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# Towards a New Type of HMG-CoA Reductase Inhibitors: Part II :[1] Dramatic Substituents Effects in the C-5 Epimerisation of Carbohydrate Derivatives

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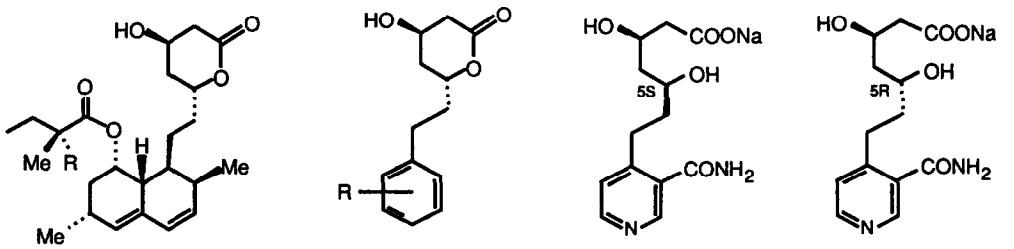
*Abstract: In the course of our search for a new class of HMG-CoA reductase inhibitors, the synthesis of reaction intermediate analogues was investigated. Compound 2, having the C-5 (R) configuration of natural mevinic acids, was prepared in enantiomerically pure form starting from levoglucosan During this synthesis, an epimerisation of the olefinic intermediate 16 was observed and was found to depend strongly both on the axial or equatorial orientation and on the nature of the C-3 substituent Biological activity of compound 2 is reported.*

## Introduction

3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGR) (EC 1.1.1.34), is the key regulatory enzyme in cholesterol biosynthesis. Inhibition of this enzyme is a powerful tool for designing new hypocholesterolemic drugs and numerous studies along this line were reported in the last decade.[2] Natural compounds such as lovastatin (mevinolin), symvastatin (synvinolin) and pravastatin are potent inhibitors of HMGR now used in clinic as hypocholesterolemic drugs.[3] The search for new synthetic inhibitors remains of interest to get new insights in the knowledge of the enzyme and its inhibition and to get new compounds with modulated activities and different tissue selectivities.[4] This prompted us to investigate a new class of inhibitors which could mimic the transition state of the enzymatic reduction of HMG-CoA by HMGR. This reduction needs the presence of NADPH and we reasoned that a molecule bearing a hydroxymethylglutarylmoiety and a NADPH analogue will be a good candidate. Indeed, one may expect a double interaction with the enzymatic site, one with the hydroxymethylglutaryl subsite and the other with a nicotinamide subsite.[5] This double interaction would give a high affinity inhibitor. Because the reducing NADPH is assumed to deliver the hydride from the *Si* face of the carbonyl group of HMG-CoA,[6] the 5(*S*) configuration of **1** would give the correct spatial disposition of the hydroxymethylglutaryl and nicotinamide moities. It is to note that this configuration was opposite to that of natural mevinic acids. Thus, we embarked in a programme aimed at the design of such inhibitors. On this basis, compound **1** was chosen as a model compound and was prepared, but unfortunately was found to be unable to inhibit HMGR even at $10^{-4}$ M.[1] To account for this

lack of biological activity, we raised two hypotheses: either the nicotinamide does not provide a sufficient energy binding to the NADPH subsite or this hydrophilic group is not adequately located, in other words the 5(*R*) configuration could be necessary to ensure correct interactions.




R = H Mevinolin
R = Me Synvinolin

Synthetic inhibitors

1

2

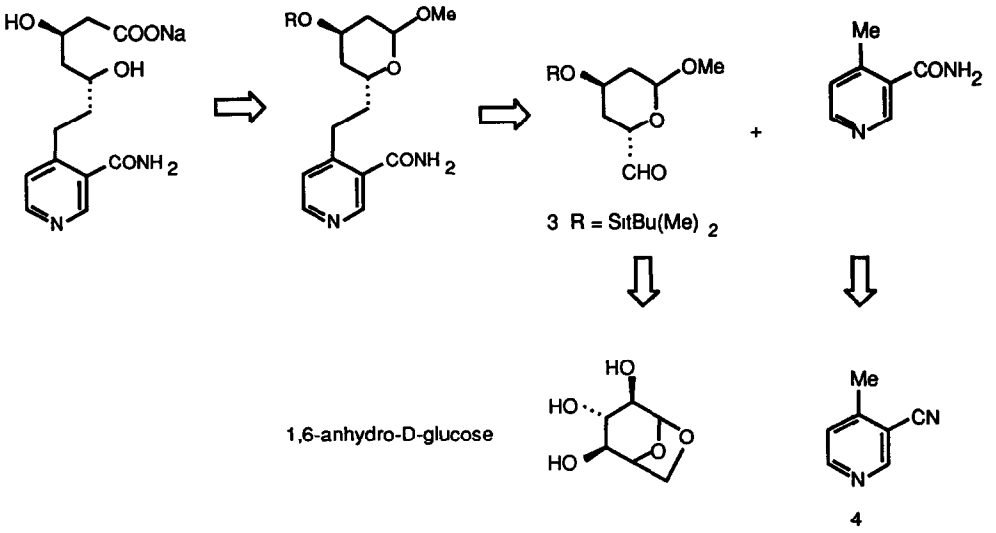
**Figure 1**

We decided to investigate the synthesis and biological evaluation of the hydroxy acid **2** that we report in this paper.

## Results and Discussion

In order to secure the correct stereochemistry at C-5, a suitable chiron could be prepared from a D-sugar. As depicted on Scheme 1, the condensation of an appropriate aldehyde with a suitable precursor of the nicotinic part was envisionned.

The aldehyde **3**, prepared from the alcohol **15** according to known chemistry,[7] was reacted with the anion derived from the nitrile **4** according to Villani procedure (**4**, NaH, DMSO, then **3**, RT, 20 min.).[8] The expected amide was obtained in an overall yield of 70% . However, to our surprise, careful analysis of the mixture revealed that *a mixture of epimers* **17** *and* **16** *was in fact obtained in a 4:1 ratio in favour of* **17**, *the 5(R) isomer*. (see Table). This was clear from proton nmr spectra which showed a typical axial proton pattern for H-1 and H-5 in **17** whereas only H-5 was found to be axial in **16**.[9] This indicates that the conformation of **17** was $^1C_4$ with all the substituents in equatorial position. This suggested that the formation of **17** might result from epimerisation of the starting aldehyde in the reaction conditions or from epimerisation of **16** to the more stable product **17** of the reaction. Thus the amide **16** may exist, to some extent, in the $^1C_4$ conformation in which two of the three substituents, at C-1 and C-3, were equatorial.

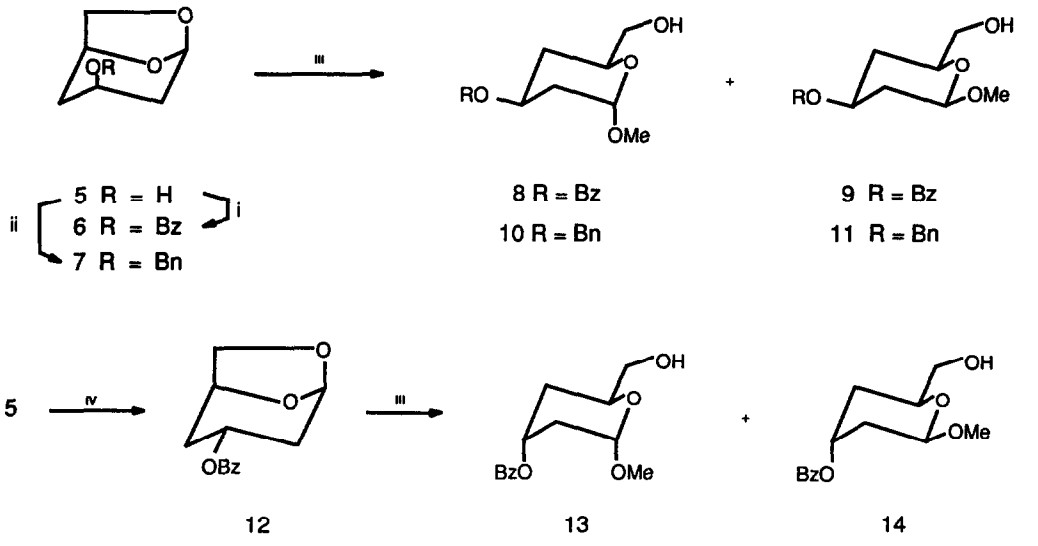



**Scheme 1**

The possible epimerisation of the starting aldehyde was ruled out first by performing the condensation in the presence of an excess of the aldehyde **3**.[10] At the end of the reaction, the crude mixture was immediately reduced with sodium borohydride and the alcohol **15** was recovered with no significant amount of the epimer at C-5 as seen from $^1$H nmr spectrum. Thus, suspecting that the bulky tert-butyldimethylsilyloxy substituent may play an important role in the conformational equilibrium of either the starting aldehyde, an intermediate or the expected amide, we decided to investigate the behaviour of some aldehydes differently substituted at C-3 in the coupling reaction. The influence of anomeric configuration was also investigated. The alcohols **8**, **9**, **13** and **14** were prepared and engaged in the above series of reactions.

*Preparation of alcohols 8, 9, 13 and 14*

To have a good entry to these alcohols, it seemed highly desirable to found a more direct route to 2,4-dideoxy sugars. 1,6-anhydro-D-glucose, (levoglucosan)[11] was found to be a good starting compound and the synthesis was realized according to Scheme 2. The alcohol **5** was easily obtained together with its C-2 hydroxy isomer (88:12), using the procedure reported by Baker et al.[12] Benzoylation of the alcohol **5** gave the benzoate **6**, and subsequent acid methanolysis gave a mixture of methyl glycosides **8** and **9**. The C-3 epimers were obtained from the key intermediate **5** through benzoylation with inversion of configuration under Mitsunobu conditions[13] giving the known benzoate **12**.[14] Acid methanolysis, again afforded a mixture of anomers **13** and **14**.[15]




**Reagents:** i) BzCl, pyridine, 80%; ii) BnCl, NaH, DMF, 89%;
iii) MeOH, Amberlite IR 120 H+, 90%; iv) $P(Ph)_3$, DEAD, PhCOOH, THF, 70%

**Scheme 2**

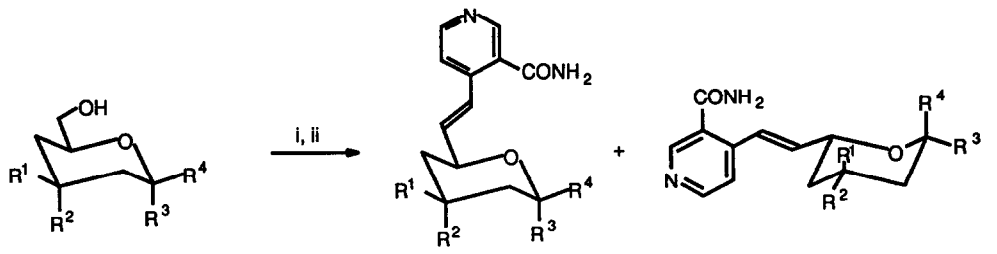
*Oxidation and condensation of the aldehydes with the anion of 4*

In order to avoid the purification and storage of the rather unstable aldehydes derived from the alcohols **8**, **9**, **13** and **14**, each condensation was performed as follows. The alcohol was submitted to Swern oxidation, conventional extractive work-up gave the crude aldehyde which was engaged in the reaction with the preformed anion of **4**. After twenty minutes of contact, the mixture was hydrolyzed and gave an unseparable mixture of isomers which were analyzed by proton nmr spectroscopy at 400 MHz. The Table summarizes the results obtained using this standard protocol.

*Discussion*

As seen from the Table, entries 1 and 2, the epimerisation dropped from 80% to only about 30% when the 3-O-t butyldimethylsilyloxy substituent in the *erythro* relative configuration (starting alcohol **15**) was replaced by 3-O-benzoyloxy in the same axial configuration (starting alcohol **13**). More interesting was the result obtained with the *threo* alcohol **8** (entry 4) which gave only 15% of epimerized compound **23**. It is clear from these results that the bulkier the substituent at C-3 in axial orientation, the larger the amount of epimerisation. It is worthy of note that simply changing a silyl group to a benzoyl group, dramatically decreased the amount of epimerization. That means that the 3-O-t butyldimethylsilyloxy group shows a marked preference for equatorial orientation thus forcing the chair in the $^1C_4$ conformation in which the nicotinic appendage was in an axial disposition. Owing to the homoenolic nature of H-5, in $\alpha$ position of the amide by vinylology, base-catalyzed epimerisation occurred

giving **17** in which all substituents were equatorial.[16] This effect is by far less pronounced for the 3-O-benzoyloxy group in **18**. Both substituents at C-3 and C-5 having approximately the same size, the conformational equilibrium between $^1C_4$ and $^4C_1$ could be shifted toward the latter because of the anomeric effect which favours the axial orientation of the aglycon.




| | | | |
|---|---|---|---|
| **15** | $R^1 = R^4 = H$, $R^2 = OSitBuMe_2$, $R^3 = OMe$ | **16** | **17** |
| **13** | $R^1 = R^4 = H$, $R^2 = OBz$, $R^3 = OMe$ | **18** | **19** |
| **14** | $R^1 = R^3 = H$, $R^2 = OBz$, $R^4 = OMe$ | **20** | **21** |
| **8** | $R^1 = OBz$, $R^2 = R^4 = H$, $R^3 = OMe$ | **22** | **23** |
| **9** | $R^1 = OBz$, $R^2 = R^3 = H$, $R^4 = OMe$ | **24** | **25** |

**Reagents:** i) DMSO, $(COCl)_2$, $NEt_3$, $CH_2Cl_2$, -60°C; ii) **4**, NaH, DMSO, 20 min., rt.;

**Scheme 3**

**Table:** *Formation of amides from aldehydes and anion of 4*

| Entry | Starting alcohol | Products | | Ratio | Yield |
|---|---|---|---|---|---|
| | | 5(*S*) | 5(*R*)[a] | *S*/*R*[b] | (%)[c] |
| 1 | **15** | **16** | **17** | 1:4 | 70 |
| 2 | **13** | **18** | **19** | 2:1 | 70 |
| 3 | **14** | **20** | **21** | 2:1 | 71 |
| 4 | **8** | **22** | **23** | 7:1 | 72 |
| 5 | **9** | **24** | **25** | 1.2:1 | 69 |

a) We have adopted the 5(*S*), 5(*R*) nomenclature which refers to carbohydrates or mevinic acids numbering. Note that the 5(*S*) compounds **16, 18, 20, 22, 24** became 5(*R*) after reduction of the double bond, in agreement with mevinic acids stereochemistry.

b) Estimated by integration of H-1, H-3 and H-5 protons

c) Overall yields for oxidation-condensation calculated from the starting alcohol

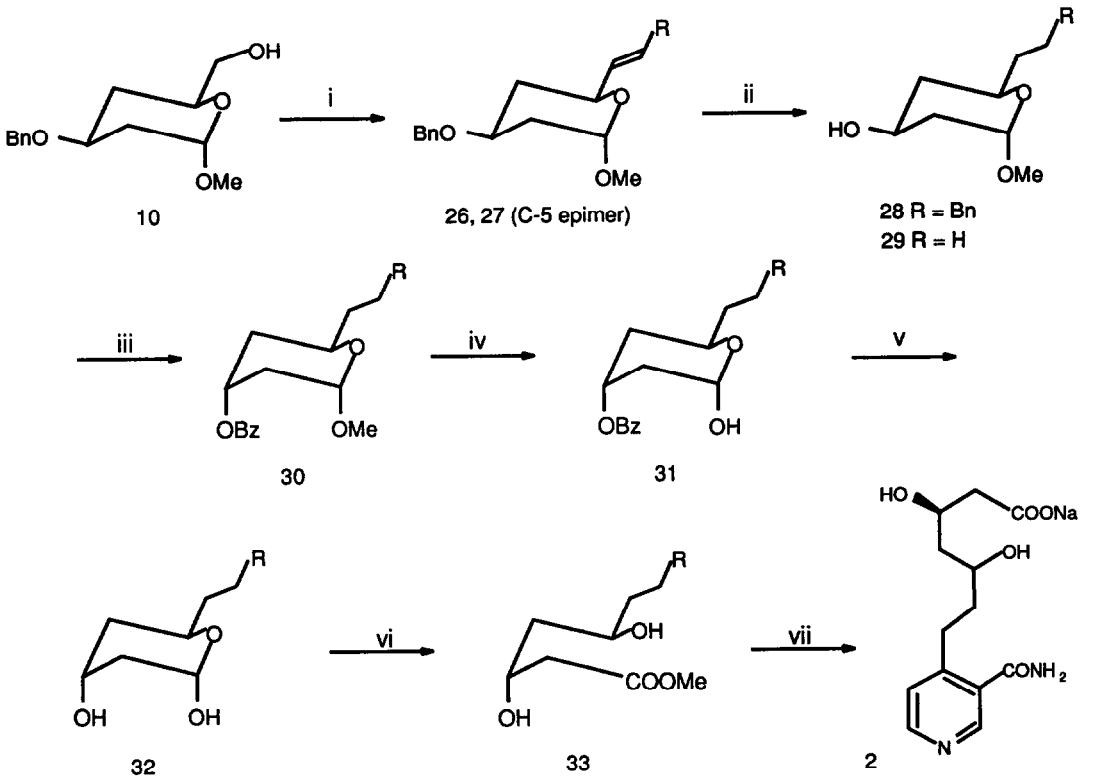
Obviously, changing the orientation of the 3-O-benzoyloxy group from axial to equatorial e.g. from **18** to **22** disfavoured the $^1C_4$ conformation (both C-3 and C-5 substituents are equatorial). The results observed with β anomers (entries 3 and 5) may be rationnalized in the same terms of conformationnal equilibria taking anomeric effect into account. For example, anomeric effect may account for the extensive epimerisation of **24**, in which the aglycon is equatorial, to **25** which satisfied this rule.

*Synthesis of the potential inhibitor* **2**

In the light of the above results, the definitive synthetic blueprint for the preparation of the potential inhibitor **2** was established as depicted on Scheme 4. The starting **10** was obtained from levoglucosan as described above for the synthesis of alcohol **8**. Expecting the same size effect, a benzyl protecting group was used instead of a benzoyl group at C-3 to allow, in the same step, the reduction of the double bond and deprotection at C-3 by hydrogenolysis. Benzylation of alcohol **5** gave **7** which was submitted to methanolysis in the presence of an acidic resin to give a 9:1 mixture of α:β anomers **10** and **11** which were separated by column chromatography. The oxidation-condensation sequence detailed above was then applied to **10** and to our good surprise the expected mixture of amides **26** and **27** was obtained in the ratio 9:1 as estimated by proton nmr spectroscopy. This unseparable mixture was then catalytically reduced to give the alcohol **29** and about 8-10% of its C-3 epimer. The correct configuration at C-5 was established using Mitsunobu inversion to give the benzoate **30** which was sequentially deprotected by acid hydrolysis of the glycoside followed by saponification of the ester group. The last and delicate step was the oxidation of the aldehyde of **32** to the methyl ester **33** which was realized using silver oxide in refluxing methanol. No attempts were made to get **33** free from its C-5 epimer (less than 10% by proton nmr spectroscopy). This compound was fully characterized by spectroscopy, high resolution mass spectrometry and elemental analysis.

The sodium salt **2** was prepared from **33** by saponification of the ester group with one equivalent of sodium hydroxide in ethanol and was directly assayed for the inhibition of HMGR: no inhibition was found even at a concentration of $10^{-4}$M. The lack of activity of both compound **1** and **2** which differ in the stereochemistry at C-5 indicates that whatever the orientation of the nicotinamide group relative to the dihydroxyacid unit it fails to bring sufficient energy binding to the active site of the enzyme.[17] This shows also that the small hydrophilic nicotinamide ring cannot strongly interact neither with the domain which binds the lipophilic hexahydronaphtalene moiety of mevinic acids, or bind the rather hydrophilic coenzyme A present in the natural substrate of HMGR.[18]

In summary, we have synthetized, from levoglucosan, a new potential inhibitor of HMGR encompassing the hydroxyacid moiety of mevinic acids of 5(R) configuration, flanked by a pyridine ring analogous to NADP. This transition state analogue as well as its previously prepared 5(S) epimer were found to be biologically inactive, suggesting that the expected double interaction in the enzymatic site cannot be realized with this kind of molecules. It is probable that the nicotinic moiety mimics only a too small part of the NADPH. Thus the use of a dihydropyridine moiety more closely related to NADPH instead of the pyridine one in **2** is probably necessary to ensure sufficient energy binding. During this study, we have demonstrated that the t-butyl dimethylsilyloxy group had a strong




**Reagents:** i) 1) DMSO, $(COCl)_2$, $NEt_3$, $CH_2Cl_2$ -60°C; 2) 4, NaH, DMSO, 20 min., rt. 70%; ii) $H_2$, Pd/C, MeOH, 55%; iii) $P(Ph)_3$, DEAD, PhCOOH, THF, 85%; iv) HCl, THF, 60°C, 80%; v) MeONa, MeOH, 75%; vi) $Ag_2O$, MeOH, reflux, 50%; vii) NaOH, EtOH

**Scheme 4**

propension to be in an equatorial orientation. This remarkable effect is by far superior to anomeric effect and was responsible of the observed epimerisation. This effect would be taken into account in planning syntheses with this widely used protecting group. The generality and the possible uses of this effect are now under current study.

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## Experimental Section

The $^1$H n.m.r spectra were recorded on a Bruker AM 400 spectrometer operating at 400 MHz. Unless otherwise stated, deuteriochloroform was used as solvent. Assignments were confirmed by double irradiation or COSY techniques. Chemical shifts are reported relative to internal $SiMe_4$. Optical rotations were measured on a Perkin Elmer 141 polarimeter at 20 °C. Melting points were measured in capillary tubes and were uncorrected. The elementary analyses and high resolution mass spectrometry were performed by the Service Central de Microanalyses du CNRS at Vernaison (France). T.l.c was performed on silica gel (Merck 6O $F_{254}$). Column chromatography used silica gel (Merck 60 70-230 mesh). Mixtures of ethyl acetate (A), ethanol (E), toluene (T) and hexane (H) were used as eluents.

### Starting compounds

Compound **15**[7], **5**[12] and 3-cyano-4-methyl pyridine[19] were prepared according to literature procedure.

### 1,6-anhydro-3-*O*-benzoyl-2,4-didesoxy-β-D-*threo*-hexopyranoside 6

To a solution of 1,6-anhydro-D-glucopyranose (600 mg, 4.5 mmol) in anhydrous pyridine (20 mL) at 0°C was added benzoyl chloride (0.8 mL, 1.7 eq) and DMAP (20 mg). After stirring at room temperature for 12 hours, ethanol (2 mL) was added and dichloromethane (100 mL). The organic layer was washed with 3N hydrochloric acid, water, 3N sodium hydroxide and water, dried over magnesium sulfate and evaporated. Column chromatography on silica gel (A/H 25:75) afforded pure **6**-. (864 mg, 80%); $R_f$0.56 (A/H 40:60); mp. 78°C; $[\alpha]_D^{20}$ - 76 (c 0.45, $CHCl_3$); $\nu_{max}$/cm$^{-1}$ 1680; $^1$H NMR δ 1.92-2.15 (m, 3H, 2 x *H*-2, *H*-4), 2.40 (m, 1H, $J_{4,4'}$ 15 Hz, *H*-4'), 3.85 (m, 1H, *H*-6), 4.35 (d, 1H, $J_{6,6'}$ 7 Hz, *H*-6'), 4.59 (m, 1H, *H*-5), 5.39 (m, 1H, *H*-3), 5.65 (s, 1H, *H*-1), 7.40-8.10 (m, 5H, *Ar*); Anal Calcd for $C_{13}H_{14}O_4$: C, 66.98; H, 5.57; Found: C, 67.06; H, 5.99.

### 1,6-anhydro-3-*O*-benzyl-2,4-didesoxy-β-D-*threo*-hexopyranoside 7

Sodium hydride (60%, 600 mg, 15 mmol), previously washed with anhydrous tetrahydrofuran, was suspended in anhydrous dimethylformamide and stirred at 0°C. A solution of **5** (1.46 g, 11.3 mmol) was added dropwise. After 10 min., benzyl bromide ( 1.74 mL, 14.7mmol) was added slowly. The mixture was stirred overnight at room temperature. The solvent was then evaporated and the residue was extracted with dichloromethane (3 x 100 mL). The organic layer was washed with 3N hydrochloric acid, water, 3N sodium hydroxide, water, dried over magnesium sulfate and evaporated. Column chromatography on silica gel (A/H 20:80) afforded pure **7**-. ( 2.33 g, 89%); $R_f$ 0.59 (A/H 2:3); mp. 108°C; $[\alpha]_D^{20}$ -36.2 (c 0.85, $CDCl_3$); $^1$H NMR δ 1.84 (m, 1H, $J_{2,2'}$ 15, $J_{2',3}$ 5, $J_{1,2'}$ 2 Hz) *H*-2') 1.94 (d, 1H, *H*-2), 2-2.20 (m, 2H, *H*-4, *H*-4'), 3.73 (m, 2H, *H*-5, *H*-6), 4.36 (d, 1H, $J_{6,6'}$ 6 Hz, *H*-6'), 4.50 (s, 1H, *H*-3), 4.52 (dd, 2H, $CH_2$Ph), 5.55 (s, 1H, *H*-1), 7.20-7.26 (m, 5H, *Ar*); Anal Calcd for $C_{13}H_{16}O_3$: C, 70.87; H, 7.33; Found: C, 68.90; H, 7.21.

**Methyl-3-*O*-benzoyl-2,4-dideoxy-D-*threo*-hexopyranoside 8, 9**

To a solution of **6** (850 mg, 3.63 mM) in methanol (50 mL) was added Amberlite IR $H^+$ form (1g). The mixture was heated for 6 hours at 30°C. When the reaction was completed, ethyl ether was added (150 mL) and the solution was filtered, washed with saturated aqueous sodium bicarbonate solution and brine. The organic layer was dried over magnesium sulfate, filtered and evaporated. The anomers **8** and **9**, obtained in a 6:1 ratio, were separated by hplc (A/H 25:75).

α anomer **8**-. (750 mg, 78%); gum; $R_f$ 0,38 (A/H 50:50); $[\alpha]_D^{20}$ + 112.7 (c 0,83, $CHCl_3$); $\nu_{max}/cm^{-1}$ 3440, 1690; $^1H$ NMR δ 1.60 (m, 1H, *H*-4a), 1.79 (m, 1H, $J_{2a,2e}$ $J_{2a,3}$ 12 Hz, *H*-2a), 2.00 (t, 1H, $J_{OH,6}$ 7 Hz, OH), 2.10 (m, 1H, *H*-4e), 2.24 (m, 1H, *H*-2e), 3.38 (s, 3H, $OCH_3$), 3.60 (dd, 1H, $J_{6,6'}$ 12, $J_{5,6}$ 5 Hz, *H*-6), 3.72 (m, 1H, $J_{5,6'}$ 3 Hz, *H*-6'), 3.99 (m, 1H, *H*-5), 4.95 (d, 1H, $J_{1,2a}$ 3 Hz, *H*-1), 5.47 (m, 1H, *H*-3), 7.40-8.10 (m, 5H, *Ar*). Anal Calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81; Found: C, 63.35; H, 6.8.

β anomer **9**-. (120 mg, 12%) gum; $R_f$ 0.32 (A/H 50:50); $\nu_{max}/cm^{-1}$ 3440, 1690; $^1H$ NMR δ 1.60 (m, 2H, *H*-2a, *H*-4a), 2.05 (m, 1H, *H*-4e), 2.20 (m, 1H, OH), 2.35 (m, 1H, *H*-2e), 3.55 (s, 3H, $OCH_3$), 3.60-3.80 (m, 3H, 2 x *H*-6 et *H*-5), 4.50 (dd, 1H, $J_{1,2a}$ 10, $J_{1,2e}$ 2 Hz, *H*-1), 5.20 (m, 1H, *H*-3), 7.40-8.10 (m, 5H, *Ar*).

**Methyl-3-*O*-benzyl-2,4-dideoxy-α-D-*threo*-hexopyranoside 10**

Compound **7** (2 g, 9 mmol) was treated according to the procedure described for the methanolysis of **6** during 12 hours. The anomers **10** and **11** (9:1 ratio) were separated using medium pressure liquid chromatography (A/H 35:65): **10**-. (1.8 g, 89%); $R_f$ 0.34; mp. 45°C; $[\alpha]_D^{20}$ +102.8 (c 0.85, $CH_3OH$); $^1H$ NMR δ 1.37 (m, 1H, *H*-4a), 1.57 (m, 1H, $J_{2a,2e}$ $J_{2a,3}$ 12 Hz, *H*-2a), 2.02 (m, 1H, *H*-4e), 2.20 (m, 1H, *H*-2e), 2.30 (m, 1H, OH), 3.38 (s, 3H, $OCH_3$), 3.60 (m, 2H, *H*-6), 3.82 (m, 1H, *H*-3), 3.99 (m, 1H, *H*-5), 4.52 (2d, 2H, $CH_2Ph$), 4.90 (d, 1H, $J_{1,2a}$ 3 Hz, *H*-1), , 7.20-7.30 (m, 5H, *Ar*); Anal Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99; Found: C, 66.70; H, 7.8.

**1,6-anhydro-3-*O*-benzoyl-2,4-dideoxy-β-D-*erythro*-hexopyranoside 12**

To a solution of **5** (720 mg, 5.5 mmol), benzoic acid (1.63 g, 2.5 eq) and triphenylphosphine (3.62 g, 2.5 eq) in anhydrous tetrahydrofuran (20 mL) stirred under argon was added dropwise DEAD (2.2 mL, 2.5eq). The mixture was stirred for 2 hours. Ethyl acetate (100 mL) was added and the organic layer was washed with aqueous sodium bicarbonate, dried over magnesium sulfate and evaporated. Column chromatography on silica gel (A/H 20:80) afforded pure **12**. (907 mg, 70%); $R_f$ 0,65 (A/H 50:50); mp. 63°C; $[\alpha]_D^{20}$ - 81.8 (c 0.15, $CHCl_3$); Litt.[8] oil; $[\alpha]_D^{20}$ - 80 (c 0.80, $CHCl_3$); $\nu_{max}/cm^{-1}$ 1750; $^1H$ NMR δ 1.80 (m, 1H, $J_{2,2'}$ 12 Hz, *H*-2), 2.00 (m, 1H, *H*-2'), 2.25 (m, 1H, $J_{4,4'}$ 14 Hz, *H*-4), 2.32 (m, 1H, *H*-4'), 3.76 (m, 1H, *H*-6), 4.00, d, 1H, $J_{6-6'}$ 7 Hz, *H*-6'), 5.60 (s, 1H, *H*-1), 7.50-8.00 (m, 5H, *Ar*).

**Methyl-3-*O*-benzoyl-2,4-dideoxy-D-*erythro*-hexopyranoside 13, 14.**

To a solution of **12** (305 mg, 1.3 mmol) in methanol (13 mL) was added Amberlite IR $H^+$ form (1g). The mixture was heated for 6 hours at 30°C. When the reaction was completed, ethyl ether was added (150 mL) and the solution was filtered, washed with saturated aqueous sodium bicarbonate solution and brine. The organic layer was dried over magnesium sulfate, filtered and evaporated. Flash chromatography on silica gel (T/H/A 35:60:5) gave an unseparable mixture of anomers **13** and **14** (4:1). Separation was cleanly effected after conventional silylation of the C-6 alcohol and careful preparative hplc (A/H 5:95). Acid hydrolysis of each isomer (THF, HCl, 1.5eq) gave almost pure **13** and **14**

α anomer **13**-. (440 mg, 63%); gum; $R_f$ 0.32 (A/H 50:50); $[\alpha]_D^{20}$ + 85 (c 0,48, $CHCl_3$); $\nu_{max}$ /$cm^{-1}$: 3480, 1720; $^1H$ NMR δ 1.81 (m, 3H, *H*-2, *H*-4, OH), 1.95 (m, 1H, *H*-2'), 2.12 (m, 1H, *H*-4'), 3.40 (s, 3H, $OCH_3$), 3.60 (m, 1H, *H*-6), 3,72 (dd, 1H, $J_{6,6'}$ 12 ; $J_{5,6'}$ 3 Hz, *H*-6'), 4.29 (m, 1H, *H*-5), 4.87 (d, 1H, $J_{1,2'}$ 4 Hz, *H*-1), 5.39 (m, 1H, *H*-3), 7.40-8.10 (m, 5H, *Ar*). Anal Calcd for $C_{14}H_{18}O_5$ : C, 63.15; H, 6.81; Found: C, 63.40; H, 6.85.

β anomer **14**-. (112 mg, 16%); gum; $R_f$ 0.32 (A/H 50:50); $[\alpha]_D^{20}$ - 39.4 (c 0.49, $CHCl_3$); $\nu_{max}$/$cm^{-1}$ 3480, 1720; $^1H$ NMR δ 1.85-1.95 (m, 4H, 2 x *H*-2, *H*-4, OH), 2.05 (m, 1H, *H*-4'), 3.48 (s, 3H, $OCH_3$), 3.52 (m, 1H, *H*-6), 3.72 (m, 1H, *H*-6'), 4.10 (m, 1H, *H*-5), 4.82 (dd, 1H, $J_{1,2}$ 5, $J_{1,2'}$ 1 Hz, *H*-1), 5.58 (m, 1H, *H*-3), 7.40-7.80 (m, 5H, *Ar*).

**General procedure for oxidation of alcohols and condensation of 3-cyano-4-methyl-pyridine.**

*Oxidation*: a solution of dimethylsulfoxide (0.18 mL, 2.2 mmol) in anhydrous dichloromethane (3 mL) was added to a cooled (-60°C) solution of oxalylchloride (0.11 mL, 1.1 mmol). The mixture was stirred for 5 min. and a solution of the alcohol (1 mmol) in anhydrous dichloromethane (5 mL) was added dropwise. After 15 min. at -60°C, triethylamine (0.8 mL) was added and the mixture was allowed to warm up to room temperature. Water (10 mL) was then added, and the aqueous phase was extracted with dichloromethane (3 x 100 mL). The organic layer was washed with 1N HCl, saturated sodium bicarbonate and water, dried over magnesium sulfate and evaporated. The crude mixture was used as such in the next step.

*Condensation*: to a suspension of sodium hydride (48 mg, 60%, 1.2 mmol) in dimethylsulfoxide (3 mL) stirred under argon, was added a solution of 3-cyano-4-methyl-pyridine (141 mg, 1.2 mmol) in dimethylsulfoxide (3 mL). The solution became dark red and after 15 min. at room temperature, a solution of the aldehyde (1 mmol) in dimethylsulfoxide (5 mL) was added. The stirring was maintained for 20 min. and the mixture was poured into 80 mL of water and extracted with ethylacetate (3 x 100 mL). The organic layer was washed with brine and dried over magnesium sulfate and evaporated. The mixture of amides was purified by column chromatography on silica gel using A/E 95:5 as eluent. $^1H$ NMR data are given below. Protons of the ethylene bridge have been noted 1' and 2'.

All amides have approximately the same $R_f$ 0.30 (A/E 90:10) and the same infrared spectra (film) $\nu_{max}$/$cm^{-1}$ 3500-3000, 1690 and 1650.

**4-[2-[(2*RS*,4*R*)-4-t butyl dimethylsilyloxy-6-methoxy-3,4,5,6-tetrahydro-2*H*-pyran-2-yl]-1 -ene-ethyl]-3-pyridine carboxamide 17** and **16** were obtained as a gum (274 mg, 70%).

**17**-. $^1$H NMR δ 0.10 (s, 6H, 2 x $CH_3$), 0.90 (m, 9H, tBu), 1.40 (m, 2H, *H*-5a, *H*-3a), 1.93 (m, 1H, *H*-3e), 2.10 (m, 1H, *H*-5e), 3.61 (s, 2.4H, $OCH_3$), 3.87 (m, 1H, *H*-4), 4.08 (m, 1H, $J_{4a,5}$ 12 Hz, *H*-2), 4.38 (dd, 0.8H, $J_{1,2a}$ 10, $J_{1,2e}$ 2 Hz, *H*-6), 6.00 (m, 1H, N-H), 6.40 (m, 1H, N-H), 6.50 (dd, 1H, $J_{5,6}$ 6, $J_{6,7}$ 15 Hz, *H*-2'), 7.10 (d, 1H, *H*-1'), 7.52 (d, 1H, *Ar*), 8.60 (d, 1H, *Ar*), 8.80 (s, 1H, *Ar*).

**16**-. $^1$H NMR δ 3.57 (s, 0.6H, $OCH_3$), 4.70 (m, 0.2H, *H*-6).

**4-[2-[(2*RS*,4*R*)-4-benzoyloxy-6-methoxy-3,4,5,6-tetrahydro-2*H*-pyran-2-yl]-1-ene-ethyl]-3-pyridine carboxamide 18, 19,** (194 mg, 70%) strating from **13** (220mg, 0.7 mmol).

**18**-. $^1$H NMR δ 1.90 (m, 1H, *H*-3a), 2.02 (m, 1H, *H*-5a), 2.10 (m, 1H, *H*-5e), 2.15 (m, 1H, *H*-3e), 3.45 (s, 2.01H, $OCH_3$), 4.65 (m, 0.66H, $J_{4a,5}$ 11 Hz, *H*-2), 4.88 (m, 0.66H, $J_{3,4a}$ 9 Hz, *H*-4), 4.92 (d, 0.66H, $J_{1,2a}$ 2 Hz, *H*-6), 6.00 (m, 2H, 2 x N-H), 6.45 (dd, 1H, *H*-2'), 7.08 (d, 1H, *H*-1'), 7.40-8.80 (m, 8H, *Ar*). Anal Calcd for $C_{21}H_{22}N_2O_5$: C, 65,96; H, 5.80; N, 7.33; Found: C, 66.11; H, 5.96. N, 7.45.

**19**-. $^1$H NMR δ 3.55 (s, 0.99H, $OCH_3$), 4.25 (m, 0.33H, $J_{4a,5}$ 9 Hz, *H*-2), 4.55 (dd, 0.33H, $J_{1,2a}$ 10, $J_{1,2e}$ 2 Hz, *H*-6), 5.25 (m, 0.33H, *H*-4).

**4-[2-[(2*RS*,4*R*)-4-benzoyloxy-6-methoxy-3,4,5,6-tetrahydro-2*H*-pyran-2-yl]-1-ene-ethyl]-3-pyridine carboxamide 20, 21** (98 mg, 71%) starting from **14** (110 mg, 0.36 mmol).

**20**-. $^1$H NMR δ 1.90 (m, 1H, *H*-3a), 2.02 (m, 1H, *H*-5a), 2.10 (m, 1H, *H*-5e), 2.15 (m, 1H, *H*-3e), 3.54 (s, 2H, $OCH_3$), 4.63 (m, 0.66H, $J_{4a,5}$ 11 Hz, *H*-2), 4.86 (dd, 0.66H, $J_{1,2a}$ 10, $J_{1,2e}$ 2 Hz, *H*-6), 5.57 (m, 0.66H, *H*-4). 6.00 (m, 2H, 2 x N-H), 6.45 (dd, 1H, *H*-2'), 7.08 (d, 1H, *H*-1'), 7.40-8.80 (m, 8H, *Ar*).

**21**-. $^1$H NMR δ 3.39 (s, 1H, $OCH_3$), 4.20 (m, 0.33H, *H*-2), 4.81 (dd, 0.33H, $J_{1,2a}$ 10, $J_{1,2e}$ 2 Hz, *H*-6), 5.60 (m, 0.33H, *H*-4).

**4-[2-[(2*RS*,4*S*)-4-benzoyloxy-6-methoxy-3,4,5,6-tetrahydro-2*H*-pyran-2-yl]-1-ene-ethyl]-3-pyridine carboxamide 22 , 23** (275 mg, 72%) starting from **8** (300 mg, 1 mmol).

**22**-. $^1$H NMR δ 1.80 (m, 2H, *H*-5a et *H*-3a), 2.27 (m, 1H, *H*-3e), 2.35 (m, 1H, *H*-5e), 3.39 (s, 2.64H, $OCH_3$), 4.60 (m, 0.88H, $J_{4a,5}$ 11 Hz, *H*-2), 5.01 (d, 0.88H, $J_{1,2a}$ 2 Hz, *H*-6), 5.50 (m, 0.88H, *H*-4), 6.00 (m, 2H, 2x N-H), 6.45 (dd, 1H, *H*-2'), 7.12 (d, 1H, *H*-1'), 7.40-8,90 (m, 8H, *Ar*).

**23**-. $^1$H NMR δ 3.55 (s, 0.36H, $OCH_3$), 4.65 (m, 0.12H, *H*-2), 4.85 (m, 0.12H, $J_{1,2a}$ 9 Hz, *H*-6), 5.58 (m, 0.12H, *H*-4).

**4-[2-[(2*RS*,4*S*)-4-benzoyloxy-6-methoxy-3,4,5,6-tetrahydro-2*H*-pyran-2-yl]-1-ene-ethyl]-3-pyridine carboxamide 24, 25** (104 mg, 69%) starting from **9** (120 mg, 0.39 mmol).

**24**-. $^1$H NMR δ 1.80 (m, 2H, *H*-5a, *H*-3a), 2.27 (m, 1H, *H*-3e), 2.35 (m, 1H, *H*-5e), 3.55 (s, 1.65H, OC*H*$_3$), 4.25 (m, 0.55H, $J_{4a,5}$ 2 Hz, *H*-2), 4.55 (dd, 0.55H, $J_{1,2a}$ 10, $J_{1,2e}$ 2 Hz, *H*-6), 5.25 (m, 0.55H, *H*-4). 6.00 (m, 2H, 2 N-H), 6.45 (dd, 1H, *H*-2'), 7.12 (d, 1H, *H*-1'), 7.40-8,90 (m, 8H, *Ar*).

**25**-. $^1$H NMR δ 3.45 (s, 1.35H, OC*H*$_3$), 4.85 (m, 0.45H, $J_{4a,5}$ 10 Hz, *H*-2), 4.90 (d, 0.45H, $J_{1,2a}$ 4 Hz, *H*-6), 5.40 (m, 0.45H, *H*-4).

**4-[2-[(2*S*,4*S*)-4-benzyloxy-6-methoxy-3,4,5,6-tetrahydro-2*H*-pyran-2-yl]-1-ene-ethyl]-3-pyridine carboxamide 26**

Oxidation of **10** (940 mg, 3.73 mmol) and condensation was performed according to the general procedure. (988 mg, 72%): $R_f$ 0.56 (A/E 70:30); mp. 57°C; $[\alpha]_D$ + 73.4 (c 0.56, MeOH); $^1$H NMR ($CD_3OD$) δ 1.46 (dd, 1H, *H*-3a), 1.61 (m, 1H, *H*-5a), 2.23 (m, 2H, *H*-2e, *H*-3e), 3.34 (s, 3H,OC*H*$_3$), 3.94 (d, 1H, C*H*$_2$Ph), 4.42 (dd, 1H, *H*-4), 4.60 (d, 1H, C*H*$_2$Ph), 4.82 (m, 1H, *H*-2'), 4.94 (d, 0.99H, J=2.0 Hz, 1H, *H*-6), 6.20 (m, 2H, N*H*), 6.44 (dd, 1H, J 16.0, J 5.0 Hz, *H*-2'), 7.10 (d, 1H, *H*-1'), 7.20-7.40 (m, 5H, *Ar*), 7.47-8.76 (m, 8H, *Ar*). Anal Calcd for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N,7.60; Found: C, 68.11; H, 6.60; N, 7.55.

**4-[2-[(2R,4S)-4-benzyloxy-6-methoxy-3,4,5,6-tetrahydro-2*H*-pyran-2-yl]-1-ene-ethyl]-3-pyridine carboxamide 27**

$^1$H NMR ($CD_3OD$) δ same signals as above except: 3.52 (s, 0.33H, OC*H*$_3$), 4.80 (dd, 0.11H, $J_{1,2a}$ 9.0 Hz, *H*-6).

**4-[2-[(2R,4S)-4-benzyloxy-6-methoxy-3,4,5,6-tetrahydro-2*H*-pyran-2-yl]-ethyl]-3-pyridine carboxamide 28**

To a solution of the epimeric mixture of **26** and **27** (800 mg, 2.2 mmol) in ethanol (80 mL) was added palladium on charcoal (10%, 250 mg) and the mixture was placed under a $H_2$ atmosphere during 4 hours. Tlc analysis indicated that the reaction was completed. The catalyst was filtered off through a pad of celite and the solvent was evaporated to afford crude **28** (627mg, 78%). An analytical sample had $R_f$ 0.52 (A/E 70:30); $[\alpha]_D^{20}$ +63,3 (c=0.62, $CH_3OH$); $\nu_{max}$/cm$^{-1}$ 3300, 3200, 1680, 1600; $^1$H NMR ($CD_3OD$) δ 1.23 (m, 1H, *H*-2'), 1.47 (m, 1H, *H*-2''), 1.70-2.30 (m, 4H, *H*-5, *H*-3), 2.90 (m, 1H, *H*-1''), 3.07 (m, 1H, *H*-1'), 3.30 (s, 3H, OC*H*$_3$), 3.72 (m, 1H, *H*-2), 3.85 (m, 1H, *H*-4), 4.55 (m, 2H), 4.82 (1H, *H*-6), 7.40-8.73 (m, 3H, *Ar*).

**4-[2-[(2*R*,4*S*)-4-hydroxy-6-methoxy-3,4,5,6-tetrahydro-2*H*-pyran-2-yl]-ethyl]-3-pyridine carboxamide 29**

To a solution of crude **28**, (585 mg, 1.57 mmol) in ethanol (60 mL) was added palladium on charcoal (10%, 500 mg) and the mixture was placed under one atmosphere of $H_2$ during 4 hours. The catalyst was filtered off through a pad of celite and the solvent was evaporated to afford crude **29** (332 mg, 75%), $R_f$ 0.34 (A/E 70:30) which was used in the next step.

**4-[2-[(2*R*,4*R*)-4-benzoyloxy-6-methoxy-3,4,5,6-tetrahydro-2*H*-pyran-2-yl]-ethyl]-3-pyridine carboxamide 30**

To a solution of **29** (280 mg, 0.99 mmol), benzoic acid (250 mg, 2mmol) and triphenylphosphine (520 mg, 2 mmol) in anhydrous tetrahydrofuran (20 mL), stirred under argon, was added dropwise DEAD (0.31 mL, 2 mmol). The mixture was stirred for 2 hours. After evaporation of the solvent the residue was chromatographed on a silica gel column (A/E 80:20) to yield pure **30**-. (326 mg, 85%); $R_f$ 0.54 (A/E 80:20); $[\alpha]_D^{20}$ +78,7 (c 0.72, $CH_3OH$). $^1H$ NMR δ 1.60-2.10 (m, 6H, 2 x *H*-5 , 2 x *H*-3, 2 x *H*-2') 2.92 (m, 1H, *H*-1'), 3.11 (m, 1H, *H*-1''), 3.38 (s, 3H, $OCH_3$), 4.20 (m, 1H, $J_{4a,5}$ 11 Hz, *H*-2), 4.92 (d, 1H, $J_{1,2a}$ 2 Hz, *H*-6), 5.25 (m, 1H, *H*-4), 7.40-8.60 (m, 8H, *Ar*); Anal Calcd for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N,7.29; Found: C, 65.45; H, 6.4; N, 7.28.

**4-[2-[(2*R*,4*R*)-4-benzoyloxy-6-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-yl]-ethyl]-3-pyridine carboxamide 31**

A solution of compound **30** (271 mg, 0.7 mmol) in tetrahydrofuran (20 mL) was added hydrochloric acid (1N, 6 mL) was gently refluxed until tlc indicated complete reaction (2 hours). Solid sodium bicarbonate was then added. After filtration, dichloromethane was added. The organic layer was washed with water and dried over magnesium sulfate. Column chromatography on silica gel (A/E 70:30) gave pure **31** (235 mg, 90%); $R_f$ 0.60 (A/E 70/30); mp 78°C; $[\alpha]_D$ + 12.5 (c 0.51 ; $CHCl_3$); $\nu_{max}/cm^{-1}$ 3500-3100, 1730, 1680, 1600 $^1H$ NMR ($CD_3OD$) δ: 1.60-2.10 (m, 6H, 2 x *H*-5 , 2 x *H*-3 2 x *H*-2'), 3.00 (m, 2H, 2 x *H*-1'), 3.88 (m, 1H, *H*-2), 5.09 (dd, 1H, *H*-6), 5.45 (m, 1H, *H*-4), 7.40-8.52 (m, 8H, *Ar*). Anal Calcd for $C_{20}H_{22}N_2O_5$: C, 64.85; H, 5.99; N,7.56; Found: C, 65.10; H, 6.0; N, 7.55.

**4-[2-[(2*R*,4*R*)-4,6-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-yl]-ethyl]-3-pyridine carboxamide 32**

To a solution of **31** (192 mg, 0.52 mmol) in anhydrous methanol (30 mL) was added a catalytic amount of sodium (40 mg). After 1 hour at room temperature, acidic resin (Dowex 50W $H^+$) was added until pH 7. The resin was filtered off and the solvent evaporated to give **32** which was purified by silica gel column chromatography (A/E 90:10)-. (110 mg, 80%); $R_f$ 0.37 (A/E 70:30); $[\alpha]_D^{20}$ -39,5 (c 0.28, $CHCl_3$); $^1H$ NMR ($CD_3OD$) 1.10 (m, 1H, *H*-2''), 1.35 (m, 1H, *H*-2'), 1.70-2.30 (m, 4H, *H*-5, *H*-3), 2.9 (m, 1H, *H*-1''), 3.00 (m, 1H, *H*-1'), 4.63 (dd, 1H, *H*-6), 7.35-8.55 (m, 3H, *Ar*).

**Methyl (3*R*,5*R*) 7-(3-aminocarbonyl-4-pyridyl)-3,5-dihydroxy heptanoate 33**

To a solution of **32** (100 mg, 0.42mmol) in methanol (25 mL) was added freshly prepared silver oxide (578 mg, 2.52 mmol). The mixture was stirred overnight at reflux in the dark. After filtration of the salts, the solvent was evaporated and the residue was chromatographed on a tlc plate ($CHCl_3$/E 85:15) to give pure **33**-. (50 mg, 50%); $R_f$ 0.42 (CHCl3/MeOH 80:20); $\nu_{max}/cm^{-1}$ 3350, 3200, 1740, 1680, 1600; $^1H$ NMR ($CD_3OD$) δ 1.42 (m, 1H, *H*-6'), 1.55 (m, 1H, *H*-6), 1.68 (m, 2H, *H*-4), 2.43 (m, 2H, *H*-2), 2.83 (m, 2H, *H*-7), 3.56 (m, 3H, $OCH_3$), 3.61 (m, 1H, *H*-3), 3.77 (m, 1H, *H*-5), 7.35-8.55 (m, 3H, *Ar*). m/z: Calcd: 296.1372; Obsd: 296.1322.

## References and Notes


1. Part I: Barth, M.; Bellamy, F. D.; Renaut, P.; Samreth, S.; Schuber, F. *Tetrahedron,* **1990**, *46*, 6731.
2. For a review see: Rosen, T.; Heathcock, C. H. *Tetrahedron,* **1986**, *42*, 4909.
3. Roth, B.D.; Sliskovic, D.R.; Trivedi, B.K. *Ann. Rep. Med. Chem.* **1989**, *24*, 147.
4. Roth, B. D.; Bocan, T. M. A.; Blankley, C. J.; Chucholowski, A. W.; Creger, P. L.; Creswell, M. W.; Newton, E. Ferguson R. S.; O'Brien, P.; Picard, J. A.; Roark, W. H.; Sekerke, C. S.; Slislovic, D. R.; Wilson, M. W. *J. Med. Chem.*, **1991**, *34*, 463 and references cited therein.
5. Nakamura, C. E.; Abeles, R. H. *Biochemistry,* **1985**, *24*, 1364.
6. Beedle, A.S.;, Munday, K.A.; Wilton, D.C. *FEBS Lett.*, **1972**, *28*, 13.
7. Rosen, T.; Taschner, M. J.; Heathcock, C. H. *J. Org. Chem.*, **1984**, *49*, 3994.
8. Villani, F.J.; Wefer, E.A.; Mann, T.A.; Mayer, J.; Peer, L.; Levy, A.S.; *J. Heterocyclic Chem.*, **1972**, *9*, 1203.
9. We have chosen to use carbohydrate numbering in the text. However, regular Chemical Abstract nomenclature rules are observed in the Experimental section.
10. For the use of such aldehydes without epimerisation in mevinic acids chemistry see ref. 7 and Yang, Y.; Falck, J. R. *Tetrahedron Lett.*, **1982**, *23*, 4305.
11. For large scale preparation see: Lafont, D.; Boullanger, P.; Cadas, O.; Descotes, G. *Synthesis*, **1988**, 191. Zottola, M.A.; Alonso, R.; Vite, G.D.; Fraser-Reid, B. *J. Org. Chem.*, **1989**, *54*, 6123 and references cited therein. For a review see: Cerny, M.; Stanek, J. Jr *Adv. Carbohydr. Chem. Biochem.* **1977**, *34*, 23.
12. Baker, R.; Boyes, R.H.O.; Broom, M.P.; O'Mahony, M.J.; Swain, C.J. *J. Chem. Soc. Perkin Trans. I*, **1987**, 1613; see also Kelly, A.G.; Roberts, J.S. *Carbohydr. Res.*, **1979**. *77*, 231.
13. Mitsunobu, O. *Synthesis*, **1981**, 1.
14. Pecka, J.; Stanek Jr, J.; Cerny, M. *Collect. Czech. Chem. Commun* , **1974**, *39*, 1192.
15. For an improved route to these precursor of the lactonic moiety of mevinic acid from levoglucosan see: Boquel, P.; Loustau Cazalet, C.; Chapleur, Y.; Samreth, S.; Bellamy, F. *Tetrahedron Lett.* **1992**, *33*, 1997. See also David, C.; Gesson, J.P.; Jacquesy, J.C. *Tetrahedron. Lett.*, **1989**, *30*, 6015. Tolstikov, G.A.; Miftakhov, M.S.; Valeev, F.A.; Ibragimova, I.R.; Gareev, A.A. *Zh. Org. Khim.*, **1991**, *27*, 415. *Chem. Abstracts*. **1991**, *115*, 182934f.
16. This epimerization may occur in the reaction medium (NaH, DMSO) but can also be catalyzed intra or inter molecularely by the nicotinamide moiety.
17. During this work was in progress, some molecules combining the dihydroxyacid moiety and different substituted pyridine residues have been reported by Hoechst; Jendralla, H.; Granzer, E.; Kerekjarto, B. v.; Krause, R.; Baader, U. Schacht E.; Bartmann, W.; Beck, G.; Bergmann,, A. *J. Med. Chem.*, **1991**, *34*, 2962 and previous references of this series. It is interesting to note that in these inhibitors of HMGR the pyridine group was flanked by a number of large lipophilic groups which can bind strongly in the lipophilic pocket of the enzyme. It seems that in our case the rather hydrophilic pyridine group could not accomodate the same binding in this site.
18. For synthetic and biological studies of irreducible analogues of HMG-CoA see: Turakhia, R. H.; Fischer, G. C.; Morrow, C. J.; Maschhoff, B. L.; Toubbeh, M. I.; Zbur-Wilson, J. L. *J. Org. Chem.*, **1986**, *51*, 1955. Fischer, G. C.; Turakhia, R. H.; Morrow, C. J. *J. Org. Chem.*, **1985**, *50*, 2011. Gordon, E. M.; Pluscec, J.; Ciosek, C. P.; Jr *Bioorganic Med. Chem. Lett.* **1991**, *1*, 61.
19. Bobbit, J.M.; Scala, D.A. *J Org. Chem.* **1960**, *25*, 560.