The Total Synthesis of Lyciumins A and B[1]

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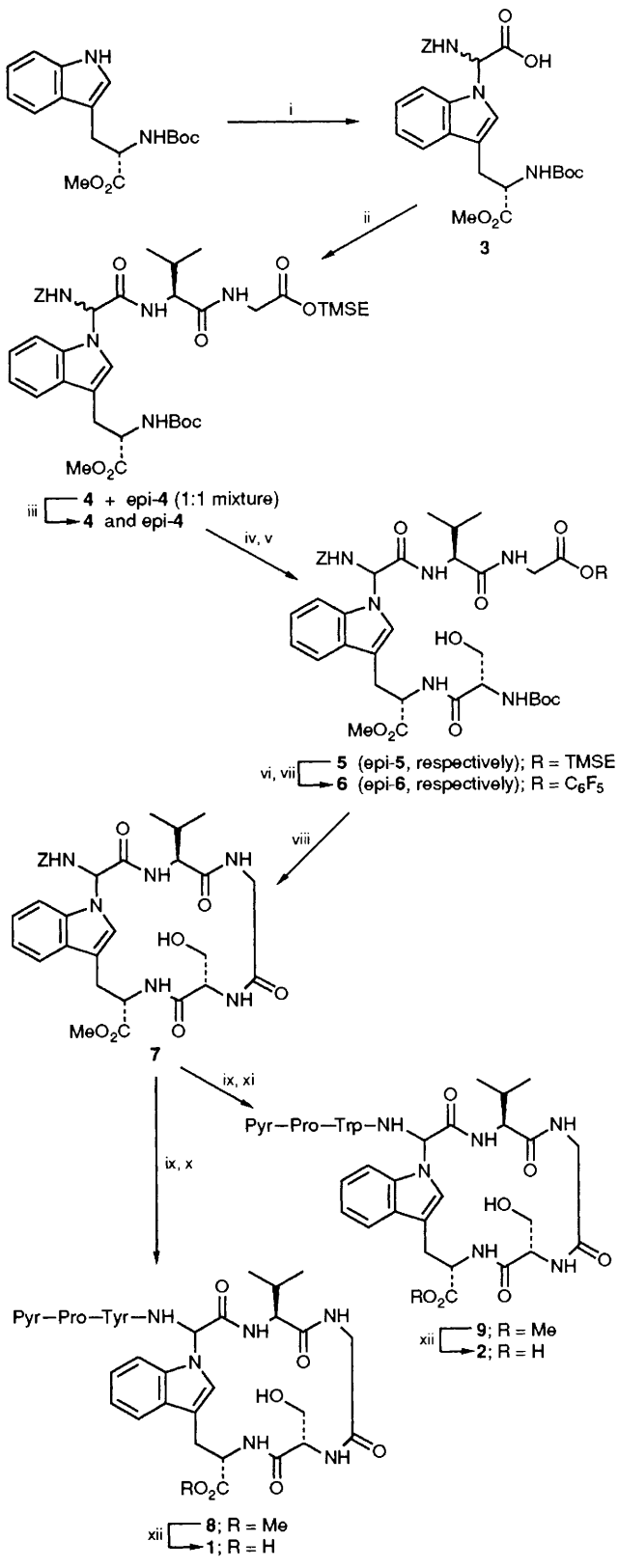
The cyclopeptides lyciumins A and B have been prepared; these compounds are inhibitors of ACE (angiotensin converting enzyme) and renin activities.

Ten *Lycium* taxa (Solanaceae) are widely distributed in East Asia, Europe and North Africa. The best known example in Europe is *Lycium halimifolinum* Mill. (Syn.: *L. barbarum*), the common boxthorn or matrimony vine. Extracts from Lycii radicis cortex, the root bark of *L. chinense* Mill., are used in traditional Chinese medicine as an antifebrile, a tonic, and a hypotensive drug. Previously, liciumamide[2] and kukoamine A[3] had been identified as constituents, isolated, and their structures elucidated. Recently, Yahara *et al.*[4] have isolated and characterised the two cyclopeptides lyciumins A and B. The structures of these compounds are unique in that both nitrogen atoms of the tryptophan are incorporated in the ring with the nitrogen atom of the indole moiety being part of an aminal functional group. Both peptides were found to inhibit renin and ACE activities. In the present communication, we report on the total syntheses of these two naturally occurring compounds.

Aminals can be prepared directly from the compounds by reactions with amides,[5] by way of thioaminals,[6] or by Curtius degradation[7] of α-acylamino acid azides. We have now found that the two epimeric aminals **3** are formed directly in a ratio of 1:1 from glyoxylic acid hydrate, *N*-Boc-tryptophan methyl ester, and benzyl carbamate. After coupling with valylglycine ester, the epimers **4** and **4a** can be separated easily; they were then subjected separately to the further reactions. In the course of these further reactions it was found in the cyclisation step that only one of the two epimers is sutiable for the construction of a cyclopeptide. We have not yet been able to clarify the configuration at the aminal carbon atoms of the two diastereoisomers **4** and epi-**4**.

For the construction of the linear substrate required for ring closure, the epimers **4** and **4a** were coupled with *tert*-butoxycarbonylserine pentafluorophenyl ester to furnish **5** and epi-**5** and subsequently transformed to the pentafluorophenyl esters **6** and epi-**6**, respectively, by conventional methods. Only one of these two isomers was able to undergo ring closure to the cyclopeptide **7**. This ring closure was realized in good yield (64% over three steps) by way of the ω-aminopentafluorophenyl ester[8] in a two-phase system of chloroform–aqueous sodium hydrogencarbonate solution without the need for high dilution conditions. The incorporation of the tripeptide side-chain proved to be difficult as a consequence of the poor solubilities of both components. After some unsuccessful attempts with the pentafluorophenyl esters, this was finally achieved using benzotriazolyltetramethyluronium tetrafluoro-



Scheme 1 *Abbreviations*: Boc = *tert*-butoxycarbonyl, Z = benzyloxycarbonyl, TMSE = trimethylsilylethyl, Pyr = pyroglutamyl, Pro = prolyl, Tyr = tyrosyl, Trp = tryptophyl. *Reagents and conditions*: i, benzyl carbamate, HOC–CO_2H·H_2O, pyridinium toluene-*p*-sulfonate, CH_2Cl_2, Dean–Stark trap, 12 h. 64%; ii, H-Val-Gly-OTMSE, diphenylphosphoryl azide (DPPA), dimethylformamide (DMF), 4 °C, 48 h, 76%; iii, medium pressure liquid chromatography, light petroleum–ethyl acetate (6:4), quantitative; iv, 6 mol dm^{-3} HCl, dioxan, 1 h, 20 °C; v, Boc-Ser-OC_6F_5, DMF, 20 °C, 16 h, 61%; vi, Bu_4NF, DMF, 20 °C, 3 h; vii, C_6F_5OH, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC), DMF, −15 to 20 °C, 14 h; viii, 6 mol dm^{-3} HCl, dioxan, 1 h, 20 °C, evaporation, $CHCl_3$–$NaHCO_3$, 20 °C, 30 min, vi–viii 64%; ix, Pd/C, H_2, DMF, 2 h, quantitative; x, Pyr-Pro-Tyr, 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), DMF, 64%; xi, Pyr-Pro-Trp, TBTU, DMF, 55%; xii, LiOH, H_2O, DMF, 20 °C, 2 h, quantitative

borate.[9] No racemization was detected by HPLC. The methyl ester **9** thus obtained and the methyl ester obtained from naturally occurring **2** after treatment with diazomethane were demonstrated to be identical by HPLC (silica gel column, Merck Hibar, LiChroSorb Si 60, 5 μ; eluent: CH_2Cl_2–MeOH 9:1). The methyl esters **8** and **9** were hydrolysed by lithium hydroxide to furnish lyciumins A and B. These synthesized products were identical with the naturally occurring compounds in every respect (NMR, optical rotation).

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