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TOTAL SYNTHESIS OF L-156,602, A NOVEL CYCLIC HEXADEPSIPEPTIDE ANTIBIOTIC

Philippe L. Durette,* Florence Baker, Peter L. Barker,[1a] Joshua Boger,[1b]
Steven S. Bondy, Milton L. Hammond, Thomas J. Lanza, Arsenio A. Pessolano,
and Charles G. Caldwell

Department of Medicinal Chemical Research, Merck Sharp & Dohme
Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065

Summary: The total synthesis of the naturally occurring cyclic hexadepsipeptide antibiotic L-156,602 (**1**) is described.

L-156,602 (**1**), isolated from cultures of *Streptomyces* spp. MA6348,[2] represents a novel 19-membered cyclic hexadepsipeptide antibiotic closely related to azinothricin[3a] and A83586C[3b] and, based on comparison of spectral data, apparently identical to PD 124,966.[4] The structure of **1** was determined by NMR spectroscopic and X-ray diffraction analysis,[2] and its absolute stereochemistry established.[2,5] The peptide backbone of **1** is comprised of Gly and five unusual amino acids [(R)- and (S)-Piz,[6] (R)- and (S)-N-hydroxy-Ala, and (2S,3S)-3-hydroxy-Leu], and is appended by a 14-carbon tetrahydropyranylpropionic acid side chain containing five asymmetric centers. We have previously reported asymmetric syntheses of the constituent amino acids[5,7] and the lipophilic side chain,[7,8] as well as studies on the semisynthetic modification of the natural product.[9] In the present communication, we describe the design and execution of a fragment-condensation strategy to the macropeptolide and incorporation of the 14-C side chain to achieve a total synthesis of this biologically interesting natural product. The methodologies developed are applicable to the syntheses of structural analogs of **1** as well as related cyclic depsipeptides.[3]

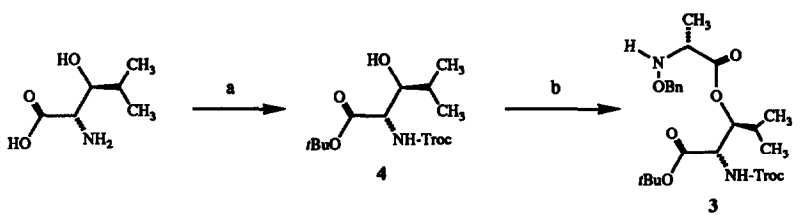
The linkage selected to effect closure of the 19-membered ring in **1** was the peptide bond between the Gly and N-OH-(S)-Ala residues since alternative sites were assessed as presenting potential synthetic difficulties as a consequence of the need for strong activation of carboxy groups in order to achieve acylation of the poorly nucleophilic nitrogens of the Piz and N-OH-Ala residues or the hindered secondary alcohol of the 3-OH-Leu. We devised an overall strategy that comprised (a) elaboration of a suitably protected linear hexadepsipeptide; (b) selective deprotection at the N- and C-termini; (c) cyclization of the resulting linear depsipeptide; (d) selective cleavage of the 3-OH-Leu N-protecting group for acylation by an activated form of the 14-C acid; and (e) removal of remaining protecting groups on the peptide lactone. Successful execution of the total synthesis was dependent on the judicious choice of protecting groups for the amino, carboxy, and hydroxy functionalities of the various amino acids and peptide fragments along the proposed pathway. Such protecting groups required variable and orthogonal degrees of "persistence", thereby allowing for the selective unmasking of reaction centers at the various coupling steps in the sequence.

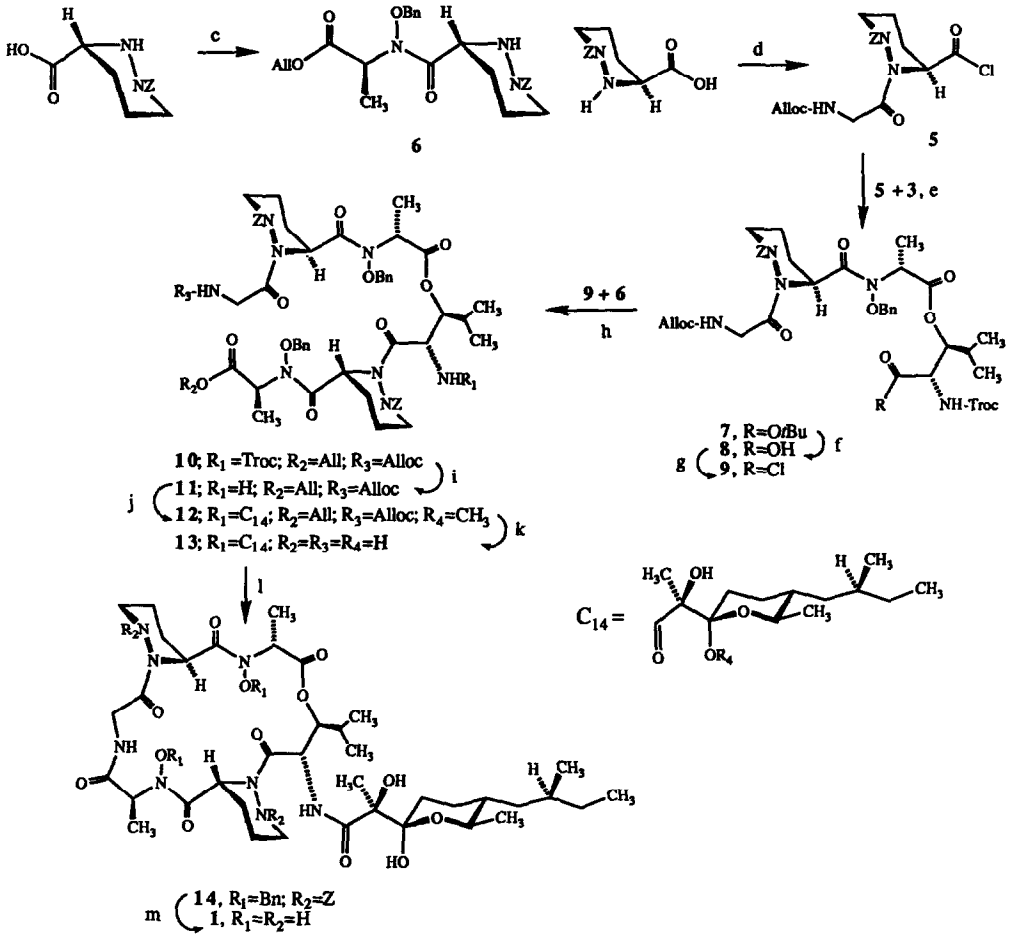
Our assembly strategy consisted of a "2 + 2 + 2" fragment condensation. The rationale for this approach was the establishment of the depsipeptide linkage between the N-OH-(R)-Ala and 3-OH-Leu residues at an early stage of the sequence. The three requisite dipeptide fragments were synthesized as shown in the Scheme below.

Taking advantage of the diminished nucleophilicity of the nitrogen in N-OBn-(R)-Ala **2**, didepsipeptide **3** was prepared in good yield without N-protection by *in situ* activation of **2** as its acyl imidazole and subsequent reaction with alcohol **4**. Condensation to form the the (R)-Piz-N-OH-(S)-Ala dipeptide fragment **6** required strong activation of the carboxy group to effect peptide bond formation due to the attenuated nucleophilicity of the N-OH-Ala nitrogen. This was readily accomplished by application of the two-phase acid chloride methodology developed for N-Fmoc protected amino acid chlorides.[10]

Formation of the peptide linkage between didepsipeptide **3** and dipeptide acid chloride **5** was efficiently carried out by AgCN-assisted amidation.[11] Cleavage of the *t*-butyl ester group in the derived fully protected tetradepsipeptide **7** yielded acid **8**. Conversion of **8** into its acid chloride and coupling with the third dipeptide fragment **6** under Schotten-Bauman conditions[10] afforded the Troc[12]-protected linear hexadepsipeptide **10** in 77% yield. The N-terminal Alloc[13] and C-terminal allyl ester groups were cleaved in a single step by palladium-catalyzed hydrostannolysis[14], which was accompanied by hydrolysis of the methyl pyranoside, to provide the corresponding linear depsipeptide. Ring closure was achieved by means of the mixed phosphonic anhydride method[15] to give protected cyclic hexadepsipeptide in 43% yield. Toward incorporation of the lipophilic side chain, the Troc group on the 3-OH-Leu residue was cleaved with Zn/AcOH, and the resulting crude amine reacted with the HOBt active ester[16] of the 14-C acid. Unfortunately, none of the desired amide was detected, and the only product isolated was the cyclic peptide alcohol resulting from *O,N*-acyl shift.[17] Consequently, resort had to be made to introducing the side chain at the linear hexadepsipeptide stage. In contrast with results obtained with the cyclic amine, reaction of the partially protected linear hexadepsipeptide amine **11** with the HOBt-ester in DMF gave the desired 14-C side chain-linked linear hexadepsipeptide **12** in 56% yield. Palladium-catalyzed hydrostannolysis then resulted in terminal N- and C-deprotection with concomitant conversion of the methyl pyranoside to the hemiketal **13**. Cyclization of the resulting crude linear depsipeptide **13** by the mixed phosphonic anhydride method gave cyclic hexadepsipeptide **14** in 57% overall yield (based on **12**) as a mixture of chromatographically resolvable-conformational isomers. Hydrogenolysis of this mixture to remove the Z and Bn protecting groups on the Piz and Ala residues, respectively, afforded synthetic L-156,602 (**1**) in 53% isolated yield, which exhibited identical spectroscopic (400 MHz ^{1}H NMR in $CDCl_3$ and CD_3CN, ^{13}C NMR, and FAB MS) and chromatographic (TLC, reverse phase HPLC) behavior as the natural product.[2]

Scheme





(a) (i) Troc-Cl, Schouten-Bauman; (ii) iPrN=C(OtBu)NiPr (63%); (b) (i) N-OBn-(R)-Ala (2), CDI, CH_2Cl_2, then 4 (67%); (c) (i) TMS-Cl, then Fmoc-Cl[20](92%); (ii) $(COCl)_2$, cat. DMF; (iii) N-OBn-(S)-AlaOAll[7], 10% $NaHCO_3$, CH_2Cl_2; (iv) Et_2NH (62% based on Fmoc-Piz); (d) (i) $(CH_3)_2C{=}CH_2$, H_2SO_4; (ii) N-Alloc-GlyCl, 10% $NaHCO_3$, CH_2Cl_2 (97%); (iii) TFA; (iv) $(COCl)_2$; (e) AgCN, toluene, 90° (77%); (f) TFA; (g) $(COCl)_2$; (h) **6**, 10% $NaHCO_3$, CH_2Cl_2 (69% based on 7); (i) Zn, AcOH; (j) HOBt-C_{14}, DMF (56%); (k) Bu_3SnH, $(Ph_3P)_2PdCl_2$, CH_2Cl_2, H_2O; (l) $[nPrP(O)O]_3$, DMAP, CH_2Cl_2, 10^{-4}M; (m) H_2, MeOH, 10% Pd(C)

References and Notes

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6. Abbreviations: Piz, piperazic acid; Fmoc, 9-fluorenylmethyloxycarbonyl; Alloc, allyloxycarbonyl; All, allyl; Troc, trichloroethyloxycarbonyl; Z, benzyloxycarbonyl; HOBt, N-hydroxybenzotriazole; BOP, benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate.
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