The Synthesis of Leualacin[1]

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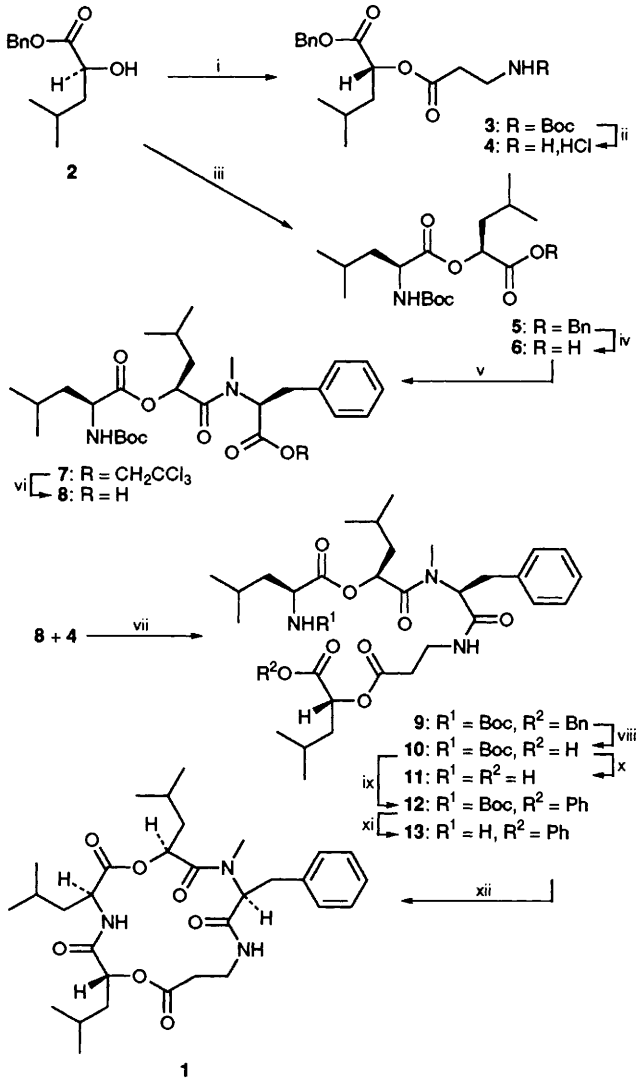
Leualacin, a new calcium blocker isolated from *Hapsidospora irregularis*, has now been synthesized.

Leualacin,[2] a novel calcium blocker has been isolated from *Hapsidospora irregularis* and elucidated to be a cyclopentadepsipeptide. In addition to (*S*)-*N*-methylphenylalanine and (*S*)-leucine, it also contains (*R*)- and (*S*)-2-hydroxy-4-methylvaleric acids and β-alanine. The structure of leualacin is completely different from those of the three classes of clinically used calcium blockers, namely dihydropyridines, benzodiazepines and verapamil derivatives. Leualacin competitively inhibits the specific binding of nitrendipine to porcine heart microsomes.



1

Scheme 1 *Reagents and conditions*: i, PPh_3, diethyl azodicarboxylate, Boc-β-alanine, toluene, 0 °C, 20 h, 69%; ii, 6 mol dm^{-3} HCl, dioxane, 0 °C, 3 h; iii, (*S*)-Boc-leucine, DMAP, DCC, CH_2Cl_2, −20 to 20 °C, 16 h, 90%; iv, MeOH, Pd/C, H_2, room temp., 4 h, 95%; v, (*S*)-H(Me)-phenylalanine trichloroethyl ester, bis(2-oxooxazolidin-*N*-yl)phosphonic chloride (BOP-Cl), *N*-ethyldiisopropylamine, CH_2Cl_2, −15 to 20 °C, 16 h, 77%; vi, Zn, 90% HOAc, room temp., 24 h; vii, *O*-(1,2-dihydro-2-oxo-1-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU), 1-hydroxybenzotriazole (HOBt), MeCN–DMF (10:1), 0 °C, 16 h, 92%; viii, MeOH, Pd/C, H_2, room temp., 4 h, 95%; ix, C_6F_5OH, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC), −15 to 20 °C, 16 h; x, 6 mol dm^{-3} HCl, dioxane, 4 h, 0 °C; xi, 6 mol dm^{-3} HCl, dioxane, 2 h, 20 °C; xii, $CHCl_3$–$NaHCO_3$, room temp., 5 h, 85%

For the construction of the ring of leualacin, we chose to close the amide bond at the unhindered nitrogen atom of leucine or β-alanine since our previous experience has revealed that cyclisation at an *N*-methylamino group (*N*-methylphenylalanine) is not advantageous. Cyclisation at the amino group of β-alanine *via* the pentafluorophenyl ester[3] only proceeded in low yield, thus confirming our previous observations[4] that cyclopeptide formation by means of the pentafluorophenyl esters in the two-phase system chloroform–aqueous sodium hydrogen carbonate solution only occurs satisfactorily at an α-amino group.

For the construction of the depsipeptides of (*R*)- and (*S*)-2-hydroxy-4-methylvaleric acid **3** and **5**, we started from the (*S*)-compound which is readily available from (*S*)-leucine[5] or *via* enantioselective hydrogenation of the corresponding α-acetoxyacrylate.[6] Formation of the (*S*)-ester **5** was smoothly effected from the (*S*)-hydroxy-carboxylate **2** by means of Boc-leucine and DCC. The (*R*)-ester **3** was easily prepared from the (*S*)-hydroxycarboxylate **2** and Boc-β-alanine *via* a Mitsunobu reaction accompanied by simultaneous inversion.

After cleavage of the benzyl protection group, reaction of **6** with *N*-methylphenylalanine trichloroethyl ester furnished the depsipeptide **7**. The ester was deblocked and the resultant carboxylic acid **8** was coupled with **4** to produce the linear depsipeptide **9**.

For the ring-closure step, we compared the activation processes involving diphenylphosphoryl azide (DPPA),[7] pentafluorophenyl diphenylphosphinate (FDPP),[8] *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluoroborate (HATU),[9] and the reaction *via* the pentafluorophenyl ester.[3] For the reaction with the former three reagents, the depsipeptide **9** was deblocked at the carboxy and amino functions. The resultant depsipeptide **12** was than allowed to react in DMF with either DPPA for 96 h or with FDPP or HATU for 18 h, respectively. The reaction solutions were then evaporated and the residues purified by flash chromatography.

Use of DPPA only gave rise to **1**† in very low yield whereas with FDPP and with HATU the yield of **1** was 60 and 50%, respectively. The highest yield for the ring-closure step was achieved *via* the pentafluorophenyl ester **13** in the two-phase system chloroform–aqueous sodium hydrogen carbonate solution, which depended upon the concentration, *i.e.* the rate of addition. The pure product was obtained in 85% yield after a reaction time of 5 h, whereas only 65 and 35% were realized after reaction times of 3 and 1 h, respectively.

The product thus synthesized was found to be identical in all respects (NMR, optical rotation and mass spectra) with the naturally occurring compound.

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Footnote

† δ_H (250 MHz; $CDCl_3$; *J* values in Hz) 7.49 (dd, *J* 9.6, 2.0, 1H), 7.28 (m, 3H), 7.10 (d, *J* 6.3, 2H), 6.20 (d, *J* 9.7, 1H), 5.18 (dd, *J* 7.9, 6.8, 1H), 4.68 (m, 2H), 4.53 (ddd, *J* 10.8, 10.0, 3.9, 1H), 4.04 (ddt, *J* 13.9, 9.9, 4.1, 1H), 3.40 (dd, *J* 14.3, 3.3, 1H), 3.37 (m, 1H), 2.96 (dd, *J* 14.5, 11.5, 1H), 2.89 (s, 3H), 2.57 (dd, *J* 6.8, 3.8, 2H), 1.83–1.42 (m, 8H),

0.95 (m, 12H), 0.68 (d, *J* 6.5, 3H), 0.57 (d, *J* 6.6, 3H), −0.44 (ddd, *J* 14.0, 8.9, 4.1, 1H).

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