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FIRST SYSTEMATIC CHIRAL SYNTHESES OF TWO PAIRS OF ENANTIOMERS WITH 3,5-DIHYDROXYHEPTENOIC ACID CHAIN, ASSOCIATED WITH A POTENT SYNTHETIC STATIN NK-104

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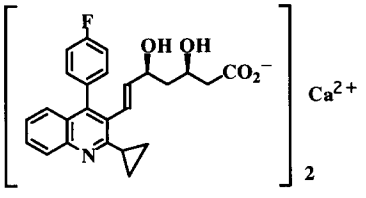
Abstract: First systematic chiral syntheses of two pairs of enantiomers with 3,5-dihydroxyheptenoic acid chain, associated with a potent synthetic statin NK-104 are reported. A pair of *syn* diol isomers (NK-104 and its enantiomer) was obtained efficiently by diastereomeric resolution. The synthesis of a pair of *anti* diol isomers (3-epimer and 5-epimer) was accomplished effectively by the asymmetric aldol reaction followed by *anti* stereoselective reduction as key steps. Their purity determinations were effected by chiral HPLC analysis.

Monocalcium bis [(3*R*, 5*S* , 6*E*) - 7 - (2 - cyclopropyl - 4 - (4 - fluorophenyl) - 3 - quinolyl) - 3, 5 - dihydroxy - 6 - heptenoate] (NK-104, **1a**)[1] is an exceedingly potent inhibitor of 3 - hydroxy - 3 - methylglutaryl coenzyme A reductase (HMGR), presently being developed as a hypolipidemic agent.

Figure 1



NK-104

It has been shown that the effective synthetic inhibitors have a 3,5-dihydroxyheptenoic or 3,5-dihydroxyheptanoic acid chain, which binds to the target enzyme active site, and that the *R* configuration at C-3 and 3, 5- *syn*- diol structure are essential for obtaining the highest affinity.[2] In common with these synthetic inhibitors, highly biological active NK-104 is the *syn*-3*R*; 5*S*-isomer, as already clarified by various chemical means of total synthesis, i.e., chiral pool methods with natural sources or asymmetric inductions.[3]

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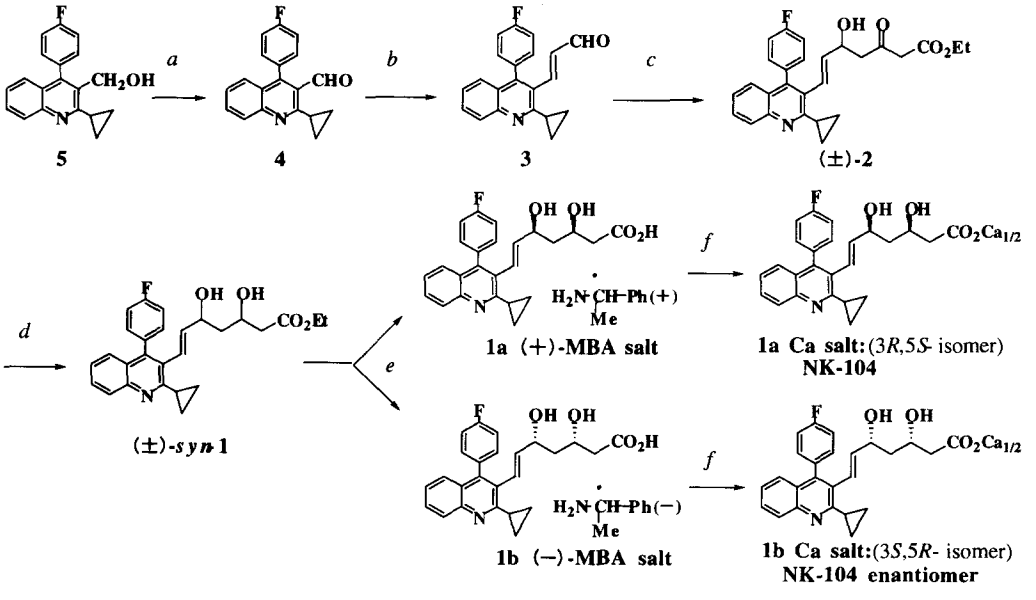
On the other hand, few systematic investigations on the syntheses of other stereoisomers have been reported. The Merck group has published a few papers on the syntheses of a pair of *syn* diol isomers and racemic epimers by partially *syn* stereoselective reduction and HPLC separation followed by diastereomeric α-methylbenzylamide resolution.[4a,b] In a development of drug, all stereoisomers in the molecule should be evaluated comparatively on various physiological and biological characterizations. In such studies, pure authentic samples with correct absolute configurations and comparable impurity contents between a pair of enantiomers are needed. In the present paper, we report synthetic methods that would be suitable for the demand described above.

The synthesis of NK-104 (3*R*, 5*S*-isomer: 1a) and its enantiomer (3*S*, 5*R*-isomer: 1b) (Scheme 1)

In order to obtain a pair of NK-104 enantiomers in high purity, we adopted a diastereomeric resolution procedure, which would be an appropriate and convenient mean. Thus, we tried to synthesize the racemic *erythro*-β, δ-dihydroxyesters (±)-***syn*-1**. Alcohol **5** required as the starting material was prepared according to our previously published procedures.[3a,5] Dimethyl sulfoxide oxidation of **5**, followed by Emmons-Horner coupling of the resulting aldehyde **4** with diethyl (cyanomethyl) phosphonate under phase transfer conditions furnished α, β-unsaturated nitrile. The Dibal reduction of the nitrile gave propenal **3**. An aldol condensation of **3** with the dianion of ethyl acetoacetate provided the racemic β-keto-δ-hydroxy esters (±)-**2**. Highly *syn* stereoselective reduction of the keto group[6] was conducted with diethylmethoxyborane and sodium borohydride at -78℃ to give the desired racemic *erythro*-β, δ-dihydroxyesters (±)-***syn*-1** with >98:2 *syn*-selectivity.[7a]

Scheme 1: Synthesis of NK-104(1a) and its enantiomer(1b) by diastereomeric resolution



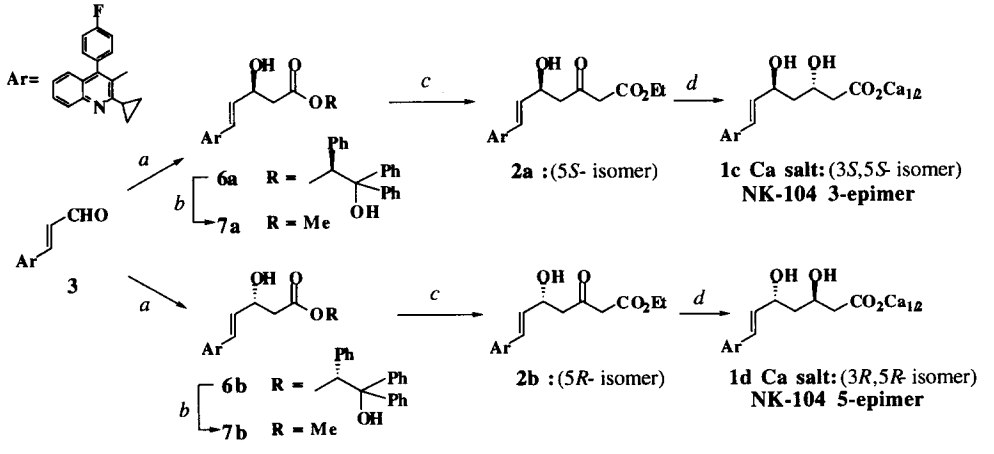
Reagents: (*a*) DMSO, P_2O_5, Et_3N; (*b*) i: $(EtO)_2POCH_2CN$, NaOH, (*n*-octyl)$_3$MeNCl, toluene and H_2O; ii: DIBAH; (*c*) $CH_3COCH_2CO_2Et$, NaH, *n*-BuLi; (*d*) $NaBH_4$, Et_2BOMe; (*e*) i: NaOHaq; ii: HClaq; iii: (+)-MBA or (−)-MBA; iv: recrystallized from MIBK and DMF; (*f*) i: HClaq; ii: NaOHaq; iii: $CaCl_2$.

The resolution procedure via diastereomeric α-methylbenzylamide[4a,b] was not appropriate for preparing the target NK-104 and its enantiomer, since the basic hydrolysis step of the amides separated needed severe conditions and injured the yield and enantiomeric purity. The resolution of (±)-***syn*-1** was accomplished via formation of the diastereomeric salts of the *erythro*- β, δ-dihydroxy acids and a chiral α-methylbenzylamine, which were readily separated by recrystallization in high yield and high purity. The resulting amine salt selectively crystallized from the solvents, was converted to the corresponding calcium salt by three-step procedure under simple and mild conditions.[8] Thus hydrolysis of (±)-***syn*-1** with NaOH followed by addition of (+)-α-methylbenzylamine ((+)-**MBA**) afforded a mixture of the diastereomeric amine salts in a quantitative yield. The **1a**·(+)-**MBA salt** was readily obtained in nearly enantiomerically pure form by three-time recrystallization from methyl isobutyl ketone- dimethyl formaldehyde (the chemical yield for the resolution step based on a mixture of the diastereomeric amine salts was nearly 30%). After acidification with HCl and hydrolysis with NaOH, the reaction of sodium salt with calcium chloride yielded the corresponding nearly pure (+)-*erythro*-β, δ-dihydroxy acid calcium salt (NK-104: **1a Ca salt**, enantiomeric excess : 99.5 % ee, *syn/anti*= 100 / 0, $[\alpha]^{20}_D$ = +23.1° , c = 1.00 in CH_3CN / H_2O = 1 / 1).[7b] The (−)-*erythro*-β, δ-dihydroxy acid calcium salt (NK-104 enantiomer: **1b Ca salt**) was obtained with (−)-α-methylbenzylamine ((−)-**MBA**) as a resolving agent in a similar manner (enantiomeric excess : 99.3 % ee, *syn/anti*= 100 / 0, $[\alpha]^{20}_D$ = −23.5° , c = 1.00 in CH_3CN / H_2O = 1 / 1).[7b]

The synthesis of 3-epimer (3*S*, 5*S*-isomer : 1c) and 5-epimer (3*R*, 5*R*-isomer : 1d) (Scheme 2)

Scheme 2 delineates the preparation of NK-104 epimers from propenal **3**. The optically active β-keto-δ-hydroxy esters **2a** and **2b**, obtained with [(*S*)-(−)-HYTRA] and [(*R*)-(+)-HYTRA] from **3** by the stereoselective asymmetric aldol procedure developed by Braun,[9] following a slightly modified procedure of Lynch et al.[10], were submitted to the *anti* stereoselective reduction to give the NK-104 epimers.

Scheme 2 : Synthesis of NK-104 epimers(1c) and (1d) by the asymmetric aldol procedure and anti stereoselective reduction



Reagents: (*a*) (S)-(-)-HYTRA or (R)-(+)-HYTRA, LDA, $MgBr_2$; (*b*) NaOMe; (*c*) CH_3CO_2Et, LDA; (*d*) i: $Me_4NHB(OAc)_3$; ii: NaOHaq; iii: $CaCl_2$.

Thus, reaction of **3** with the magnesium (II) enolate of (*S*) and (*R*)-2-acetoxy-1,1,2-triphenylethanol gave the chiral aldol products **6a** and **6b** respectively in good yield (**6a**: 92.8% de; **6b**: 92.2% de, HPLC).[7c] The diastereomeric excesses of **6a** and **6b** were not significantly improved by recrystallization. They were transformed into the corresponding methyl esters **7a** and **7b** with MeONa in methanol (**7a**: 91.6% ee; **7b**: 91.2% ee, HPLC on chiral column).[7d] Respective Claisen condensation of **7a** and **7b** with ethyl lithioacetate yielded the corresponding chiral β-keto-δ-hydroxy esters **2a** and **2b** (**2a**: 5*S*-isomer, 92.6% ee ; **2b**: 5*R*-isomer, 94.0% ee, HPLC on chiral column).[7e] The absolute configuration at C-5 of **2a** was also corroborated by the transformation of it to NK-104 (3*R*, 5*S*-isomer; **1a**) according to the *syn* stereoselective reduction of the 3-position carbonyl group with $NaBH_4$ and Et_2BOMe. Although enantiomerically enriched **2a** and **2b** were available by this method, we explored alternative ways to obtain them in a nearly enantiomeric pure form for various evaluations. Thus, the racemic β-keto-δ-hydroxy esters (±)-**2** were resolved by a preparative chiral HPLC to provide **2a** and **2b** in good yield.[11] Both enantiomers had enantiomeric excesses of more than 99.0% ee. Highly *anti* stereoselective reduction[12] of **2a** and **2b** with $Me_4NHB(OAc)_3$ in acetic acid gave the *threo*-β, δ-dihydroxyesters **1c** and **1d** respectively (**2a** → **1c**, **2b** → **1d**) with >93:7 *anti*-selectivity.[7a] After recrystallization from dichloromethane and *c*-hexane, they were transformed to the corresponding calcium salts in a manner analogous to that employed in the syntheses of the *erythro*-β, δ-dihydroxy acid calcium salts. The enantiomeric purities of **1c Ca salt** and **1d Ca salt** were nearly in agreement with the enantiomeric excesses of precursors **2a** and **2b** (3-epimer: **1c Ca salt**, enantiomeric excess : 99.8 % ee, *syn* / *anti* = 0.28 / 99.73, $[\alpha]^{20}_D$ = +2.0° , c = 1.05 in CH_3CN / H_2O = 1 / 1, 5-epimer; **1d Ca salt**, enantiomeric excess : 99.5 % ee, *syn* / *anti* = 0.71 / 99.29 , $[\alpha]^{20}_D$ = −0.4° , c = 1.05 in CH_3CN / H_2O = 1 / 1).[7b]

In respect of NK-104, the synthetic sequence permitted the selective preparation of both of diastereomers and enantiomer with the 3,5-dihydroxyheptenoic acid chain conveniently, and afforded pure authentic samples with correct absolute configurations and comparable impurity contents between a pair of enantiomers to the various physiological and biological evaluations.

Acknowledgment: We thank Daicel Chemical Industries, Ltd. for supplying **2a** and **2b**.

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