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Studies toward luzopeptins: a key tripeptide subunit selectively deprotectable under neutral conditions

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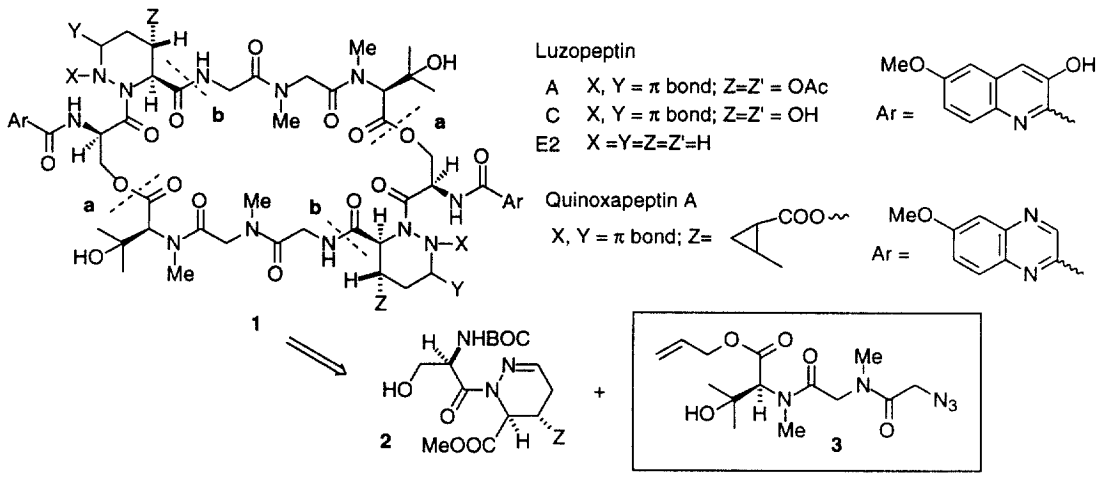
ABSTRACT

We describe a protocol for the multigram preparation of a tripeptide found in peptin antibiotics. The *N*-terminus is an azido group, while the *C*-terminus is an allyl ester. The molecule may be cleanly and selectively deblocked under neutral conditions, facilitating strategic planning for the creation of the macrocyclic sector of all peptins.

Keywords: *luzopeptins, peptides, anti-HIV compounds, azidoacids, N-methyl-3-hydroxyvaline*

Luzopeptins [1] belong to a group of dimeric cyclodepsipeptide natural products (the "peptins", Scheme 1) that includes quinoxapeptins [2] and sandramycin [3]. Interest in these cytotoxic molecules derives especially from their significant antiretroviral activity [4]. The macrocyclic framework of peptins conceals difficult chemical problems, resolution of which

Scheme 1



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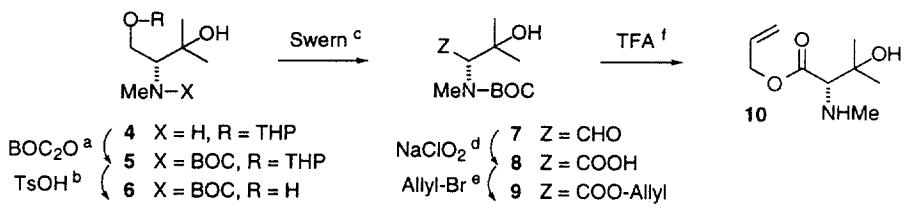
has required development of new chemistry [5-7]. An avenue to **1** may be envisioned through macrolactonization (cf. disconnection **a**, Scheme 1) or macrolactamization (cf. **b**) of an appropriate monomeric segment. Either approach requires fragments **2** [5] and **3**. Both oxygenated piperazic acids ("piz", cf. **2**, Z = OR) [8] and (L)-*N*-methyl-3-hydroxyvaline ("mvh") subunits of **1** are sensitive and especially intolerant of basic agents, which tend to induce β-elimination of the oxygenated functionality. The tertiary OH group also renders mvh somewhat labile under acidic conditions, though BOC deblocking in mvh derivatives may still be effected with TFA. The development of a unified approach to the peptins is thus clearly subordinate to the creation of a form of **3** bearing carboxy– and amino protecting groups that may be easily and selectively released under mild, neutral conditions, so as not harm sensitive advanced intermediates. We now describe methods for the preparation of multigram batches of a variant of **3** in which the C-terminus is blocked as an allyl ester and an azidoacetamide functions as an N-terminal glycine equivalent, demonstrating, *inter alia*, the potential of α-azidoacyl units as latent aminoacids [9].

Scheme 2



(a) CH_2Cl_2, rt. 99%; (b) 10 mol %, MeOH, rt, 2h, 95%; (c) 1.1 equiv. of Swern reagent, THF, –78°C, then Et_3N; (d) Aq. *t*BuOH, 2-Me-2-butene, NaH_2PO_4, 0°C to rt; (e) 3 equiv., Et_3N, acetone, rt., 3h, 78% c-e.; (f) 50% in CH_2Cl_2, then aq. $NaHCO_3$, 96%.

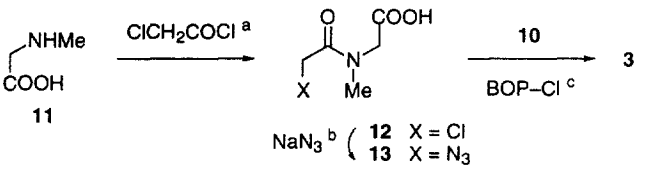
Compound **4** was advanced to **8** by a modification of a previously described [10] route (Scheme 2). Scale-up of the original sequence revealed difficulties with a crucial oxidation of a primary alcohol to a carboxylic acid either with basic $KMnO_4$ under Garner [11] conditions or with RuO_4 according to Sharpless [12]. These problems were especially troublesome when the amino center in **4** was blocked with groups other than BOC. However, Swern oxidation [13] of intermediate **6** to the sensitive aldehyde **7**[1] followed by treatment with $NaClO_2$ in buffered aqueous solution [14] furnished acid **8** in 85 % overall yield and in optical purity corresponding to 90% ee.[2] Only BOC derivatives gave high yields in this sequence, whereas Cbz, Fmoc and Troc analogues of **6** performed poorly. Reaction of **8** with allyl bromide furnished allyl ester **9** in 90% yield. Cleavage of the BOC group afforded **10**.

Reaction of sarcosine, **11**, with chloroacetyl chloride in a biphasic medium of CH_2Cl_2 and aq. Na_2CO_3 and afforded acid **12** in 89 % yield (Scheme 3). This material was easily purified by chromatography (silica, 100% EtOAc). Subsequent reaction of water-soluble **12**

[1]Significant degradation of this delicate substance occurred during attempted chromatography. It was best to advance the crude aldehyde to acid **8** without purification or extensive characterization.

[2]Acid **8** was condensed with (*R*)-(+)-*N*-methylbenzylamine of 99+% ee (Acros) by using BOP-Cl (Et_3N, CH_2Cl_2, 0°C to rt). The compound thus obtained existed as a mixture of rotamers of the tertiary carbamate at rt ($CDCl_3$, 500 MHz ^1H NMR). At 55°C ($CDCl_3$) the spectrum (rotamer-free, well resolved, integrable) clearly showed the two diastereomers of the amide in a ratio of 95:5.

Scheme 3

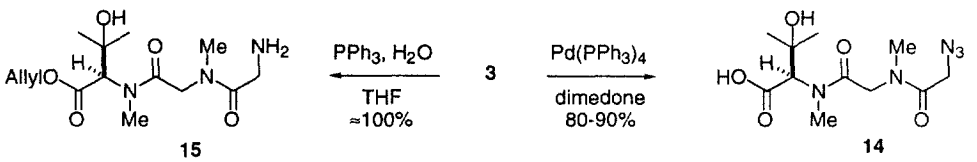


(a) 2 equiv. of acid chloride, 1 equiv. $NaHCO_3$, 1.2 equiv. NaOH, CH_2Cl_2, 0°C, 30 min, 79%.; (b) water, rt. 36 h, 86%; (c) 1.2 equiv.; 1 equiv. of **10**, Et_3N, CH_2Cl_2, 0°C, 1h, 63%.

with NaN_3 afforded azido dipeptide **13** in 85% yield. The final coupling of **13** with **10** was best effected with BOP-Cl as the condensing agent. Dipeptides akin to **13**, but containing an expressed, N-protected glycine, suffered from unfavorable solubility properties in organic media. This created awkward difficulties with their processing. More importantly, tripeptides of the type **3** displaying a free terminal amino group proved to be labile under basic conditions or in the presence of Lewis acidic metal ions. This ruled against the use N-protecting groups such as, e.g., TROC. The use of an azidoacetyl group in lieu of a terminal glycine removed all such difficulties.

Selective deprotection (Scheme 5) of the allyl ester in **3** may be smoothly accomplished using catalytic $Pd(PPh_3)_4$ and dimedone as the acceptor [15].[1] Acid **14** may be purified by chromatography. Complex mixtures were obtained when dimedone was replaced by amines,

Scheme 4



[1]Data for key intermediates [^1H & ^{13}C NMR in $CDCl_3$ with coupling constants J on Hz, IR as films, MS in EI mode, $[\alpha]_D^{25}$ in CH_2Cl_2. **8**: $[\alpha]_D^{25}$ = –31.3 (0.054g/mL). ^1H (50°C): 1.26 (3H, s), 1.38 (3H, s), 1.46 (9H, s), 2.94 (3H, s), 4.55 (1H, s), 6.94 (1H, br). 13C (50°C): 26.2, 28.3, 28.6, 34.2, 65.9, 73.3, 81.1, 157.0, 173.0. IR: 3455-2599, 1689. MS: 115 (100), 248 (M+H). HRMS (EI): calcd. 248.1498; obs.: 248.1503 (M+H). **9**: $[\alpha]_D^{25}$ = – 58.7 (0.143 g/mL). ^1H (50°C): 1.24 (3H, s), 1.36 (3H, s), 1.46 (9H, s), 2.92 (3H, s), 4.59 (1H, br), 4.65 (2H, dt, J_1 = 5.6, J_2 = 1.5), 5.24 (1H, dq, J_1=10.5, J_2 = 1.5), 5.32 (1H, dq, J_1 = 17.3, J_2 = 1.5), 5.91 (1H, ddt, J_1 = 17.3, J_2 = 10.5, J_3 = 5.6). ^{13}C: two rotamers at rt. Major rot.: 25.9, 28.2, 28.8, 33.7, 64.8, 65.5, 72.8, 80.3, 118.5, 131.4, 156.5, 170.8. Minor rot.: 25.8, 28.2, 28.6, 33.1, 65.2, 65.6, 72.8, 80.6, 118.8, 131.1, 155.3, 170.8. At 50°C: 26.2, 28.3, 28.9, 33.2, 65.4, 65.5, 73.0, 80.4, 118.6, 131.6, 170.8. IR: 3488, 1743, 1691. MS (FAB): 57 (100), 288 (M+H). HRMS calcd. 288.1811; obs.: 288.1806. **10**: ^1H : 1.09 (3H, s), 1.33 (3H, s), 2.43 (3H, s), 3.05 (1H, s), 4.68 (2H, dd, J_1 = 6.0, J_2 = 1.5), 5.30 (1H, br. d, J = 10.2), 5.36 (1H, dq, J_1 = 16.8, J_2 = 1.5), 5.93 (1H, ddt, J_1 = 16.8, J_2 = 10.2, J_3 = 6.0). **13**: 3:1 mixture of rotamers at 25°C (NMR). ^1H, major rot.: 3.02 (3H, s), 4.03 (2H, s, overlapping with minor rot.), 4.15 (2H, s), 10.88 (1H, br, overlapping with minor rot.). Minor rot.: 2.98 (2H, s), 3.93 (2H, s), 4.03 (2H, s, overlapping with major rot.), 4.15 (2H, s), 10.88 (1H, br, overlapping with major rot.) ^{13}C, major rot.: 35.8, 49.6, 50.2, 168.9, 172.3; minor rot.: 35.4, 50.3, 50.7, 168.8, 171.5. IR: 3465, 2113, 1735, 1650. MS: 88 (100), 99, 102, 116, 145, 155, 173. **3**: $[\alpha]_D^{25}$ = – 64.7 (0.077g/mL). ^1H (50°C): 1.16 (3H,s), 1.37 (3H, s), 3.00 (3H, s), 3.08 (3H, s), 3.95 (2H, s), 4.22 (2H, s), 3.55 (1H, br), 4.63 (2H, dd, J_1 = 5.9, J_2 = 1.5), 5.02 (1H, br), 5.23 (1H, br. d, J = 10.5), 5.30 (1H, dq, J_1 = 17.3, J_2 = 1.5), 5.88 (1H, ddt, J_1 = 17.3, J_2 = 10.5, J_3 = 5.9). ^{13}C (50°C): 26.4, 28.8, 33.4, 35.7, 49.4, 50.3, 63.7, 65.8, 72.7, 119.0, 131.4, 167.8, 168.7, 169.8. IR: 3414, 2109, 1732, 1650. MS (CI): 155(100), 342 (M+H). HRMS (EI): calcd. 342.1777; obs.: 342.1778 (M+H). **14**: $[\alpha]_D^{25}$ = – 20° (0.023g/mL) ^1H: 1.18 (3H, s), 1.38 (3H, s), 2.99 (3H, s), 3.10 (3H, s), 4.03 (2H, s), 4.16 (1H, d, J = 16.8), 4.43 (1H, d, J = 16.8), 5.02 (1H, s), 7.58 (1H, br). ^{13}C: 26.1, 28.6, 33.6, 35.9, 49.7, 50.2, 63.6, 72.8, 168.5, 169.3, 171.5. IR: 3442.2, 2107.4, 1649.2. MS (FAB): 154 (100), 302 (M+H), 324 (M+Na). HRMS(FAB): calc. 302.1464; obs. 302.1445. **15**: ^1H : 1.19 (3H, s), 1.41 (3H, s), 3.01 (3H, s), 3.11 (3H, s), 3.54 (2H, s), 4.28 (2H, s), 4.69 (2H, br), 5.09 (1H, s), 5.28 (1H, br. d, J = 10.5), 5.34 (1H, dq, J_1 = 17.3, J_2 = 1.5), 5.90 (1H, ddt, J_1 = 17.3, J_2 = 10.5, J_3 = 5.9).

apparently because of sensitivity of mvh esters to base-promoted β-elimination. Reduction of the azido unit is best effected (≈ quantitative yield, NMR) under Staudinger conditions [16] with PPh_3 in the presence of water. Although the byproduct $O{=}PPh_3$ is difficult to separate from **15**, it appears not to interfere with subsequent peptide coupling reactions, and indeed, it might even assist them [17]. Azide reduction may also be effected with Zn/acid. However, residual organic acids (e.g., AcOH, pivalic acid) and metal ions were not removed easily from the crude amine. Base treatment was especially damaging, inducing variable degrees of degradation of the product. Reduction with Zn and inorganic acids such as aq. HCl or aq. NH_4Cl gave mixtures of products.

In summary, the protocols described herein allow the preparation of multigram amounts (>10g) of **3**, thus resolving a significant difficulty associated with work on the synthesis of peptins.

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