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Total synthesis of luzopeptin C

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Abstract—The synthesis of luzopeptin C has been accomplished by self-assembly of the macrocycle via activation of a pentapeptide monomer. The present work underscores the generality of the spontaneous macrocyclization approach to the peptins, a strategy introduced by us in connection with the synthesis of luzopeptin E2.

Luzopeptins[1] and quinoxapeptins[2] constitute what may be termed the 'peptin' family of natural products. These substances display extremely interesting biological activities. For instance, luzopeptin C and quinoxa-peptins are potent inhibitors of HIV replication at non-cytotoxic levels in human T-cells in vitro,[2,3] while luzopeptin A may be of interest as an antitumor agent, due to its 1000-fold greater cytotoxicity relative to mitomycin C.[1] Peptins exhibit a largely invariant depsipeptide macrocycle composed of two identical subunits and containing piperazic acid (*piz*),[4] *N*-methyl-3-hydroxyvaline (*mhv*), D-serine, sarcosine and glycine. The structures of four luzopeptins have been firmly established and are shown in Fig. 1.[5] Quinoxapeptins differ from luzopeptins for the nature of the heteroaroyl 'wings' bound to the serine NH_2 groups and of the acyloxy substituents Z/Z' on the *piz* units.[2]

The first reports detailing synthetic studies toward luzopeptins date from the mid-1980s; yet, the extreme difficulties associated with the endeavor have been conquered only very recently. The first syntheses of **1**–**3** and of quinoxapeptins were announced in 1999 by Boger,[6] who also explored various aspects of the bioactivity of the peptins,[7] and who has recently disclosed full details of this work.[8] Our own involvement in the peptin field has generated a number of principles for the formulation of a synthetic plan;[9] in particular, the establishment of methodology for the formation of a problematic *piz*–D-serine dipeptide.[10] These efforts have recently culminated in the total synthesis of **4**.[11] A key aspect of this work is an especially concise solution to the problem of macrocycle assembly. Thus, it was found that the 32-membered ring of luzopeptin E2 self-assembles upon carboxy terminus activation of a

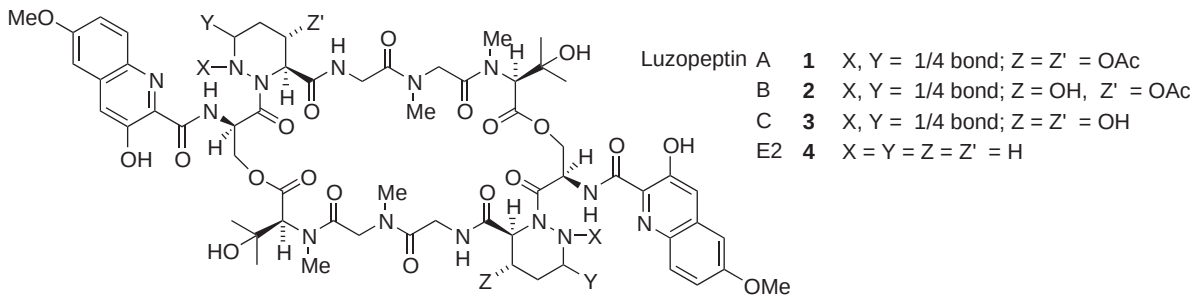

Figure 1.

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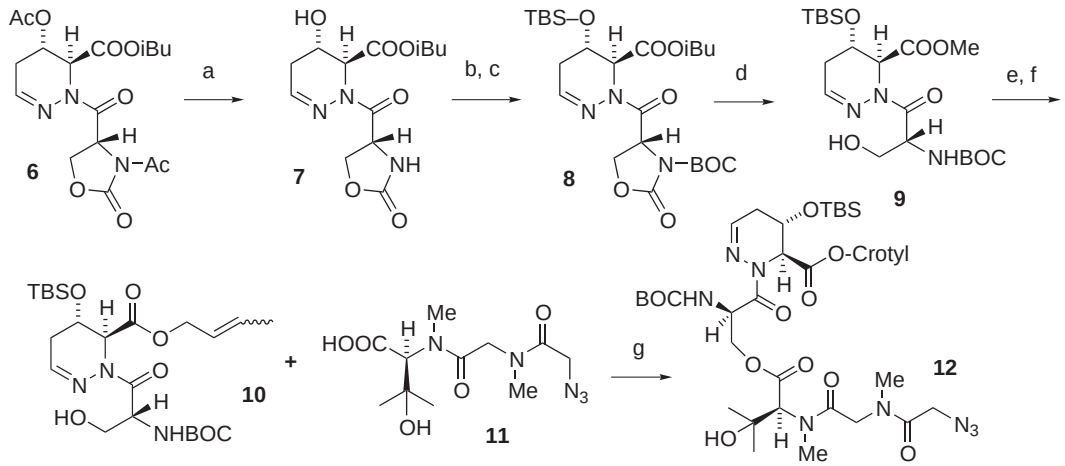
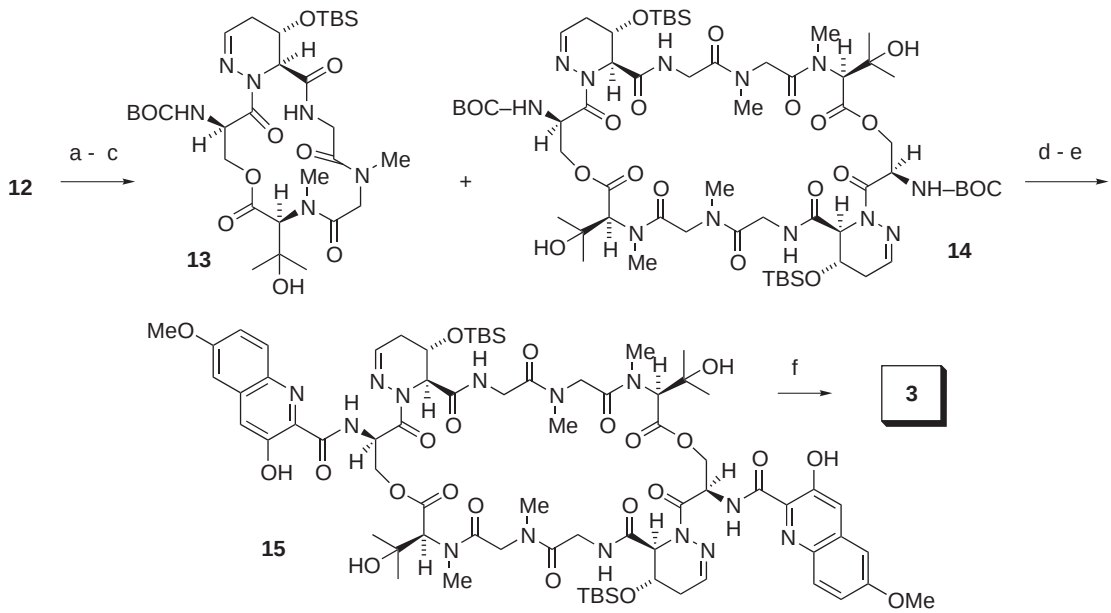
pentapeptide of the type **12**. However, the *piz* component of **4** lacks the oxygen functionality at the β-position of the carboxy unit, and it is thus considerably sturdier than the analogous component of luzopeptins A–C and quinoxapeptins. Earlier work from our group had raised some doubts concerning the applicability of the strategy devised for luzopeptin E2 to the more complex and sensitive C series of peptins. In particular, we had concluded that β-elimination of the OH group in the *piz* unit may complicate base-promoted oxazolone cleavage in substrates of the type **8**,[10a] which are obligatory intermediates toward the ultimate goals. We have now elaborated conditions suitable for the conduct of these operations in the oxygenated series of substrates, and we have verified that macrocyclodimerization of **12** itself is possible. In this Letter, we wish to describe the total synthesis of luzopeptin C.

Oxazolone cleavage in system **8** may be conducted without untoward consequences if the OH group of the *piz* unit is protected as a TBS ether (Scheme 1).[12] Accordingly, standard methods were employed to advance the previously described **6** to intermediate **8**, which upon reaction with Cs_2CO_3 in MeOH suffered not only release of the oxazolone ring, but also transesterification to methyl ester **9**.[13] Peptides incorporating *mhv* are sensitive to the basic conditions required for methyl ester cleavage. Prior to the union of fragment **9** with tripeptide acid **11**,[9e] the methyl ester was therefore exchanged with a crotyl ester, which may be released at



Scheme 1. (a) $N_2H_4{\cdot}H_2O$, MeCN, rt, 4 h, 99%; (b) TBS-Cl, imidazole, DMF, 16 h, 70%; (c) BOC_2O, Et_3N, DMAP, CH_2Cl_2, 95%; (d) 10% w/w Cs_2CO_3, MeOH, 6 h; (e) LiOH, aq. THF, 2 h; (f) crotyl-Br, Et_3N, Me_2CO, 24 h, 65% d–f; (g) DCC (3 equiv.), DMAP (2 equiv.), 0° to rt, 16 h, 60%.



Scheme 2. (a) Cat. $Pd(PPh_3)_4$, dimedone, THF, rt, 5 h; (b) PPh_3, H_2O, THF, rt, 18 h; (c) EDCI (4 equiv.), HOAt (4 equiv.), CH_2Cl_2, 0°C to rt, 16 h, 26% of **14**, 9% of **13** over three steps (a–c); (d) TFA, CH_2Cl_2, 30 min; (e) 3-hydroxy-6-methoxyquinaldic acid, EDCI, HOBt, DMF, $NaHCO_3$, rt, 12 h, 55% d–e; (f) Py-HF, CH_2Cl_2, rt, 12% after extensive purification.

an opportune later stage of the synthesis under neutral conditions (cat. Pd(0)).[14] The reasons for our choice of a crotyl, rather than an allyl, ester, have been addressed elsewhere.[11] Esterification[6] of **10** with free acid **11** afforded pentapeptide **12**: a protected monomeric precursor to the peptin macrocycle.

Carboxy and amino termini in **12** were deblocked to yield the corresponding free aminoacid, an extremely polar substance, which was neither purified[15] nor extensively characterized. Rather, it was immediately subjected to the macrocyclization conditions devised for luzopeptin E2 (70 mg/mL in CH_2Cl_2, EDCI, HOAt), whereupon the desired macrocyclic dimer **14** emerged in 26% chromatographed yield, together with undesired cyclic monomer **13** (ca. 9%) (Scheme 2). Unreacted starting aminoacid (10–15%) and high molecular mass byproducts were also recovered. The BOC groups in **14** were cleaved (TFA) and the now free amino units were acylated with 3-hydroxy-6-methoxyquinaldic acid[11] (EDCI/HOBt). This resulted in formation of **15**, i.e. the bis-TBS ether of luzopeptin C. Desilylation could not be conducted via the customary TBAF treatment, because this reagent inflicted extensive damage to the molecule. We attribute this to the basicity of TBAF and to the vulnerability of intermediates incorporating *mhv* esters and 4-hydroxy-*piz* subunits to basic agents. On the other hand, exposure of **15** to the acidic HF/pyridine complex provided fully synthetic **3**, whose properties were identical to those described in the literature for natural material. Luzopeptins A and B may be obtained by selective acetylation of **3**.[1,6] Therefore, a synthesis of **3** represents a formal synthesis of **1** and **2**.

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