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CONVENIENT TWO-STEP STEREOSPECIFIC HYDROXY-SUBSTITUTION WITH RETENTION IN ß-HYDROXY-δ-LACTONES.

4 (R)-HETEROSUBSTITUTED MEVINOLIN AND -ANALOGS

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Abstract: Michael additions of mercaptanes and amines to optically pure 6-alkyl-5,6-dihydro-2H-pyran-2-ones of the mevinolin type [6(R)]-5 and the aromatic analog [6(S)]-7 are stereospecific to give 4(R)-substituted mevinolin analogs.

Compactin 1a and mevinolin 1b, metabolites isolated from culture broths of *Penicillium* and *Monascus* strains, inhibit HMG CoA reductase and thus are capable to block cholesterol biosynthesis in mammals on an early stage.[1] An abnormally high level of plasma cholesterol is a primary risk factor for development of atherosclerosis and coronary artery disease.[1] The potential of 1a and 1b to be of therapeutic value against these pathological states has provoked the development of several total syntheses and numerous synthetic studies.[2] While the replacement of the hexalin portion of these compounds by substituted biphenyls and the replacement of the saturated ethylene bridge by an ethene bridge have been reported,[3] ether bridged systems of type 2 have not.[4]

This paper describes the substitution of the 4R-hydroxy group of 1b [5] and 3b [4,5] by several mercaptyl- and amino-groups with retention of configuration. Heating a solution of 1 mmol of 1b or 3b and 2 mmol of the Burgess reagent 4 [6] in 30 ml of dry benzene to 60°C (1,5 h) gave the α,ß-unsaturated lactones 5 (mp. 128-129°C) and 7 (mp. 79°C) in 61 and 93% yield, respectively.[7,8] The compound 7 was produced in 79% yield [8], when a solution of 1 mmol of 3a in 30ml of THF was treated with 3 mmol of tetrabutylammonium fluoride and 1 mmol of p-toluenesulfonic acid- monohydrate (25°C, 12 h). The 4R-addition product 6 was obtained stereospecifically in 74% yield [8] when 5 was treated with 1 equiv. of thiolacetic acid and 0.1 equiv. of triethylamine (0°C, 2 h).[9] Similar treatment of 7 with mercaptanes in the presence of base or with primary amines (Table 1) gave stereospecifically the 4R-substituted addition products 8.[10] The 4R-configuration is obvious from a comparison of the ^{1}H-nmr spectra of 1b, 3b, 6 and 8a-d [11], as well as from the stereospecificity of the reaction. Neither tlc analyses of the reaction mixtures nor 270 MHz-^{1}H-nmr spectra of crude or purified 6 or 8 indicated the presence of any 4S-isomers. Inhibition data of HMG CoA reductase activity are summarized in Table 2.

Acknowledgement: We are indebted to Dr. Fehlhaber and Dr. Kogler for the interpretation of nmr spectra.

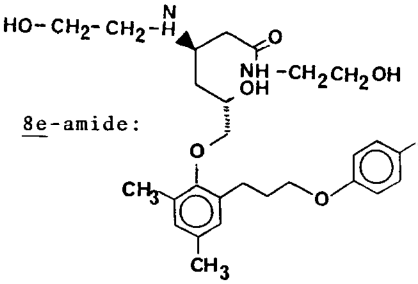
Table 1: Stereospecific Michael additions of nucleophiles R^8YH to α,β-unsaturated lactones 5 and 7

rct.	lactone	R^8YH (equiv)	base (equiv)	solvent	°C	time (h)	product	yield (%)[8]
1	5	CH_3COSH (1.0)	NEt_3 (0.1)	none	0	2	6	74[9]
2	7	CH_3COSH (1.6)	NEt_3 (0.2)	none	25	0.5	8a	94[7]
3	7	$HOCH_2CH_2SH$ (1.8)	NEt_3 (0.4)	none	25	0.5	8b	65[7]
4	7	$C_6H_5CH_2SH$ (2.5)	NEt_3 (0.5)	none	25	2	8c	95[7]
5	7	L-Cystein (2.0) ·HCl	Na_2CO_3 (1.5) NEt_3 (1.8)	$CHCl_3$/ CH_3OH	25	1	8d	97[7]
6	7	$HOCH_2CH_2NH_2$ (1.0)	none	DME	25	12	8e	68[12]
7	7	$HOCH_2CH_2NH_2$ (10)	none	DME	25	1	8e-amide	91[7]
8	7	$C_6H_5CH_2NH_2$ (2.0)	none	C_6H_6	50	12	8f-amide	98[7]

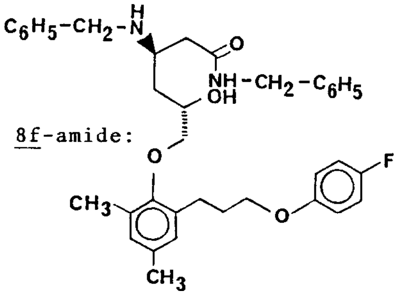
Table 2: Inhibition of solubilized HMG CoA reductase from rat liver microsomes

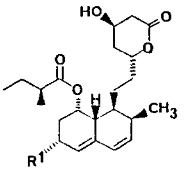
Compound	IC_{50} (mol/l)	Compound	IC_{50} (mol/l)
1b-Na^+-salt	$8 \cdot 10^{-9}$	8c	$\sim 10^{-4}$
1b	$2 \cdot 10^{-7}$	8d	24% inhib. at 10^{-7} 37% inhib. at 10^{-6}
3a-Na^+-salt	$3.6 \cdot 10^{-7}$	8e-ethanolamide	$> 10^{-4}$
3a	$1 \cdot 10^{-6}$	8f-benzylamide	$> 10^{-4}$
6	$1.5 \cdot 10^{-6}$	9	$3 \cdot 10^{-6}$
8a	$3 \cdot 10^{-7}$	10	$3 \cdot 10^{-6}$
8b	$1 \cdot 10^{-6}$		

8e-amide:



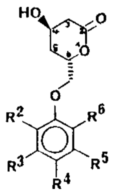
8f-amide:





1a R¹ = H

1b R¹ = CH₃



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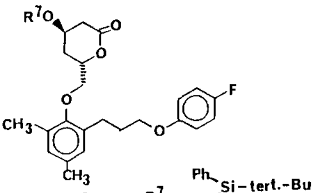
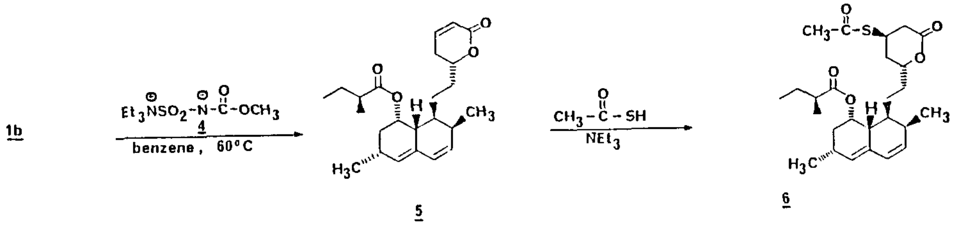
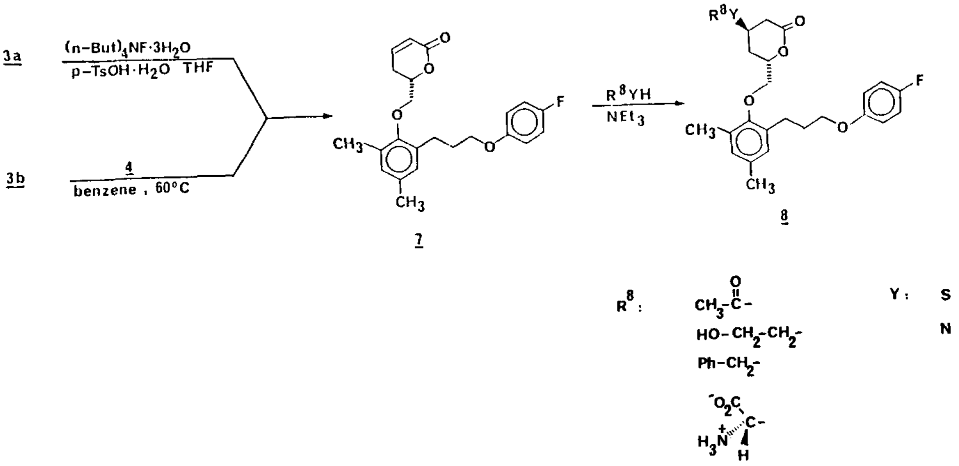


3a R⁷ = Ph₂Si-tert.-Bu

3b R⁷ = H





1 3-Hydroxy-3-methylglutarylcoenzyme A Reductase, J.R.Sabine Ed., CRC Press, Boca Raton (1983), and references cited therein.

2 T.Rosen, C.H.Heathcock, J.Am.Chem.Soc. 107, 3731 (1985) and references cited in footnotes 9 and 10.

3a G.E.Stokker et.al., J.Med.Chem. 29, 170 (1986).

b W.F.Hoffman et.al., J.Med.Chem. 29, 159 (1986).

4 A report on compounds 2, including experimental details of the synthesis of 3a,b is in preparation for J.Med.Chem..

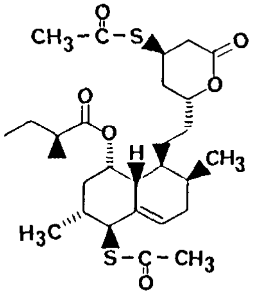
5 1b and 3a,b were optically pure (4R,6S), as drawn.

6 E.M.Burgess, H.R.Penton Jr., E.A.Taylor, J.Org.Chem 38, 26 (1973).

7 No by-products were observed on tlc analysis of the reaction mixture.

8 All yields refer to purified products after flash chromatography. All products were characterized by 270 MHz ^{1}H-nmr and ms spectra.

9 With an excess of reagent (1.7 equiv. CH_3COSH, 0.2 equiv. NEt_3) and longer reaction time (25°C, 2d) the 1,4-addition products 9 and 10 were obtained additionally.
tlc (30% AcOEt/ 70% petroleum ether): 6 (40% yield, R_f = 0.32), 5, 9 (0% and 20% yield, R_f = 0.27), 10 (25% yield, R_f = 0.23).



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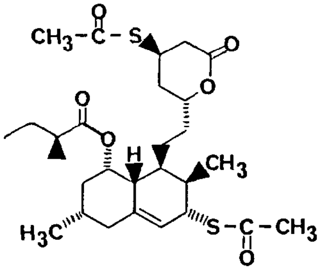

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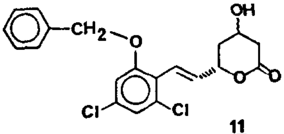
10 K. Torssell, M.P. Tyagi, Acta Chem. Scand. B31, 297 (1977) did observe comparable trans-selectivities in nucleophilic additions to 6-methyl-5,6-dihydro-2H-pyran-2-one.

11 In lit. 3b (page 168) the distinction of cis- and trans-11 has been made based on the chemical shift of the proton at C-6 and the coupling constants of the proton at C-4. It was observed that 6-H trans-11 is deshielded 0.47 ppm relative to 6-H of cis-11 and that the vicinal coupling constants of trans-11 are 3-5.2 Hz compared to 5-9.2 Hz for cis-11. We have found δ= 4.53 ppm for 6-H and J= 5.1, 3.9, 3.9 and 3.4 Hz for 4-H in mevinolin 1b In 6, 9 and 10 6-H had chemical shifts of δ= 4.37, 4.40, and 4.39 ppm, respectively. 4-H had average coupling constants (treatment as qui) of 5.8, 5.9 and 5.9 Hz, respectively.
In 3b 6-H had δ= 4.98 ppm and 4-H an average coupling constant of 3.9 Hz. In 8a-8d the resonance of 6-H was in the range δ= 4.78 - 4.88 and average J-values were in the range 5.6 - 5.8 Hz, respectively.

12 Addition to the double bond is accompanied by some opening of the lactone to give the amide. Better yield is obtained according to reaction 7 with excess amine, followed by saponification of the resulting ethanolamide (conc. NaOH /H_2O/ EtOH, reflux, 3h), acidification and reflux with benzene.



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