Arch. Pharm. Res. Vol. 17, No. 2, pp. 104-108, 1994

Aza-Analogue of Mevinolin: Synthesis of Substituted Octahydroisoquinoline, the Bottom Half of Aza-analogue of Mevinolin

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(Received November 17, 1993)

trans-Ethyl 1,2,3,4a,5,6,8a-octahydro-2-benzyl-4-hydroxy-6-methyl-5-isoquinoline-carboxylate was prepared by intramolecular Diels-Alder reaction as a precursor of newly designed aza-analogue of mevinolin.

Key words: Mevinolin, Aza-analogue of Mevinolin, IMDA

INTRODUCTION

The mevinic acids, represented by compactin (**1a**) (Brown *et al.*, 1976; Endo *et al.*, 1976) and mevinolin (**1b**) (Alberts *et al.*, 1980; Endo, 1979), have been attractive because of its effect in lowering plasma cholesterol levels. This hypocholesterolemic activity of **1** and related compounds (Kathawala, 1991) stems from the inhibition of the enzyme, 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase in its conversion of HMG-CoA to mevalonate and coenzyme A, which is the rate-limiting step in the biosynthesis of cholesterol (Grundy, 1988). Recent inferences on the HMG-CoA reductase binding site (Heathcock *et al.*, 1989) as well as studies on structure-activity relationship of **1** and related systems spur us on designing **2**, aza analogue of **1**, as a potential target molecule for investigation of its biological properties. Herein, we wish to report the synthesis of octahydroisoquinoline portion of **2** (Figure 1).

MATERIALS AND METHODS

Melting points were determined on Yanaco micro 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 shift 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). All solvents were reagent grade and used directly without further purification.

N-Benzyl-*t,t*-2,4-hexadienylamine (3c)

After stirring a solution of 3.20 g (0.034 mol) of *t,t*-2,4-hexadienal and equimolar of benzylamine in 30 ml of CH_3OH for 2 h at room temperature, the reaction mixture was cooled to 0℃ and allowed to be stirred for additional 30 min.. To the mixture was added 0.49 g (0.051 mol) of $NaBH_4$, and the resulting mixture was allowed to be stirred for an additional hour. After evaporation of methanol, the reaction mixture was diluted with 100 ml of CH_2Cl_2 and treated with 10% NaOH. The organic layer was washed with water and brine. Evaporation of CH_2Cl_2 gave 4.06 g of yellow liquid, which was distilled under reduced pressure to afford 3.85 g (65%) of pale yellow liquid: bp 136℃ (7.5 mmHg); IR (thin film) υ 3010, 2960, 1600, 1450, 1120, 990, 740, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5H), 6.10 (m, 2H), 5.50 (m, 2H), 3.78 (s, 2H), 3.27 (d, J=6.7 Hz, 2H), 1.74 (d, J=6.7 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 17.9, 50.8, 53.2, 126.7, 128.1, 128.3, 128.6, 129.0, 131.1, 132.0, 140.3.

(E)-5-Bromo-4-oxo-2-pentenoic Acid (4a)

To an ice cold mixture of 3.00 g (0.03 mol) of chromic anhydride in 5 ml of H_2O and 4.75 g of H_2SO_4 in 8.5 ml of H_2O, the solution of 5.28 g (0.027 mol) of (E)-5-bromo-4-hydroxy-2-pentenoic acid (Jahng *et al.*,

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1989) in 25 ml of acetone was slowly added with stirring. After the addition was completed, reaction mixture was stirred for additional 15 h. The reaction mixture was then extracted with ether and the combined ether layers were washed with brine. Evaporation of solvent gave an oily material, which was chromatographed on silica gel, eluting with n-hexane : CH_2Cl_2 (1 : 1), followed by CH_2Cl_2. The early fractions of CH_2Cl_2 gave 4.81 g (92%) of white solid; mp 102-103℃; IR (thin film) υ 3200-2500 (br.), 1680, 1400, 1260, 1055, 970 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, J=18 Hz, 1H), 6.73 (d, J=18 Hz, 1H), 6.43 (br. s, OH), 4.16 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 32.6, 133.5, 136.1, 165.8, 190.2.

Ethyl (E)-5-bromo-4-oxo-2-pentenoate (4b)

Method A: The same procedure described above for **4a**, employed with the mixture of 6.30 g (0.063 mol) of chromic anhydride in 9.5 ml of water, 9.50 g of H_2SO_4 in 17 ml of H_2O, and the solution of 13.31 g (0.066 mol) of ethyl (E)-5-bromo-4-hydroxy-2-pentenoate in 50 ml of acetone. After stirring for additional 15h, the reaction mixture was extracted with ether. The combined ether layers were washed with brine and dried over $MgSO_4$. Evaporation of solvent gave an oil, which was chromatographed on silica gel, eluting with CCl_4 : EtOAc (4 : 1). The early fractions provided 10.10 g (76%) of white crystals; mp 51-53℃; IR (thin film) 3050, 2990, 1715, 1690, 1640, 1440, 1370, 1300, 1180, 1030, 980, 840, 740, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (d J=15.9 Hz, 1H), 6.81 (d, J=15.9 Hz, 1H), 4.28 (q, J=6.7 Hz, 2H), 4.08 (s, 2H), 1.28 (t, J=6.7 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 32.5, 61.5, 133.2, 135.7, 164.7, 190.2.

Method B: The compound **4a** was esterified as an usual manner to afford **4b** in 82-85% of yields. Spectral data were identical with those obtained from method A.

***trans*-Ethyl 1,2,3,4,4a,5,6,8a-octahydro-2-benzyl-4-oxo-6-methyl-5-isoquinolinecarboxylate ($6c_1$)**

The solution of 1.74 g (0.01 mol) of N-benzyl-*t,t*-2,4-hexadienylamine, 2.42 g (0.01 mol) of **4b** and 1.10 g of triethylamine in 20 ml of Et_2O was refluxed for 1.5 h under N_2 atmosphere. To the cooled reaction mixture was added 100 ml of Et_2O and 50 ml of EtOAc. The resulting mixture was washed with saturated aq. K_2CO_3 and dried over $MgSO_4$. Removal of the solvent afforded a sticky material, which was chromatographed on alumina eluting with n-hexane : EtOAc (9 : 1) to provide two major fractions. The spectral data of early fractions are as follows: IR (thin film) υ 3010, 2950, 1700, 1450, 1350, 1280, 1170, 1150, 1040, 1020, 850, 730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.00 (d, 3H, J=6.7 Hz), 1.21 (t, 3H, J=7.2 Hz), 2.31 (dd, 1H, J=11.7, 9.4 Hz), 2.60 (m, 1H), 2.57 (t, 1H, J=3.4 Hz), 2.76 (d, 2H, J=8.7 Hz), 2.85 (dm, 1H, J=11.7 Hz), 3.03 (d, 1H, J=14.5 Hz), 3.17 (d, 1H, J=14.5 Hz), 3.58 (s, 2H), 4.10 (q, 2H, J=7.2 Hz), 5.53 (dm, 1H, J=9.9 Hz), 5.61 (dd, 1H, J=10.3, 1.3 Hz), 7.30 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 19.9, 32.7, 35.6, 46.1, 50.1, 54.5, 60.7, 62.16, 62.2, 125.3, 127.4, 128.4, 128.9, 133.1, 137.1, 173.3, 206.7.

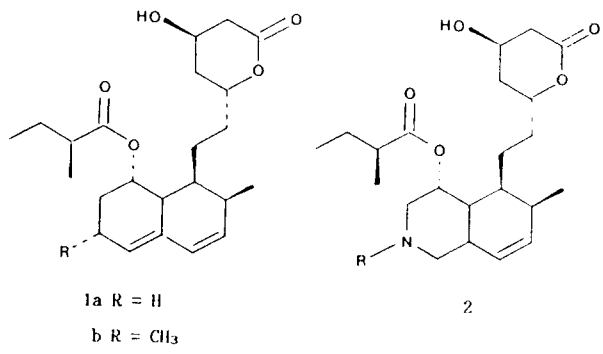

Figure 1

***cis*-Ethyl 1,2,3,4,4a,5,6,8a-octahydro-2-N-benzyl-4-oxo-6-methyl-5-isoquinolinecarboxylate ($6c_2$)**

The spectral data of the latter eluent are as follows: IR (thin film) υ 3010, 2950, 1700, 1450, 1350, 1260, 1150, 1130, 1060, 1020, 910, 850, 730, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 1.05 (d, 3H, J=6.7 Hz), 1.21 (t, 3H, J=7.1 Hz), 2.89 (t, 1H, J=6.0 Hz), 2.98 (dd, 1H, J=15.3, 6.0 Hz), 3.25 (dd, 1H, J=12.0, 2.0 Hz), 3.42 (dm, 1H, J=15.0 Hz), 3.71 (dd, 1H, J=14.8, 7.5 Hz), 3.74 (s, 2H, H_3), 4.09-4.25 (overlapped m, 3H, $-OCH_2-$ and H_{1A}), 4.53 (d, 1H, J=15.0 Hz), 4.80 (d, 1H, J=15.0 Hz), 5.33 (ddd, 1H, J=10.0, 2.7, 0.8 Hz), 5.80(dm, 1H, J=10.3 Hz), 7.28-7.33(m, 5H).

Ethyl (E)-4,5-epoxy-2-pentenoate (7)

To a mixture of 91.40 g (0.41 mol) of ethyl (E)-5-bromo-4-hydroxy-2-pentenoate in 50 ml of 95% EtOH was added 17.70 g(0.55 mol) of NaOH in 50 ml of water and resulting mixture was allowed to be stirred for 15 h at room temperature. Reaction mixture was concentrated and extracted with ether. The combined organic layer was dried and flitered. The filtrate was chromatographed on silica gel, eluting with n-hexane : CH_2Cl_2 (9 : 1). The early fractions were afforded 35.50 g (61%) of colorless liquid; IR (thin film) υ 3040, 2970, 2900, 1710, 1650, 1460, 1380, 1260, 1180, 1150, 1030, 970, 840, 720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.63 (dd, J=15.5, 7.5 Hz, H_3), 6.18 (d, J=15.5 Hz, H_2), 4.19 (q, J=6.7 Hz, 2H), 3.46 (ddd, J=7.5, 3.9, 2.7 Hz, H_4), 3.06 (dd, J=4.8, 3.9 Hz, H_{5A}), 2.72 (dd, J=4.8, 2.7 Hz, H_{5B}), 1.30 (t, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 49.1, 50.2, 124.3, 144.6, 165.4.

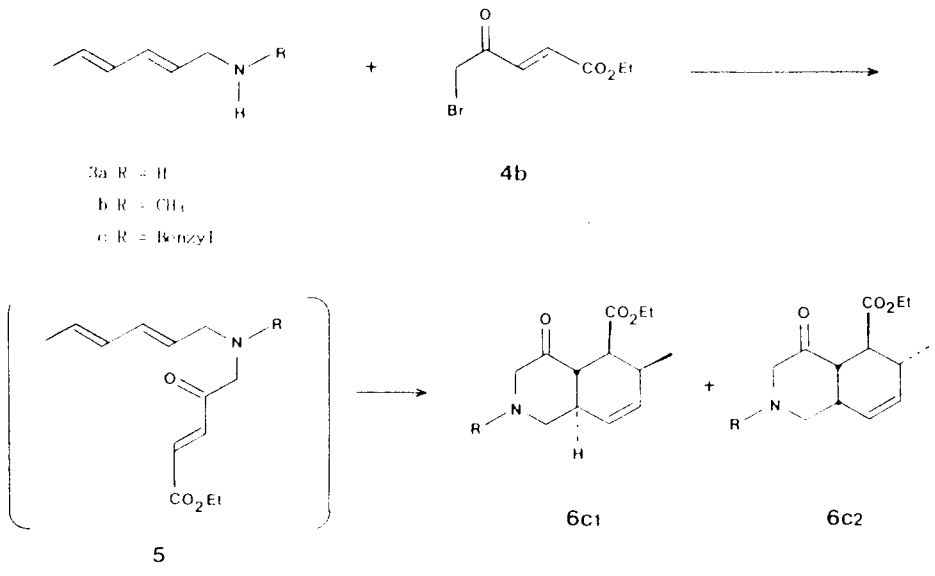

Figure 2

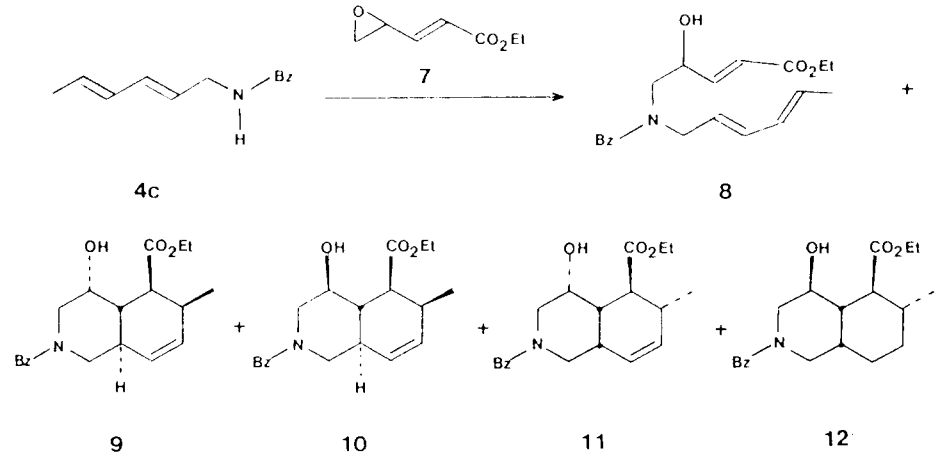

Figure 3

trans-Ethyl 1,2,3,4,4a,5,6,8a-octahydro-2-benzyl-4-hydroxy-6-methyl-5-isoquinolinecarboxylate (9)

The solution of 0.35 g (2 mmol) of **3c**, 0.28 g (2 mmol) of ethyl (E)-4,5-epoxy-2-pentenoate in 10 ml of absolute methanol was refluxed for 46 h. Removal of solvent afforded an oily material, which was chromatographed on silica gel, eluting with n-hexane : EtOAc (9 : 1). The early fractions gave 0.21 g (30%) of ethyl 5-(N-benzyl-N-t,t-2,4-hexadienyl)-amino-4-hydroxy-2-pentenoate (**8**): IR (thin film) υ 3430, 3010, 1700, 1440, 1380, 1260, 1150, 1140, 1050, 1000, 990, 910, 850, 730, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36-7.26 (m, 5H), 6.84 (dd, J=15.0, 4.5 Hz, H_3), 6.42 (dd, J=15.0, 11.6 Hz, H_2), 6.01-6.13 (m, 2H), 5.63-5.69 (m, 1H), 5.49-5.52 (m, 1H), 4.58 (br. s, OH), 4.29-4.32 (m, 1H, methine H), 4.18 (q, J=7.4 Hz, 2H), 3.52-3.80 (AB quartet, benzylic H), 3.29 (dd, 1H), 3.12 (dd, J=14.4, 8.1 Hz, 1H), 2.62 (dd, J=12.9, 3.9 Hz, 1H), 2.50 (dd, J=12.9, 9.9 Hz, 1H), 1.74 (d, J=6.9 Hz, 3H), 1.26 (t, J=7.4 Hz, 3H).

The later fractions afforded 0.05 g (0.94%) of **9** as a crystalline plate: mp 74-76℃ and mixture of **10** and **11**. The spectral data of **9** are as follows: IR (thin film) υ 3430, 3010, 2950, 2890, 2790, 1700, 1440, 1370, 1280, 1170, 1140, 1060, 1020, 990, 910, 880, 730, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (d, 3H, J=7.1 Hz), 1.29 (t, 3H, J=7.1 Hz), 1.56 (td, 1H, J=10.5, 10.2 Hz), 1.76 (t, 1H, J=11.2 Hz), 1.97 (dd, 1H, J=10.3, 10.2 Hz), 2.66 (m, 1H), 2.79 (overlapped dd, 2H, J=11.1, 5.7 Hz), 3.16 (ddd, 1H, J=10.2, 4.5, 1.7

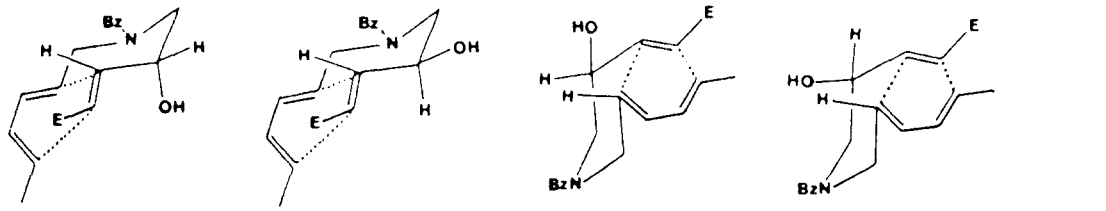

Figure 4

Hz), 3.53 (d, 1H, J=13.0 Hz), 3.57 (d, 1H, J=13.0 Hz), 3.63 (td, J=13.0, 4.4 Hz, 1H), 4.07 (d, 1H, J=3.9 Hz, OH), 4.19 (q, 2H, J=17.1 Hz), 5.33 (br. d, 1H, J=9.8 Hz), 5.59 (ddd, 1H, J=9.8, 4.4, 3.0 Hz), 7.36-7.27 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.1, 17.5, 33.2, 39.4, 42.2, 48.4, 58.3, 61.1, 61.8, 62.5, 70.8, 126.8, 127.1, 128.2, 129.2, 137.9, 177.0; mass spectrum, m/e (rel. intensity) 330 (16.5, M+1), 329 (61.8, M), 314 (8, M-CH_3), 311 (3, M-H_2O), 300 (4, M-C_2H_5), 284 (21.0), 257 (20.0), 256 (66, M-CO_2Et), 238 (9, M-91), 188 (11), 134 (37.5), 120 (45.0), 102 (20.0), 91 (100).

RESULTS AND DISCUSSION

Key of our plan for the synthesis of **2** involved construction of the bottom half by intramolecular Diels-Alder reaction of aza trienoate (eg. **5**, **8**). In this strategy, cyclization of **5** to **6**, via an endo transition state, would introduce each of the stereochemical features in hydroisoquinoline ring in a single step. In addition, proper choice of substituting group on N would be expected to control such a stereochemical aspect.

(E)-2,4-Hexadienylamines (**3**) were prepared by either classical reductive amination method (Borch, 1972) from commercially available (E)-2,4-hexadienal, or azidation of *t,t*-2,4-hexadienyl bromide followed by LAH reduction. Reactions of **3a** and **3b** with ethyl (E)-5-bromo-4-oxo-2-pentenoate (**4b**) was too sluggish to afford the corresponding products, **6a** and **6b**. On the other and, amine **3c** afforded only 4% yield of isolable products, whose structure were chracterized by spectroscopic analysis to show $\mathbf{6c_1}$: $\mathbf{6c_2}$ in 7 : 3 ratio (Figure 2).

As previously have been reported, intramolecular Diels-Alder reaction of diene with activated dienophile proceed with a significant degree of stereoselective to provide an increased ratio of *trans : cis*-fused system, which are oriented from *endo*- and *exo*-transition state, respectively (Martin *et al.*, 1983; Roush *et al.*, 1981). Aza trienoate (**5**), in which the dienophile is highly activated by conjugation with an acyl carbon in the chain connecting the diene and dienophile as well as with ethoxycarbonyl carbon, is expected to provide more portion of $\mathbf{6c_1}$. The reaction would not stop at alkylation stage, but instead to provide the final Diels-Alder adducts. Although stereoselectivity was somewhat achieved, the original synthetic approach was plagued with low yields and arduous procedures to isolate the products. Thus, it was necessary to develop a new approach which involved epoxide ring-opening reaction by amine as a nucleophile. Treatment of **3c** with ethyl (E)-4,5-epoxy-2-pentenoate (**7**) in refluxing MeOH afforded 10% of N-alkylated only product (**8**) plus 90% of a 4 : 1 : 0.2 mixture of coincident N-alkylation and cycloaddition adducts **9**, **10**, and **11**, respectively (Kim, 1993) (Figure 3).

The intramolecular Diels-Alder reaction of aza trienoate is expected to proceed through chair-like endo transition state A and B rather than alternative exo mode especially under the low reaction temperature. The precise nature of the factors responsible for the increase of selectivity is uncertain at present. We, however, reason that the pseudoaxial OH in the transition state A is oriented for maximum hyperconjugative overlap (σ^*_{C-O}-π^*), leading to transition state stabilizing effect as well as the possible 1,3-diaxial interaction between OH and CO_2Et, which might destabilize transition state B (Figure 4).

The coupling constant of H_{4a} would afford structural information of the compound isolated. A one proton triplet of doublet ($J_{4a,5}=J_{4a,8a}=11.0$, $J_{4a,4}=4.4$ Hz) at δ 3.63 was assigned to H_{4a} by 2D NMR analysis. The large vicinal coupling constant shows that the substituted hydroisoquinoline molecule contains *trans*-fused at the fused position. In addition, coupling consatant to H_4 elicits that C_4-OH group is oriented to equatorial, thus having correct stereochemistry required in system 2. Attempts to convert **9** into designed molecule are in progress, which will be reported in the near future.

ACKNOWLEDGEMENT

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

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