Arch. Pharm. Res. Vol. 17, No. 3, pp. 161-165, 1994

Synthesis of (±)-*trans*-6-[2-(Benzotriazolyl)ethyl]tetrahydro-4-hydroxy-2H-pyran-2-ones as Potential HMG-CoA Reductase Inhibitors

Jin-Il Kim, Soo Kyung Lee and Yurngdong Jahng*

College of Pharmacy, Yeungnam University, Kyongsan 712-749, Korea

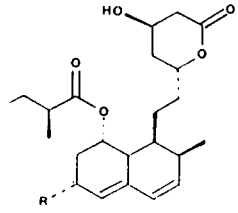
(Received March 24, 1994)

New hypolipaemic agents, in which benzotriazole moiety is connected to tetrahydro-4-hydroxy-2H-pyran-2-one by a two-carbon bridge, were designed and synthesized to show significant cholesterol-lowering effect comparable to mevinolin.

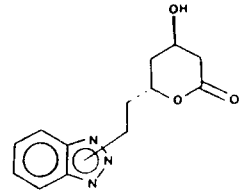
Key words: Hypolipaemic Agent, HMG-CoA reductase inhibitor, Benzotriazole

INTRODUCTION

The discoveries of compactin (**1a**) (Endo *et al.*, 1976; Brown *et al.*, 1976) and mevinolin (**1b**) (Endo, 1979; Alberts *et al.*, 1980) opened new era for the treatment of hypercholesterolemia by inhibiting cholesterol biosynthesis at the level of the major rate-limiting enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. The structure-activity relationship (SAR) studies upon these molecules as well as related compounds revealed that the chiral β-hydroxy-δ-lactone moiety or its equivalents is essential for the maximum activity(Stokker *et al.*, 1986; Jendralla *et al.*, 1991). The dehydrodecalin moiety of **1**, however, can be replaced by carbocycles, nitrogen- and/or oxygen-containing heterocycles without losing the activity in the case that such a moiety can impose suitable physicochemical factors in binding inhibitors to the enzyme (Roth *et al.*, 1989 and 1991). As a part of our research to develop antihypercholesterolemic agents, in this paper, we present the synthesis and preliminary biological activity of **2**, in which benzotriazole moiety is connected to β-hydroxy-δ-lactone moiety by a two-carbon bridge.



1a R=H (Compactin)
b R=CH_3 (Mevinolin)



2a 1-Substituted
b 2-Substituted

MATERIALS AND METHODS

Melting points were determined on Fisher-Jones melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained on a Perkin Elmer 1310 spectrophotometer in KBr, except where noted. Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker AM-300 (300 MHz for ^1H NMR and 75.5 MHz for ^{13}C NMR) spectrometer and chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) as an internal standard. Mass spectra were obtained by direct sample introduction into a Hewlett-Packard 5933 A GC-mass spectrometer and are reported herein as m/e (relative intensity). Dry THF was obtained by distilling over LAH and all other solvents were reagent grade and used directly without further purification. 1H-Benzotriazole was prepared by literature method (Damschroder *et al.*, 1955).

1-(3,3-Diethoxypropyl)-1H-benzotriazole (4a) and 2-(3,3-Diethoxypropyl)-2H-benzotriazole (4b)

To a suspension of 0.48 g (10 mmol) of 50% NaH in 10 ml of dry DMF was added a solution of 1.20 g (10 mmol) of 1H-benzotriazole in 10 ml of DMF under N_2. When the gas evolution had ceased, 0.38 g (2.5 mmol) of NaI was added, followed by the dropwise addition of 1.67 g (0.01 mol) of 3-chloropropionaldehyde diethyl acetal in 10 ml of DMF. The resul-

Correspondence to: Yurngdong Jahng, College of Pharmacy, Yeungnam University, Kyongsan 712-749, Korea

ting solution was heated at 85℃ for 60 h. The reaction mixture was poured into 100 ml of ice-water and extracted with ether (3×50 ml). Work-up as usual gave 1.87 g of crude material, which was chromatographed on silica gel, eluting with n-hexane: EtOAc (1 : 1). The early fractions (R_f=0.48) afforded 0.68 g (27%) of 2-(3,3-diethoxypropyl)-2H-benzotriazole (**4b**): IR(thin film) υ 3040, 2960, 1550, 1460, 1405, 1365, 1115, 1050, 745 cm^{-1}; ^1H NMR($CDCl_3$, 300 MHz) δ 1.13(t, J=7.0 Hz, 6H), 2.38(q, J=6.8 Hz, H_2), 3.42(qm, J=7.2 Hz, 2H), 3.59(qm, J=7.2 Hz, 2H), 4.50(t, J=5.5 Hz, H_3), 4.77(t, J=6.9 Hz, H_1), 7.29(dd, J=6.4, 3.2 Hz, 2H), 7.79(dd, J=6.4, 3.2 Hz, 2H); ^{13}C NMR($CDCl_3$, 75.5 MHz) δ 15.1(CH_3), 33.8(C_2), 52.3(C_1), 61.6(OCH_2), 100.1(C_3), 117.7($C_{4\&7}$), 125.9($C_{5\&6}$), 144.1($_{4a\&7a}$).

The latter fractions (R_f=0.25) afforded 0.92 g (36%) of 1-(3,3-diethoxypropyl)-benzotriazole (**4a**): IR(thin film) υ 3040, 2960, 1590, 1460, 1405, 1365, 1115, 1050, 945 cm^{-1}; ^1H NMR($CDCl_3$, 300 MHz) δ 1.06(t, J=7.1 Hz, 6H), 2.18(dt, J=7.0, 5.5 Hz, H_2), 3.34(qm, J=6.7 Hz, 2H), 3.51(qm, J=6.7 Hz, 2H), 4.34(t, 1H, J=5.5 Hz, H_3), 4.59(t, J=7.0 Hz, H_1), 7.20(dd, 1H, J=8.7, 6.9, 1.1 Hz, $H_{5'}$), 7.34(dd, 1H, J=8.7, 6.9 Hz, $H_{6'}$), 7.43(d, 1H, J=8.7 Hz, $H_{7'}$), 7.90(d, 1H, J=8.7 Hz, $H_{4'}$); ^{13}C NMR($CDCl_3$, 75.5 MHz) δ 15.1(CH_3), 33.8(C_2), 43.8(C_1), 62.0(OCH_2), 100.3(C_3), 109.3($C_{7'}$), 119.8($C_{4'}$), 123.6($C_{5'}$), 127.0($C_{6'}$), 133.0(C_{7a}), 145.8(C_{4a}).

1-(3-Oxopropyl)-1H-benzotriazole (5a)

A solution of 0.50 g (2.0 mmol) of the acetal and 0.42 g (2.2 mmol) of *p*-TsOH·H_2O in 20 ml of acetone-water (5 : 1) was refluxed for 48 h. The cooled mixture was concentrated and extracted with Et_2O (3×50 ml). The combined organic layer was washed with satd. aq. $NaHCO_3$ and brine, and dried over $MgSO_4$. Removal of the solvent gave 0.30 g of crude material, which was chromatographed on silica gel, eluting with *n*-hexane : CH_2Cl_2 (2 : 3). The early fractions afforded 0.14 g (40%) of 1-(3-oxopropyl)-1H-benzotriazole as a white semisolid: IR(thin film) υ 3040, 2960, 2840, 1700, 1440, 1355, 1270, 1140, 1065, 1000, 740 cm^{-1}; NMR($CDCl_3$, 300 MHz) δ 3.28(t, 2H, J=6.8 Hz, H_2), 4.87(dd, 2H, J=6.8 Hz, H_1), 7.34(t, J=7.8 Hz, $H_{5/6}$), 7.48(t, J=7.8 Hz, $H_{6/5}$), 7.70(d, H_7), 7.99(d, H_4), 9.92(s, 1H, CHO); ^{13}C NMR($CDCl_3$, 75.5 MHz) δ 40.7(C_2), 42.8(C_1), 109.4, 119.7, 124.0, 127.4, 133.4, 145.7, 198.4(C_3).

2-(3-Oxopropyl)-2H-benzotriazole (5b)

The same procedure described above for 1-(3-oxopropyl)-1H-benzotriazole (**5a**) was employed for 2-(3,3-diethoxypropyl)-2H-benzotriazole to provide 2-(3-oxopropyl)-2H-benzotriazole as thick syrup: IR(thin film) υ 3040, 2920, 2900, 2720, 1710, 1555, 1440, 1370, 1320, 1270, 1160, 1070, 970, 830, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.35(t, 2H, J=6.8 Hz, H_2), 5.09(t, 2H, J=6.8 Hz, H_1), 7.35(dd, 2H, J=6.8, 3.1 Hz), 7.83(dd, 2H), 9.93(s, 1H, CHO); ^{13}C NMR($CDCl_3$, 75.5 MHz) δ 42.4(C_2), 49.5(C_1), 117.8($C_{4'}$), 126.3($C_{5'}$), 144.2(C_{4a}), 198.0(C_3).

(±)-Ethyl 7-(benzotriazol-1-yl)-5-hydroxy-3-oxo-6-heptanoate (7a)

To a chilled mixture of 0.24 g (0.37 mmol, 60% suspension in mineral oil) of NaH in 100 ml of dry THF under N_2 atmosphere, was added 0.49 g (0.38 mmol) of ethyl acetoacetate in 10 min. The homogeneous, clear solution was stirred at 0℃ for 30 min, followed by the dropwise addition 3.93 ml (0.37 mmol) of n-BuLi in hexane (1.6 mol) solution over 15 min. The orange anion solution was stirred at 0℃ for an additional hour. The acetone-dry ice bath was controlled at -78℃ and a THF solution containing 0.65 g (0.37 mmol) of 1-(3-oxopropyl)-1H-benzotriazole was added with stirring at −78℃ for 1 h. The mixture was, then, diluted with 0.5 N HCl solution (until pH= 5), and extracted with ether (3×50 ml). The combined organic layer was washed with H_2O, sat. $NaHCO_3$, and dried over anhyd. $MgSO_4$. Concentration under reduced pressure gave 0.75 g of crude material, which was chromatographed on silica gel, eluting with *n*-hexane : CH_2Cl_2(3 : 2). The latter fractions gave 0.51 g (48%) of red oil: IR(thin film) υ 3380, 3060, 2940, 1700, 1440, 1400, 1370, 1300, 1270, 1240, 1150, 1050, 745 cm^{-1}; ^1H NMR($CDCl_3$, 300 MHz) δ 1.24(t, 3H, J=6.7 Hz), 2.12-2.22(m, H_6), 2.64-2.77(m, H_4), 3.46(s, H_2), 3.88(m, H_5), 4.13(t, J=6.9 Hz, CH_2), 4.81(m, H_7), 7.34(t, J=7.8 Hz, 1H), 7.45(t, 1H), 7.60(d, 1H), 8.00(d, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.8, 35.9, 44.3, 49.4, 49.5, 61.3, 64.2, 109.4, 119.4, 123.8, 127.2, 133.0, 145.4, 166.7, 202.8.

(±)-Ethyl 7-(benzotriazol-2-yl)-5-hydroxy-3-oxo-6-heptanoate (7b)

The same procedure described above in compound **7a** was employed for the preparation of **7b** with 0.53 g (3.0 mmol) of 2-(3-oxopropyl)-2H-benzotriazole to give 0.40 g (52%) of **7b** as a red oil: IR(thin film) υ 3450, 3040, 1940, 2870, 1710, 1430, 1320, 1260, 1130, 1050, 1020, 740 cm^{-1}; ^1H NMR($CDCl_3$, 300 MHz) δ 1.24(t, 3H, J=7.2 Hz), 2.15-2.31(m, 2H, H_6), 2.72-2.75 (AB quartet, 2H, H_4), 3.44(s, 2H, H_2), 4.13(m, 1H), 4.16 (q, 2H), 4.88-4.96(m, 2H, H_7), 7.37(dd, 2H, J=6.4, 3.2 Hz), 7.84(dd, 2H); ^{13}C NMR($CDCl_3$, 75.5 MHz) δ 13.9 (CH_3), 36.1(C_6), 49.3(C_4), 49.8(C_2), 52.9(C_7), 61.5(OCH_2), 64.6(C_5), 117.9($C_{4'}$), 126.3($C_{5'}$), 144.2(C_{4a}), 166.8(C_1), 202.7(C_3).

(±)-Ethyl *cis*-7-(benzotriazol-1-yl)-3,5-dihydroxy-6-heptanoate (8a)

To a solution of 0.17 g (0.060 mmol) of ethyl 7-

(benzotriazol-1-yl)-5-hydroxy-3-oxo-6-heptanoate in 20 ml of dry THF at 0℃ under Ar atmosphere, was added 0.6 ml (0.060 mmol) of 1M triethylborane solution in THF in one portion. The cooling ice-water bath was replaced with an acetone-dry ice bath, and then to the reaction mixture was added 0.03 g (0.72 mmol) of $NaBH_4$ in one portion. The reaction suspension was stirred at −78℃ for 2 h, forming a clear, homogeneous pale yellow solution. The reaction mixture was diluted with 0.8 ml of CH_3OH and the solution was allowed to stir at −78℃ for an additional 1.5 h. The reaction mixture was, then, diluted with 100 ml of 1N HCl, followed by extractions with ether (3×50 ml). The combined organic layer was washed with H_2O, dried over $MgSO_4$, concentrated under reduced pressure to give 0.28 g of crude product as a thick syrup. The crude syrup was chromatographed on silica gel, eluting with *n*-hexane : $CHCl_3$(4 : 1). The later fractions afforded 0.18 g (46.5%) of **8a** as a red oil: IR(thin film) υ 3400, 2960, 2860, 1700, 1610, 1520, 1470, 1400, 1220, 1150, 1040, 830, 740 cm^{-1}; ^1H NMR($CDCl_3$, 300 MHz) δ 1.24(t, J=6.8 Hz, 3H), 1.56(td, J=12.0, 2.0 Hz, 1H), 1.63-1.69(m, 1H), 2.05-2.13(m, 1H), 2.15-2.21 (m, 1H), 2.45(d, J=6.9 Hz, 2H), 3.82(tm, J=9.0, 2.4 Hz, 1H), 3.93(m, 1H), 4.16(q, 2H), 4.20-4.23(m, 1H), 4.76-4.87(m, 2H), 7.36(t, J=8.3 Hz, 1H), 7.47(t, 1H), 7.60(d, 1H), 8.03(d, 1H); ^{13}C NMR($CDCl_3$, 75.5 MHz) δ 14.1, 37.3, 41.5, 42.2, 44.3, 60.8, 68.5, 68.6, 109.9, 119.8, 123.9, 127.2, 133.2, 145.7, 172.4; mass spectrum, m/z (rel. intensity) 308(0.14, M+1), 307(1.8, M), 289(0.5), 262(39.0), 176(12.0), 148(31.0), 133(100), 121 (51.5), 106(52.0), 91(43.0), 77(47.6).

(±)-Ethyl *cis*-7-(benzotriazol-2-yl)-3,5-dihydroxy-6-heptanoate (8b)

The same procedure described above in compound **8a** was employed for **8b** with 1.23 g (4.0 mmol) of ethyl 7-(benzotriazol-2-yl)-5-hydroxy-3-oxo-6-heptanoate to give 0.85 g of crude product as a syrup, which was chromatographed on silicagel, eluting with *n*-hexane : $CHCl_3$ (4 : 1). The early fraction afforded 0. 50 g (56%) of dialkoxyethylborane complex (**9b**) as a red oil: IR(thin film) υ 3400, 2960, 2860, 1700, 1605, 1530, 1450, 1400, 1240, 1150, 1040, 830, 740 cm^{-1}; ^1H NMR($CDCl_3$, 300 MHz) δ 0.68(q, 2H, J=7.8 Hz), 0.85(t, 3H, J=7.8 Hz), 1.24(t, 3H, J=7.2 Hz), 1.39-1.51 (m, 1H), 2.00(dt, 1H, J=15.9, 3.0 Hz), 2.17-2.23(m, 1 H), 2.35-2.46(m, 2H), 2.58(dd, 1H, J=16.0, 6.9 Hz), 4.02-4.06(m, 1H), 4.13(q, 2H, J=7.2 Hz), 4.33-4.39(m, 1H), 4.92-4.97(m, 2H), 7.34-7.39(m, 2H), 7.83-7.88(m, 2H); ^{13}C NMR($CDCl_3$, 75.5 MHz) δ 7.39, 14.0, 37.0, 37.9, 42.0, 52.5, 60.4, 67.6, 67,9, 117.8, 126.1, 144.2, 170.5.

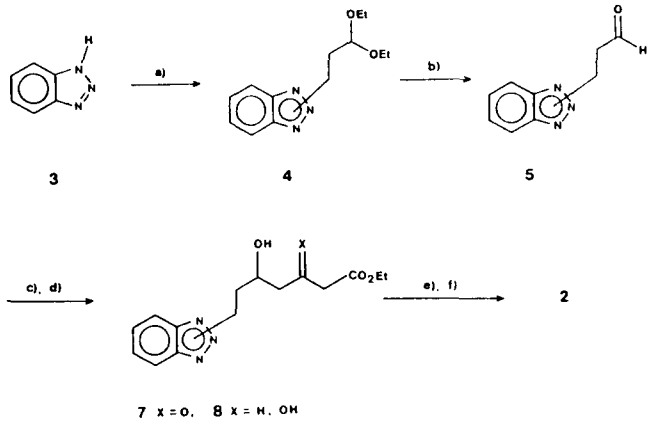
The latter fractions gave 0.25 g (28%) of a product as an oil: IR(thin film) υ 3400, 2940, 1700, 1400, 1340, 1140, 1080, 940, 845, 740 cm^{-1}; ^1H NMR($CDCl_3$, 300 MHz) δ 1.24(t, 3H, J=7.2 Hz), 1.56(dt, 1H, J=14.2, 2.9 Hz, H_{4A}), 1.65(dt, 1H, J=14.2, 9.6 Hz, H_{4B}), 2.16-2.21(m, 1H), 2.23-2.31(m, 1H), 2.43-2.47(m, 2H), 3.86-3.92(m, 1H), 3.98(br. s, 1H, OH), 4.13(q, 2H), 4.15(s, 1H, OH), 4.20-4.27(m, 1H), 4.85-4.99(m, 2H, H_7), 7.38 (m, 2H), 7.85(m, 2H); ^{13}C NMR($CDCl_3$, 75.5 MHz) δ 14.0(CH_3), 37.3(C_6), 41.6(C_4), 42.1(C_2), 53.0(C_7), 61.0 (OCH_2), 68.6(C_5), 68.7(C_3), 117.8($C_{4'}$), 126.3($C_{5'}$), 144.2 (C_{4a}), 172.4(C_1); mass spectrum, m/z (rel. intensity) 307 (10.2, M), 290(5), 262(12), 120(100), 104(8), 91(12), 43 (21).

(±)-*trans*-6-[2-(Benzotriazol-1-yl)ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one (2a)

To the solution containing 0.66 g (0.23 mmol) of (±)-ethyl *cis*-7-(benzotriazol-1-yl)-3,5-dihydroxy-6-heptanoate in 15 ml of THF was added 1.42 ml of MeOH and followed by the dropwise addition of 4 ml of 3N LiOH. The resulting solution was allowed to be stirred overnight. To the reaction mixture was added 50 ml of Et_2O and stirred for additional 20 min. The organic layer was separated and the aq. phase was diluted with 5 ml of H_2O and extraced with 50 ml of Et_2O. The organic layer was washed with 2N LiOH and the aq. layer was separated. The combined aqueous layer was acidified with 6N HCl (pH=3) and extracted with EtOAc (3×100 ml). The combined organic layer was washed with saline, dried over $MgSO_4$. The removal of the solvent afforded 0.60 g (94%) of white solid, which was directly subjected to lactonization. To the solution of 0.60 g (0.22 mmol) of dried ethyl *cis*-7-(benzotriazol-1-yl)-3,5-dihydroxy-6-heptanoic acid in 20 ml of CH_2Cl_2 was added 1.40 g (0.66 mmol) of 1,3-dicyclohexylcarbodiimide and the resulting mixture was allowed to be stirred for 8 h. After removing the solvent, the resulting solid was dissolved in minimum amount of water, and extracted with Et_2O (3×70 ml). The oily material was purified by column chromatography, eluting with CH_2Cl_2. The latter fractions afforded 0.21 g (37%) of the product as a colorless oil: IR(thin film) υ 3400, 3040, 2960, 1700, 1350, 1260, 730, 700 cm^{-1}; ^1H NMR($CDCl_3$, 300 MHz) δ 1.77(ddd, J_{gem}=14.3, J_{H5A-H6}=11.4, J_{H5A-H4}=3.0 Hz, H_{5A}), 1.98(dm, J_{gem}=14.3 Hz, H_{5B}), 2.34-2.38(m, 2H, H_7), 2.67(AB quartet, 2H, H_3), 2.75-2.83(m, 2H), 4.40(quintet, 1H, J=3.7 Hz, H_4), 4.71(t, 1H, J=6.9 Hz, H_6), 4.84-4.88(m, 2H, H_8), 7.38(t, J=7.6 Hz, 1H), 7.51(t, 1H), 7.63(dd, J=7.6, 4.5 Hz, 1H), 8.04(dd, J=7.6, 4.5 Hz, 1H).

(±)-*trans*-6-[2-(Benzotriazol-2-yl)ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one (2b)

The same procedure described above in compound **2a** was employed for the preparation of **2b** with 0.29



Key: a) i) NaH, ii) $ClCH_2CH_2CH(OEt)_2$, b) H_2O, *p*-TsOH, c) $^-CH_2CO^-CHCO_2Et$ (**6**), d) $NaBH_4$, Et_3B, e) i) 3N aq. LiOH, ii) H_3O^+, f) DCC, toluene.

Scheme 1

g (0.1 mmol) of (±)-ethyl cis-7-(benzotriazol-2-yl)-3,5-dihydroxy-6-heptanoate to give 0.15 g (52%) of **2b** as white platelets: mp 77-78℃, IR(thin film) υ 3400, 3040, 2960, 1700, 1420, 1355, 1260, 1220, 1070, 730, 700 cm^-; ^1H NMR($CDCl_3$, 300 MHz) δ 1.74(ddd, J_{gem}=14.3, J_{H5A-H6}=11.4, J_{H5A-H4}=3.0 Hz, H_{5A}), 1.94(dm, J_{gem}=14.3 Hz, H_{5B}), 2.42-2.52(m, 2H, H_7), 2.67(AB quartet, 2H, H_3), 2.97(s, 1H, OH), 4.37(quintet, 1H, J=3.7 Hz, H_4), 4.80-4.86(m, 1H, H_6), 4.94(t, 2H, J=6.9 Hz, H_8), 7.34-7.40(m, 2H), 7.61-7.86(m, 2H); ^{13}C NMR($CDCl_3$, 75.5 MHz) δ 35.57, 35.62, 38.5, 52.3, 62.4, 72.9, 117.9, 126.4, 144.3, 169.9; mass spectrum, m/z (rel. intensity) 262 (0.4, M+1), 261(2.61, M), 225(0.5), 189(22.0), 146(12.5), 120(100), 105(13.0), 104(38.0), 91(25.0).

RESULTS AND DISCUSSION

The synthetic sequence is quite straightforward as shown Scheme 1. The prerequisite 1H-benzotriazole (**3**) was prepared from *o*-phenylenediamine by previously reported method. The alkylation of benzotriazole by 3-chloropropionaldehyde diethyl acetal (Büchi *et al.*, 1969) in the presence of NaH yielded N_1- and N_2-alkylated products **4** in 4 : 3 ratio. This distribution of the alkylated products is presumably due to the resonance of the deprotonated species. These products can be readily separated and assigned to two isomeric partners by ^1H NMR spectra, of which N_2-alkylated product has a plane of symmetry and by comparing to the reported spectral data of 1H-benzotriazole (Roberts, 1963), thus showing characteristic A_2B_2 system. Hydrolysis of acetal afforded the corresponding aldehyde **5**, which was reacted with dianion **6**, generated from ethyl acetoacetate, to lead hydroxyketo ester **7** in 52% of two-step yield. The keto group was, then, stereoselectively reduced by the previously reported method (Narasaka *et al.*, 1980 and 1984) (i.e. $NaBH_4$ in the presence of triethylborane) to yield *cis*-3,5-dihydroxy ester **8**. No diastereomeric isomer was observed in 300 MHz ^1H NMR spectrum thus confirming a high stereoselectivity of the reduction. During the work-up of the reaction mixture, was isolated dialkoxyethylborane complex, which can also be readily converted to cis-3,5-dihydroxy ester by treating with 30% H_2O_2. Dihydroxy esters **8** were, then, hydrolyzed by treating with 3N LiOH, followed by acidification to give free acids almost quantitatively. The free acids were not fully characterized, but instead lactonized by known method in the presence of DCC to afford **2** as final products.

In vivo antihypercholesterolemic activities of these compounds were evaluated by the method (Hulcher *et al.*, 1973; Zak *et al.*, 1954; *et al.*, 1951) described previously and the preliminary results showed compound **2a** is 85% as potent as mevinolin, in lowering plasma low density lipoprotein (LDL) level. Designed molecules, thus, can be a lead compound for potential hypolipaemic agents. Chiral synthesis of these molecules as well as biological studies will be reported in the near future.

ACKNOWLEDGEMENT

Financial support from the Research Center for New Drug Development (1993) is gratefully acknowledged.

REFERENCES CITED

Alberts, A. W., Chen, J., Kuron, G., Hunt, V., Huff, J., Hoffman, C., Rothrock, J., Lopez, M., Joshua, H., Harris, E., Patchett, A., Monaghan, R., Currie, S., Stapley, E., Albers-Schoenberg, G., Hensens, O., Hirshfield, J., Hoogsteen, K., Liesch, J. and Springer, J., Mevinolin: a highly potent competitive inhibitor of hydroxymethylglutarylcoenzyme A reductase and a cholesterol lowering agent. *Proc. Natl. Acad. Sci., U.S.A.*, 77, 3957-3961 (1980).

Brown, A. G., Smale, T. C., King, T. J., Hasenkamp, R. and Thompson, R. H., Crystal and molecular structure of compactin, a new antifungal metabolite from *Penicillium brevicompactum*. *J. Chem. Soc., Perkin Trans 1*, 1165-1170 (1976).

Büchi, G. and Wuest, H., Synthesis of (±)-nuciferol, J. Org. Chem., 34, 1122-1123 (1969). 3-Chloropropionaldehyde diethyl acetal can be readily prepared by employing the method described therein.

Damschroder, R. E. D. and Peterson, W. D., 1,2,3-Benzotriazole. *Org. Syn. Coll.* Vol. III, 106-108 (1955).

Endo, A., Kuroda, M. and Tsujita, Y., ML-236A, and ML-236B, new inhibitors of cholesterogenesis produced by *Penicillium citrinum*. *J. Antibiotics*, 29, 1346-

1348 (1976).
Endo, A., Monacolin K, a new hypocholesterolemic agent produced by a monascus species. *J. Antibiotics*, 32, 852-854 (1979).
Jendralla, H., Granzer, E., V. Kerekjarto, B., Krause, R., Schacht, U., Baader, E., Bartmann, W., Beck, G., Bergmann, A., Kesseler, K., Wess, G., Chen, L.-J., Granata, S., Herchen, J., Kleine H., Schüssler, H. and Wagner, K., Synthesis and biological activity of new HMG-CoA reductase inhibitors. 3., *J. Med. Chem.*, 34, 2962-2983 (1991), and references therein.
Hulcher, F. H. and Oleson, W. H., Simplified spectrophotometric assay for microsomal 3-hydroxy-3-methylglutaryl CoA reductase by measurement of coenzyme A. *J. Lipid Res.*, 14, 625-631(1973).
Lowry, O. H., Rosenbrough, N. J., Farr, A. L. and Randall, R. J., Protein measurement with the folin-phenol reagents. *J. Biol. Chem.*, 193, 265-275 (1951).
Narasaka, K. and Pai, H. C., Stereoselective synthesis of meso (or *erythro*) 1,3-diols from β-hydroxyketones. *Chem. Lett.*, 1415-1418 (1980).
Narasaka, K. and Pai, F.-C., Stereoselective reduction of β-hydroxyketones to 1,3-diols. *Tetrahedron* 40, 2233-2238 (1984).
Roberts, N. K., Nuclear magnetic resonances and ultraviolet spectra of benzotriazole and its 1- and 2-methyl derivatives. *J. Chem. Soc.*, 5556-5558 (1963) and references therein.
Roth, B. D., Sliskovic, D. R. and Trivedi, B. K., Treatment of hypercholesterolemia. *Ann. Rep. Med. Chem.*, 24, 147-156 (1989).
Roth, B. D., Bocan, T. M. A., Blankley, C. J., Chucholowski, A. W., Creger, P. L., Creswell, M. W., Ferguson, E., Newton, R. S., O'Brien, P., Picard, J. A., Roark, W. H., Sekerke, C. S., Sliskovic, D. R. and Wilson, M. W., Relationship between tissue selectivity and lipophilicity for inhibitors of HMG-CoA reductase. *J. Med. Chem.*, 33, 463-466 (1991), and references therein.
Stokker, G. E., Alberts, A. W., Gifillan, J. L., Huff, J. W., Smith, R. L., 3-Hydroxy-3-methyl-glutarylcoenzyme A reductase inhibitors. 5., *J. Med. Chem.*, 29, 29, 852-855 (1986), and references therein.
Zak, B. and Dickman, R. C., Rapid estimation of free and total cholesterol. *Am. J. Clin. Pathol.*, 24, 1307-1315 (1954).