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Enantioselective synthesis of the lactone moiety of HMG-CoA reductase inhibitor: stereoselective synthesis of (+)-(4*R*,6*R*)-4-hydroxy-6-(2-phenylethyl)-tetrahydro-2*H*-pyran-2-one

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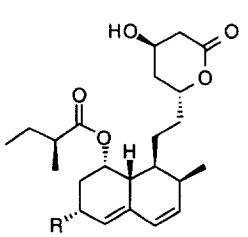
Abstract: The enantioselective synthesis of the lactone moiety of (+)-compactin and (+)-mevinolin was established starting from a *meso*-3,5-dihydroxycyclohexanone derivative by employing an enantioselective deprotonation strategy. © 1997 Elsevier Science Ltd. All rights reserved.

The recent discoveries of compactin **1**,[1] mevinolin **2**[2] (Figure 1) and their relatives provided impetus to the design of general strategies for the synthesis of these HMG-CoA reductase inhibitors due to the significant biological activity. The important synthetic feature for such compounds is the stereocontrolled construction of the stereogenic centers bearing the two hydroxy groups for the (3*R*,5*R*)-3,5-dihydroxy-6-alkanoic acid 1,5-lactone system, which are essential for activity. Consequently, a number of enantioselective or enantiospecific syntheses of natural products including the syntheses of the lactone moiety have appeared[3] by elaboration of chiral pool materials, such as tartaric acid,[4] L-amino acids,[5] (*S*)-malic acid,[6] and carbohydrates[7] and by asymmetric syntheses involving an asymmetric Diels–Alder reaction,[8] a diastereoselective aldol reaction,[9] an asymmetric epoxidation,[10] enantioselective reductions of prochiral β,δ-diketo esters[11] or a 1,3-diketone,[12] and a diastereoselective reduction of a chiral β,δ-diketo ester.[13] Recently we have been involved[14] in the exploitation of an enantioselective deprotonation reaction for the synthesis of physiologically active natural products, since the enantioselective deprotonation of prochiral compounds with chiral bases[15] is one of the most reliable methods to synthesize optically active compounds. As a continuation of our work on the enantioselective deprotonation strategy, we have further studied the asymmetric synthesis of the lactone moiety of HMG-CoA reductase inhibitors and report here an enantioselective synthesis of (+)-(4*R*,6*R*)-4-hydroxy-6-(2-phenylethyl)-tetrahydro-2*H*-pyran-2-one.

The requisite starting prochiral ketone **7** was synthesized as described below (Scheme 1).



1 R = H
2 R = Me

Figure 1. Structures of (+)-compactin **1** and (+)-mevinolin **2**.

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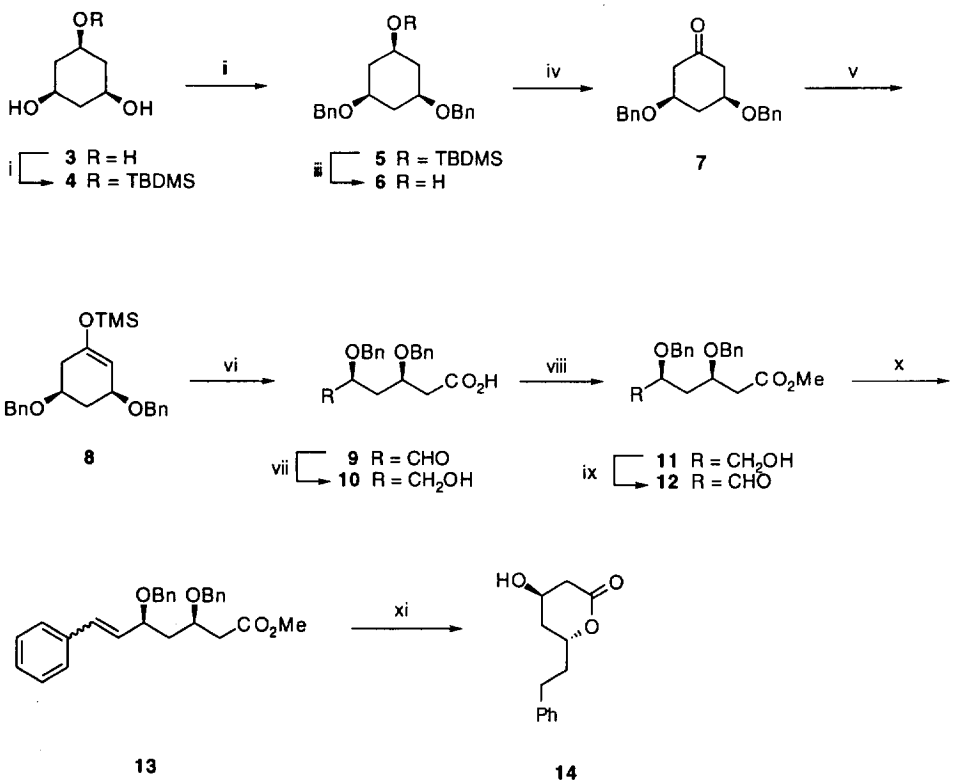

Scheme 1. *Reagents and conditions*: i) NaH, pyridine, room temp., then TBDMSCl, THF, 0°C; ii) NaH, BnBr, $^{n}Bu_4NI$, THF, room temp.; iii) TBAF, THF, room temp.; iv) PCC, AcONa, Celite, CH_2Cl_2, room temp.; v) lithium (*S,S'*)-α,α'-dimethyldibenzylamide, TMSCl, THF, −100°C; vi) O_3, CH_2Cl_2, −78°C, then PPh_3; vii) $NaBH_4$, MeOH, room temp.; viii) MeI, K_2CO_3, DMF, room temp.; ix) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 to −45°C; x) $PhCH_2PPh_3Cl$, $^{n}BuLi$, THF, 0°C to room temp.; xi) H_2, $Pd(OH)_2$, EtOH, room temp., then *p*-TsOH, benzene, room temp.

Mono-sodium salt, derived from *cis,cis*-1,3,5-trihydroxycyclohexane **3** on treatment with 1 equivalent of sodium hydride in pyridine, was treated with *tert*-butyldimethylsilyl chloride in tetrahydrofuran at 0°C to give the mono-silyl ether **4**, in 84% yield, which was further alkylated with benzyl bromide and sodium hydride in the presence of tetrabutylammonium iodide to furnish the dibenzyl ether **5** in quantitative yield. Desilylation of **5** with tetrabutylammonium fluoride, followed by oxidation of the resulting alcohol **6** with pyridinium chlorochromate on Celite in the presence of sodium acetate afforded the ketone **7** in 76% yield from **5**. The ketone **7** was also prepared from the much cheaper starting material, a mixture of *cis,trans*- and *cis,cis*-1,3,5-trihydroxycyclohexanes, by four steps using essentially the same procedure as described above involving silylation, benzylation, desilylation and oxidation in about 20% overall yield.

With the desired prochiral ketone in hand, we investigated an enantioselective deprotonation reaction of **7** with lithium (*S,S*)-α,α'-dimethyldibenzylamide as the chiral base in the presence of trimethylsilyl chloride in tetrahydrofuran at −78°C to give the silyl ether **8** in 62% yield. Since the enantiomeric excess of the silyl ether **8** could not be determined at this stage, unfortunately, we decided to use this silyl ether in the next step. Ozonolysis of the ether **8** in dichloromethane at −78°C, followed by treatment with triphenylphosphine provided the aldehyde **9**, in 71% yield. Although an esterification of **9** was first attempted under the various reaction conditions, e.g. treatment with iodomethane and potassium carbonate in *N,N*-dimethylformamide, with *p*-toluenesulfonic acid in methanol, and thionyl chloride in methanol, a partial epimerization of the hydroxy group at the 5-position was observed. Thus,

the aldehyde **9** was converted into the alcohol **10** on reduction with sodium borohydride in methanol in 68% yield. Esterification of the acid-alcohol **10** with iodomethane in *N,N*-dimethylformamide in the presence of potassium carbonate afforded the ester **11** in 90% yield. The enantiomeric excess of this ester was determined to be 70.2% by HPLC analysis with the chiral column CHIRALPAK AD (Daicel Chemical Industries, Ltd.). When the above enantioselective deprotonation of **8** was carried out at −100°C, the enantiomeric excess of the ester **11**, $[\alpha]_D$ +12.0 (c=0.9, $CHCl_3$), was increased to 73.8%. Although the stereocontrolled construction of 1,3-*syn* dihydroxy system was thus achieved by employing an enantioselective deprotonation of *cis*-3,5-dihydroxycyclohexanone derivative and the stereostructure of the hydroxy groups could be assumed based on the consideration of previous results,[14,15] the determination of its absolute configuration still remained obscure. In order to determine the absolute configuration of the stereogenic centers on **11** unambiguously, we attempted the conversion of **11** into a compactin analogue. Swern oxidation of the alcohol **11** gave the aldehyde **12**, in 95% yield, which on treatment with benzyltriphenylphosphonium chloride and *n*-butyllithium in tetrahydrofuran furnished the olefin **13**, $[\alpha]_D$ −29.1 (c=1.1, $CHCl_3$), as a mixture of *E/Z* isomers, in a ratio of 1/4, in 95% yield. Finally, deprotection of the benzyl ethers of **13** under the catalytic hydrogenation reaction condition using palladium hydroxide as a catalyst, followed by lactonization of the resulting hydroxy-ester with *p*-toluenesulfonic acid in benzene afforded the desired (+)-(4*R*,6*R*)-4-hydroxy-6-(2-phenylethyl)-tetrahydro-2*H*-pyran-2-one **14**, in 67% yield, whose spectroscopic data were identical with those reported.[6,7c,10,12] Since the sign of rotation of our synthetic product, m.p. 104.2–105.8°C, $[\alpha]_D$ +64.6 ($CHCl_3$) (after one recrystallization), m.p. 106–106.5°C; $[\alpha]_D$ +69.5 ($CHCl_3$) (after two recrystallization), corresponds to that of the literatures, {m.p. 108°C, $[\alpha]_D$ +71 ($CHCl_3$)[13] and m.p. 106–107°C, $[\alpha]_D$ +67.2 ($CHCl_3$)[12]}, its absolute stereochemistry can now be assigned as 4*R* and 6*R*.

Thus we could disclose an alternative synthetic approach to compactin analogue by employing an enantioselective deprotonation of a prochiral cyclohexanone derivative as a key step. The methodology described in this paper should be applicable to the enantioselective synthesis of the other types of physiologically active compounds including natural products.

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