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Enantioconvergent Synthesis of a Promising HMG Co-A Reductase Inhibitor NK-104 from Both Enantiomers of Epichlorohydrin

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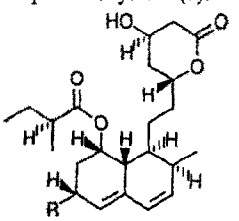
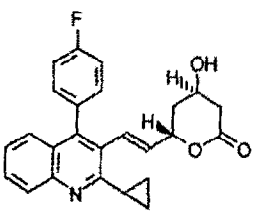
Abstract: An enantioconvergent synthesis of (+)-NK-104 (**3**), a promising HMG Co-A reductase inhibitor, has been developed from both enantiomers of epichlorohydrin.

Fungal metabolites such as compactin (**1**) and mevinolin (**2**) and their derivatives have been shown to be highly effective low-density lipoprotein (LDL) cholesterol lowering agents through their ability to inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-Co-A) reductase, the rate-limiting enzyme in the biosynthesis of cholesterol, and are used for treatment of hypercholesterolaemia.[1] Since it has been found that their biological activity depends largely on the β-hydroxy-δ-lactone subunit, a number of unnatural compounds bearing this essential subunit have been prepared[2] and among these (+)-NK-104 (**3**) was reported to be a promising product by exhibiting 10 fold more activity than the representative products from the fungal metabolites[3] (**Figure 1**). Synthesis of **3**, however, is not an easy task owing to the presence of *E*-olefin conjugated to the quinoline ring which makes introduction of the requisite β-hydroxy-δ-lactone subunit more difficult. We report here an enantioconvergent synthesis of optically pure (+)-NK-104[4] (**3**) utilizing both (*R*)- and (*S*)-enantiomers of epichlorohydrin[5] (**7**).



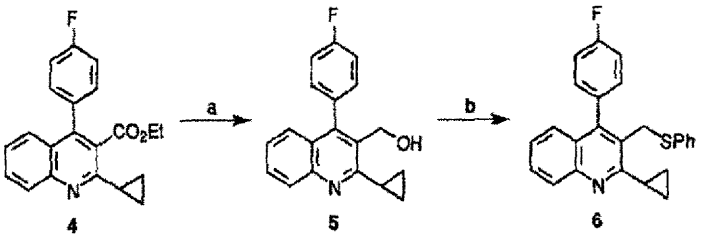
compactin (R=H) (1)
mevinolin (R=Me) (2)



NK-104 (3)

Figure 1

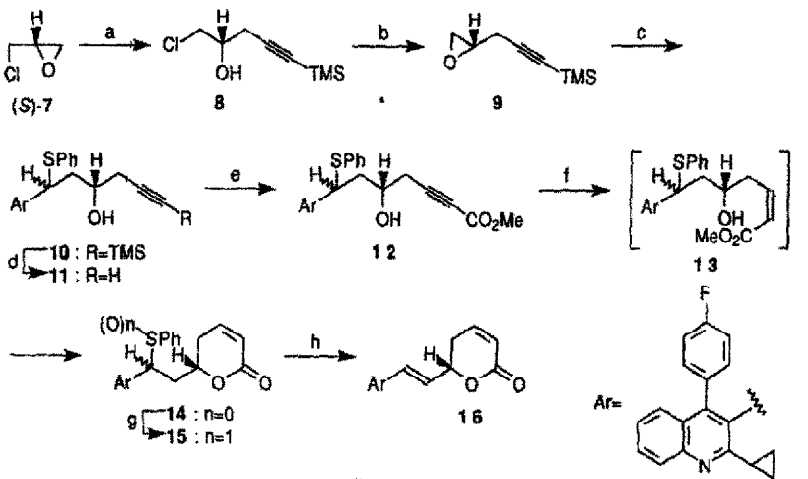
We first transformed the known ester[6] (**4**) into the phenyl sulfide (**6**) in an excellent overall yield (>95%) by reduction with lithium aluminum hydride followed by treating the resulting alcohol (**5**) with diphenyl disulfide and tri-*n*-butylphosphine[7] (**Scheme 1**). The sulfide (**6**), thus obtained, was then reacted with the epoxide[8] (**9**), prepared from (*S*)-epichlorohydrin [(*S*)-**7**] in two steps *via* the chlorohydrin (**8**), in the presence of *n*-butyllithium[8] to give the secondary alcohol (**10**) in 41% yield (83% based on consumed **6**) as an inseparable diastereomeric mixture at the benzylic carbogenic center with some recovery of the sulfide (**6**) (~40%). After removal of the trimethylsilyl group of **10** on brief exposure to methanolic potassium carbonate,[9] the resulting terminal acetylene (**11**) (94%) was stirred with copper(II) chloride in methanol under an atmosphere of carbon monoxide in the presence of a catalytic amount of palladium(II) chloride to furnish the methyl ester (**12**) in 67% yield by carbomethoxylation.[8,10,11] Partial hydrogenation of **12** on Lindlar catalyst yielded the Z-olefin (**13**) which gave the α,β-unsaturated δ-lactone (**14**) in 92% overall yield on refluxing in toluene in the presence of pyridinium *p*-toluenesulfonate. To install the requisite *E*-double bond,[8] the sulfide (**14**) was first treated with *m*-chloroperbenzoic acid to give the sulfoxide (**15**). On thermolysis with



Scheme 1

Reagents and conditions: a) $LiAlH_4$, THF, 0 °C – room temp.; b) phSSph, *n*-Bu_3P, pyridine, room temp.

calcium carbonate in refluxing toluene,[8,12 15] **15** afforded the single product (**16**), mp 168-168.5 °C, $[\alpha]_D^{29}$ –57.84 (*c* 1.49, $CHCl_3$), having the requisite *E*-olefin bond in 96% overall yield from the sulfide (**14**) (**Scheme 2**).

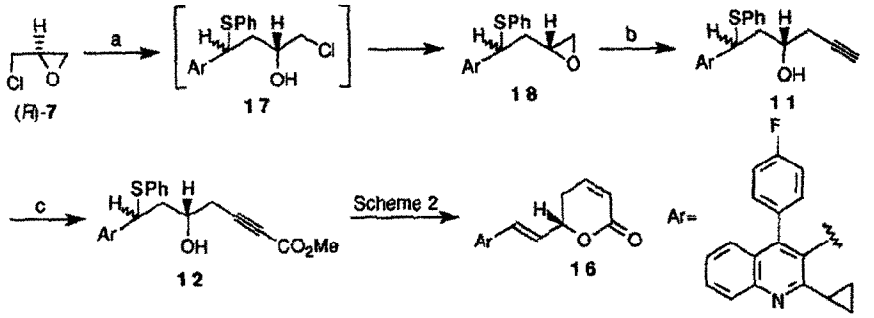


Scheme 2

Reagents and conditions: a) trimethylsilylacetylene, *n*-BuLi, then BF_3·OEt_2, then (*S*)-**7**, THF, –78 °C (25 min), –30 °C (18 h); b) KOH, THF, 0 °C, 4 h; c) **6**, *n*-BuLi, then **9**, THF, –78 °C (1.5 h), –20 °C (10 h); d) K_2CO_3, MeOH, room temp., 9 h; e) $PdCl_2$ (cat.), $CuCl_2$, NaOAc, CO, MeOH, room temp., 3 h; f) H_2, Lindlar cat., MeOH, room temp., 25 h, then PPTS (cat.), toluene, reflux, 1.5 h; g) *m*-CPBA, CH_2Cl_2, –78 °C, 1 h, –40 °C, 30 min, then Me_2S; h) $CaCO_3$, toluene, reflux, 30 min.

On the other hand, the sulfide (**6**) was treated directly with (*R*)-epichlorohydrin [(*R*)-**7**] in the presence *tert*. butyllithium to give the crude chlorohydrin (**17**) with some recovery of the sulfide (**6**) (~40%). Crude **17** was then treated with potassium hydroxide to give the epoxide (**18**) in 49% overall yield (78% yield based on consumed **6**) as a diastereomeric mixture at the benzylic stereogenic center. On reaction with lithium acetylide ethylenediamine complex in DMSO,[13] **18** furnished the terminal acetylene (**11**) in quantitative yield. This compound could also be transformed into the unsaturated δ-lactone (**16**) in a comparable overall yield by following the established route including the palladium catalyzed carbomethoxylation as shown in **Scheme 2**. Attempts to obtain the ester (**12**) directly by treating **18** with methyl lithiopropiolate,[14] however, failed even in the presence of boron trifluoride[15] (**Scheme 3**).

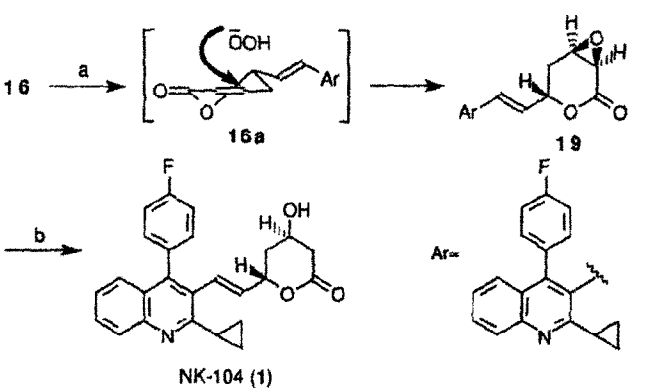
Having obtained the common key intermediate (**12**) bearing the requisite *E*-olefinic bond convergently from both (*S*)- and (*R*)-enantiomers of epichlorohydrin (**7**), we next carried out the introduction of the β-hydroxy group on the δ-lactone moiety. Since we have established an efficient two-step method for the stereospecific introduction of a β-hydroxy group on a δ-lactone system *via* an epoxide precursor starting from an α,β-unsaturated δ-lactone,[8,11,14,16] this was applied to **16** with a slight modification of using a different



Scheme 3

Reagents and conditions: a) (i) **6**, *t*-BuLi, then (*R*)-**7**, THF, –78 °C, 1 h; (ii) KOH, THF, room temp., 3.5 h; b) HC≡CLi ($CH_2NH_2)_2$, DMSO, room temp., 30 min; c) $PdCl_2$ (cat.), $CuCl_2$, NaOAc, CO, MeOH, room temp., 3 h.

solvent system. Thus, treatment of **16** with an excess (3 equiv.) of 30% hydrogen peroxide and 4N NaOH (5 equiv.) in a 4:1 mixture of methanol and dichloromethane allowed chemo- and stereospecific epoxidation at the lactone double bond to afford the α,β-epoxy lactone (**19**), mp 170-171 °C, $[\alpha]_D^{28}$ +43.15 (*c* 1.13, $CHCl_3$), in 81% yield as a single stereoisomer. The stereochemistry of **19** could readily be assigned as shown by ^{1}H-nmr spectral comparison with those of the related materials[8,11,14,16] which indicated that the hydroperoxide ion was introduced specifically from the stereoelectronically favored[17] *anti*-face to the δ-substituent. The following conversion of **19** into (+)-NK-104 (**3**) further confirmed the stereochemistry of the epoxy bond. To avoid solvolytic cleavage of the lactone ring under the reductive cleavage[8,11,14,16] of the epoxide bond, the selenolate complex was generated in THF in place of alcoholic solvents which were employed in the original procedure.[18] Thus, the epoxide (**19**) was treated with the complex, generated in THF in the same reaction flask by treating diphenyl diselenide with sodium borohydride in the presence of a catalytic amount of acetic acid, to afford NK-104 (**3**), mp 138-139 °C, $[\alpha]_D^{32}$ +8.84 (*c* 0.92, $CHCl_3$) [authentic material[3]: mp 136-139 °C, $[\alpha]_D^{20}$ +9.0 (*c* 1.0, $CHCl_3$)], in 61% yield. Optical and diastereomeric purities of the product were confirmed by hplc analysis using chiral columns [Chiralpack AS and Nucleosil 50-5; *i*-PrOH-hexane (1:9 v/v)] and (+)-**1** obtained was shown to be 97.8% ee and free of diastereomers (**Scheme 4**).



Scheme 4

Reagents and conditions: a) 30% H_2O_2, 4N NaOH, MeOH-CH_2Cl_2 (4:1), 0 °C, 40 min; b) phSeSeph, $NaBH_4$, THF, 40 °C, 10 min, then AcOH (cat.), 0 °C, then **19**, 20 min.

In conclusion, although the present synthesis of (+)-NK-104 (**3**) has still to be improved at the coupling stage between the non-chiral and the chiral epoxide segments, it has produced the optically pure material enantioconvergently from both (*R*)- and (*S*)-enantiomers of epichlorohydrin whose large scale production has been established.[19]

References and Notes

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