; Liesch, J.; Springer, J. Proc. Natl. Acad. Sci. USA 1980, 77, 3957.

2. Endo, A.; Kuroda, M.; Tsujita, Y.; J. Antibiot. 1976, 29, 1346.

3. Compactin-Hsu, C.-T.; Wang, N.-Y.; Latimer, L.H.; Sih, C.J. J. Am. Chem. Soc., 1983, 105, 593. Hirama, M.; Uei, M. ibid, 1982, 104, 4251. Girota, N.N.; Wendler, N.L. Tetrahedron Lett. 1982, 5501. Girota, N.N.; Wendler, N.L. ibid 1983, 3687. Grieco, P.A.; Zelle, R.E.; Lis, R.; Finn, J. J. Am. Chem. Soc. 1983, 105, 1403. Mevinolin-Hirama, M.; Iwashita, M. Tetrahedron Lett. 1983, 1811.

4. Lee, T.-J.; Holtz, W.J.; Smith, R.L. J. Org. Chem. 1982, 47, 4750. Kuo, C.H.; Patchett, A.A.; Wendler, N.L. ibid 1983, 48, 1991, Yang, Y.L.; Manna, S.; Falck, J.R., Yang, Y.-L. Tetrahedron Lett. 1984, 3563; T.-J. Lee, ibid 1985, 4995.

5. Stokker, G.E.; Hoffman, W.F.; Alberts. A.W.; Cragoe, Jr., E.J.; Deana, A.A.; Gilfillan, J.L.; Huff, J.W.; Novello, F.C.; Prugh, J.D.; Smith, R.L.; Willard, A.K., J. Med. Chem. 1985, 28, 347.

6. Sletzinger, M.; Verhoeven, T.R., Volante, R.P.; McNamara, N.M.; Corley, E.G.; Liu, T.M.H., Tetrahedron Lett. 1985, 2951.

7. Prugh, J.D.; Deana, A.A., Tetrahedron Lett. 1982, 281. Yang, Y.-L.; Falck, J.R. ibid 1982, 4305. Danishefsky, S.; Kerwin, J.R.; Kobayshi, S. J. Amer, Chem. Soc. 1982, 104, 358. Prasad, U.; Repic, O. Tetrahedron Lett. 1984, 2435 and 3391. Rosen, T.; Taschner, M.J.; Heathcock, C.H. J. Org. Chem. 1984, 49, 3994. Majewski, M.; Clive, D.L.J.; Anderson, P.C., Tetrahedron Lett. 1984, 2106. Guindon, Y.; Yoakim, C.; Bernstein, M.A.; Morton, H.E. Tetrahedron Lett. 1985, 1185.

8. Morrison, J.D. and Mosher, H.S. "Asymmetric Organic Reactions" Am. Chem. Soc.; Washington D.C. 1976, p. 142-152. Soladie, G. in "Asymmetric Synthesis: Vol. 2. ed. J.D. Morrison, 1983, Academic Press, New York, N.Y., pp-188-199. Evans, D.A.; Nelson, J.V.; Taber, T.R. in Topics in Stereochemistry, 1982, 13, 1. Heathcock, C.H., in "Asymmetric Synthesis" Vol, 3., ed. J.D. Morrison, 1984, Academic Press, New York, N.Y., pp 174-190.

9. Iwasawa, N.; Mukaiyama, T. Chem. Lett., 1983, 297. Braun, M.; Devant, R. Tetrahedron Lett. 1984, 5031. Nagao, Y.; Yamada, S.; Kumagai, T.; Ochiai, M.; Fujita, E. J. Chem. Soc. Chem. Comm.; 20, 1418 (1984). Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E.; J. Org. Chem.; 51, 2393 (1986). Helmchen, G.; Leifkauf, U.; Tauter Knopfel, I., Angew. Chem. Int. Ed. Ingl.; 24, 874 (1985).

10. G.E. Stokker, A.W. Alberts, P.S. Anderson, E.J. Cragoe, Jr., A.A. Deana, J.L. Gilfillan, J. Hirshfield, W.J. Holtz, W.F. Hoffman, J.W. Huff, T.J. Lee, F.C. Novello, J.D.Prugh, C.S. Rooney, R.L. Smith, and A.K. Willard, J.Med.Chem. 1986, 29, 170.