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Novel synthetic strategy for HMG-CoA reductase inhibitors

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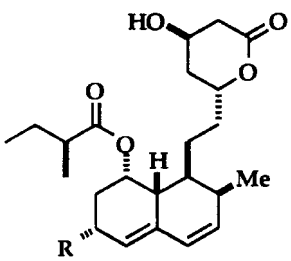
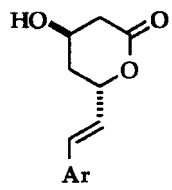
Abstract
Strategies for the synthesis of HMG-CoA reductase inhibitors are discussed with the emphasis on (1) asymmetric reduction of β,δ-diketo esters of a chiral auxiliary alcohol, (2) synthesis and olefination of optically pure 3,5-*syn*-isopropylidenedioxy-6-oxohexanoate ester, and (3) hydrometalation of 3,5-*syn*-isopropylidenedioxy-7-heptynoate followed by cross-coupling reaction with aryl halide.

INTRODUCTION

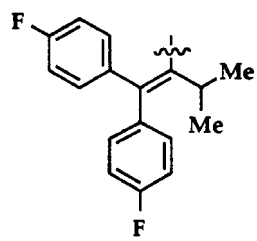
Since compactin (**1a**) and mevinolin (**1b**) were shown to be highly potent inhibitors of 3-hydroxy-3-methylglutaryl Coenzyme A (HMG Co-A) reductase,[1] a number of synthetic analogs have been designed and synthesized to improve activity and suppress side effect. We have been studying general synthetic methods which allow us to prepare a variety of the target molecules, all of which consist of aromatic part and a *trans*-β-hydroxy-δ-lactone moiety, both connected by *trans*-1,2-ethylidene bridge.[2] Our retrosynthetic analysis led to novel strategies based on (1) stereoselective (one-pot) reduction of β,δ-diketo esters of a chiral auxiliary alcohol, (2) synthesis and olefination of optically pure 3,5-*syn*-isopropylidenedioxy-6-oxohexanoate ester, and (3) hydrometalation of 3,5-*syn*-isopropylidenedioxy-7-heptynoate followed by cross-coupling reaction.



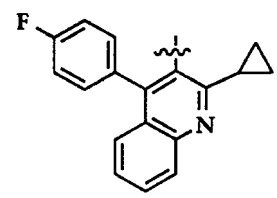
1a: R = H, compactin
1b: R = Me, mevinolin



2: synthetic analogs
': mirror image
2a: Ar = Ph
2b: Ar = **i**
2c: Ar = **ii** (NK-104)



i

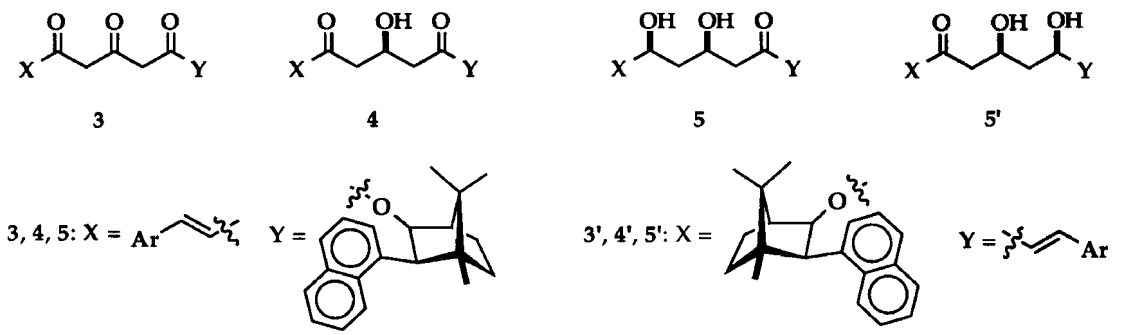


ii

ASYMMETRIC REDUCTION OF β,δ-DIKETO ESTERS

The requisite substrates 7-aryl-substituted 3,5-diketo esters (**3** or **3'**, Y = *t*-Bu) were prepared by the reaction of *N*-methoxy amides and the dianion of *t*-butyl acetoacetate.[3] Since discrimination between the *re* and *si* face of the two carbonyls in β,δ-diketo esters by a chiral borane chelating reagent turned out to be extremely difficult, we considered it should be essential to produce a dissymmetric environment around the diketo ester by reducing the

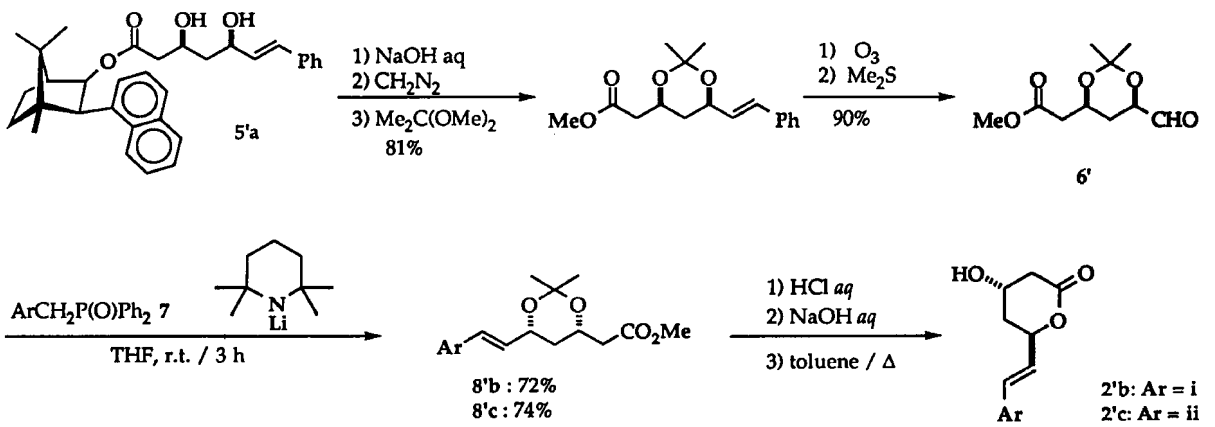
conformational freedom of the molecule. To fulfil these criteria, we have chosen β,δ-diketo esters derived from the Taber's chiral alcohol.[4] Herein *gem*-dimethyl groups at C(7) of bicyclo[2.2.1]heptane control the conformation of the diketo esters, and the naphthalene ring acts as a steric shield of one face of the carbonyls. Thus, the substrate **3'a** was prepred by the condensation discussed above and was reduced in methanol-tetrahydrofuran (THF) with sodium borohydride in the presence of diethylmethoxyborane to give *syn*-diol **5'a** highly selectively, which after hydrolysis and lactonization afforded lactone **2'a**. Percentage of enantiomeric excess (ee) was 56% ee, but the absolute configurations were opposite to the desired. When 9-methoxy-9-BBN or dimethyl(ethoxy)borane was used in lieu of diethylmethoxyborane, no or opposite asymmetric induction was observed, respectively.[4]



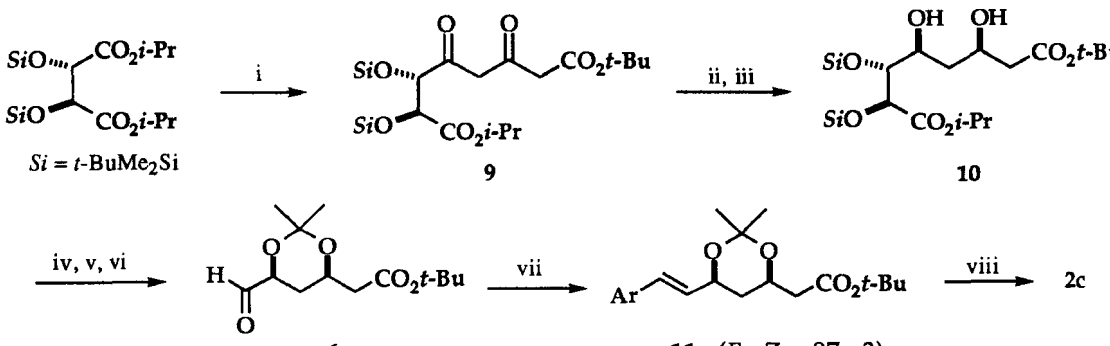
In order to improve the selectivity, we studied the reduction of the diketo esters to give hydroxy keto esters **4'**. For the reducting agent diisobutylaluminium hydride was found to give the best results, and thus hydroxy keto ester **4'a** with isomer ratio of >95 : 5 was obtained at -78 °C in THF. Subsequent *syn*-reduction with Et_2BOMe-$NaBH_4$ gave **5'a** which was hydrolyzed and lactonized to give rise to a *trans*-lactone **2'a** of 95% ee. The sequence was repeated starting with **3a** to give **2a** having correct absolute configuration and was applied to the synthesis of **2c** in optically active form.

OLEFINATION STRATEGY

The Wittig-type olefination of 6-oxo-3,5-*syn*-dihydroxyhexanoate (**6** or its enantiomer **6'**)[5] should be an alternative route to provide various artificial analogs. To test the feasibility of this approach, we first hydrolyzed **5'a** to give a carboxylic acid, whose active hydrogens were protected by esterification and acetalization. Ozonolysis of the remaining C=C bond gave **6'**, which was then converted into **8'b** or **8'c** by the reaction of the phosphine oxide reagent **7b** or **7c** and butyllithium or lithium amide base. Hydrolysis followed by lactonization gave rise to **2'b** or **2'c** respectively. Olefination with phosphorus ylide or phosphonate anion was less stereoselective or less efficient.



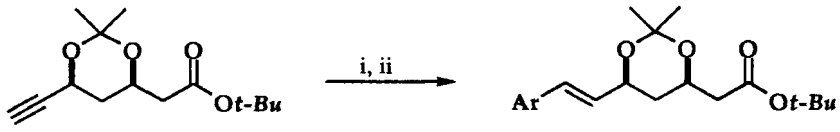
Now that this synthetic route was shown to be feasible, the key intermediate **6** having correct absolute configuration was prepared from tartaric acid. The bis(*t*-butyldimethyl)silyl ether of diisopropyl D(-)-tartrate was allowed to react with the dianion of *t*-butyl acetoacetate to give **9** in good yields. Even if excess amount of the dianion was used, only **9** was produced. Reduction of **9** with diisobutylaluminium hydride afforded a hydroxy keto ester with an isomeric purity of 99 : 1. *Syn*-reduction as above produced **10**, whose 1,3-diol moiety was protected as an acetonide. Desilylation followed by glycol cleavage gave the desired aldehyde **6**. Olefination of **6** with **7c** affored **11c**, a seco derivative of **2c**.[6]



i: $MeCOCH_2COOt$-Bu, NaH, *n*-BuLi, -78 °C, 20 h, 74%; ii: $(i\text{-Bu})_2AlH$, THF, hexane, -78°C, 4 h, 60%
iii: Et_2BOMe, $NaBH_4$, THF, MeOH, -78 °C~r.t., 12 h, 76%; iv: $(CH_3)_2C(OCH_3)_2$, *p*-TsOH, r.t., 2 h, 98%
v: $(n\text{-Bu})_4NF$, THF, r.t., 3 h, 99%; vi: $NaIO_4$, ether, H_2O, r.t., 2 h, 85%
vii: Li[ArCHP(O)Ph_2], THF, r.t., 3 h, 67%; viii: CF_3COOH

HYDROMETALATION–CROSS-COUPLING STRATEGY

We have shown that organosilicon compounds undergo palladium-catalyzed cross-coupling reaction when activated with fluoride ion.[7] This reaction was applied to a terminal acetylene **12**, which was prepared in an optically active form by chemical synthetic elaboration from tartrate,[8] resolution,[9] or asymmetric reduction of an acetylenic ketone with baker's yeast.[10] Hydrosilylation of **12** with $HSiMe_2Cl$ and the Pt catalyst having divinylsiloxane ligand proceeded smoothly to give an alkenylsilane with regioselectivity of 96 : 4. This intermediate was, without further purification, allowed to couple with Ar-I using $(allylPdCl)_2$ catalyst and TBAF to give the desired coupled product **11**.[8] Use of $HSiMe(OEt)_2$ or H_2PtCl_6 catalyst resulted in inferior regioselectivity of hydrosilylation, although cross-coupling successfully took place in these cases also.



12

11a: Ar = Ph, 81% (96 : 4)
11c: Ar = ii, 83% (96 : 4)

i: Me_2ClSiH (1.2 eq), $t\text{-}Bu_3PPt(CH_2{=}CHSiMe_2)_2O$ (0.5 mol%), r.t., 1 h
ii: Ar-I (1.1 eq), $n\text{-}Bu_4NF$ (2.0 eq), $(allylPdCl)_2$ (2.5 mol%), THF, 60 °C, 0.5 h

The same transformation was achieved using 9-BBN or disiamylborane as the hydrometalating reagent.[9]

Acknowledgment: The author is totally indebted to his coworkers whose names are listed in the literatures.

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