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An Efficient Synthesis of Enantiopure SDZ 267-489 via a Resolution/Racemization Method

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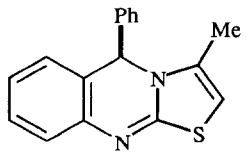
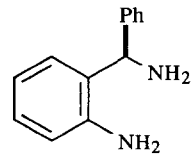
Absract: A new synthesis of (*R*)-3-methyl-5-phenyl-5H-thiazolo[2,3-b]quinazoline **1**, a serum HDL cholesterol raising agent, is described utilizing a resolution of the racemic compound with D-tartaric acid. The undesired S-enantiomer was recycled using either a photochemical or thermal electrocyclic ring opening/closing reaction making the synthesis economical. Copyright © 1996 Elsevier Science Ltd

Although asymmetric synthesis has seen an explosive development during the last decade,[1] classical resolution via crystallization of diastereomeric salts still remains a widely accepted method for obtaining enantiopure compounds on large scale.[2] Most of the asymmetric syntheses require sophisticated operations and unless they provide ≥98% *ee*, further enrichment of the desired enantiomer is often necessary when one deals with drug substances. Conversely, the classical resolution method, owing to its simplicity, is easy to carry out and becomes even more attractive if the undesired enantiomer can be racemized *in situ* or recycled by a simple operation. The synthesis of SDZ 267-489 (**1**) described herein serves as one such example to demonstrate the effectiveness of this strategy.



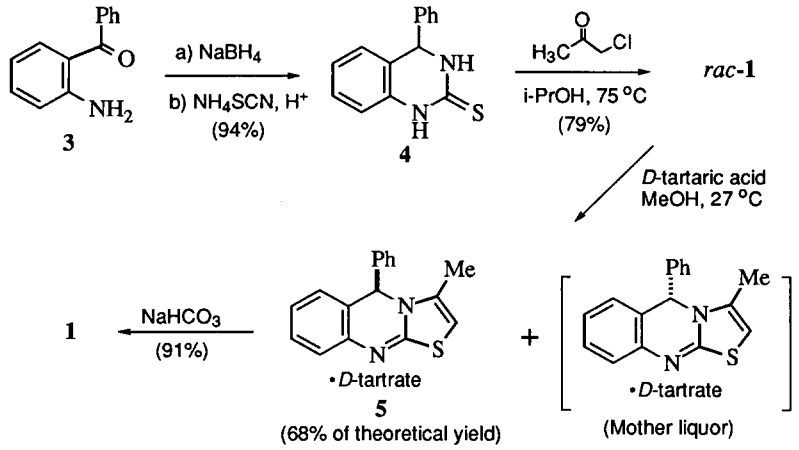
1



2

The original route[3] utilized diamine **2** as the key intermediate and provided **1** only in low yield. Attempts to fix the stereochemistry at the benzylic position via asymmetric synthesis prior to the central ring closure were not successful, and at this stage we turned our attention to classical resolution methodology. Racemic **1** used in the present studies was obtained in high yield by a modified procedure[3] shown in the Scheme 1. Reduction of

2-aminobenzophenone **3** with $NaBH_4$ in 95% ethanol cleanly generated the intermediate alcohol which, without isolation, upon treatment with ammonium thiocyanate and hydrochloric acid gave thiourea **4** in 94% yield. Compound **4** was then condensed with chloroacetone in the presence of a catalytic amount of NaBr and

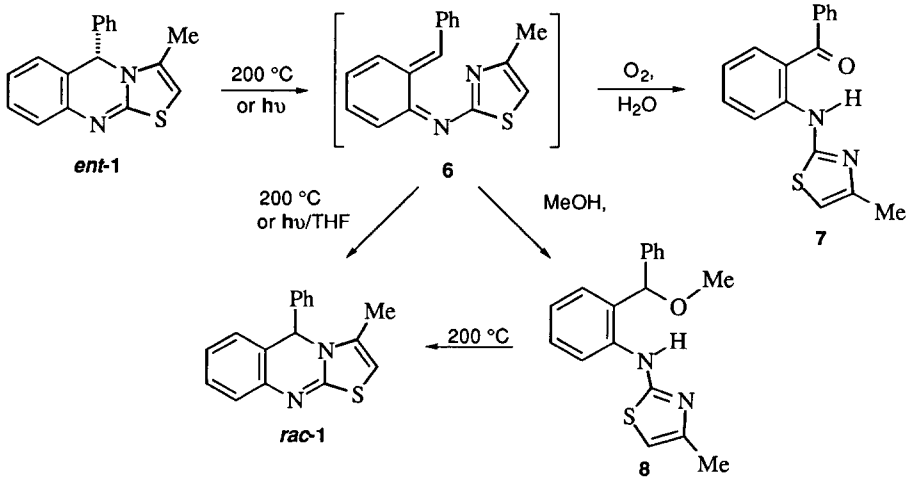


Scheme 1

dehydrated *in situ* to furnish racemic **1** in 79% isolated yield. At this juncture we investigated the resolution of compounds **4** and *rac*-**1**. In our hands, we were unable to effect the resolution of **4**. However, racemic **1** could be resolved into either the pure *R*-enantiomer (**1**) or S-enantiomer (*ent*-**1**) using D or L-tartaric acid respectively. For the desired **1**, *rac*-**1** was dissolved along with a stoichiometric amount of D-tartaric acid in methanol at 35-40 °C, then cooled to 27 °C whereupon crystallization of the diastereomeric salt **5** occurred. Optimization studies indicated that methanol was superior to ethanol as the solvent medium, and that the temperature at which crystallization occurred was critical. The free base **1** (>99% *ee*) was obtained upon basification of **5** with $NaHCO_3$ in 31% yield (62% of the available R-enantiomer).

With an efficient resolution process in hand, methods to recycle the mother liquors from the resolution step were investigated to make the synthesis economical. The doubly benzylic methine proton (also α to nitrogen) at the stereogenic center in compound **1** was found to be resistant toward deprotonation under basic[4] or radical-generating conditions. This is most likely due to the resultant antiaromaticity of the central pyrimidine ring. Limited success was achieved in epimerizing the stereogenic center by first oxidizing the compound with bromine followed by $LiAlH_4$ reduction, which generated racemic thiazoloquinazoline in low yields.

A serendipitous observation led to the discovery of a practical racemization procedure. It was noticed that **1** slowly changed color on a TLC plate (silica gel) when allowed to stand under fluorescent light. On eluting this silica gel plate, we observed a yellow spot with an R_f much higher than that of the parent compound. The ^1H NMR of this new compound prepared deliberately by loading **1** on silica gel and irradiating with a 500 W tungsten lamp revealed that the signal due to the C-5 proton of **1** had disappeared and that a new signal appeared at a much lower field (11.96 ppm in C_6D_6). The ^{13}C resonance was shifted accordingly from 61.0 ppm in **1** to 199.7 ppm. The new compound, a result of oxidative ring opening of the central pyrimidine ring, was assigned structure **7** based on NMR and mass spectra. Our difficulty in oxidizing the C-5 position with a variety of reagents in our earlier studies suggested that **1** could not directly transform to **7**. We thus speculated that the central pyrimidine ring probably undergoes an electrocyclic ring opening (Scheme 2) to give the *o*-quinone methide imine **6** prior to air oxidation. This electrocyclic ring opening is likely promoted by the fluorescent



Scheme 2

light. Further experimentation confirmed this hypothesis. Photolysis of a solution of **1** or *ent*-**1** in methanol, using a medium-pressure Hg lamp and Pyrex filter, afforded the anticipated racemic methanol adduct **8** in almost quantitative yield. With the confirmation of the existence of the the *o*-quinone methide imine **6**, it naturally followed that the reversible electrocyclic process should lead to racemization under the photochemical condition. To our satisfaction, when no trapping agent (methanol) was present, *ent*-**1** cleanly racemized under the photochemical conditions in THF under nitrogen. The formation of *o*-quinone methide imines is well documented in the literature.[5,6] Most of the examples involve thermolysis of the appropriate precursors at

temperatures of about 500 °C.[6] Surprisingly, the thermal electrocyclic ring opening/ring closure of *ent*-**1** was realized under milder conditions, i.e., at a temperature as low as 200 °C. Aromatic stabilization in the thiazole ring during the central-ring opening probably serves to lower the transition state energy.

The thermal racemization can be accomplished by either heating the free base *ent*-**1** neat or as a suspension in an inert medium. In practice, a suspension of the free base in a vegetable oil is heated at 200 °C for 3 hours. The racemic product is collected by filtration and washed with heptane to give analytically pure material in almost quantitative yield. The racemic sample obtained was re-subjected to the resolution sequence thus completing the recycle process.

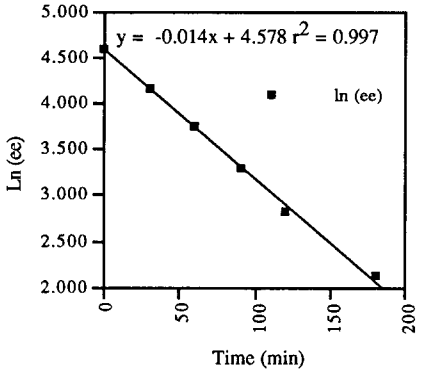


Figure 1. Plot of Ln (ee) vs Time for the photochemical racemization

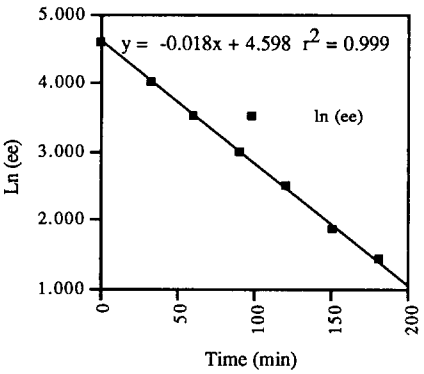


Figure 2. Plot of Ln (ee) vs Time for the thermal racemization

The photochemical racemization was shown to exhibit first order kinetics (Figure 1) with a reaction constant k = 0.014 min^{-1} at 25 °C. Similarly, the thermal racemization also followed first order reaction kinetics (Figure 2) with a reaction constant k = 0.018 min^{-1} at 200 °C. It is very likely that the same intermediate **6** is involved in both racemization processes. Attempts to trap the o-quinonemethide intermediate under thermal conditions were not successful as the intramolecular ring closure competes favorably.

In conclusion, a practical and efficient method for the synthesis of the drug substance SDZ 267-489 has been developed based on a resolution/racemization strategy. Two simple processes to recycle the undesired enantiomer have been devised, thus making the present method a viable alternative to asymmetric synthesis.

EXPERIMENTAL SECTION

Melting points were determined on a Büchi 535 instrument and are uncorrected. NMR spectra were recorded on a Bruker AC 300 NMR spectrometer. IR spectra were obtained on a BioRad FTS-40 FTIR spectrophotometer. Mass spectra were recorded on a Finnigan 4600 spectrometer. HPLC analyses were performed on a Rainin Dynamax apparatus at 254 nm, using a Chiracel OD column and hexane/isopropanol (95:5) with a flow rate of 1 mL/min. Microanalytical data were obtained on a EA 1108 elemental analyzer from Carlo Erba instruments. Commercially available compounds from Aldrich were used in this work .

3,4-Dihydro-4-phenyl-2(1H)-quinazolinethione (4). A solution of 301 g (1.53 mol) of 2-aminobenzophenone **3** in 0.65 L of 95% ethanol was heated to 65 °C under a nitrogen atmosphere. To the mixture was added portionwise over 5 min 30.4 g (0.804 mol) of $NaBH_4$, and the orange mixture was stirred at 65-70 °C for 1.5 h. The resulting off-white suspension was diluted with 0.55 L of water and followed by the dropwise addition of a solution of 125 g (1.64 mol) of ammonium thiocyanate in 0.25 L of water. The temperature was maintained at 65 °C throughout the addition. The reaction mixture was then treated with 0.205 L of concentrated hydrochloric acid in 0.40 L of water and stirred at 65 -70 °C for 2 h. The mixture was cooled to 45 °C and vacuum filtered. The solid was washed with 1.50 L of warm water followed by a wash with 0.60 L of 95% ethanol. The damp solid was suspended in a solution of 0.27 L of methanol and 1.10 L of water. The suspension was stirred at 50 °C for 45 min and filtered hot. The solid was rinsed with 0.50 L of warm water followed by 0.15 L of cold (5 °C) methanol and was dried at 45 °C to afford 343 g (93.5%) of **4** as a white solid: mp 226-229 °C (lit.[3] mp 226-229 °C); ^1H NMR (300 MHz, DMSO-d_6) δ 5.60 (1H, d *J*= 2.5 Hz), 6.93-7.08 (2H, m), 7.13-7.37 (7H, m), 9.19 (1H, s), 10.65 (1H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 56.6, 114.2, 121.2, 123.1, 126.1, 126.9, 127.5, 128.2, 128.6, 134.1, 144.2, 174.6.

(±) - 3-Methyl-5-phenyl-5H-thiazolo[2,3-b]quinazoline (*rac-1*). A mixture of 173.7 g (0.723 mol) of **4** and 13.7 g (0.133 mol) of NaBr was suspended in 0.965 L of 2-propanol and heated to 75 °C under a nitrogen atmosphere. To the rapidly stirred mixture was added 75.2 mL (0.907 mol) of chloroacetone, and the resulting white suspension was stirred at 75 °C for 3 h. The mixture was concentrated *in vacuo*, and the residue was diluted with 0.565 L of ethyl acetate. The suspension was warmed to 45 °C, and a solution of 126 g (1.50 mol) of $NaHCO_3$ in 1.13 L of water was added. The mixture was stirred at 45 °C for 1 h then cooled to 20 °C and filtered. The solid was washed with 1.25 L of warm water and followed by 0.22 L of cold (0 °C)

ethyl acetate. The damp solid was suspended in 2.1 L of acetonitrile and heated to reflux to effect dissolution. The solution was cooled to 10 °C, filtered and washed with 0.25 L of chilled (0 °C) acetonitrile. Vacuum drying of the solid at 45 °C afforded 158 g (78.5%) of ***rac*-1** as a light amber solid: mp 184-185 °C (lit.[3] mp 184-187 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.93 (3H, d, J = 1.3 Hz), 5.67 (1H, q, J = 1.3 Hz), 6.18 (1H, s), 6.85-7.33 (9H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 61.0, 61.0, 96.7, 96.8, 121.4, 123.3, 123.3, 125.2, 126.5, 128.2, 128.7, 129.3, 134.6, 141.1, 143.7, 163.4.

(R)-3-Methyl-5-phenyl-5H-thiazolo[2,3-b]quinazoline, D-tartaric acid salt (5). A mixture of 185 g (0.665 mol) of ***rac*-1** and 3.33 L of methanol was heated to 35-40 °C, and 100 g (0.666 mol) of D-(−)-tartaric acid was added. The mixture was heated at 40 °C to effect dissolution, then cooled to 27 °C and stirred for 2 h at this temperature. The solid was collected by vacuum filtration and washed with 0.20 L of chilled (0 °C) methanol. The solid was vacuum dried at 45 °C to give 96.1 g (34%) of **5** as a white solid: mp 99 °C dec.; $[\alpha]_D^{25}$ −108.5 (c = 1.0, MeOH); IR (KBr) 3200 (br), 1724, 1662, 1530 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.93 (3H, d, J = 1.3 Hz), 3.17 (MeOH, solvated), 4.29 (2H, s), 6.17 (1H, d, J = 1.3 Hz), 6.55 (1H, s), 6.86-6.92 (2H, m), 7.07-7.17 (2H, m), 7.22-7.37 (6H, m); ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.4, 48.4 ($\underline{C}H_3OH$, solvated), 58.8, 71.9, 97.0, 121.9, 122.9, 124.7, 126.7, 127.8, 128.2, 129.0, 134.8, 140.4, 143.7, 162.4, 173.0; CIMS (NH_3) *m/z* 279 (free base, M^+ +1). Anal. Calcd for $C_{21}H_{20}N_2O_6S$+1.55 CH_3OH: C, 56.65; H, 5.52; N, 5.86, S, 6.71. Found: C, 56.52; H, 5.15; N, 5.98; S, 6.47.

(R)-3-Methyl-5-phenyl-5H-thiazolo[2,3-b]quinazoline (1). A suspension of 75 g (0.175 mol) of **5** in 0.875 L of ethyl acetate was heated to 35 °C. To the mixture was added a solution of 56.3 g (0.67 mol) of sodium bicarbonate in 0.57 L of water. The biphasic mixture was stirred at 35 °C for 1 h. The phases were separated, and the organic phase was washed with a total of 0.30 L water, in three equal portions. It was then concentrated *in vacuo*, and the residue was diluted with 0.375 L of heptane and cooled to −10 °C. The product was collected by filtration and washed with 0.10 L of chilled (0 °C) heptane and vacuum dried at 50 °C to afford 44.2 g (91%) of **1** as a white solid: mp 177-179 °C (lit.[3] mp 174-177 °C); 99% *ee* (HPLC); $[\alpha]_D^{25}$ −181.1 (c = 1.0, MeOH) [lit.[3] $[\alpha]_D^{25}$ −181.1, (c = 1.0, MeOH)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.93 (3H, d, J = 1.3 Hz), 5.67 (1H, q, J = 1.3 Hz), 6.18 (1H, s), 6.85-7.33 (9H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 61.1, 96.7, 121.5, 123.3, 123.4, 125.2, 126.5, 128.2, 128.7, 129.3, 134.6, 141.3, 143.7, 163.4.

Thermal racemization of *ent*-1. A mixture of 0.50 L of vegetable oil and 100.0 g ***ent*-1** (66% *ee*, which was obtained by basification of the mother liquor from the resolution step) was heated at 200 °C under nitrogen

for 2 h. The reaction mixture was initally a suspension and became a homogeneous solution when the temperature rose over 120 °C. After 2 h, the mixture was cooled to 50 °C and diluted with 0.2 L of heptane. The suspension was further cooled to room temperature and was vacuum filtered through a Buchner funnel/polypropylene filter pad. The filter cake was washed with 0.3 L of heptane in two equal portions. The collected solid was dried under vacuum to give 97.0 g (97%) of ***rac*-1** as a white solid: HPLC (>99% purity); *R/S* = 49.7 : 50.3.

[2-(4-Methyl-2-thiazolyl)amino]phenylphenylketone (7): (Photochemical oxidation of *rac*-1). A solution of 20.0 g (71.9 mmol) of ***rac*-1** was dissolved in 1 L of THF containing 10 mL of water and deposited on 600 g of silica gel (230-400 mesh). The mixture was irradiated with a 500 W tungsten lamp in a crystallizing dish with external cooling and occassional mixing for a period of 6 days. The silica gel was transfered to a fritted filter and washed with hexane. About 8.5 g (43%) of the starting material was recovered from the silica gel after the hexane washing. The crude product was further purified by flash chromatography on silica gel (hexane) and recrystallized from hexane at -20 °C to give 3.62 g (17%) of **7** as yellow needle-like crystals: mp 60.3-61.3 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38 (3H, s), 6.31 (1H, t, *J* = 0.9 Hz), 6.92 (1H, tt, *J* = 7.4, 0.8 Hz), 7.44-7.50 (2H, m), 7.54-7.59 (3H, m), 7.66-7.69 (2H, m), 8.59 (1H, d, *J* = 8.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.6, 104.0, 117.9, 119.3, 120.4, 128.2, 129.6, 131.7, 134.4, 134.9, 139.2, 143.9, 149.4, 162.4, 199.7; IR (KBr) 3435, 1630, 1587, 1530, 1310, 1260 cm^{-1}; CIMS (NH_3) *m/z* 295.2 (M^+ +1). Anal. Calcd for $C_{17}H_{14}N_2OS$: C, 69.36; H, 4.79; N, 9.52. Found: C, 69.31; H, 4.71; N, 9.50.

N-[2-[(Methoxy)phenylmethyl]phenyl]-4-methyl-2-thiazolamine (8): (Photolysis of *ent*-1 in methanol). A quantity of 2.00 g (7.19 mmol, 66% *ee*) of ***ent*-1** was dissolved in 1 L of methanol in an immersion photoreactor. The solution was purged with nitrogen for 10 minutes and photolyzed with a medium pressure Hg lamp through a Pyrex filter. Analysis of a sample of the mixture after 3 h of photolysis showed that about 50% of the ***ent*-1** had transformed to **8**, and the remaining ***ent*-1** was found to be a 1:1 mixture of the two enantiomers. The solvent was removed after 6.5 hours of photolysis. The residue was purified by flash chromatography (80:20 hexane/ethyl acetate) to afford 2.155 g (97%) of **8** as a white solid: mp 76.0-76.8 °C, ^{1}H NMR (300 MHz, C_6D_6) δ 2.06 (3H, s), 2.98 (3H, s), 5.03 (1H, s), 5.62 (1H, s), 6.71-6.76 (1H, m), 6.86-6.92 (2H, m), 6.96-7.01 (2H, m), 7.06-7.12 (2H, m), 8.30 (1H, d, *J* = 8.2 Hz), 8.72 (1H, s, br); ^{13}C NMR (75 MHz, C_6D_6) δ 17.6, 56.67, 85.7, 102.2, 119.9, 122.2, 127.1, 127.9, 128.6, 129.5,

130.2, 140.5, 140.6, 149.6, 164.1; CIMS (NH_3) *m/z* 311 (M^+ +1); IR (KBr) 701, 747, 754, 776, 974, 982, 1075, 1107, 1132, 1192, 1257, 1312, 1376, 1493, 1580, 1600, 2734, 2828, 2929, 3052, 3148, 3434 cm^{-1} Anal. Calcd for $C_{18}H_{18}N_2OS$: C, 69.65; H, 5.84; N, 9.02, S, 10.34. Found: C, 69.85; H, 5.92; N, 9.02; S, 10.62.

Kinetic Study of Photochemical and Thermal Racemization of *ent*-1.

A) Photochemical Racemization: A quantity of 1 g (3.6 mmol, 99% ee) of ***ent*-1** was dissolved in 1000 mL of THF in an immersion photoreactor. The solution was purged with nitrogen for 10 minutes and photolyzed with a medium pressure Hg lamp through a Pyrex filter at 25 °C. Aliquots of samples were withdrawn and analyzed directly by the HPLC method to determine the optical purities. A plot of Ln(ee) vs Time is shown in **Figure 1**.

B) Thermal Racemization: A quantity of 2.00 g (7.19 mmol, 99% *ee*) of ***ent*-1**, was added to a pre-heated vegetable oil solution (10 mL) at 200 °C under nitrogen. Aliquots of samples were withdrawn, diluted with hexane and analyzed by the HPLC method to determine the optical purities. A plot of Ln(ee) vs Time is shown in **Figure 2**.

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