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TOWARDS A NEW TYPE OF HMG-CoA REDUCTASE INHIBITOR

M. Barth[b], F.D. Bellamy[a], P. Renaut[a]*, S. Samreth[a], F. Schuber[b]

[a] Laboratoires Fournier, Research Center, 21121 Daix (France)
[b] Laboratoire de Chimie Bioorganique CNRS-URA 1386, Faculté de Pharmacie, 74 route du Rhin, 67400 Illkirch (France)

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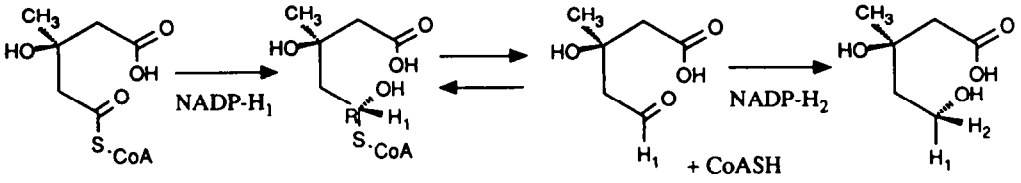
In an attempt to design a novel class of HMG-Co A reductase inhibitors, we have synthesized compound 3 as a reaction intermediate analogue of the enzymatic reduction of mevaldic acid by NADPH. A 15 steps, enantioselective sequence allowed us, from commercial R-(+)-malic acid to prepare aldehyde 4 in an optically pure form and to couple it with the nicotinamide moiety affording the target molecule.

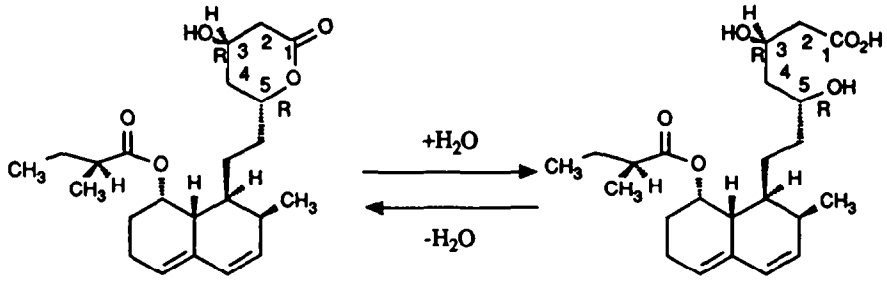
3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (EC 1.1.1.34), a key regulatory enzyme in the biosynthesis of cholesterol (1), represents an attractive target for the design of hypocholesterolemic drugs (2). This enzyme catalyzes the two-step reduction of HMG-CoA into mevalonic acid via a mevaldic acid-CoA hemithioacetal intermediate (Scheme 1). It is generally accepted that this tightly bound intermediate, which has an (R) configuration at C-5 (3), is converted into the corresponding aldehyde and CoASH prior to the second hydride transfer (4, 5). During this final reduction step, the second hydrogen added to the aldehyde carbonyl assumes a pro-S configuration (6). In both reductions a hydrogen is transferred to the same face of the carbonyl of HMGCoA or mevaldic acid.



Scheme 1

Among the most potent reversible inhibitors of HMG-CoA reductase are fungal metabolites, i.e. compactin 1 and related compounds (7). Nakamura and Abeles (8) have provided arguments suggesting that these compounds which all have the (R) configuration at C-5 (9), interact simultaneously with two separate domains of the active site : i) the one which binds the hydroxymethylglutarate moiety of HMG-CoA, ii) a hydrophobic pocket interacting with the decalin moiety of the inhibitors which binds CoA. This double interaction could account for their high affinity for the active site of the reductase.

In order to design a new class of inhibitors we have used an alternate approach which consists in exploring the third domain, i.e., the NADPH subsite. Thus, compound 3 which mimics the transition state of the enzymatic reduction of mevaldic acid by NADPH appeared to be a good candidate.



Compactin 1 2

Figure 1

Compared to all other synthetic inhibitors of HMG-Co A reductase, the general structure of which can be represented as in Figure 2, our compound presents two major differences :

- the configuration at carbon 5 is 5(S) instead of 5(R) (10)
- the aromatic group, nicotinamide, bears an amide function.

The retrosynthetic scheme we have elaborated is outlined in Scheme 2, the key step being the olefination type reaction between 3-cyano-4-methylpyridine and the optically pure aldehyde 4.

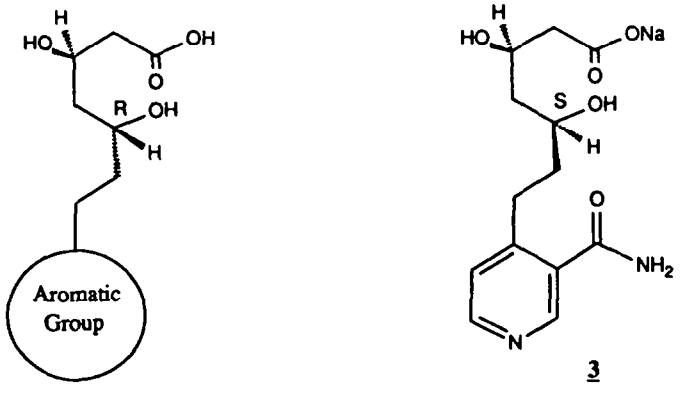


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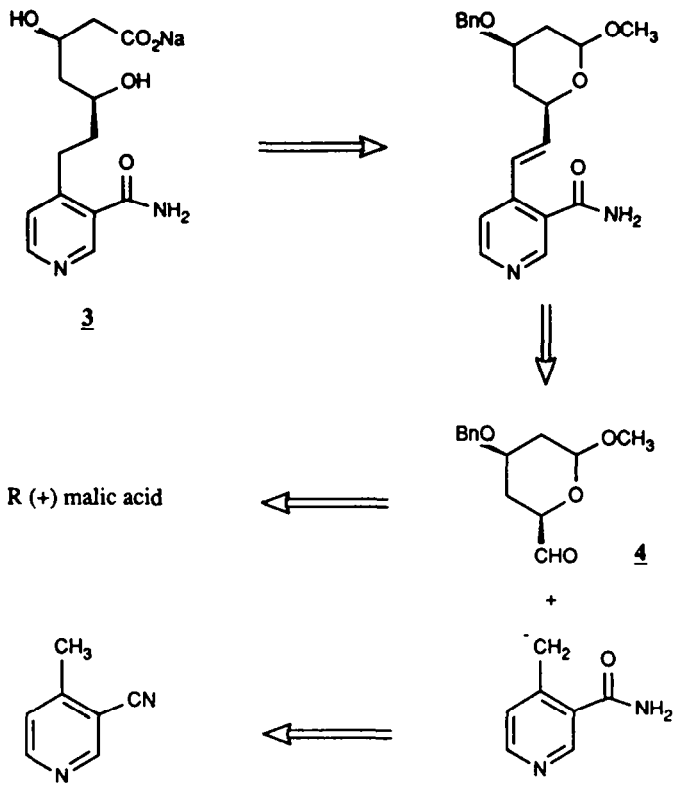
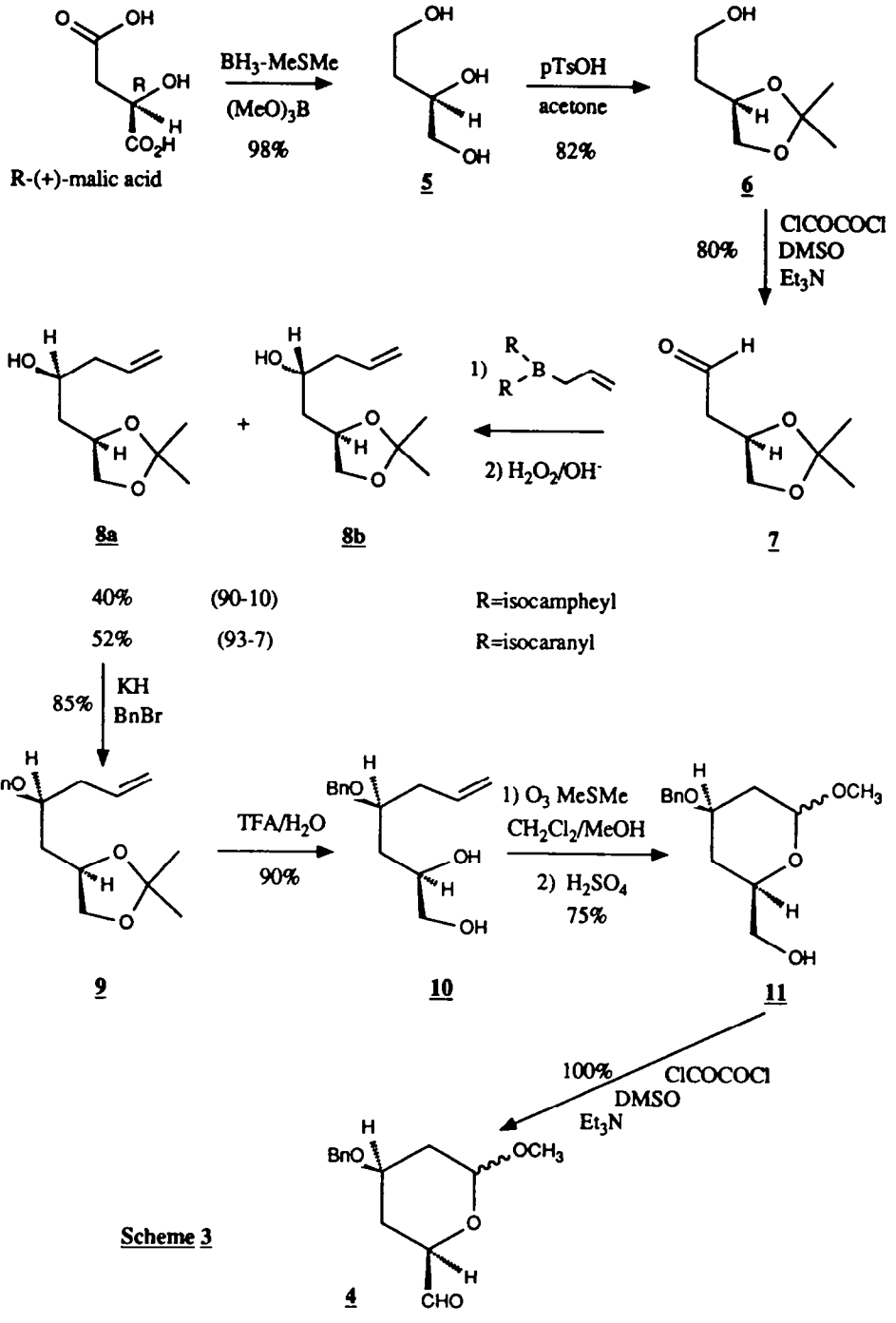
Figure 2



Scheme 2

Usually, creation of the C_6-C_7 bond is performed by attack of an organometallic species borne by the aromatic residue on a leaving group attached to the adequately protected lactone ring. The presence of a primary amide group in 3 precluded this kind of strategy and forced us to find a more suitable way. We were successful in using the procedure developed by chemists at Schering starting with 4-methylnicotinonitrile (11).

Synthesis of 5(S)-epi-compactin and mevinolin had already been described by two different groups (10) : Rosen and Heathcock, using a very different strategy obtained, in an intermediary step, a mixture of diastereoisomers they had to separate, whereas chemists at Merck have developed a method for inverting C_5 in the lactone ring of mevinolin. Our synthetic scheme required the synthesis of aldehyde 4 in an optically pure form. In this purpose we took advantage of Hanessian's chemistry of Avermectin related compounds for which he performed the synthesis of the opposite enantiomer of 4 (12).


R-(+)-malic acid
BH3-MeSMe
(MeO)3B
98%
5
pTsOH
acetone
82%
6
80%
ClCOCOCl
DMSO
Et3N
7
1)
2) H2O2/OH-
8a
8b
40%
(90-10)
R=isocampheyl
52%
(93-7)
R=isocaranyl
85%
KH
BnBr
9
TFA/H2O
90%
10
1) O3 MeSMe
CH2Cl2/MeOH
2) H2SO4
75%
11
100%
ClCOCOCl
DMSO
Et3N
4

Scheme 3

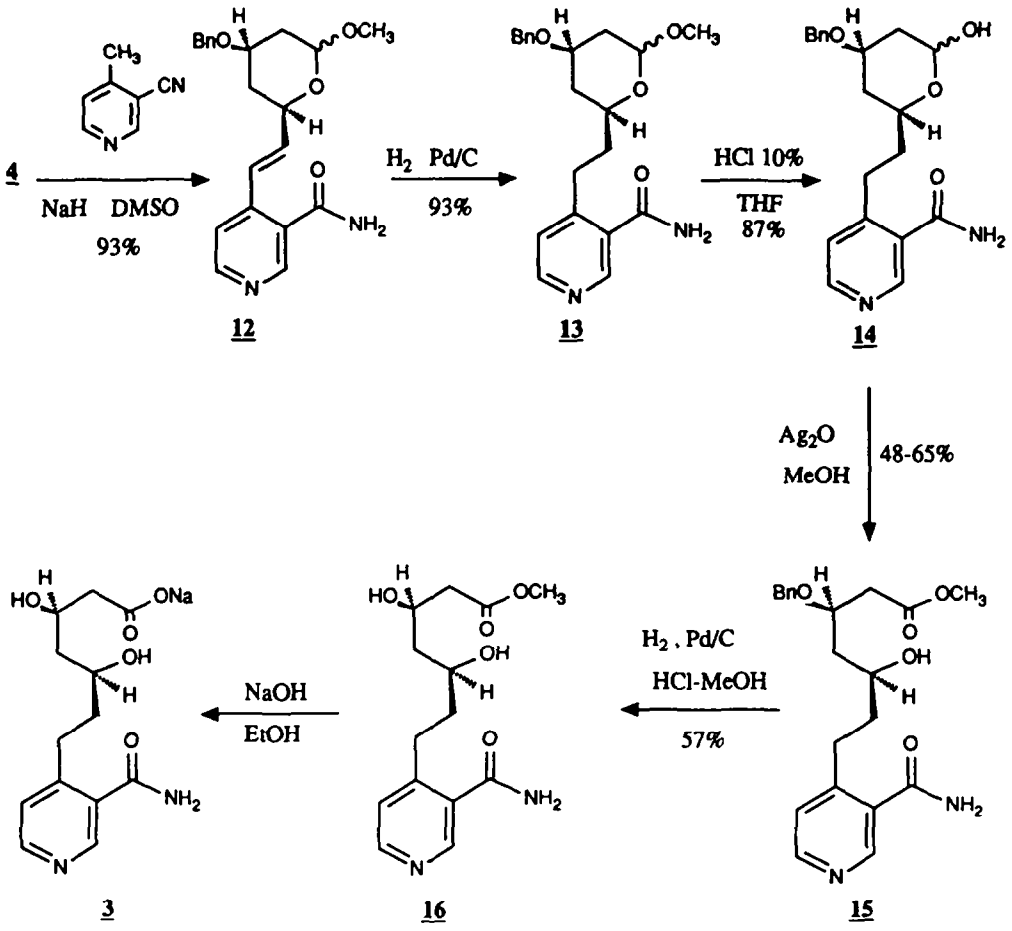
Reduction of commercially available (R)-(+)-malic acid with borane-methylsulfide complex in presence of trimethylborate (13) afforded, in quantitative yield, triol 5. Dioxolane 6 was obtained in 82% yield by p-toluene sulfonic acid catalyzed ketalization with anhydrous acetone. We found Swern's procedure to be superior to PCC oxidation (12) for the transformation of 6 into aldehyde 7. The next step involves introduction of an allyl group by means of an organometallic reagent. In order to avoid the tedious chromatographic separation of the 1:1 mixture of diastereoisomeric alcohols formed when allylmagnesium bromide is used as reagent (12), we used Brown's methodology (14) : thus, treatment of 7 with β-allyldiisopinocampheylborane derived from (+) α-pinene gave a 90:10 mixture of allylic alcohols 8 (15). This stereoselectivity could be further increased to 93:7 when using β-allyldiisocaranylborane (16) and, in this case, alcohol 8a was easily isolated by a simple chromatography. Protection of the free alcohol with benzylbromide and potassium hydride in THF, followed by removal of the acetal group by trifluoroacetic acid, afforded diol 10 in 76.5% overall yield. Then, 11 was obtained in a one pot procedure with 75% yield. Ozonolysis of the double bond was carried out in a mixture of methylene chloride and methanol, the resulting ozonide was reduced by dimethylsulfide and the cyclized hemiacetal was etherified by acidification of the medium. The final step gave the desired aldehyde 4 in quantitative yield by means of a Swern's oxidation (Scheme 3).

Coupling this aldehyde with 3-cyano-4-methyl-pyridine was performed according to the procedure used for the coupling of the same pyridine derivative with benzaldehyde (11). Whereas Schering's chemists could use either potassium t-butoxide in t-butylalcohol or sodium methoxide in methanol, the yield of the coupling reaction of 4 proved to be very dependent on the base used. The best yield, 93%, was obtained when using sodium hydride in DMSO at room temperature.

Since aldehyde 4 might be expected to be prone to epimerization under such strongly basic conditions, we checked the absolute configuration of 12 at C-5 as follows : this compound was

submitted to an ozonolysis reaction prior to reduction with sodium borohydride. The resulting alcohol was identical to 11 in all respects, thus confirming the absence of epimerization during the coupling reaction.

Our target compound 3 was then obtained in a straightforward manner : catalytic hydrogenation of the double bond and subsequent hydrolysis of the ketal with 10% HCl gave the lactol 14, the oxidation of which proved to be rather tricky. After having tried many oxidation reagents we found out that only silver oxide in methanol could lead to the expected hydroxy ester 15 which was debenzylated by catalytic hydrogenation in acidic medium affording 16 after neutralization of the mixture.



Scheme 4

The sodium salt 3 was obtained by saponification of the ester group with one equivalent of NaOH in ethanol and was directly assayed for the inhibition of HMG-Co A reductase : at 10^{-4} M, it did not inhibit the enzyme. This might indicate that the nicotinamide moeity does not provide a sufficient energy binding to the NADPH subsite.

Acknowledgement

We want to thank the C.N.R.S. for a grant to one of us (M. Barth) and F. Cermelj for typing this manuscript.

EXPERIMENTAL SECTION

^1H NMR spectra were obtained on Bruker WP 80 (80 MHz), Bruker AC 300 (300 MHz), Bruker WM 400 (400 MHz) spectrometers with Me_4Si as the internal reference; attributions were confirmed by COSY techniques. IR spectra were recorded on a Perkin-Elmer 782 spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Microanalyses were performed on a Perkin-Elmer 240c apparatus. Mass spectra were recorded on a Varian MAT 311 spectrometer. Melting points were obtained on a Electrothermal apparatus and are uncorrected.

(2R)-1,2,4-butanetriol 5

To a solution of 100 g (750 mmol) of (R)-malic acid ($[\alpha]_D^{20}$ = + 28°C, c=5.6 in pyridine) in 1 l of THF was added, under a N_2 atmosphere, 325 ml (3150 mmol) of trimethylborate and the resulting mixture was stirred at room temperature for one hour. Then 170 ml (1770 mmol) of borane methyl sulfide were slowly added and stirring was maintained for 20 hours. After evaporation of the solvent under reduced pressure, the residue was dissolved in 1 l of MeOH to which 300 g of SiO_2 was added and the suspension stirred 5 hours at room temperature. Removal of the SiO_2 by filtration and evaporation of the methanol afforded 77.9 g (98%) of 5 as a colorless oil. $[\alpha]_D^{20}$ = + 26.5° (c=1.33, EtOH); Litt. (17) for the opposite enantiomer $[\alpha]_D$ = - 28°C (c=1.07, MeOH); ^1H NMR (80 MHz, $CDCl_3$) δ 4.4 (s, 3H, OH), 3.6 (m, 1H), 3.5 (m, 2H), 3.24 (m, 2H), 1.54 (m, 2H).

(4R)-2,2-dimethyl-4-ethanol-1,3-dioxolane 6

To a solution of 36.7 g (346 mmol) of butanetriol in 1.8 l of anhydrous acetone was added 2.16 g (12.5 mmol) of p-toluene sulfonic acid. After 15 hours stirring at room temperature, 1.7 ml of triethylamine was added and the resulting solution filtered on a short column of silica gel. The column was thoroughly washed with a mixture (7:3) of hexane and acetone, the solvent removed under vacuum giving 41.5 g (82%) of 6 as an oil. ^1H NMR (80 MHz, $CDCl_3$) δ 4.4-3.6 (m, 5H), 2.99 (s, 1H, OH), 1.81 (q, J=5Hz, 2H), 1.42 (s, 3H), 1.36 (s, 3H). The chemical shifts are in good agreement with those found for the opposite enantiomer (18).

(4R)-2,2-dimethyl-4-ethanal-1,3-dioxolane 7

18 ml of DMSO in 60 ml of anhydrous CH_2Cl_2 were added at -60°C and under N_2 atmosphere, to a solution of 10.5 ml (122 mmol) of oxalylchloride in 75 ml of methylene chloride. After 5 min stirring at - 60°C, 15 g (103 mmol) of 6 in 75 ml of CH_2Cl_2 were slowly added and stirring was maintained for 45 min. Then 75 ml (543 mmol) of triethylamine were added and after 15 min stirring at - 60°C the reaction mixture was allowed to warm up to room temperature. Then 20 ml of water were added, the aqueous phase extracted with CH_2Cl_2, the combined extracts washed successively with 1N HCl, a saturated aqueous solution of $NaHCO_3$, distilled water and dried over $MgSO_4$. Evaporation of the solvent gave 11.9 g (80%) of 7 as an oil. ^1H NMR (80 MHz, $CDCl_3$) δ 9.82 (t, J=1.6 Hz, 1H), 4.54 (m, 1H), 4.18 (dd, J=6Hz, J=8Hz, 1H), 3.6 (dd, J=6Hz, J=8Hz, 1H), 2.75 (m, 2H), 1.42 (s, 3H), 1.37 (s, 3H).

(4R)-2,2-dimethyl-4-[(2S)-2-α propenyl]-ethanol-1,3-dioxolane (8a)

All manipulations must be carried out under a carefully controlled argon atmosphere. To a solution of 2.6 ml (25 mmol) of BMS is 25 ml of anhydrous THF were added, at 0°C, 7.95 ml (50 mmol) of (+)-α-pinene. Keeping the resulting mixture overnight at 4°C gave rise to the formation of crystals which were collected by filtration, washed three times with ether under argon and dried in vacuo to give 3.3 g (46%) of a white powder which was dissolved in 15 ml of anhydrous THF. To this solution was added, at 0°C, 950 µl of methanol and the resulting mixture was stirred at room temperature for 3 hours. Evaporation of the solvent gave a white solid which was dissolved in 11 ml of anhydrous ether followed by carefull addition at - 65°C of 21 ml (11.5 mmol) of a freshly prepared 0.5 M solution of allylmagnesium bromide in ether. The reaction mixture was first allowed to warm up to room temperature and then cooled down to - 75°C. To this cooled solution were added dropwise 1.6 g (11.1 mmol) of 7 in 5 ml ether. After 2 hours stirring at -75°C, were added 8.5 ml of a 3N NaOH solution and 3.5 ml of 30% H_2O_2 and the resulting mixture refluxed for 1 hour. Dilution with water, extraction of the aqueous phase with ether, washing of the combined organic extracts with water and brine, drying over $MgSO_4$ and removal of the solvent afforded a 90:10 mixture of alcohols 8a and 8b from which 0.86 g (40%) of 8a was obtained by column chromatography on silica gel (hexane:ethyl acetate ; 8:2). Following a very similar procedure but

using (+)-3-carene instead of (+)-α-pinene, alcohols 8a and 8b were obtained in a 93:7 ratio from which 8a was isolated in 52% yield. $[\alpha]_D^{20}$ = + 9.05° (c=1.5, CH_2Cl_2); ^1H NMR (80 MHz, $CDCl_3$) δ 5.8 (m, 1H), 5.2 (m, 1H), 5.03 (m, 1H), 4.3 (m, 2H), 3.87 (m, 1H), 3.56 (m, 1H), 2.3 (m, 2H), 2.18 (s, 1H, OH), 1.7 (m, 2H), 1.4 (s, 3H), 1.36 (m, 3H); IR (neat), ν (cm^{-1}) : 3400, 3100, 1650; Anal. ($C_{10}H_{18}O_3$) found : C 64.48, H 9.83; calcd : C 64.49, H 9.74).

(4R)-2,2-dimethyl-4-[(2S)-2-benzyloxy-4-pentenyl]-1,3-dioxolane 9

To a suspension of 1.44 g (36 mmol) of KH in 100 ml anhydrous THF was added, at 0°C and under argon, 6 g (32 mmol) of alcohol 8a in 30 ml THF and stirring was maintained for 20 min before addition of 4.6 ml (39 mmol) of benzylbromide. The reaction mixture was allowed to return slowly to room temperature before hydrolysis with 100 ml of brine. Extraction with ether, backwashing of the combined extracts with water, drying over $MgSO_4$ and evaporation of the solvent gave 10.37 g of a crude oil which was purified by column chromatography (hexane-ethylacetate ; 95:5) to leave 7.5 g (85%) of oily 9. $[\alpha]_D^{20}$ = + 48.26° (c=1.5, CH_2Cl_2) ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.26 (m, 5H), 5.85 (m, 1H), 5.12 (m, 2H),4.65 (d, J=12.6 Hz, 1H), 4.47 (d, J=12.6 Hz, 1H), 4.25 (m, 1H), 4.04 (dd, J=5 Hz, J=7.6 Hz, 1H), 3.69 (m, 1H), 3.51 (t, J=7.6 Hz, 1H), 2.36 (m, 2H), 1.76 (ddd, J=14 Hz - J= 8 Hz - J=4 Hz, 1H), 1.66 (ddd, J=14 Hz, J=8 Hz, J=4 Hz, 1H),1.37 (s, 3H), 1.32 (s, 3H) ; IR (neat) : ν (cm^{-1}) :1650, 1500, 920; Anal. ($C_{17}H_{24}O_3$) found : C 73.34 H, 8.67; calcd C : 73.88, H 8.75).

(2R,4S)-4-benzyloxy-6-hepten-1,2-diol 10

A mixture of 15 ml of trifluoroacetic acid and 10 ml water was added at 0°C to a solution of 6.4 g (23.2 mmol) of 9 in 32 ml of THF. The resulting mixture was then allowed to warm up to room temperature and stirred for 7 hours before neutralization with 1N NaOH, followed by extraction with ether. The organic extracts were backwashed with brine, dried over $MgSO_4$ and the solvent removed under vacuo leaving 4.9 g (90%) of 10 as a pale yellow oil. $[\alpha]_D^{20}$ = + 47.3° (c=1.07, CH_2Cl_2); ^1H NMR (80 MHz, $CDCl_3$) δ 7.34 (s, 5H), 5.84 (m, 1H), 5.20-5 (m, 2H), 4.7 (d, J=12 Hz, 1H), 4.47 (d, J=12 Hz, 1H), 3.8 (m, 2H), 3.4 (m, 2H), 2.4 (m, 2H), 1.9 (m, 2H, OH), 1.66 (m, 2H) ; IR (neat), ν (cm^{-1}) : 3400, 1650, 1510, 1470 ; MS(HR), $C_{14}H_{20}O_3$: found 236.1399, calcd 236.1412.

(2R,4R)-4-benzyloxy-6-methoxy-3,4,5,6-tetrahydro-2-methanol-2H-pyrane 11

Ozone was bubbled for 2 hours through a solution of 5.47 g (23.2 mmol) of diol 10 in 160 ml of a 1 to 1 mixture of CH_2Cl_2 and MeOH cooled at -78°C. The reaction was then quenched with 32 ml of dimethyl-sulfide, stirred 20 hours at room temperature, acidified with 1 ml of concentrated H_2SO_4, stirred for 5 hours and poured onto 200 ml of an aqueous saturated solution of $NaHCO_3$. Extraction with ethylacetate, backwashing of the combined extracts with water and brine, drying ($MgSO_4$) and evaporation of the solvent afforded a crude residue which was purified by chromatography on silica gel eluted with hexane-ethylacetate (1:1) to give 4.38 (75%) of 11 as a colorless oil. $[\alpha]_D^{20}$ = - 89° ; (c=2.9, CH_2Cl_2) ; ^1H NMR (400 MHz, $CDCl_3$) : δ 7.36-7.31 (m, 5H), 4.9 (m) and 4.35 (m) (total 1H), 4.55 (m, 2H), 3.9 (m, 1H), 3.82 (m, 1H), 3.62 (m, 2H), 3.52 (s) and 3.33 (s) (total 3H), 2.25 (s, 1H, OH), 2.19 (m, 1H), 1.98 (m, 1H), 1.57 (ddd, J=12 Hz, J=12 Hz, J=6 Hz, 1H), 1.37 (q, J=12 Hz, 1H) ; IR (neat), ν (cm^{-1}) : 3450, 1505, 1460 ; MS 270 (MNH_4^+) 253 (MH^+) 238 (MH^+-CH_3) 221 (MH^+-CH_3-H_2O); MS(HR) : $C_{14}H_{20}O_4$, found : 252.1365 calcd : 252.1361.

(2R,4R)-4-benzyloxy-6-methoxy-3,4,5,6-tetrahydro-2-methanal-2H-pyrane 4

To a solution of 618 µl (7.2 mmol) of oxalylchloride in 8 ml of CH_2Cl_2 was added, at - 60°C, under argon, 1.1 ml (15 mmol) of DMSO in 4 ml CH_2Cl_2. A solution of 1.55 g (6 mmol) of alcohol 11 in 12 ml CH_2Cl_2 was then added and the resulting mixture stirred for 20 min followed by addition of 4.55 ml (33 mmol) of triethylamine. Stirring was continued at -60°C for 1 hour and the solution allowed to warm up to room temperature. Addition of 10 ml H_2O, extraction with CH_2Cl_2, successive backwashings of the extracts with 1N HCl, water, saturated $NaHCO_3$, brine, drying over $MgSO_4$ and evaporation of the solvent at low temperature gave the aldehyde 4 in quantitative yield. ^1H NMR (80 MHz, $CDCl_3$) δ 9.68 (s, 1H), 7.3 (m, 5H), 4.98 (m, 1H), 4.56 (s, 2H), 3.87 (m, 2H), 3.55 (s) and 3.3. (s) (total 3H), 2.19 (m, 2H), 1.48 (m, 2H).

4-[2-[(2R,4R)-4-benzyloxy-6-methoxy-3,4,5,6-tetrahydro-2H-pyran-2-yl]-1-ene-ethyl]-3-pyridinecarboxamide 12

To a suspension of 0.18 g (6mmol) of NaH in 17 ml of DMSO was added, under argon, a DMSO (17 ml) solution of 0.708 g (6 mmol) of 3-cyano-4-methylpyridine and stirring was maintained for 20 min. Then 1.5 g (6 mmol) of aldehyde 4 in 30 ml of DMSO were slowly added. After 20 min stirring, the reaction mixture was poured onto 200 ml of water, extracted with ethylacetate. After washing the extracts with brine, drying over $MgSO_4$ and evaporation of the solvent, 2.7 g of crude 12 were obtained. Purification by column chromatography afforded 2.05 g (93%) of pure 12. $[\alpha]_D^{20}$ = - 55.5° (c=2.01, CH_2Cl_2) ; ^1H NMR (300 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.59 (d, J=5.3 Hz, 1H), 7.45 (d, J=5.3 Hz, 1H), 7.3 (m, 5H), 7.08 (d, J=16 Hz, H_8), 6.43 (dd, J=16 Hz, J=5.7 Hz, H_7), 4.94 (d, J=3.1 Hz, H_6), 4.57 (m, 2H), 4.42 (m, H_2), 3.95 (m, H_4), 3.34 (s, 3H, OCH_3), 2.22 (m, H_{3eq}, H_{5eq}), 1.63 (dt, J=13 Hz, J=3.6 Hz, H_{5ax}) 1.45 (q, J=17.8 Hz, H_{3ax}) ; IR (neat), ν (cm^{-1}) : 3200, 3100, 1690, 1630, 1600, 1550 ; Anal. ($C_{21}H_{24}N_2O_4$) found : C 67.91, H 6.64, N 7.34; calcd : C 68.46, H 6.56, N 7.60).

4-[2-[(2S,4R)-4-benzyloxy-6-methoxy-3,4,5,6-tetrahydro-2H-pyran-2-yl]-ethyl]-3-pyridinecarboxamide 13

A solution of 1.61 g (4.4 mmol) of 12 in 80 ml of anhydrous methanol was hydrogenated in the presence of 350 mg of 10% palladium on charcoal at 40°C, in a Parr apparatus, under 3 bars, for one hour. After removal of the catalyst by filtration and evaporation of the solvent, one got 1.5 g (93%) of a light-yellow oil. $[\alpha]_D^{20}$ = - 61.6° (C=2.09, $CHCl_3$) ; ^1H NMR (300 MHz, $CDCl_3$), δ 8.67 (s, 1H), 8.53 (d, J=5.1 Hz, 1H), 7.29 (m, 6H), 6.07 (broad, 1H, NH), 5.96 (broad, 1H, NH), 4.85 (d, J=2.8 Hz, H_6), 4.53 (m, 2H, CH_2Ph), 3.85 (m, H_4), 3.74 (m, H_2), 3.29 (s, 3H, OCH_3), 3.0 (m, H_8), 2.94 (m, H_8), 2.22 (m, H_{5eq}), 2.09 (m, H_{3eq}), 1.84 (m, 2H, H_7), 1.56 (dt, J=16.6 Hz, J=3.7 Hz, H_{5ax}), 1.31 (q, J=11.8 Hz, H_{3ax} ; IR (neat), ν (cm^{-1}) : 3450, 3400, 1700, 1600; Anal.($C_{21}H_{26}N_2O_4$) found: C 68.11, H 7.36, N 7.78; calcd : C 68.08, H 7.07, N 7.56).

4-[2-[2S,4R)-4-benzyloxy-6-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-yl]-ethyl]-3-pyridinecarboxamide 14

A solution of 1.4 g (3.78 mmol) of 13 and 130 ml of 3N HCl in 200 ml of THF was refluxed for 30 min, neutralized with 1N NaOH and extracted with ethylacetate. The organic phase was washed with brine, dried over $MgSO_4$ and evaporated to give 1.16 g (87%) of a pale yellow oil. $[\alpha]_D^{20}$ = - 24.7° (c=1.22, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.52 (m, 1H), 7.28 (m, 6H), 6.49 (s) and 6.14 (s) (total 2H), 5.39 (s, 0.5H), 4.60 (d, J=8.1 Hz, 0.5H), 4.52 (m, 2H), 3.86 (m, 0.5H), 3.71 (m, 0.5H), 3.53 (m, 0.5H), 3.22 (m, 2H), 3.06 (m, 0.5H), 2.84 (m, 0.5H), 2.3 (dd, J=12.7 Hz, J=4.6 Hz, 0.5 H), 2.19 (dd, J=12.7 Hz, J=4.6 Hz, 0.5H), 2-1.6 (m, 3.5H), 1.52-1.20 (m, 2.5H); IR ($CHCl_3$), ν (cm^{-1}) : 1680, 1600; Anal. ($C_{20}H_{24}N_2O_4$) found: C 66.71, H 6.79, N 7.50; calcd : C 67.39, H6.79, N 7.86.

Methyl (3R,5S) 7-(3-aminocarbonyl-4-pyridyl)-3-benzyloxy-5-hydroxy heptanoate 15

A mixture of 630 mg (1.77 mmol) of 14 and 2.6 g of Ag_2O in 150 ml of anhydrous methanol was refluxed under nitrogen for 3 hours in the dark. Filtration on celite followed by removal of the solvent under vacuo left a residue which was purified by column chromatography on silica gel (eluant : $CHCl_3$-MeOH ; 95:5). 330 mg (48%) of 15 was obtained as a colorless oil. The NMR spectrum shows the presence of small amounts of the corresponding lactone, the quantity of which increases with time when the solution is kept at room temperature. ^1H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.53 (m, 1H), 7.38-7.16 (m, 6H), 6.64 (broad, 1H, NH), 6.18 (broad, 1H, NH), 4.55 (d, J=11.9 Hz, 1H), 4.47 (d, J=11.9 Hz, 1H), 4.16 (m, 1H), 3.72 (m, 1H), 3.66 (s, 3H), 3.03 (m, 1H), 2.85 (m, 1H), 2.66 (dd, J=17.9 Hz, J=5.9 Hz, 1H), 2.51 (dd, J=17.9 Hz, J=5.9 Hz, 1H), 1.83 (m, 3H), 1.68 (m, 2H); IR (neat), ν (cm^{-1}) : 1750, 1680.

Methyl (3R,5S) 7-(3-aminocarbonyl-4-pyridyl)-3,5-dihydroxy heptanoate 16

A solution of 90 mg (0.23 mmol) of 15 and 38 µl of 12 N HCl in 15 ml of anhydrous methanol was hydrogenated in the presence of 50 mg of 10% Pd/C at 30°C in a Parr apparatus, under 3 bars, for one hour. After filtration on celite and neutralization with 587 µl of a solution of $NaHCO_3$ (70 g/l), the reaction mixture was poured onto 150 ml of water. Lyophilization of the solution and column chromatography of the residue (eluant : $CHCl_3$-MeOH ; 95:5) gave 39 mg (57%) of 16 as a colorless

oil. $[\alpha]_D^{20}$ = - 46.5° (c=0.2, THF) ; ^{1}H NMR (400 MHz, DMSO) : δ 8.53 (m, 2H), 8.05 (broad, 1H, NH), 7.66 (broad, 1H, NH), 7.35 (d, J=6 Hz, 1H), 4.69 (d, J=6 Hz, 1H, OH), 4.66 (d, J=6Hz, 1H, OH), 4.12 (m, 1H), 3.65 (m, 1H), 3.63 (s, 3H), 2.93-2.74 (m, 2H), 2.47 (dd, J=15 Hz, J=6 Hz, 1H), 2.36 (dd, J=12 Hz, J=9 Hz, 1H), 1.67 (m, 2H), 1.42 (m, 2H); IR (neat), ν (cm^{-1}) : 3200, 1740, 1680; Anal. ($C_{14}H_{20}N_2O_5$, H_2O) found : C 53.97, H 6.87, N 8.78; calcd: C 53.49, H 7.05, N 8.91.

Sodium (3R,5S) 7-(3-aminocarbonyl-4-pyridyl)-3,5-dihydroxy heptanoate 3

A mixture of 15 mg (0.05 mmol) of 16 and 50 µl (0.05 mmol) of N NaOH in 1,1 ml of ethanol was stirred at 50° for 1 h. and then evaporated to dryness. Dilution of the residue with 10 ml of water followed by lyophilization gave 12.5 mg (82%) of the sodium salt 3 as a colorless oil. $[\alpha]_D^{20}$ = -14° (c=0.1, MeOH) ; ^{1}H NMR (400 MHz, d_6-DMSO) : δ 8.51 (m, 2H), 8.04 (broad, 1H, NH), 7.60 (broad, 1H, NH), 7.34 (d, J=6Hz, 1H), 4.68 (broad, 1H, OH), 4.44 (broad, 1H, OH), 3.85 (m, 1H), 3.65 (m, 1H, 2.88 (m, 1H), 2.79 (m, 1H), 2.14 (dd, J=14.7 Hz, J=4.7 Hz, 1H), 3.85 (dd, J=14.7 Hz, J=8.8 Hz, 1H), 1.65 (m, 2H), 1.34 (m, 2H). The salt was used in the HMGCo-A reductase inhibition assay without further purification.

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