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# SYNTHESIS OF SUBSTRATE-BASED INHIBITORS OF HMG CoA REDUCTASE (II).

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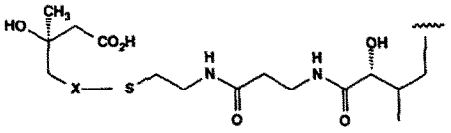
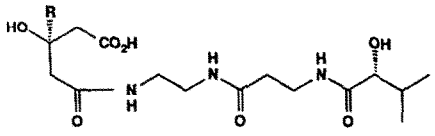
**Abstract:** A synthesis is reported for the preparation of a chemically stable, hydroxyethylamine analog (**5a**) of hemithioacetal (**2**), an intermediate in the HMG CoA reductase enzymatic reaction. Syntheses are also described for two sub-structure analogs of substrate HMG CoA (**1**) in which the scissile thioester bond normally acted upon by the enzyme is replaced by an amide linkage (**3,4**).

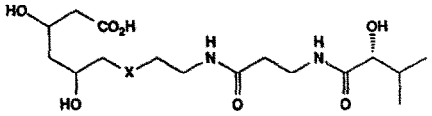
Recent approaches to the problem of designing novel HMG CoA reductase (HMGR) inhibitors have emphasized the relationship of new enitities to known natural product inhibitors [1]. Many potent inhibitors ( $K_i = 10^{-9}$ M range) have been identified, and these substances have almost exclusively [2] conformed to a 3,5 dihydroxyheptanoic acid skeleton, in which a "hydrophobic anchor" [3] has been appended to a dihydroxy HMG surrogate. As part of our efforts in this area, we have sought to design inhibitors of HMGR which are based on the structure of the actual enzyme substrate or intermediates, rather than on the mevinic acids [4]. This approach to



**1** X= C=O
**2** CHOH



**3** R= -H
**4** R= $-CH_3$

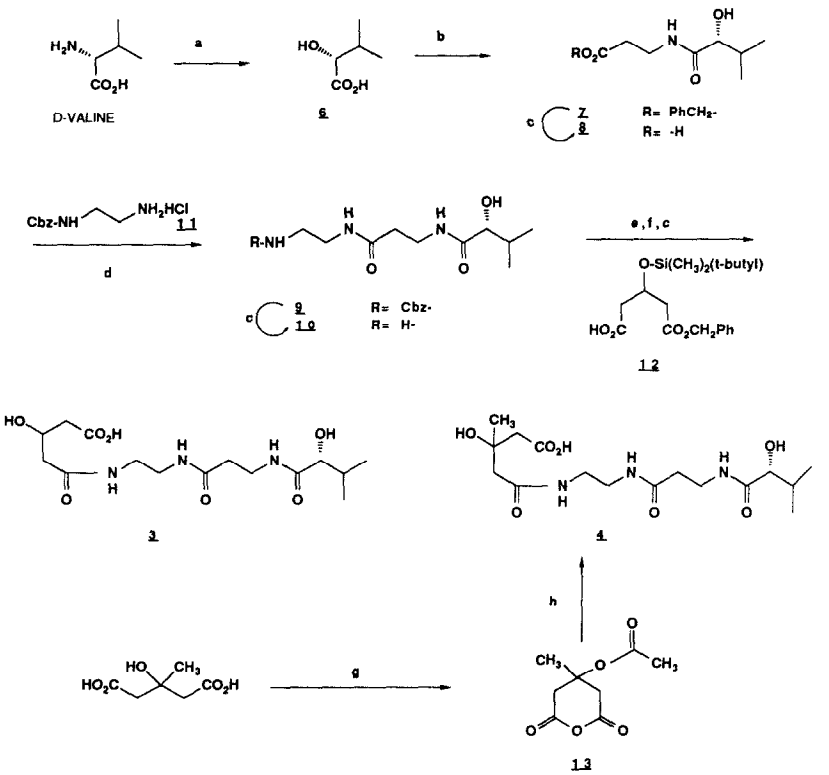


**5a** X= NH
**5b** X= S

HMGR inhibition has received relatively little attention [5,6]. In the present letter we describe the synthesis of two chemically stabilized substrate mimics (**3,4**), and another chemically stable molecule (**5a**) designed to mimic the hemithioacetal intermediate (**2**) of the enzyme reaction . In a previous report we outlined the design and synthesis of several potential substrate/intermediate modelled, inhibitor targets based on **1** and **2** [7] including hydroxy sulfide **5b**. In the design of

inhibitor **5a**, amine nitrogen is introduced in order to engage a new hydrogen bond interaction, which should be an unavailable option with **5b** due to the poorer hydrogen bond acceptor ability of divalent sulfur. Other strategic considerations were discussed previously[7].

**Scheme 1**

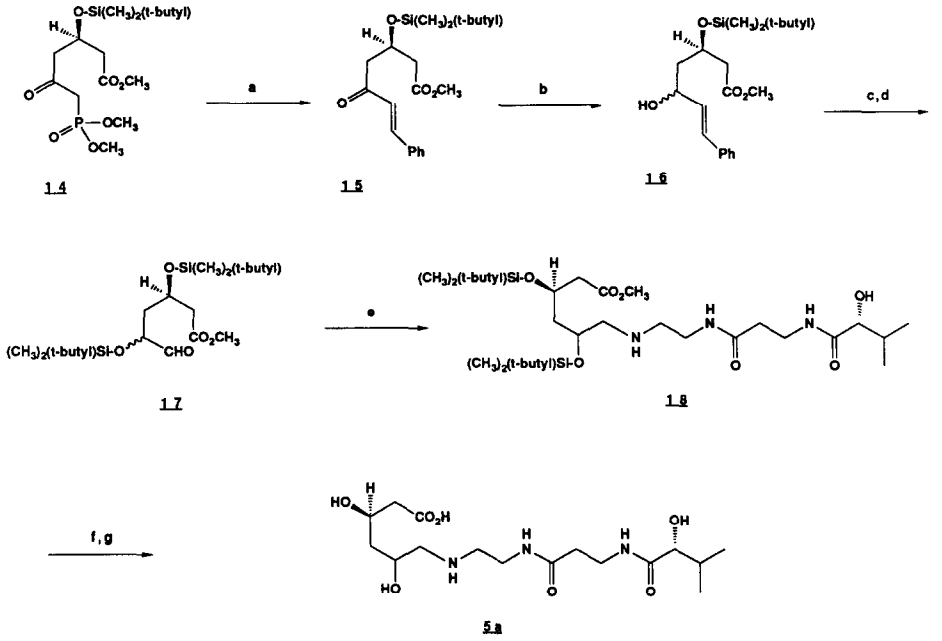



a)HCl, $NaNO_2$, HOAc (98%) ; b)β- Ala-Obz hydrochloride, DCC, HBT, diisopropylethylamine,THF (47%); c) $H_2$,10% Pd/C, 95% EtOH (100 %); d) Cbz-NH-$CH_2$-$CH_2$-$NH_2$ HCl, diisopropylethylamine, DCC, HBT, THF (70%); e) compound **12** DCC, HBT, THF (50%); f) HF, $CH_3CN$ (40%); g) acetic anhydride, benzene, reflux, 1h (61%); h) i) compound **10**, THF, reflux 12h , ii) 1N NaOH, $CH_3OH$,(15-20%)

The synthesis of substrate mimics **3** and **4** , which differ by the introduction of a C-3 methyl substitutent is summarized in **Scheme 1.** Preparation of substance **8** from D-valine and β-alanine benzyl ester proceeds as previously described[7]. Coupling of **8** with mono-Cbz-ethylenediamine (DCC/ HBT/ THF), followed by hydrogenolysis gave in pure chiral form, amine **10** as a key intermediate (mp 134-135 °C; $^{13}C$ NMR ($CDCl_3$) δ 16.5, 19.5, 32.9, 36.4, 36.5, 41.9, 42.9, 76.9, 174.0, 176.8 ppm; $[\alpha]^{25}_D$= +34.0° (c= 0.615, $CH_3OH$); CI-MS : m/e 232 (M+H)). This material is a close analog of the ubiquitious mercaptan, pantetheine, a major component of Co-enzyme A. Amide bond formation between half acid **12** [7] and **10**, followed by

deprotection of silyl and ester groups afforded (des-methyl) substrate analog **3**. In order to prepare **4**, 3-hydroxy-3-methylglutaric acid was simultaneously dehydrated and acylated with acetic anhydride to give anhydride **13** [8]. Ring opening of **13** with amine **10** in hot THF, followed by hydrolysis of the tertiary ester, produced target **4** as the sodium salt.

**Scheme 2**




**14** **15** **16** **17** **18** **5a**

a) benzaldehyde, LiCl, DBU, $CH_3CN$ (71%), b) $Li(t\text{-}OBu)_3AlH$, THF(92%), c) $t\text{-}Bu(CH_3)_2Si\text{-}Cl$, imidazole, $CH_2Cl_2$ (62%), d) $O_3$, $CH_3OH$, $Me_2S$, -78°C (100%); e) compound **8**, isopropanol, THF, $NaBH_3CN$ (25%), f) 1 N NaOH, $CH_3OH$, g) HF, $CH_3CN$.

Aminoalcohol **5a** is another example of a "hyperextended" design element, being applied to a substrate which undergoes cleavage (separation) in the course of enzymatic transformation [9]. Our synthesis of **5a** also required amine **10**, and additionally demanded access to a protected α-hydroxy aldehyde such as **17**. It was anticipated that reductive alkylation of **10** and **17** would lead to the protected target skeleton. In practice this proved to be a viable route to **5a**. Substance **17** was synthesized by the route shown in **Scheme 2.** Ketophosphonate **14** [10] reacted with benzaldehyde to give **15** which underwent ketone reduction, followed by ozonolysis, and silylation. Attempts were not made to control the hydroxyl group stereochemistry resulting from reduction of **15**, since we wished to obtain both diastereomers of **5a**. Reductive amination of **17** with **10** produced **18** as a mixture of diastereomers. It was found that if ester saponification preceeded desilylation, a cleaner product was obtained following HP-20 purification[11] (**5a**) [12].

Testing of **3**, **4**, or **5a** against a rat hepatic microsomal HMG CoA reductase for enzyme inhibition[13], showed that these materials lacked significant ($I_{50}$ > 1.0 mM) enzyme inhibitory activity.

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