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Total Synthesis and Absolute Stereochemistry of the Antifungal Dipeptide Sch 37137 and its 2*S*,3*S* - Isomer

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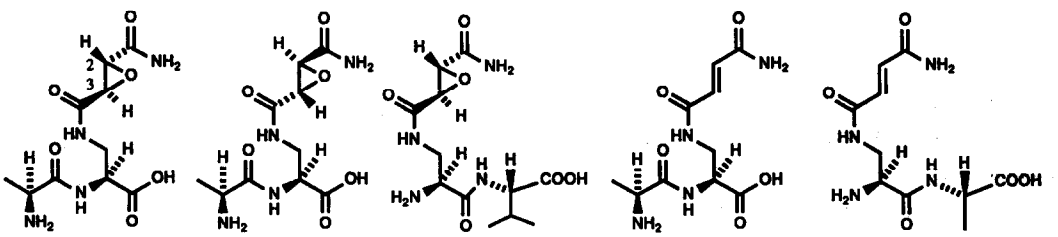
Abstract: The absolute stereochemistry of the epoxide moiety in Sch 37137 has been established as 2*R*, 3*R* by its synthesis from L-tartaric acid.

Sch 37137 (**1**) and A 19009 (**4**), isolated respectively from *Micromonospora Sp.*[1] and *Streptomyces Sp.*,[2] are derivatives of the non-protein amino acid L-2,3-diaminopropanoic acid (L- DAP). Recently, the structurally related CB-25-1 (**3**) was isolated from *Serratia Plymuthica*.[3] The most intensively studied of these compounds, which all display interesting antifungal activities, is A 19009 the structure of which was initially assigned incorrectly as (**5**) but was later revised to (**4**) in the course of its total synthesis.[4] The antifungal activity of (**4**) arises, in part, from its ability to inhibit selectively the glucosamine-6-phosphate synthase from *Candida albicans*.[5] Sch 37137 (**1**) and CB-25-1 (**3**), which differ from (**4**) by having an epoxide ring in place the double bond, showed similar activities, suggesting a common mechanism for their antifungal action.



(1) (2) (3) (4) (5)

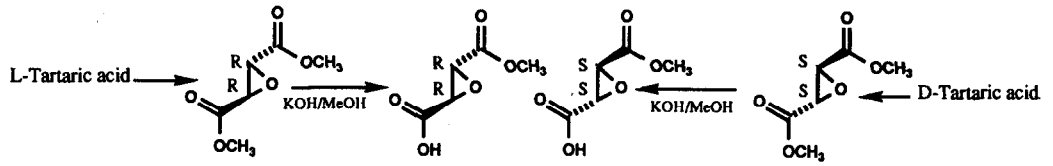
Scheme 1

Spectroscopic and chemical degradation studies in this laboratory[1] firmly established the structure and stereochemistry of Sch 37137, except for the absolute configurations at the C-2 and C-3 epoxy chiral centers. Initially, Sch 37137 was obtained in small amounts because of difficulties in isolating it from the fermentation broth. In order to obtain sufficient quantities for further biological evaluation and to determine the overall absolute stereochemistry, we have carried out a total synthesis of Sch 37137 and its (2*S*,3*S*) isomer (**2**).

The basic strategy for our synthesis of Sch 37137 was the coupling of enantiomerically pure *trans*-2,3-epoxy-succinic acid with L-2,3-diaminopropanoic acid, a reaction which also served as a route for the preparation of a large

number of analogs.

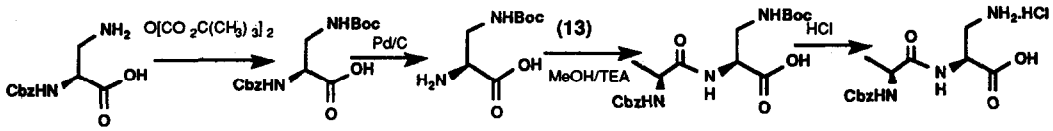
Synthesis of *trans* (2*R*,3*R*)- and (2*S*,3*S*)-epoxy succinic acid monomethyl esters (**6**) and (**7**), respectively, originated with the known corresponding diesters (**8**) and (**9**), which were easily prepared in three steps from L- and D-tartaric acids (Scheme 2) based on the elegant synthesis of Mori and coworkers.[6] Treatment of (**8**) and (**9**) with one equiv. of KOH in MeOH at 0°C and acidic work up with continuous extraction with ethylacetate provided (**6**) and (**7**),[9] respectively, in 69% yield.



(8) (6) (7) (9)

Scheme 2

The amino acid part of the molecule was synthesized in a straightforward manner from the known L-DAP derivative (**10**)[7] (Scheme 3). Thus, treatment of (**10**) with di-*t*-butyldicarbonate at 0°C at pH 9 (with 1N NaOH) in MeOH/H_2O (1:1)[8] gave N^2-benzyloxycarbonyl-N^3-*t*-butoxycarbonyl-L-2,3-diaminopropanoic acid (**11**) in 78% yield. Deprotection of the CBZ group was achieved quantitatively by catalytic hydrogenation on Pd/C in MeOH. Coupling of the amino acid (**12**) with N-carbobenzyloxy-L-alanine-N-hydroxysuccinimide ester (**13**) in MeOH using Et_3N, followed by deprotection of the BOC group in (**14**) with 4N HCl in dioxane overnight at room temperature provided N^2-benzyloxycarbonyl-L-2,3-diaminopropanoic acid hydrochloride (**15**) in 81% yield.

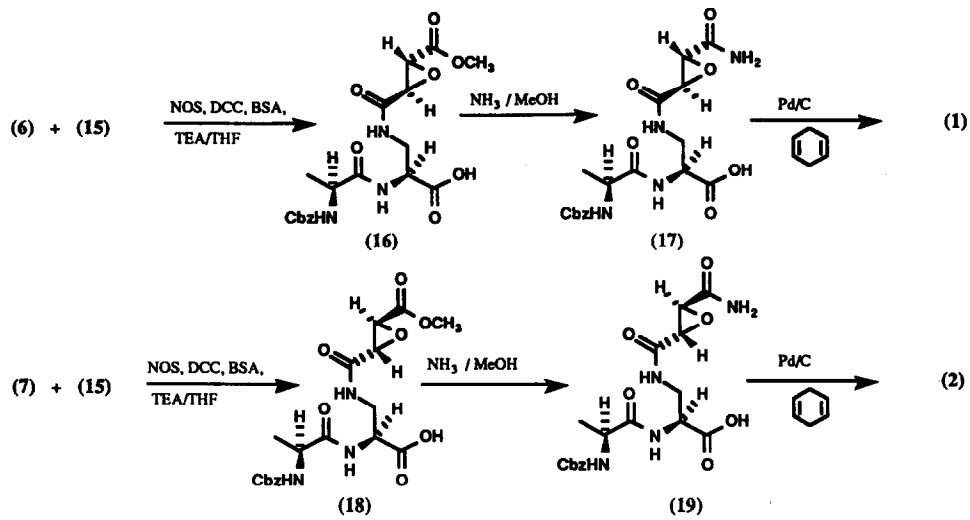


(10) (11) (12) (14) (15)

Scheme 3

The total synthesis of Sch 37137 was achieved by coupling (**6**) with (**15**) using DCC, NOS, TEA, and BSA in THF followed by flash chromatography of the crude product on a reversed phase column eluting with 40% MeOH/H_2O to give the intermediate ester (**16**)[9] in 32% yield. The ester (**16**) was treated with five equiv. of NH_3 in MeOH and the ammonium salt of (**17**) was passed through a CG-50 H^+ resin column to give the crystalline amide (**17**)[9] in 73% yield. A large excess of NH_3 was needed to convert the ester to amide. Interestingly, under anhydrous conditions no evidence of epoxide opening was observed. The CBZ group in (**17**) was then removed by transfer hydrogenolysis using 10% Pd/C and cyclohexadiene in MeOH to provide Sch 37137 (**1**)[9] in 96% yield. Spectroscopic data for synthetic Sch 37137 were identical with those reported for naturally-derived material. This synthesis of Sch 37137 also revealed the absolute stereochemistry to be as depicted in structure (**1**) (i.e 2*R*,3*R*).

In a similar manner, the (2*S*,3*S*) isomer (**2**) of Sch 37137 (**1**) was prepared by coupling (**7**) with (**15**) under the same conditions. The β-protons of the DAP moiety of (**2**)[9] showed a difference in chemical shifts, whereas the remainder of the ^1H NMR spectrum was almost superimposable with that of the natural product (**1**).



Scheme 4

X-ray crystallographic analysis[10] of the synthetic intermediate (17) verified the overall stereochemistry. A view of the structure is provided in Fig. 1. No racemization took place during the coupling reaction.

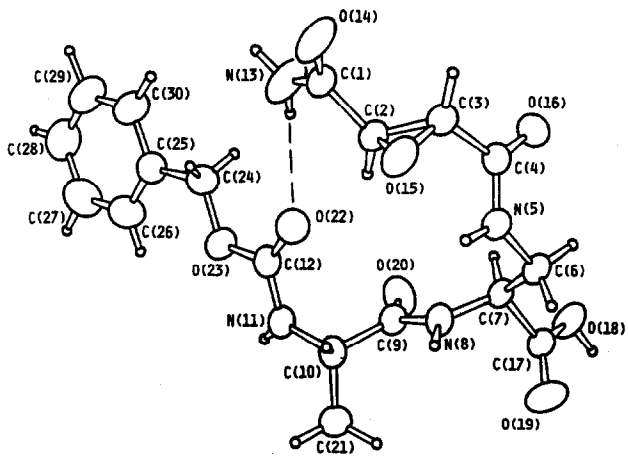


Fig 1. Structure and solid-state conformation of intermediate (17); the broken line indicates an intramolecular N-H...O [N(13)...O(22) = 3.113(3) Å] hydrogen bond.

In conclusion, we have prepared the natural 2*R*,3*R*-epoxy dipeptide Sch 37137 and its 2*S*,3*S*-epoxy isomer, thus establishing the absolute stereochemistry of the epoxide moiety. The synthetic route has provided a means for the preparation of a large number of analogs of Sch 37137 and CB-25-1 for biological investigations and SAR studies, the results of which will be reported elsewhere.

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References and Notes

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9. **Selected spectral and physical data.**

(**1**) : ^{1}H NMR (D_2O) δ 1.55 (d, J = 7.0 Hz, 3H), 3.55 (dd, J = 14.0, 7.0 Hz, 1H), 3.76 (dd, J = 14.0, 4.5 Hz, 1H), 3.67 (d, J = 2.0 Hz, 1H), 3.70 (d, J = 2.0 Hz, 1H), 4.04 (q, 7.0 Hz, 1H), 4.36 (dd, J = 7.0, 4.5 Hz, 1H).
(**2**) : ^{1}H NMR (D_2O) δ 1.52 (d, J = 7.0 Hz, 3H), 3.58 (dd, J = 14.0, 7.0 Hz, 1H), 3.68 (d, J = 2.0 Hz, 1H), 3.70 (d, J = 2.0 Hz, 1H), 3.72 (dd, J = 14.0, 4.5 Hz, 1H), 4.04 (q, J = 7.0 Hz, 1H), 4. 38 (dd, J = 7.0, 4.5 Hz, 1H).
(**6**) : Oil, $[\alpha]_D^{23}$ -99.1° (*c* 0.58, $CHCl_3$) ; ^{1}H NMR ($CDCl_3$) δ 3.75 (s, 2H), 3.85 (s. 6H), 7.20 (s, broad, 1H).
(**7**) : Oil, $[\alpha]_D^{23}$ +91.3° (*c* 0.79, $CHCl_3$) ; ^{1}H NMR ($CDCl_3$) δ 3.72 (s, 2H), 3.83 (s, 6H), 9.50 (s, broad,1H).
(**16**) : Oil, ^{1}H NMR ($CDCl_3$) δ 1.34 (d, J = 7.0 Hz. 2H), 3.68 (m, 2H), 3.69 (s, 1H), 3.7 (s, 1H), 3.70 (s, 3H), 4.21 (q, 1H), 4.60 (m, broad, 1H), 5.02 (q, J = 12.0, 12.0 Hz, 2H), 5.82 (d, J = 7.5 Hz, 1H), 7.3 (s, 5H), 7.62 (d, J = 7.5 Hz, 1H).
(**17**) : Mp 210-212 °C (MeOH); $[\alpha]_D^{23}$ -69.5° (*c* 0.57, MeOH); ^{1}H NMR (CD_3OD) δ 1.34 (d, J = 7.0 Hz, 3H), 3.38 (dd, J = 14.0, 8.0 Hz, 1H), 3.52 (d, J = 4.0 Hz, 1H), 3.53 (d, J = 4.0 Hz, 1H), 3.87 (dd, J = 14.0, 4.0 Hz, 1H), 4.13 (q, J = 7.0 Hz, 1H), 4.60 (dd, J = 8.0, 4.0 Hz, 1H), 5.10 (dd, J = 12.0, 12.0 Hz, 2H), 7.34 (s, 5H).
(**18**) Oil, ^{1}H NMR ($CDCl_3$) δ 1.38 (d, J = 7.0 Hz, 2H), 3.69 (m, 2H), 3.7 (s, 1H), 3.72 (s, 1H), 3.8 (s, 3H), 4.24 (q, 1H), 4.60 (m, broad, 1H), 5.12 (q, J =12.0, 12.0 Hz, 2H), 5.68(d, J = 7.4 Hz, 1H), 7.30 (s, 5H), 7.48 (d, J = 7.5 Hz, 1H).
(**19**) : Mp 208-210 °C (MeOH); $[\alpha]_D^{23}$ + 17.5° (*c* 0.3, MeOH); ^{1}H NMR(CD_3OD) δ 1.40 (d, J = 7.0 Hz, 3H), 3.55 (dd, J = 14.0, 8.0 Hz, 1H), 3.57 (d, J = 4.0 Hz, 1H), 3.59 (d, J = 4.0 Hz, 1H), 3.70 (dd, J = 14.0, 4.0 Hz, 1H), 4.13 (q, 1H), 4.58 (m, 1H), 5.11 (s, broad, 2H), 7.40 (s, 5H).

10. *Crystal data for* (**1**): $C_{18}H_{22}N_4O_8$, M = 422.40, triclinic, space group $P\bar{1}$ (No.1), a = 9.047(1) Å, b = 11.450(1) Å, c = 5.031(1) Å, α = 100.10(1)°, β = 98.00(1)°, γ = 86.47(1)°, V = 507.7(2) Å^3, Z = 1, $D_{calcd.}$ = 1.381 g cm^{-3}, μ(Cu-*K*α radiation, λ = 1.5418Å) = 8.9 cm^{-1}. Intensity data (±*h*,±*k*,+*l*; 2092 non-equivalent reflections; $\theta_{max.}$ = 75°) were recorded on an Enraf-Nonius CAD-4 diffractometer [Cu-*K*α radiation, graphite monochromator; ω-2θ scans, scanwidth (1.00 + 0.14tanθ)°] from a crystal of dimensions 0.20 x 0.26 x 0.50 mm. The crystal structure was solved by direct methods (RANTAN). Full-matrix least-squares refinement (Enraf-Nonius SDP) of atomic positional and thermal parameters (anisotropic C, N, O; isotropic H) converged (max. shift:esd = 0.02) at R = 0.029 (R_w = 0.041) over 2052 absorption-corrected ($T_{max.}$:$T_{min.}$ = 1.00:0.92) reflections with I>3.0σ(I). Atomic parameters, bond lengths, bond angles, and torsion angles for (**1**) have been deposited at the Cambridge Crystallographic Data Centre, Cambridge CB2 1EZ, U.K.

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