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SELECTIVE SEMISYNTHETIC MODIFICATION OF L-156,602, A NOVEL CYCLIC HEXADEPSIPEPTIDE ANTIBIOTIC

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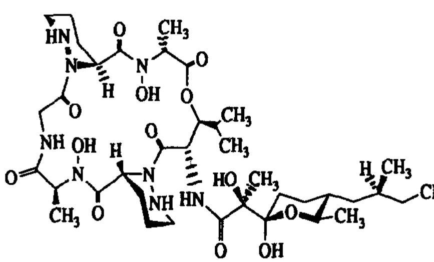
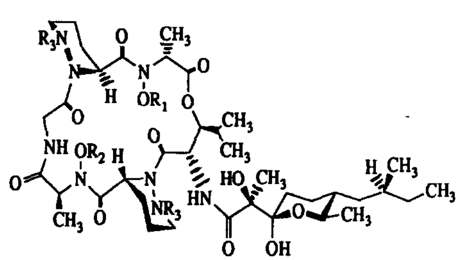
Summary: The cyclic hexadepsipeptide antibiotic L-156,602 has been found to be amenable to a wide variety of selective oxidation, reduction, acylation and alkylation reactions. Both the peptide nucleus and lipophilic side chain displayed remarkable selectivity towards a variety of chemical modifications under acid or neutral conditions.

The antibiotic L-156,602 1, isolated from cultures of *Streptomyces ssp.* MA6348[1a], represents a novel 19-membered cyclic hexadepsipeptide related to azinothricin[1b] and A83586C.[1c] The depsipeptide ring contains five unusual amino acids; (R)-and (S)-piperazic acid (Piz), (R)-and (S)-N-hydroxy-alanine (Ala) and (2S,3S)-3-hydroxy-leucine (Leu). The NMR assignments and X-ray crystal structure of L-156,602 have been determined,[2a] and the absolute stereochemistry established by comparison of 3-OH Leu obtained from acid hydrolysis of 1 with authentic synthetic samples of (2R,3R)-and (2S,3S)-3-OH Leu.[2a,b] Asymmetric syntheses of the constituent amino acids and the lipophilic side chain,[3a] as well as a total synthesis of 1,[3b] have been reported from our laboratories. The interesting biological properties of 1 prompted us to develop methodology for its selective modification with specific analogs targeted to define structure-activity profiles. Inspection of the literature revealed little precedence for the selective modification of such base sensitive depsipeptides.[4] The results of our studies on the modification of the lipophilic side chain and peptide portions of 1 are described below.

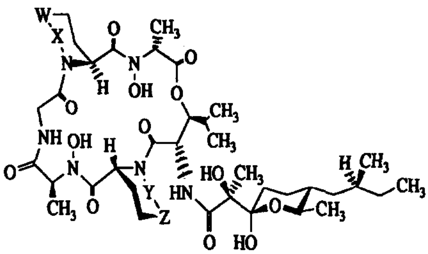


1

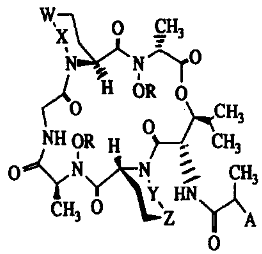


2; R_1= H; R_2= CBZ; R_3= H
3; R_1= R_2= CBZ; R_3= H
4; R_1= R_2= H; R_3= CH_3

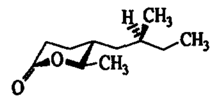
The N-OH-Ala residues were selectively mono- or bis-protected as the corresponding benzyl carbonates 2 and 3, respectively,[5] which were readily removable by catalytic hydrogenolysis. Interestingly, both of the (R)- and (S)-Piz secondary nitrogens resisted acylation, even under forcing conditions. However, both (R)-and (S)-Piz secondary nitrogens were reductively methylated under Borch[6] conditions to give 4 in fair yield. The Piz residues of natural product 1 could be oxidized to yield either the monodehydro product 5 or the bis-dehydro compound 6 with meta-chloroperbenzoic acid (mCPBA). Oxidation of 1 or 3 with other organic peracids, peroxides or hypochlorite either gave back starting material or resulted in decomposition. The lipophilic side chain of 3 was readily cleaved at the vicinal diol function with periodic acid with concomitant oxidation of the Piz residues to give bis-dehydropyruvamide 7 and C-11 lactone 8[3a] in good yield. Reaction of 1 with various oxidizing agents gave a complex mixture of products, indicating the requirement for initial protection of the N-OH Ala residues.



5; W-X = [CH=N]; Y-Z = [NHCH$_2$]
6; W-X = [CH=N]; Y-Z = [N=CH]



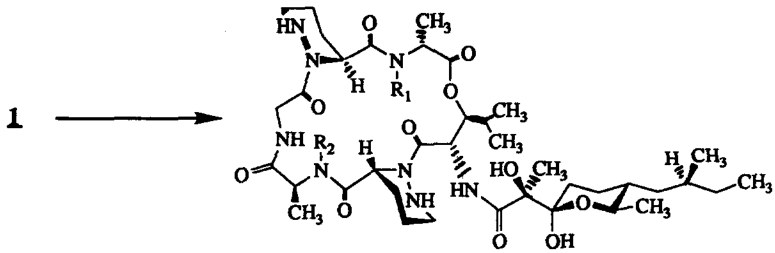
7; A= [=O]; R= [CBZ]; W-X; Y-Z; = [N=CH]
9; A= [H,OH]; R= [CBZ]; W-X; Y-Z; = [NHCH$_2$]
10; A= [(OEt)$_2$]; R= [CBZ]; W-X; Y-Z; = [N=CH]
11; A= [(OEt)$_2$]; R= [CBZ]; W-X; Y-Z; = [NH-CH$_2$]
12; A= [(OEt)$_2$]; R= [H]; W-X; Y-Z; = [NH-CH$_2$]
13; A= [=O]; R= [H]; W-X; Y-Z; = [NH-CH$_2$]



8; $[\alpha]_D = +90°$

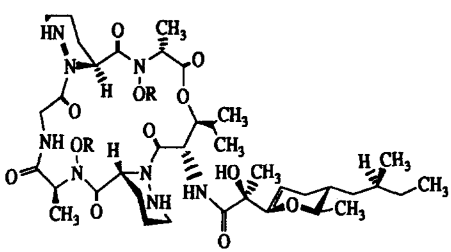
Sodium cyanoborohydride reduction of 7 in glacial acetic acid afforded a diastereomeric mixture of the bis-reduced-Piz alcohols 9 in low yield. A method was needed to selectively reduce the bis-dehydro-Piz residues of 7 in the presence of the 2-keto function of the pyruvamide. A workable solution consisted of forming the pyruvamide diethyl ketal 10, and reducing the dehydro-Piz residues to 11 with sodium cyanoborohydride in glacial acetic acid. The (R)-and (S)-N-O-carbobenzyloxy (CBZ)-Ala residues were readily hydrogenolyzed to 12, and ketal hydrolysis proceeded cleanly in aqueous HCl to give 13 [6 N HCl, 55°, 6h]. Both the (R)- and (S)-N-OH-Ala and the pyruvamide keto group were remarkably stable to strong aqueous acid. Reductive reactions on 1 or derivative fragments proceeded slowly under weakly acidic conditions with sodium cyanoborohydride, whereas sodium borohydride in THF, ethanol or glacial acetic acid cleaved the depsipeptide ester bond.

The (R)- and (S)-N-hydroxy-Ala residues of 1 displayed a marked regioselectivity for O-alkylation and deoxygenation. Treatment of 1 with phenyldiazomethane gave the (S)-N-OBn-Ala derivative 14 as the only product. This preference, as well as the selectivity seen in the formation of 2, can be rationalized in terms of hydrogen bonding between the N-OH of the (R)-Ala with the hydroxy group of the lactic acid side chain that rests under the peptide ring (2.83A) and the neighboring glycine amide carbonyl observed in the crystal structure (2.63A).[2a] Deoxygenation of the (R)-N-OH-Ala to give 15 was achieved by treatment of 14 with titanium trichloride in acetate-buffered methanol.[7] Subsequent hydrogenolysis with 5% platinum-on-carbon gave the (R)-Ala, (S)-N-OH-Ala derivative 16.[8] Titanium trichloride deoxygenation of 1 gave the bis-alanine derivative 17.

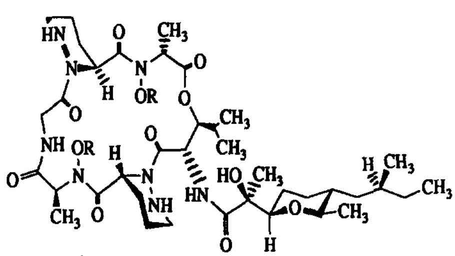


14; R_1= OH; R_2= OBn
15; R_1= H; R_2= OBn
16; R_1= H; R_2= OH
17; R_1= H; R_2= H

Our semisynthetic efforts also included selective modification of the C_{14} side chain of the L-156,602 parent skeleton. Attempted formation of the acetonide of 3 with acetone and a catalytic quantity of PPTS (pyridinium-4-toluenesufonate) gave no reaction, while treatment with 2,2-dimethoxypropane afforded dihydropyran 18, presumably through an acid catalyzed elimination of the hemiketal hydroxyl group. In turn, 18 was hydrated with aqueous acid to give a single product which corresponded to 3. Reductive cleavage of 3 with sodium cyanoborohydride in acetic acid gave the pyran 19 as a single diastereomer, presumably due to preferential axial attack by hydride on the intermediate oxonium ion. A similar observation has been recently reported for the reduction of 2-deoxypyranosides with sodium cyanoborohydride in an aqueous HCl-ether suspension to form 1,5-anhydroalditols.[9] As expected, pyran 19 was not cleaved by periodic acid.



18; R=CBZ



19; R=CBZ

It should be noted that many of the synthetic transformations described above gave the desired products in fair to excellent yields essentially uncontaminated by reaction side products. Many products did not require purification for subsequent reactions[2, 3, 5, 10, 11, 12, 13,] since HPLC analysis indicated at least 90% purity; some were purified by normal phase chromatography [4, 6, 7, 8, 9, 14], while 15 and 16 were purified by recrystallization from ethanol.

In conclusion, we have demonstrated that L-156,602 can undergo selective and synthetically useful functional group transformations which should prove applicable to a wide variety of other synthetic and naturally occurring polypeptides.

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5. Structural assignments of compounds synthesized in this report are based on high field NMR (200 and 300 MHz) studies and FAB mass spectroscopy of samples purified by isocratic or gradient reverse phase HPLC Whatmann RAC Partisil-5 ODS-3 4.6mm x 10cm RP column. The structural assignments of the products reported herein are correlated with intermediates and positional isomers of depsipeptide analogs made by total synthesis. [**1** to **2**: a) 1.2 eq CBZ-Cl, 2.2 eq Et_3N, CH_2Cl_2, b) H_3O^+, 80%]; [**1** to **3**: a) 2.2 eq CBZ-Cl, 2.4 eq Et_3N, 5% 4-dimethylaminopyridine (DMAP), CH_2Cl_2, b) H_3O^+, 74%]; [**2**, **3** to **1**: 5% Pd/C, H_2, atm.pressure, 15 min, 95%]; [**1** to **4**: 10X $NaCNBH_3$, 10x 37% formaldehyde, AcOH, 25°, 6h, acetonitrile, 30%]; [**1** to **5**: 1.2-2 eq 78% mCPBA 4:1 acetonitrile/water, 25°, 2h, 85%]; [**1** to **6**: 4 eq 78% mCPBA 4:1 acetonitrile/water, 55°, 10h, 98%]; [**3** to **7** and **8**: a) 1.4 mole ratio H_5IO_6, THF, 10° 2h, b) 10% $NaHSO_3$, **7** =48% **8** =70%, $[a]_D$= +90° (c 0.97,$CHCl_3$); **8** by total synthesis [3a] $[a]_D$=+94.1, (c 0.90, $CHCl_3$)]; [**7** to **10**: Amberlyst 15 resin, ethyl orthoformate (excess) 25°, 18h, 67%]; [**10** to **11**: $NaCNBH_3$, AcOH, 25°, 3h, 90%]; [**11** to **12**: 5% Pd/C, H_2, atmospheric pressure, 6h, 90%]; [**12** to **13**: 6 N HCl: acetone 1:1, 55°, 6h, 70%]; [**1** to **14**: a) phenyldiazomethane, ether, 18h, b) AcOH, 31%]; [**14** to **15**, **16**: a) $TiCl_3$ (excess), NaOAc, 3:2 MeOH:H_2O, 60°, 30min, 30%, b) 5% Pt/C, H_2, 40psi, 18h, 35%]; [**1** to **17**: $TiCl_3$ (excess), NaOAc, 3:2 MeOH:H_2O, 60°, 6h, 67%]; [**1** to **18**: 5% pyridinium-4-toluenesufonate (PPTS), 2,2-dimethoxypropane, 60°, 2h, 62%]; [**1** to **19**: $NaCNBH_3$, AcOH, 25°, 1h, 95%].
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