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Total Synthesis of Luzopeptin E2**

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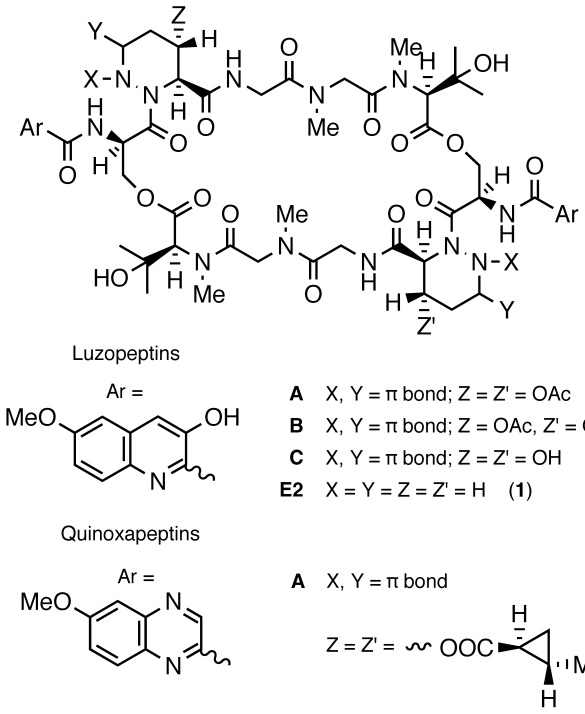
Luzopeptins are symmetric, dimeric macrocyclic depsipeptide antibiotics, which were first described in 1981.[1] Initially, these compounds attracted attention because of their antitumor activity, but the subsequent discovery of their potency as inhibitors of HIV replication in vitro at non cytotoxic doses has stimulated increased interest.[2] The biomolecular target of luzopeptins appears to be reverse transcriptase (RT). This enzyme is found only in retroviruses and it is crucial for their replication. Consequently, it is a prime target for antiretroviral therapy. Anti-HIV activity is even more pronounced in the structurally related quinoxapeptins,[3] which together with luzopeptins constitute what may be referred to as the "peptin" family of natural products. Most known RT inhibitors are nucleoside analogues (e.g, AZT); not so the peptins. This raises a number of questions concerning the mode of action and other details of their bioactivity.

Peptins exhibit an essentially invariant macrocyclic portion that incorporates two unusual components: piperazic acids (piz)[4] and *N*-methyl-3-hydroxyvaline. These delicate subunits complicate the planning of the synthesis, and indeed, peptins have remained elusive goals for a long time. Recently, Boger et al. reported total syntheses of luzopeptins A – C[5] and of the quinoxapeptins.[6, 7] Our own involvement in the peptin area has produced a number of guiding principles for the formulation of a synthetic plan[8] and it has now resulted in the total synthesis of luzopeptin E2 (**1**).[9]



Our strategy is based on the hypothesis that the 32-membered macrocycle of the peptins may self-assemble by spontaneous cyclodimerization of a suitable monomeric precursor.[10] This goal could be accomplished in a macrolactonization (simultaneous formation of both depsi bonds) or a macrolactamization (simultaneous formation of two peptide bonds) mode. Experiment ultimately ruled in favor of the latter approach.

Background work identified pentapetide **10** as our primary subtarget. Oxazolone cleavage[11] of the protected serine – piperazic acid dipeptide **4** obtained from **2**[12] produced the methyl ester **5**, which was converted to the crotyl ester **7** (Scheme 1). This operation was mandated by the sensitivity of later intermediates incorporating an *N*-methyl-3-hydroxyva-

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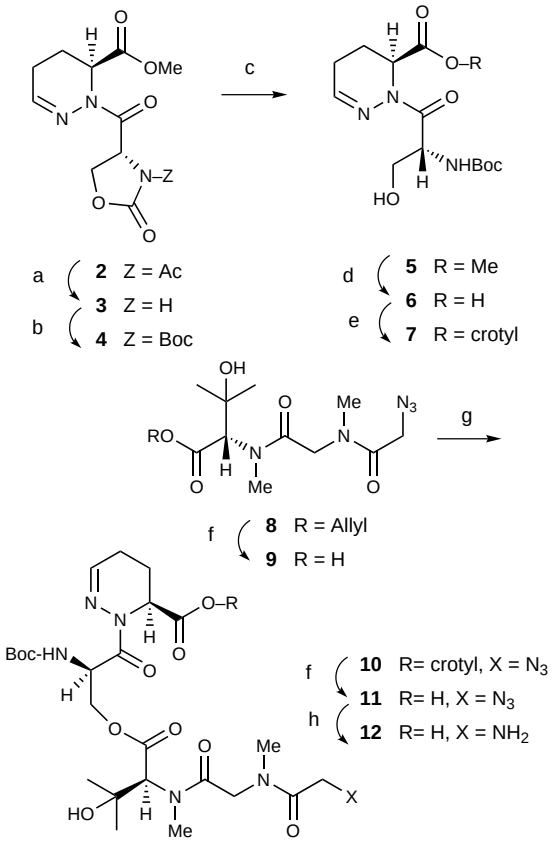
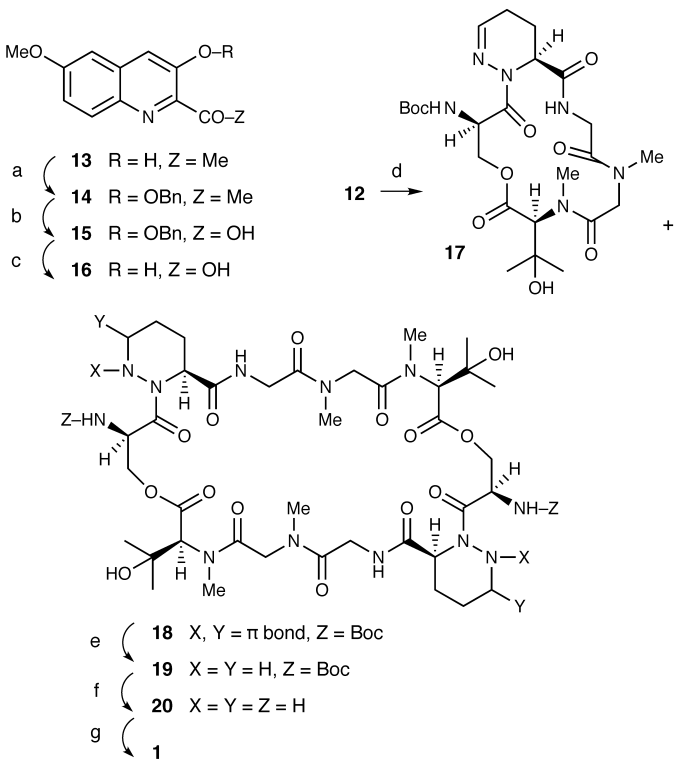


Scheme 1. a) N_2H_4, MeCN, room temperature, 90%; b) BOC_2O, Et_3N, cat. DMAP, CH_2Cl_2, 0°C then room temperature, 100%; c) Cs_2CO_3, MeOH, room temperature, 88%; d) LiOH, THF/H_2O, room temperature, 90%; e) crotyl-Br, Et_3N, Me_2CO, room temperature, 91%; f) [$(Ph_3P)_4Pd$], dimedone, THF, room temperature, yield of **9:** 85%; yield of **11** calculated at the stage of **18** (Scheme 2); g) **7**, DCC, DMAP, CH_2Cl_2, 0°C then room temperature, 95%; h) Ph_3P, H_2O, THF, room temperature. DCC. Abbreviations: Boc = *tert*-butoxycarbonyl; DMAP = 4-dimethylaminopyridine; dimedone = 5,5-dimethyl-1,3-cyclohexandione; DCC = dicyclohexylcarbodiimide.



Scheme 2. a) BnBr, K_2CO_3, acetone, room temperature, 82%; b) aq. NaOCl (bleach), dioxane, H_2O, room temperature, 99%; c) H_2, cat. Pd(C), EtOAc, 60%; d) EDCI, HOAt, 0°C to room temperature, yield of **17**: 10%; yield of **18**: 26% from **10** over three steps; e) H_2, 50 bar, cat. PtO_2, EtOAc, room temperature, 99%; f) TFA, CH_2Cl_2, room temperature; g) **16**, EDCI, HOBt, $NaHCO_3$, DMF, room temperature, 50% from **19** over two steps. Abbreviations: EDCI = 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide; HOAt = 1-hydroxy-7-aza-1*H*-benzotriazole; HOBt = 1-hydroxy-1*H*-benzotriazole; TFA = trifluoroacetic acid.

line unit to the basic conditions normally employed for methyl ester cleavage,[8e] and by the consequent requirement for an ester cleavable under neutral conditions. An allyl ester, the obvious choice, was unsuitable in the present case, due to its propensity to undergo cleavage during subsequent coupling operations. The reasons for this remain unclear, but circumstantial evidence suggested that deallylation was due to S_N'-type displacement of the piz carboxylate group. Increased steric bulk at the terminal olefinic carbon atom cured the problem.[13]

The base-sensitive tripeptide **8**[8e] was selectively deblocked at the C-terminus under neutral conditions, and the resulting acid **9** was esterified[5–7] with fragment **7**. Amino and carboxy termini of the emerging product **10** were deblocked to give **12**—the monomer of the macrocyclic sector of **1**.[14]

Quinaldic acid **16** was obtained in a straightforward manner from quinoline **13**[15] (Scheme 2). Exposure of **12** to EDCI and HOAt[16] produced the desired product **18** in 26% chromatographed yield from **10** over three steps. Undesired cyclic monomer **17** (10% yield) and unreacted **12** (10–15%) were also obtained, together with a mixture of high-molecular-mass substances. The moderate yield of **18** seems acceptable in light of the conciseness of the macrocyclization sequence.

Reduction of the unsaturated piperazic acids was best effected by hydrogenation over PtO_2, which caused no damage to the potentially sensitive N–N bonds. The Boc groups in the resulting **19** were cleaved (TFA) to furnish intermediate **20**. Completion of the synthesis entailed selective acylation of the primary amino groups in **20** with **16** (EDCI, HOBt) to afford fully synthetic luzopeptin E2, whose ^1H and ^{13}C spectra were identical and superimposable with those of natural **1**.[17]

An analogue of **1** that can be considered as an "unnatural" luzopeptin was obtained from **18** by Boc release (TFA) and installation of the quinaldoyl units on the serine amino groups. Chemical reduction of this substance ($NaBH_3CN$, TFA) afforded **1** in mediocre yield, whereas attempted catalytic hydrogenation inflicted extensive damage to the quinolines. It thus appears that the E series of natural products is best accessed by adjusting the oxidation state of the macrocycle prior to introduction of the quinaldic acids.

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[14] Compounds **11** and **12** obtained in this way were contaminated with $Ph_3P{=}O$. These substances were extremely polar and difficult to purify; accordingly, they were not fully characterized. By contrast, macrocyclic materials were easily purified by chromatography. It appears that $Ph_3P{=}O$ does not interfere with subsequent coupling operations, and indeed, it might even assist them; cf.: V. A. Efimov, O. G. Chakhmakhcheva, Y. A. Ovchinnikov, *Nucl. Acids Res.* **1985**, *13*, 3651.
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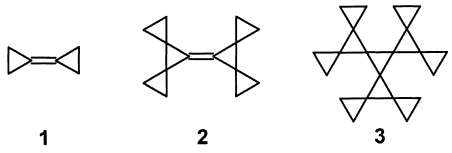
A Third-Generation Bicyclopropylidene: Straightforward Preparation of 15,15′-Bis-(hexaspiro[2.0.2.0.0.0.2.0.2.0.1.0]pentadecylidene) and a C_{2v}-Symmetric Branched [15]Triangulane**

Malte von Seebach, Sergei I. Kozhushkov, Roland Boese, Jordi Benet-Buchholz, Dmitrii S. Yufit, Judith A. K. Howard, and Armin de Meijere*

Dedicated to Professor Paul von Ragué Schleyer on the occasion of his 70th birthday

Bicyclopropylidene (**1**), an interesting laboratory curiosity when first prepared in milligram quantities in 1970,[1] has since become easily available,[2] and due to its unique reactivity, developed into a versatile C_6 building block for organic synthesis.[3] Among other applications, it serves as the best starting material for various branched [*n*]triangulanes—hydrocarbons consisting exclusively of spiroannelated cyclopropane units.[4] The perspirocyclopropanated analogue of **1**, a second-generation bicyclopropylidene **2**, had previously been prepared along a tedious 14-step sequence,[5] and **2** had been further transformed into the perspirocyclopropanated [3]rotane **3** which, with its 10 spiroannelated cyclopropane rings, at that time was the largest achievable [*n*]triangulane.[6]



The classical approach to substituted bicyclopropylidenes by dimerization of 1-halo-1-lithiocyclopropanes generated by treatment of 1,1-dihalocyclopropanes with alkyllithium reagents,[7] has recently been significantly improved by Neu-

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