Tetrahedron Letters,Vol.29,No.8,pp 929-930,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

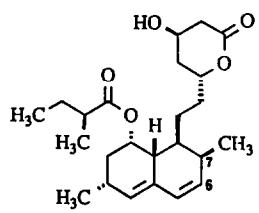
SYNTHESIS OF A NOVEL HMG-COA REDUCTASE INHIBITOR

E. Baader, W. Bartmann, G. Beck, A. Bergmann, H. Jendralla, K. Kesseler, G. Wess, W. Schubert, E. Granzer, B. v. Kerekjarto, R. Krause

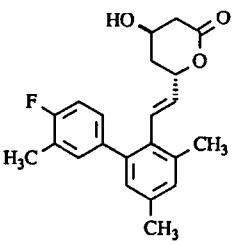
Hoechst AG, Pharma Forschung, Postfach 80 03 20, D-6230 Frankfurt a.M. 80

Abstract: The synthesis of a new 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor starting from 4,4'-difluorobenzophenone is described.

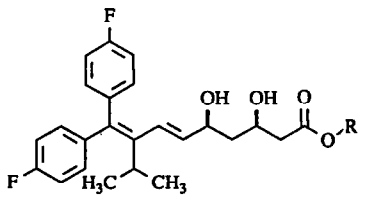
Mevinolin 1 and its congeners are potent inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate limiting enzyme in cholesterol biosynthesis[1]. Mevinolin lowers cholesterol levels in man and might be useful in the treatment of hypercholesterolemia [2]. Efforts have been made to replace the hexahydronaphthalene part by simple aromatic structures and some biphenyl analogs e.g. 2 emerged as the most prominent examples. It seemed that high in vitro and in vivo activity is limited to structures closely related to the biaryl system of 2 with an appropriate substitution pattern [3].



1



2

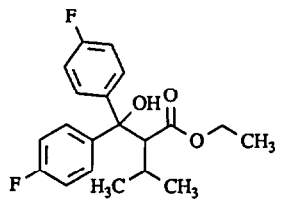


3 R = Na
4 R = C_2H_5

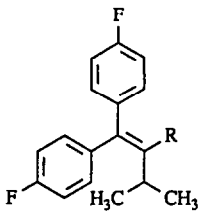
Our interest was focused on HMG-CoA reductase inhibitors with novel structures. Compound 3 [4] was selected for synthesis because of promising molecular modelling data: The 4-fluorophenyl rings match the ester and the diene of mevinolin, and the isopropyl group corresponds to carbon 6-C, 7-C and 7-CH_3 of 1.

4,4'-Difluorobenzophenone was reacted with α-lithio ethyl isovalerate (LDA, THF, -70°C, 30 min) in THF for 1.5 h at -78°C and 5 min at 0°C to give 5 (85%, mp. 116-118°C) which was treated with a cat. amount of p-toluenesulfonic acid (toluene, reflux, 1h) providing unsaturated ester 6 (100%, mp. 48-50°C). 6 was converted to aldehyde 10 in 46% yield via intermediates 7-9: Reduction of 6 with 3 equiv. diisobutylaluminum hydride in methylene chloride at 0°C for 45

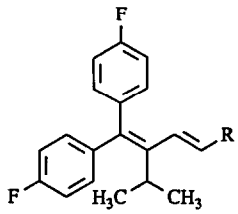
min gave 7 (mp. 70°C) which was oxidized (1.5 equiv. pyridinium chlorochromate, methylene chloride, 23°C, 1h) to aldehyde 8 (mp. 69°C). 8 was converted to nitrile 9 (mp. 113°C) with 1.2 equiv. diisopropyl cyanomethylphosphonate [5], 1.2 equiv. sodium hydride in THF at 23°C for 1.5 h. Reduction of nitrile 9 with 2.0 equiv. diisobutylaluminum hydride in THF at 5°C for 2 h and flash chromatography on silicagel (cyclohexane/ethyl acetate/trietylamine = 80:20:1) gave aldehyde 10 (mp. 108°C). 10 was converted to 4 in two steps: Reaction of 10 with 1.5 equiv. ethyl acetoacetate dianion (1 equiv. sodium hydride, 1 equiv. n-butyllithium, THF, -5°C) in THF (-70°C, 2 h and 0°C, 5 min) yielded 11. Subsequent stereospecific reduction [6] ((1) 1.6 equiv. triethylborane in THF at 23°C for 10 min, (2) 2.0 equiv. sodium borohydride at -70°C followed by 24 equiv. methanol, 2 h at -70°C, (3) 18 equiv. aqueous hydrogen peroxide in water at 0°C for 5 min, extraction and flash chromatography on silicagel, cyclohexane/ethyl acetate/triethylamine = 60 : 40 : 1) provided predominantly syn dihydroxy ester 4 in 53% yield (syn/anti 9:1). Saponification of 4 (1.0 equiv. 1M aqueous sodium hydroxide in ethanol at 23°C for 1h) gave 3 in 93% yield, mp.>230°C.



5



6 R = $CO_2C_2H_5$
7 R = CH_2OH
8 R = CHO



9 R = CN
10 R = CHO
11 R = $CH(OH)CH_2COCH_2CO_2C_2H_5$

Sodium carboxylate 3 and mevinolin sodium have similar inhibitory activity on solubilized microsomal rat liver HMG-CoA reductase [7] (IC_{50} (mol/l): 1.4 x 10^{-8} (3) [8], 8.0 x 10^{-9} (mevinolin sodium)) and in the suppression of sodium acetate incorporation in liver cell cultures (HEP-G2). After oral administration of 3, 10 mg/kg for 19 days and 20 mg/kg for 13 days, LDL-cholesterol levels in rabbits were decreased by 33% [8] (mevinolin, 10 mg/kg for 32 days,-40%).

Acknowledgment: We wish to thank K. Bock, H. Kleine and M. Schlette for technical assistance, Dr. Fehlhaber and Dr. Kogler for analytical support.

References and Notes:

1. A. Endo, J.Med.Chem. 28, 401 (1985)
2. The Lovastatin Study Group II, JAMA 256, 2829 (1986)
3. Drugs of the Future 12, 437 (1987); 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, A.K. Willard, J.Med.Chem. 29, 170 (1986) and cit. ref.
4. The open chain dihydroxy acid is the biologically active form
5. R.W. Dugger, C.H. Heathcock, Synth.Comm. 10, 509 (1980)
6. K. Narasaka, H.C. Pai, Chem.Lett. 1980, 1415
7. B.W. Philipp, D.J. Shapiro, J.Lipid Res. 20, 588 (1979)
8. Enantiomerically pure 3 is expected to have twice the potency of racemic 3.

(Received in Germany 10 December 1987)