Tetrahedron Letters,Vol.30,No.38,pp 5115-5118,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

ENANTIOSELECTIVE SYNTHESIS OF A NEW FLUORO-SUBSTITUTED HMG-COA REDUCTASE INHIBITOR

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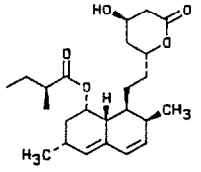
Abstract: The synthesis of a new fluoro-substituted 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor 3 in high optical purity via addition of the chiral enolate 12 to fluoro aldehyde 8Z is described.

Fluorination of biologically active compounds can have profound and unexpected results on their activity [1]. Enhancement of biological activity and improved selectivity along with reduction of undesired properties and side effects have been achieved e.g. with a number of fluorinated steroids [2], prostaglandins and prostacyclins [3,4], as well as in carbohydrate chemistry [5].

With these objectives in mind, we focused our interest on the synthesis of novel inhibitors of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase containing a fluoro-olefin bridge.

Inhibition of HMG-CoA-reductase by mevinolin (Mevacor^{R}) 1 in man results in a marked decrease in plasma levels of atherogenic low-density lipoproteins (LDL), via increased hepatic LDL-receptor synthesis [6].



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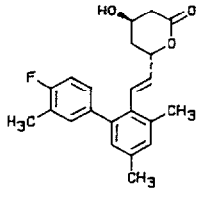

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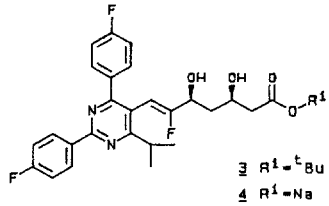
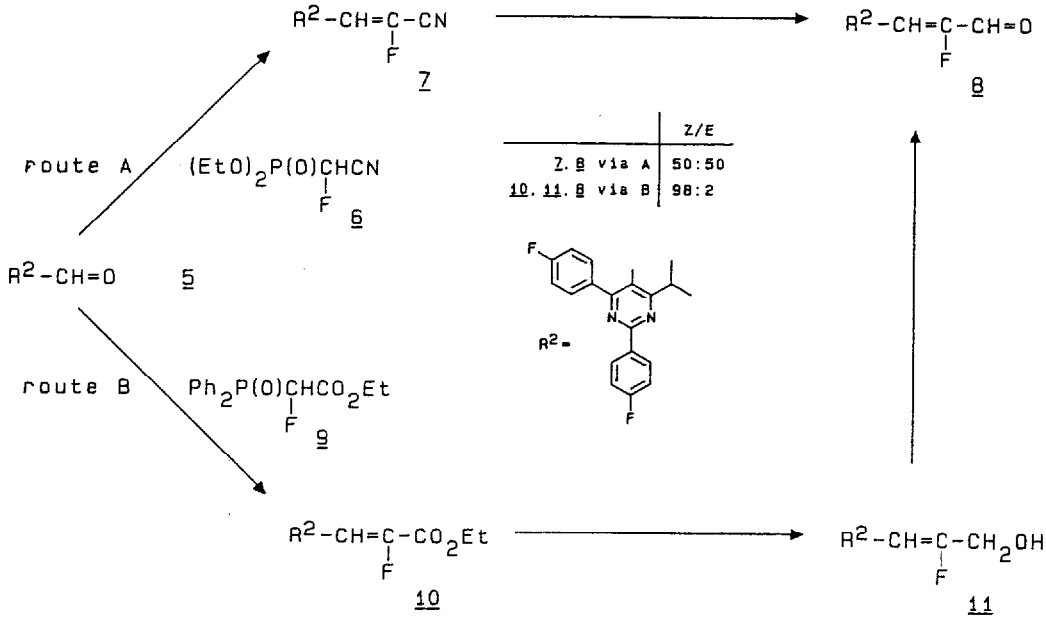


3 $R^1 = {}^tBu$
4 $R^1 = Na$

Analogues of 1, e.g. 2, also show potent in vitro and in vivo activity [7]. The heterocyclic fluoro analogue 3 has been selected for synthesis, because the corresponding 6-desfluoro analogue [8] was already a potent inhibitor of HMG-CoA reductase both in vitro and in vivo.

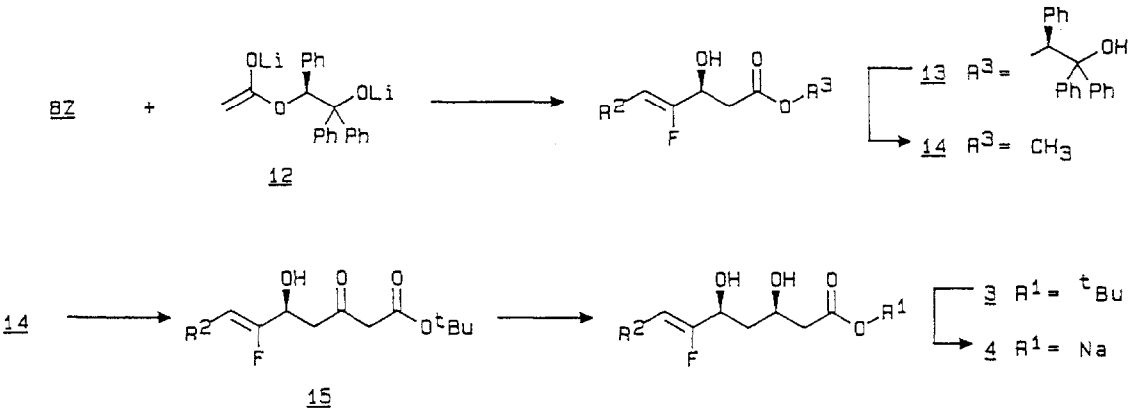
Compound 3 has been synthesized from 8 in four steps via a highly enantioselective synthesis [9-11]. Fluoro aldehyde 8 could be prepared via route A or B starting from aldehyde 5 [12]. Treatment of 5 (route A) with the sodium salt



of 2-(O,O-diethyl-phosphono)-2-fluoro-acetonitrile 6 [13] (6, DME, 1 equiv.NaH, 20°C, 2h) gave α-fluoro-nitrile 7 (72%, mp. 112°C) as an unseparated 1:1 mixture of E and Z isomers (R_f = 0.49 cyclohexane/ethyl acetate = 10:1). Reduction of the E/Z mixture 7 with 2 equiv. diisobutylaluminium hydride in THF at -10°C for 2h and chromatography on silicagel (cyclohexane/ethyl acetate = 10:1) gave pure aldehydes 8E [14] (R_f = 0.45, oil) and 8Z [14] (R_f = 0.27, mp. 159-162°C) in 85% yield in a 1:1 ratio.

Stereoselective conversion of 5 to 8Z was achieved in 3 steps (route B): (1) Horner reaction of 5 with the lithium salt of ethyl diphenyl phosphinoxy-fluoroacetate 9 [15] (9 in THF, 1 equiv. BuLi, 0°C, 30 min), provided 10 (75%, mp. 85-89°C), (2) reduction of the fluoro ester 10 with 2 equiv. diisobutyl-aluminium hydride in methylene chloride at 0°C for 2h yielded 11 (90%, mp. 112-114°C), (3) oxidation of 11 (5 equiv. CrO_3, Pyr., methylene chloride, 23°C, 2h) gave aldehyde 8Z [14] (93%, mp. 159-163°C).

Conversion of 8Z to 3 started with a highly diastereoselective aldol reaction [9,10]. Dianion 12 (generated from (S)-(-)2-hydroxy-1,2,2-triphenyl-acetate [16] and 2 equiv. LDA, THF, -70°C, 1h) was reacted with 8Z yielding 13 in 87% (mp.193-195°C). 13 was transformed into the corresponding methyl ester 14 with 1 equiv. sodium methanolate in methanol at 23°C for 16h (97%, oil R_f= 0.25 [17]). Reaction of 14 with 4 equiv. tert.-butyl acetate anion (4 equiv. LDA, THF, -70°C) in THF for 1h yielded 15 (82%, oil, R_f = 0.54 [17])



Stereospecific reduction [18] of 15 ((1) 1.2 equiv. triethylborane/24 equiv. methanol in THF at -70°C for 1h, (2) 1.2 equiv. sodium borohydride at -70°C for 1h), followed by repeated evaporation with methanol and flash chromatography on silicagel (cyclohexane/ethyl acetate 2:1), provided 6Z-fluoro syn dihydroxy ester 3 in 92% yield, mp. 148°C, $[\alpha]_D^{25}$ = -13.2° (CH_3OH, c=1), ee=92% [19].

Saponification of 3 (1 equiv. 1 M aqueous sodium hydroxide in ethanol at 20°C for 3h) gave 4 in 95% yield, mp. 210°C.

On inhibition of solubilized microsomal rat liver HMG-CoA reductase [20] sodium carboxylate 4 was more potent than mevinolin sodium. (IC_{50} (mol/l) 2.9 x 10^{-9} 4, 8.0 x 10^{-9} (mevinolin sodium)). Results from animal studies will be reported separately.

Acknowledgement: We wish to thank S. Jäger and K. Hohm for skillful technical assistance, Dr. Fehlhaber, Dr. Kogler and M. Weber for analytical support, Dr. Granzer and Dr. v. Kerekjarto for biological data. Special thank goes to Dr. Gigliotti (Roussel Uclaf, Paris) for generous gift of 2-(0,0-diethyl-phosphono)-2-fluoro-acetonitrile 6.

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14) The distinction of E and Z isomers has been made based on the chemical shift and the coupling constants of the proton at C-7. 8Z: = 6.92 ppm, J = 34 Hz for 7-H, 8E: = 7.31 ppm, J = 16 Hz for 7-H
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(Received in Germany 28 June 1989)