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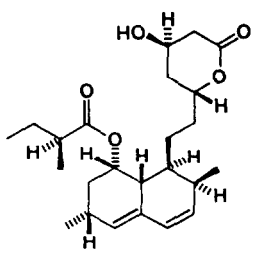
Asymmetric Synthesis via Acetal Templates. 15.[1] The Preparation of Enantiomerically Pure Mevinolin Analogs

William S Johnson,[a]* Andrew B Kelson[a] and John D Elliott[b]

[a]*Department of Chemistry, Stanford University, Stanford, California 94305*
[b]*Department of Medicinal Chemistry, Smith Kline and French Laboratories, P O Box 1539, King of Prussia, Pennsylvania 19406-0939*

Abstract *An efficient asymmetric synthesis of the hydroxylactone moiety of mevinolin* ***1*** *is described The key step is the $TiCl_4$-catalyzed coupling reaction of acetals* ***3a*** *and* ***3b*** *derived from (R)-1,3-butanediol with 1,3-bis(trimethylsilyloxy)-1-methoxybuta-1,3-diene* ***4*** *to give the δ-alkoxy-β-keto ester* ***5***

The natural product mevinolin **1** is an extremely potent reversible inhibitor of (3*S*)-3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase, the rate-limiting enzyme in the cholesterol biosynthetic pathway [2] The beneficial effect displayed by mevinolin **1** in reducing serum cholesterol levels and its consequent potential for the mitigation of atherosclerosis, has elicited much synthetic interest both in the natural product itself[3] and in structurally simplified congeners [4a] Some of the most potent inhibitors to have emerged from these studies have structures exemplified by compound **2**, in which the biphenyl nucleus is variously substituted An invariant feature of these molecules, shared by mevinolin **1** in its active form, is a 5-substituted-3,5-dihydroxypentanoic acid moiety with the absolute configuration shown in **2**



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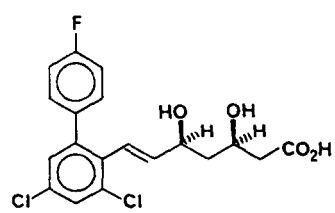
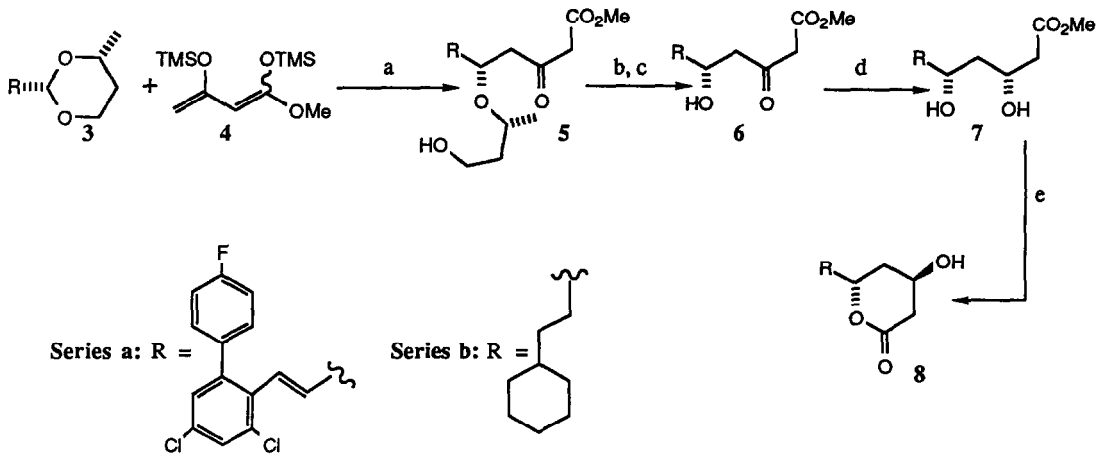


2

Despite the prodigious synthetic efforts in this area there remains the need for new efficient routes to such compounds in enantiomerically pure form[3,4b] and it was towards this objective that we directed our attention

In planning a synthetic strategy to afford molecules of type **7** we were mindful of the excellent method which already exists for the diastereoselective reduction of an aldol, via a dialkylboron chelate, to the corresponding *syn*-1,3-diol (*e g* , **6** → **7**)[5] Thus the key objective became the development of an asymmetric synthesis of aldols of type **6** which in turn would yield hydroxy lactones **8** Compound **8a** is representative of a series of potent synthetic analogs of mevinolin, and **8b** is a model for the elaboration of the lactone portion of mevinolin itself



Reagents **Series a** [a]$TiCl_4$, 2,6-di-*t*-butylpyridine, CH_2Cl_2, -78 °C, [b]Dess-Martin periodinane, CH_2Cl_2, 25 °C, [c]dibenzylammonium trifluoroacetate, 25 °C, [d]$Et_2BOMe/NaBH_4$, -78 °C, [e]as in ref 4a **Series b** Same as **series a** except [a]base omitted, [e]HF/pyridine, CH_3CN, 4 h, 25 °C

The acetal **3a**[6] was prepared in 90% yield from the corresponding aldehyde[4] and the readily available (3*R*)-butane-1,3-diol[7] (benzene/reflux/cat *p*-TsOH/azeotropic water removal) The crucial coupling reac-tion between **3a** and 1,3-bis(trimethylsilyloxy)-1-methoxybuta-1,3-diene **4**[8] gave **5a**[6a] (71%) as a single diastereoisomer[9a,10] The configuration at C-5 of **5a** was expected to be *S* based upon previous experience with acetals of this type[1,5d]

The chiral auxiliary of **5a** was removed by a two-step sequence involving oxidation with Dess-Martin periodinane followed by selective β–elimination promoted by dibenzylammonium trifluoroacetate to give the desired aldol **6a** [6a,9b] The diastereoselective reduction was carried out on this crude material, as previously described,[5c] to give the diol **7a** (54% from **5a**) [6a,10] Saponification and lactonization gave *syn* lactone **8a** (82%),[10] m p 113-115° (reported,[4] 108-109 5°) The ^{1}H NMR, IR and mass spectra of this material were identical to the corresponding characteristics reported for substance **8a** [4] The optical rotation $[\alpha]_D^{25}$ +40° (c = 0 8, $CHCl_3$), was in excellent agreement with the reported value $[\alpha]_D^{25}$ +38 8° ($CHCl_3$),[4] thus confirming the expected stereochemical course of the coupling reaction to give **5a**

The preparation of lactone **8b** was performed along similar lines Thus the coupling of acetal **3b**[6] with nucleophile **4** proceeded to give **5b** in 81% yield [6a,9a] Removal of the chiral auxiliary afforded the aldol **6b**[6a,9b] which was reduced[5c] to give **7b** (51% from **5b**) [6a] Lactonization was achieved by treatment with HF/pyridine[12] to give 8b (78%),[6a] m p 72-74° (reported,[13] 72-73°) The optical rotation of **8b** $[\alpha]_D^{25}$ +33 5° (c = 0 7, $CHCl_3$) was in good agreement with that of an authentic sample[13] $[\alpha]_D^{25}$ +29° (c = 0 28, $CHCl_3$)

In conclusion, an efficient synthetic route to the lactones of 5-substituted 3,5-dihydroxypentanoic acids has been developed utilizing the readily accessible (3*R*)-butane-1,3-diol to furnish products of the correct antipodal form for inhibition of HMGCoA reductase

Acknowledgements We thank the National Institutes of Health and the National Science Foundation for support of this research We are also grateful to Professor C H Heathcock for providing us with an authentic sample[13] of the lactone **8b**

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6 (a) ^{1}H NMR, IR and mass spectra were entirely consistent with the structural assignment (b) A satisfactory combustion analysis was obtained for an appropriately purified sample of this compound

7 Available, inexpensively, by the lithium aluminum hydride reduction of commercial (3*R*)-polyhydroxybutanoate See Seebach, D , Züger, M *Helv Chim Acta* , **1982**, *65*, 495

8 Prepared according to the method of Brownbridge, P , Chan, T H , Brook, M. A , Kang, G J *Can J Chem* , **1983**, *61*, 688 The crude material was approximately 95% pure by ^{1}H NMR and was not purified before use

9 (a) A solution of acetal **3a** (0 273 g, 0 74 mmol), nucleophile **4** (1 17 g, 4 5 mmol) and 2,6-di-*t*-butylpyridine (0 168 ml, 0 75 mmol) in dry CH_2Cl_2 (15 ml) was cooled to -78 °C under argon. To this stirred solution was added, rapidly dropwise, $TiCl_4$ (0 33 ml, 3 0 mmol) After stirring for 5 min the reaction was quenched by the addition of methanol (2 ml) Extractive work-up and column chromatography gave **5a** (0 256 g, 71%) ^{1}H NMR ($CDCl_3$) showed **5a** to be an approximately 95 5 mixture of keto/enol tautomers The procedure used for acetal **3b** did not involve the use of 2,6-di-*t*-butylpyridine but was otherwise identical

(b) A mixture of **5a** (0 128 g, 0 27 mmol) and Dess-Martin periodinane (0 128 g, 0 3 mmol) in dry CH_2Cl_2 (3 ml) was stirred at 25 °C for 1 h, then $NaHCO_3$ (0 5 g, 5 95 mmol) and a solution of $Na_2S_2O_3$ (0 5 g, 3 16 mmol) in water were added and stirring was continued for 30 min The crude aldehyde (0 125 g), obtained by extractive work-up, was dissolved in benzene (3 ml) and cooled to 6 °C Dibenzylammonium trifluoroacetate (0 091 g, 0 29 mmol) was added and, after stirring at 6 °C for 90 min, the product was partitioned between water and EtOAc The aqueous layer was further extracted with EtOAc, then the combined organic layers were washed with 1 N HCl, water, saturated $NaHCO_3$ and brine Evaporation of the dried solution gave crude **6a** (0 117 g) which was subjected to the diastereoselective reduction (ref 5c) without further purification An identical procedure was followed for the conversion of **5b** to **6b**

10 The product was purified by low-pressure column chromatography on silica gel

11 Dess, D B , Martin, J C *J Org Chem* , **1983**, *48*, 4155

12 Available from the Aldrich Chemical Company

13 The authentic sample was a specimen from the stereorational synthesis of Rosen, T., Taschner, M J , Heathcock, C H *J Org Chem* , **1984**, *49*, 3994

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