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α,α-DIFLUOROKETONE INHIBITORS OF HMG CoA REDUCTASE

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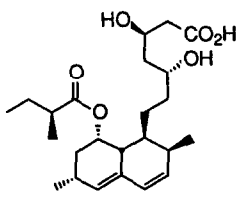
Abstract: The rationale for a new class of HMG CoA reductase inhibitors, represented by α,α-difluoroketones **3** and **4**, is described. The syntheses of **3**, **4**, and their nonfluorinated analogue **5** are presented.

The importance of mevinolin (**1**; acid form), a naturally occurring HMG CoA reductase inhibitor, as an antihypercholesterolemic agent[1] has inspired an extensive search for simplified analogues lacking the structurally complex hexalin ring system of **1**[2], resulting in the discovery of potent inhibitors such as **2**[2a]. In contrast, more limited structure-activity studies have indicated that the 3R,5R-dihydroxyheptanoic acid portion of **1** is much less tolerant of variation than the hexalin system[3]. The dihydroxy acid portion of **1** and **2** most likely interacts with the hydroxymethylglutaryl binding domain of the reductase enzyme[4], possibly mimicking the enzyme-generated hemithioacetal of mevaldic acid and coenzyme A[5]. A similar binding interaction could be provided by α-fluoroketones, which are potent inhibitors of several classes of enzymes by virtue of their propensity to form stable hydrates and adducts with enzyme active-site nucleophiles[6]. It has been demonstrated that an analogue of **2** and CoASH can bind to yeast HMG CoA reductase simultaneously[4]. One might therefore expect α,α-difluoroketone **3** or **4** to form a hemithioketal with CoASH in the enzyme active site[7]. Alternatively, **3** or **4** could bind as a ketone hydrate. We describe herein the synthesis in racemic form of α,α-difluoroketones **3** and **4**, and their nonfluorinated analogue, **5**.



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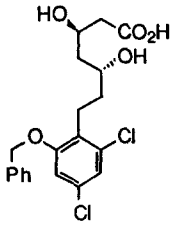

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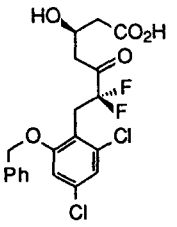

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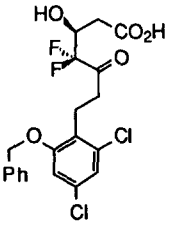

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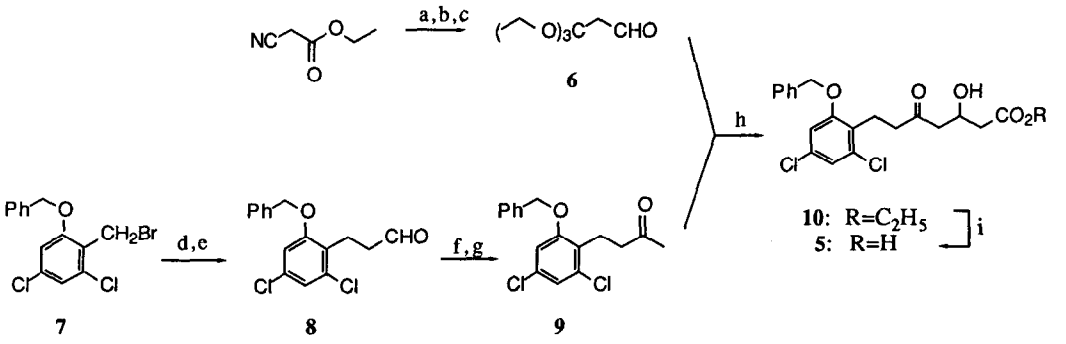
The synthesis of the nonfluorinated compound **5**, shown in Scheme I[8], was achieved using the triethyl orthoester of malonaldehyde (**6**). Reagent **6**, readily prepared from ethyl cyanoacetate by orthoester formation[9] followed by reduction with diisobutylaluminum hydride (DIBAL), serves as a convenient synthon for 3-hydroxyesters via its reaction with lithium reagents[10,11]. Thus, alkylation of bromide **7**[12] with lithio t-butyl

acetate and subsequent DIBAL reduction provided aldehyde **8**, which was converted in two steps to ketone **9**. Aldol condensation of **6** with the enolate of **9** followed by acid workup led directly to 3-hydroxy-5-ketoester **10** in good yield[13]. Saponification provided the acid **5**.

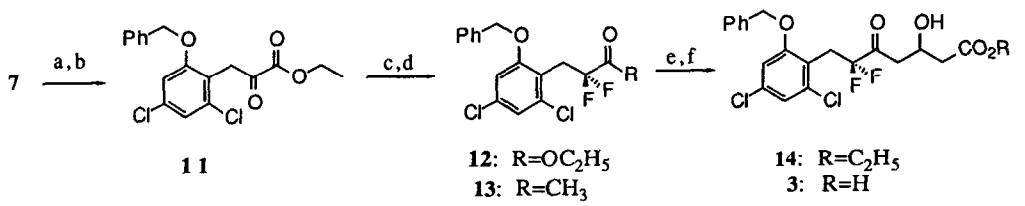
Scheme I



a. HCl, ethanol; 95%. b. ethanol, 10 days; 79%. c. DIBAL, toluene, -78°; 80%. d. t-BuOAc, LDA, THF, -78°; 88%. e. DIBAL, toluene, -78°; 83%. f. CH_3Li, THF, 0°; H_3O^+; 98%. g. Jones oxidation; 79%. h. **9**, LDA, THF; **6**, -78°; H_3O^+; 80%. i. NaOH, H_2O, CH_3OH, THF; H_3O^+; 85%.

A strategy similar to that of Scheme I was used in the synthesis of **3** (Scheme II)[8]. Alkylation of bromide **7** with 2-carboethoxy dithiane[14] and hydrolysis of the dithiane yielded 2-ketoester **11**, which was treated with diethylaminosulfur trifluoride (DAST)[15] to provide a moderate yield of difluoroester **12**. Difluoroester **12** led cleanly to ketone **13** upon treatment with methyllithium. Aldol condensation of **13** with **6**, as before, provided the 3-hydroxy-5-keto-6,6-difluoroester **14**, although the yield was significantly lower than in the case of **10**[16]. Saponification of **14** (1.1 equiv. NaOH, 1:1:1 THF-methanol-water) to give **3** was remarkably facile, being complete within seconds. By comparison, it is suggestive that the corresponding reaction of **10** to give **5** required over 2 hours for completion under the same conditions (vide infra).

Scheme II

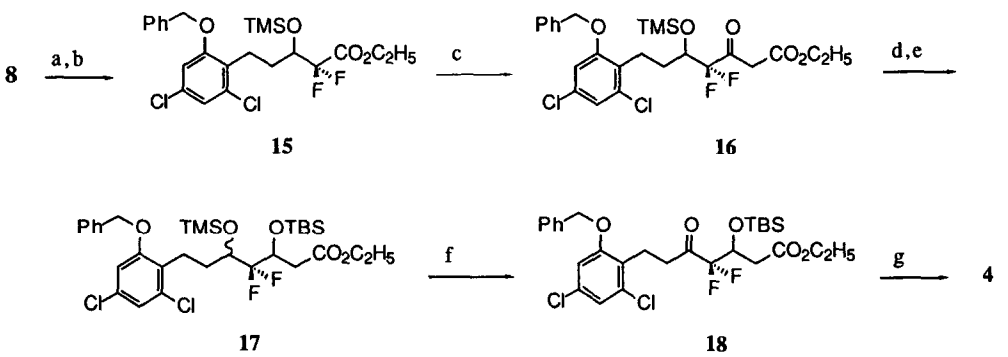


a. ethyl-1,3-dithiane-2-carboxylate, KH, DMF, C_6H_6; 92%. b. NBS, H_2O, acetone; 95%. c. DAST (neat), 60°; 33%. d. CH_3Li, THF, -78°; H_3O^+; 99%. e. $LiN(TMS)_2$, THF; **6**, -78°;H_3O^+; 20%. f. NaOH, H_2O, CH_3OH, THF; H_3O^+; 99%.

Synthesis of the 4,4-difluoro compound **4** was effected by a somewhat different route, shown in Scheme III[8]. Reformatsky reaction of aldehyde **8** with ethyl bromodifluoroacetate[17] and trimethylsilyl protection yielded the difluoroester **15**, which underwent smooth condensation with lithio ethyl acetate to afford 3-ketoester **16**. Borohydride reduction of **16** and protection with the t-butyldimethylsilyl group led to the protected 1,3-diols **17**. Selective oxidation of the trimethylsilyl ether of **17** with Jones reagent provided 3-t-butylsiloxy-4,4-difluoro-5-ketoester **18**. Treatment of **18** with 1.2 equivalents of tetrabutylammonium fluoride in THF led to a rapid and quantitative reaction to produce the *free acid* **4**. De-esterification presumably resulted from fluoride ion-induced attack by water which is present in the commercial tetrabutylammonium fluoride employed. In support of this suggestion, basic aqueous hydrolysis of **18**, as with **14**, was exceptionally rapid. It is likely that the enhanced reactivity observed in hydrolysis of esters **14** and **18**, as compared with **10**, involves neighboring group participation: attack of hydroxide on the electrophilic difluoroketone group, subsequent cyclization, and loss of ethoxide would form a transient pseudoacid (a δ-hydroxy δ-lactone), which would open to the acyclic carboxylate.

Compounds **3** - **5** proved to be effective inhibitors of HMG CoA reductase in vitro[18]. These results will be presented elsewhere.

Scheme III



a. $BrF_2CCO_2C_2H_5$, Zn, THF; 70%. b. TMSOTf, 2,6-lutidine, CH_2Cl_2; 92%. c. $LiCH_2CO_2C_2H_5$, THF, -78°; 77%.
d. $NaBH_4$; 100%. e. TBSOTf, 2,6-lutidine, CH_2Cl_2; 83%. f. Jones oxidation; 75%. g. n-Bu_4NF, THF; 98%.

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[8]New compounds were characterized by ^{1}HNMR, IR, and mass spectral analyses and combustion analysis.

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[10]A 1.5M solution of DIBAL in toluene (40ml) was added over 10 min to a -78° solution of 11.7 g cyanoacetic acid triethyl orthoester (prepared according to ref. 9) in 100 ml toluene with stirring under Ar. After 90 min, 40 ml cold (dry ice-chilled) ethanol was added rapidly. The solution was stirred with warming to 0° over 40 min, then was treated successively with 2.3 ml water, 2.3 ml 15% NaOH, and 6.9 ml water. After 20 min, filtration, drying over $MgSO_4$, and concentration at 45°/15 torr yielded a residue which was distilled (55°/0.5 torr) to provide 7.22 g **6** as a colorless liquid (76%). d. 0.936. ^{1}HNMR($CDCl_3$): δ 9.72(1H,t), 3.55(6H,q), 2.76(2H,d), 1.20(9H,t). MS(NF_3 neg): m/z 189$(M-H)^-$. Anal. calc. for $C_9H_{18}O_4$: C, 56.82; H, 9.54. Found: C, 56.66; H, 9.59. Although acid- and base-labile, aldehyde **6** can be stored indefinitely at -20° without appreciable decomposition.

[11]Orthoester-based reagents of a similar nature are described in ref. 7 and: (a) B. Rousseau, J.-P. Beaucourt, and L. Pichat, Tetrahedron Lett., **1982**, 2183. (b) F. Bohlmann and W. Sucrow, Chem. Ber., **1964**, *97*, 1839.

[12]Bromide **7** was prepared from 2,4-dichloro-6-benzyloxybenzaldehyde (ref. 2a) by the following sequence: (a) $NaBH_4$, ethanol; 98%. (b) $P(Ph)_3$, CBr_4, THF; 81%.

[13]To 0.44 mmol LDA in 1 ml THF at -78° was added 129 mg **9** in 1 ml THF with stirring. After 10 min 97 µl **6** in 0.5 ml THF was added; 1 hr later the cold reaction mixture was diluted with 10% HCl. Extractive workup and flash chromatography (2:1 ether:hexanes) provided 140 mg **10** (80%).

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[16]Bearing on this result, the enolate of **13** is readily generated with $LiN(TMS)_2$ and trapped with TMSCl to yield the expected difluoro enol silyl ether. The surprisingly low yield of **14** might reflect diminished nucleophilicity of the enolate of **13** when compared to that of **9**. The other principal reaction products consisted of a diastereomeric mixture of δ-lactols from condensation of **14** with a second molecule of **6**, and the aldol dimer of **13**.

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[18]W. Karsten and T. Meek, unpublished results.

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