A Simple Stereoselective Synthesis of the Cholesterol Absorption Inhibitor (−)-SCH 48461

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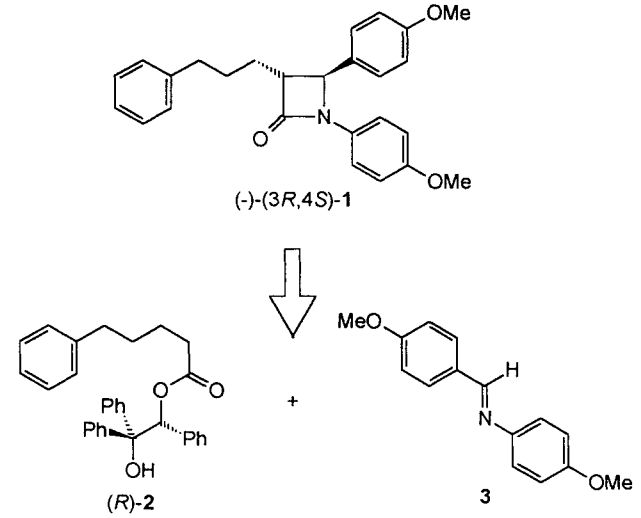
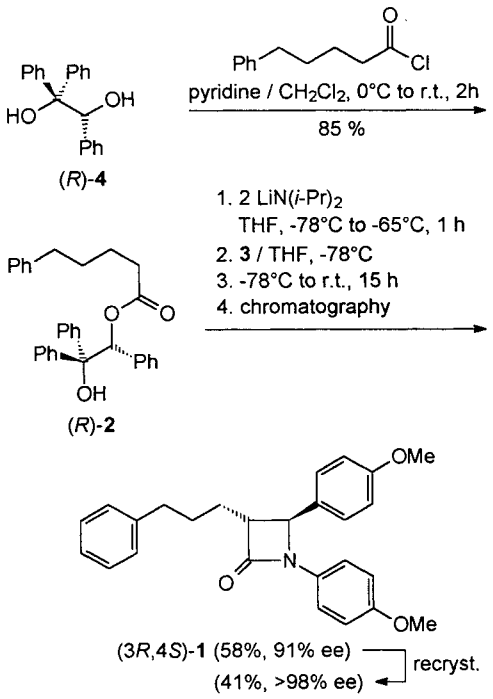
The cholesterol absorption inhibitor (3*R*,4*S*)-**1** is synthesized in 91% ee by a stereoselective condensation of doubly deprotonated ester **2** and imine **3**. The optical purity of the *trans*-diastereomer **1** obtained as the major isomer (*trans*/*cis*, 94:6) is enhanced to > 98% ee by a single recrystallization.

For decades, β-lactams have been known as highly efficient antibiotics.[1] However, the azetidinone **1** has been found to display a completely different biological activity. Thus, a Schering–Plough research group reported recently that **1** acts as a potent inhibitor of intestinal cholesterol absorption, presumably by a novel mechanism of action.[2] The β-lactam **1** was first synthesized as a racemate, the resolution of which was accomplished by chromatography on a Chiracel OD column. A comparison of (−)-(3*R*,4*S*)-**1**, named SCH 48461, with *ent*-**1** revealed that the former stereoisomer provides dramatically greater *in vivo* activity. Although an asymmetric synthesis described recently[3] afforded (−)-**1** it led to the formation of the undesired *cis*-diastereomer (93% ee) which had to be epimerized to a *cis*/*trans*-mixture (1:4) and finally separated. Considering this protocol to be fairly tedious, we decided to apply our esterenolate-imine condensation[4] in order to synthesize SCH 48461 by a facile route (Scheme 1).



Scheme 1

For this purpose, readily available (*R*)-triphenylglycol **(4)**[5] is esterified by treatment with 5-phenylpentanoic chloride[6] to the chiral ester **2**. When ester **2** is doubly deprotonated by treatment with 2 equivalents of lithium diisopropylamide and subsequently allowed to react with imine **3**,[7] the azetidinone **1** is obtained besides triphenylglycol **(4)** which is removed by column chromatography. The *trans*-β-lactam **1** is formed predominantly (94:6) according to the ^{1}H NMR spectra[8] of the crude mixture of **1** and **4**. After removal of the diol **4** and the minor *cis*-diastereomer by chromatography, the enantiomeric excess of *trans*-azetidinone **1** is determined to be 91% ee by ^{1}H NMR measurement in the presence of the chiral shift reagent Eu(hfc)$_3$.[9] The enantiomeric purity of **1** is enhanced to > 98% ee by a single recrystallization from hexane/ethyl acetate. Thus, a straightforward, two-step route is opened to the novel drug SCH 48461 based on the versatile[10] chiral reagent triphenylglycol **(4)**.



Scheme 2

The absolute configuration of the azetidinone **1** obtained from (*R*)-ester **2** is not only assigned by comparison of its optical rotation with the data described,[2,3] but also by the CD spectrum which shows a strong negative Cotton effect. When the octant rule[11] is applied to (3*R*,4*S*)-**1**, the structure of which has been optimized by MOPAC-AM1 calculations,[12] both the aryl substituent at C-4 and the phenylpropyl side chain at C-3 turn out to be located in negative octants. The negative Cotton effect thus predicted is clearly confirmed by the circular dichroism.

Melting points (uncorrected) were determined with a Büchi melting point apparatus 510. Specific rotations were determined with a Perkin–Elmer 341 polarimeter. CD spectra: Jasco J 600. Mass spectra: Varian MAT CH-5. ^{1}H NMR spectra: Varian VXR 300. TLC: Silica gel 60 F_{254} (Merck). Column chromatography: MN-Kieselgel 60, mesh size 0.04–0.063 mm (Macherey-Nagel). General remarks concerning the handling of lithium enolates are given in Ref.[13]

(1′*R*)-5-Phenylpentanoic Acid 2′-Hydroxy-1′,2′,2′-triphenylethyl Ester [(*R*)-2]:

A 500-mL two-necked flask, connected to a combined nitrogen-vacuum line, was equipped with a magnetic stirrer and a dropping funnel and charged with diol **4** (15.1 g, 52.0 mmol), pyridine (4.95 mL, 57 mmol) and anhyd CH_2Cl_2 (200 mL). The mixture was stirred at 0 °C, and a solution of 5-phenylpentanoic chloride (10.3 g, 52.0 mmol) in CH_2Cl_2 (50 mL) was added through the dropping funnel. A white precipitate formed gradually. After stirring for 2 h at r.t., water (200 mL) was added in order to dissolve the hydrochloride, and the organic solvent was removed in a rotary evaporator. The product precipitated thereby and was collected in a suction filter, washed several times with water (300 mL), and air dried with suction for 1 h. The resulting cake was transferred to a 1-L flask and dissolved in toluene (500 mL). The mixture was concentrated by distillation of the solvent at atmospheric pressure until precipitation of the product started. Hexane (100 mL) was added and the mixture was kept in a freezer (−18 °C) overnight. The crystalline product was collected in a suction filter, washed with hexane, and dried in vacuo (oil pump) to give (*R*)-**2** (20 g, 85%); mp 191–192 °C; $[\alpha]_D^{20}$ +166 (*c* = 0.5, $CHCl_3$).

$C_{31}H_{30}O_3$	calc.	C 82.63	H 6.72
(450.6)	found	82.45	6.70

MS (70 eV): *m/z* = 450 (M^+, 0.3), 183 (100).

^{1}H NMR ($CDCl_3$/TMS): δ = 1.41–1.58 (m, 4H, 3-H, 4-H), 2.24–2.27 (m, 2H, 2-H), 2.48–2.52 (m, 2H, 5-H), 2.79 (s, 1H, OH), 6.69 [s, 1H, PhC*H*(OH)], 7.02–7.57 (m, 20 H_{arom}).

(3*R*,4*S*)-1,4-Bis(4-methoxyphenyl)-3-(3-phenylpropyl)-2-azetidinone [(3*R*,4*S*)-1]:

A 100-mL two-necked flask, connected to a combined nitrogen-vacuum line, was equipped with a magnetic stirrer and a septum. During the following manipulations, N_2 atmosphere was maintained in all flasks. Anhyd THF (40 mL) and *i*-Pr_2NH (3.04 mL, 21.8 mmol) were injected through the septum by a syringe. The mixture was stirred at −78 °C, and a 1.6 M solution of BuLi in hexane (14 mL, 21.8 mmol) was added. Stirring was continued for 30 min at 0 °C in order to complete the formation of LDA. In a 250-mL two-necked flask, connected to the combined nitrogen-vacuum line, a solution of the ester **2** (4.7 g, 10.8 mmol) in anhyd THF (100 mL) was stirred at −78 °C. The precooled (−78 °C) solution of LDA, prepared as described above, was added by a cannula, whereby the 250-mL flask was slightly evacuated. The stirred mixture reached −65 °C within 2 h and was then cooled again to −78 °C. A solution of **3** (2.48 g, 10.8 mmol) in anhyd THF (40 mL) was precooled to −78 °C and added by means of a cannula. The mixture was allowed to reach r.t. within 15 h and transferred to a separatory funnel. Et_2O (200 mL) was added, and the mixture was washed with 1 N HCl (2 × 80 mL). The combined aqueous layers were extracted with Et_2O (2 × 50 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), and concentrated in a rotary evaporator. The crude product thus obtained was purified by column chromatography on silica gel (hexane/$CHCl_3$/EtOAc, 8:4:1). The fraction corresponding to R_f 0.35 (diol **4**: R_f 0.25) was collected to give crystalline **1** as a pure diastereomer; ee 91% according to ^{1}H NMR measurement with Eu(hfc)$_3$; yield: 2.5 g (58%); $[\alpha]_D^{20}$ −17.3 (*c* = 0.51, MeOH), corresponding to 90% ee [Lit.[2] $[\alpha]_D$ −19.3 (*c* = 0.623, MeOH)]. Recrystallization (hexane/EtOAc, 1:1) afforded (3*R*,4*S*)-**1** in >98% ee; yield: 1.8 g (41%); mp 47–48 °C [Lit.[2] 46.5–48 °C]; $[\alpha]_D$ −19.0 (*c* = 0.48, MeOH). The spectroscopic data were in accordance with those described in Lit.[2]

^{1}H NMR ($CDCl_3$/TMS): δ = 1.75–1.94 (m, 4H, CH_2CH_2), 2.63 (t, *J* = 7 Hz, 2H, $PhCH_2$), 3.09–3.07 (m, 1H, 3-H), 3.71 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 4.54 (d, *J* = 2.4 Hz, 1H, 4-H), 6.75 (d, *J* = 9 Hz, 2 H_{arom}), 6.87 (d, *J* = 8.7 Hz, 2 H_{arom}), 7.12–7.29 (m, 9 H_{arom}).

^{1}H NMR ($CDCl_3$/TMS): Mixture of **1** (91% ee; 40 mg) and Eu(hfc)$_3$ (75 mg): (3*R*,4*S*)-**1**: δ = 3.78 (s, 3H, OCH_3); (3*S*,4*R*)-**1**: δ = 3.94 (s, 3H, OCH_3).

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(8) In the *cis*-isomer of **1**, the doublet (*J* = 6 Hz) of 4-H is observed at δ = 5.11 (see Ref. 2) which differs distinctly from the corresponding signal of **1** synthesized by us (see experimental).
(9) Eu(hfc)$_3$ = Tris[3-(2,2,3,3,4,4,4-heptafluoro-1-hydroxybutylidene)-*d*-camphorato]europium (Aldrich)
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(12) MOPAC 6.0 package: Stewart, J.J.P. QCPE #455.
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