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Epsilon-lactam Analogs of the Anthelmintic Cyclodepsipeptide PF1022A

Fred E. Dutton* and Byung H. Lee

Animal Health Discovery Research, Pharmacia & Upjohn, Inc., Kalamazoo, MI 49001

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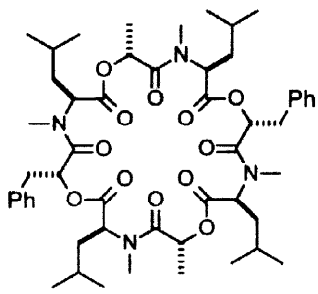
Abstract: Conformationally restricted analogs of the anthelmintic cyclodepsipeptide PF1022A **1** were prepared by fusing a seven-membered lactam ring onto the macrocycle. Following the preparation of cyclodepsipeptide (CDP) **2** by classical chemical methods, CDPs **2** and **3** were synthesized using solid phase methodology involving cyclization-cleavage from an oxime resin.

Helminths, especially parasitic nematodes, cause substantial health problems in humans and domestic animals. The potent antiparasitic activity of cyclodepsipeptide PF1022A **1** and its analogs was discovered by Japanese scientists.[1] Because PF1022A is unique both structurally and in its mode of action, it represents a promising new class of anthelmintics. PF1022A consists of eight residues in a floppy, 24-membered ring: four



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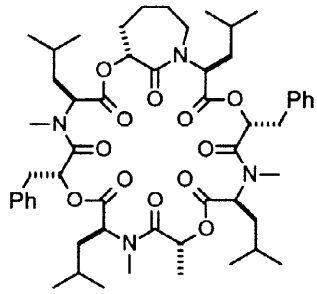

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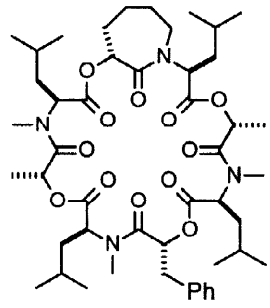

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N-methyl-L-leucines (MeLeu), two D-lactates (Lac) and two 3-phenyl-D-lactates (PhLac). Following our total synthesis of PF1022A[2] we began investigating the effects on biological activity resulting from restricting the number of conformations that PF1022A can adopt. This was accomplished by constructing a molecular bridge between the *N*-methyl group of a leucine residue and the methyl group of its adjacent lactic acid residue. The effect was to fuse a lactam ring to the macrocycle. In earlier work we produced gamma-lactam and delta-lactam analogs of PF1022A.[3] We have now introduced an ethylene bridge producing a seven-membered (epsilon) lactam ring attached to the macrocycle and have developed combinatorial chemistry methods which allow for the rapid preparation of the variety of analogs required for SAR studies.

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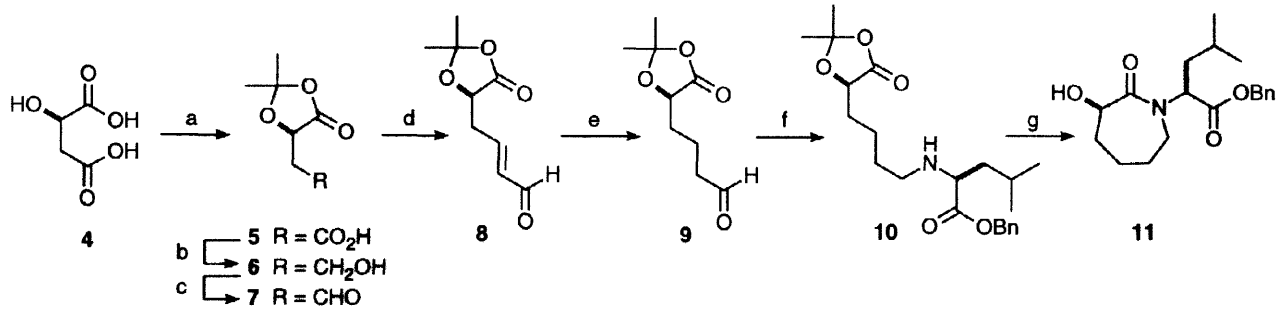
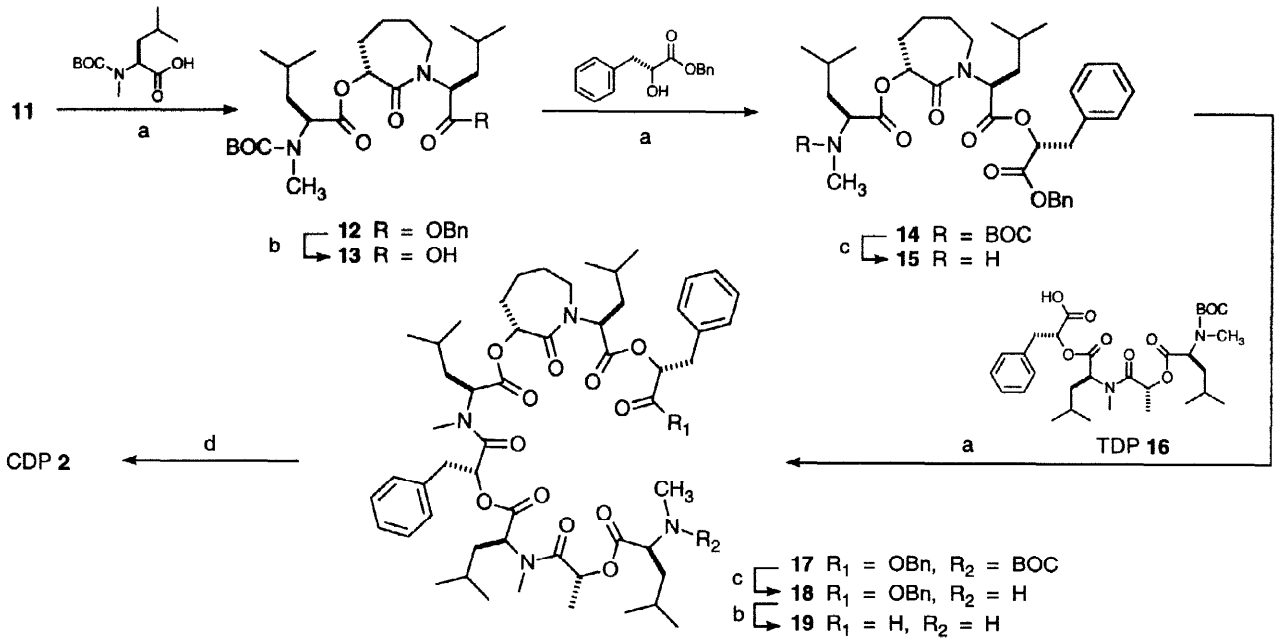
Our strategy was to prepare CDP **2** by joining together tetradepsipeptides (TDP) **15** and **16**. We prepared TDP **16** using classical methods of peptide synthesis.[3] TDP **15** required the synthesis of epsilon-lactam (Lactam) **11** which contains two chiral centers. This was prepared in seven steps from D-malic acid **4** and L-leucine benzyl ester. D-Malic acid upon treatment with pyridinium *p*-toluenesulfonate in 2,2-dimethoxypropane



a) 2,2-Dimethoxypropane, PPTS, 25 °C; b) BH_3·THF; c) PCC, CH_2Cl_2; d) (triphenylphosphoranylidene)acetaldehyde, toluene, 80 °C; e) H_2, 5% Pd on C, EtOAc; f) L-leucine benzyl ester, HOAc, $NaBH_3CN$; g) mixed xylenes, reflux, 115-215 h.

as both reactant and solvent gave the dioxolanone acid **5** in 97% yield. The dioxolanone ring not only protects the carboxyl group against reduction and its adjacent hydroxyl group against oxidation in subsequent reactions, but also is more reactive toward nucleophilic displacement than an ordinary ester. This enhanced reactivity made possible the conversion of amine **10** to epsilon-lactam **11**. The dioxolanone intermediate **5** was reduced to



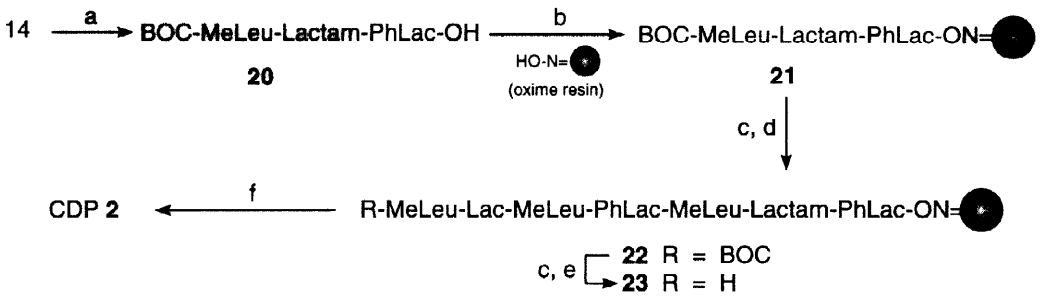
a) DCC, DMAP, CH_2Cl_2; b) H_2, 10% Pd on C, EtOH; c) 20% TFA in CH_2Cl_2; d) BOP-Cl, DPEA, CH_2Cl_2, 1 mM.

alcohol **6** with BH_3•THF (~100%) and then oxidized with PCC to aldehyde **7** (47%). The required two-carbon homologation to aldehyde **8** was achieved by heating aldehyde **7** with (triphenylphosphoranylidene)acetaldehyde in toluene at 80 °C for 90 minutes (54%). Catalytic hydrogenation at balloon pressure (5% Pd on C, EtOAc) gave the saturated aldehyde **9** (72%) which underwent reductive amination with L-leucine benzyl ester

(HOAc, $NaBH_3CN$, CH_2Cl_2) to give secondary amine **10** in 74% yield. This material when heated at reflux in xylene for 115-215 hours produced the epsilon-lactam **11** in 79% yield; $[\alpha]_D^{25} = -37°$ (c 1.12, MeOH).

Epsilon-lactam **11** was coupled (DCC) with *N*-BOC-*N*-methyl-L-leucine and the resulting tridepsipeptide **12** (71%) deprotected at the C-terminus by hydrogenolysis to give acid **13** (~100%). Coupling (DCC) with 3-phenyl-D-lactic acid benzyl ester produced TDP **14** (42%). The BOC group was removed (TFA) to give TDP **15** (95%) which was coupled (DCC) with TDP **16** resulting in octadepsipeptide **17** (78%). Removal first of the BOC group (TFA) to give **18** (97%) and then of the benzyl group (H_2) to give **19** (94%) followed by macrolactamization (BOP-Cl, diisopropylethylamine (DPEA), CH_2Cl_2) at high dilution (1 mM) gave CDP **2** in 43% yield.[4]

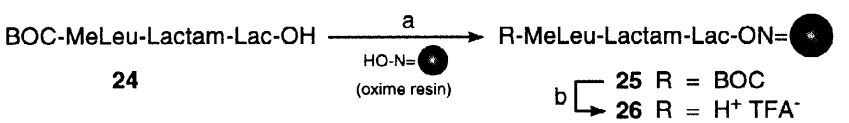
CDP **2** was also prepared using resin-based chemistry.[5] The benzyl group was removed (H_2) from TDP **14** and the resulting free acid **20** (~100%) bound to oxime-functionalized, polystyrene resin developed by Kaiser[6] using (diisopropylcarbodiimide (DIC)) to give **21**. The BOC group was removed (TFA) to give the amine salt, which was then condensed (PyBrop) with TDP **16** to give the resin-linked octadepsipeptide **22**. The BOC group was removed (TFA) and the salt converted (DPEA) to free amine **23**. The challenge posed in adapting this synthesis to resin-based chemistry suitable for application of combinatorial techniques stems from the steric



a) H_2, 10% Pd on C, EtOH; b) DIC, DMAP, CH_2Cl_2; c) 20% TFA, CH_2Cl_2; d) TDP **16**, PyBrop, DPEA, CH_2Cl_2; e) DPEA; f) EtOAc, reflux, 2 days.

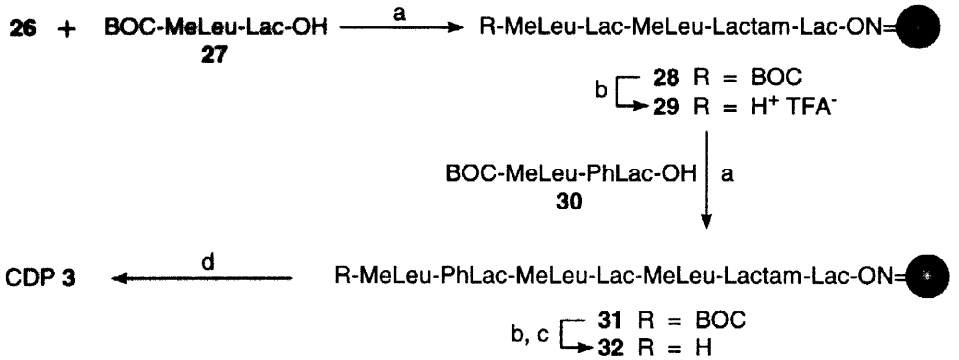
hindrance at the peptide-resin interface which impedes cleavage-cyclization from the oxime resin. Nonetheless, the resin-bound peptide **23** upon heating in refluxing ethyl acetate for two days underwent cyclization to give CDP **2** (30% pure by HPLC, 4.5 mg/100 mg resin). The HPLC retention time and electrospray mass spectrum of this compound were identical with those of the classically prepared material described above.

In a similar fashion, TDP **24**[7] was attached to oxime resin (DIC) to give **25**. The BOC group was removed (TFA) to give amine salt **26** which was then condensed with BOC-MeLeu-Lac-OH **27**[2] (PyBrop) to give resin-linked hexadepsipeptide **28**. Removal of the BOC group gave amine salt **29**. Condensation with BOC-MeLeu-



a) DIC, DMAP, CH_2Cl_2; b) 20% TFA in CH_2Cl_2.

PhLac-OH **30**[2] (PyBrop) gave the resin-linked octadepsipeptide **31** from which the BOC protecting group was removed (TFA) and the amine salt converted (DPEA) to amine **32**. Heating amine **32** in ethyl acetate under reflux for two days gave CDP **3**[8] (45% pure by HPLC, 6.0 mg/100 mg resin).



a) PyBrop, DPEA, CH_2Cl_2; b) 20% TFA, CH_2Cl_2; c) DPEA; d) EtOAc, reflux, 2 days.

It should be noted that further purification of the products from this resin-based chemistry is desirable before SAR studies be undertaken.

In conclusion, we have prepared an epsilon-lactam containing two chiral centers and used this compound to prepare conformationally restricted analogs of PF1022A by employing both classical and resin-based methods of synthesis.

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4. Crude product from the macrolactamization was purified by silica gel chromatography (50% EtOAc in hexane) followed by high vacuum drying to give CDP **2** (628 mg, 43%) as a white solid foam. $[\alpha]_D^{25}$ = -97° (c 0.92, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.70-1.08 (m, 27 H), 1.20-2.20 (m, 18 H), 2.65 (s, ~0.2 H), 2.75 (s, ~0.2 H), 2.78 (s, ~2.8 H), 2.80 (s, ~0.1 H), 2.82 (s, ~2.8 H), 2.90 (s, ~0.2 H), 2.97 (s, ~2.7 H), 3.00-3.49 (m, 6 H), 4.45 (t, *J* = 7.5 Hz, 1 H), 5.06 (dd, *J* = 6.8, 13.8 Hz, 1 H), 5.30 (dd, *J* = 4.3, 11.8 Hz, 1 H), 5.36 (dd, *J* = 2.7, 12.9 Hz, 1 H), 5.44 (dd, *J* = 4.2, 12.3 Hz, 1 H), 5.53 (dd, *J* = ~3, 8.1 Hz, 1 H), 5.65 (t, *J* = 7.6 Hz, 1 H), 5.71 (t, *J* = 7.7 Hz, 1 H), 7.23 (m, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.47, 16.15, 21.39, 21.48, 21.57, 22.10, 23.68, 23.76, 24.49, 25.04, 25.59, 27.26, 28.43, 29.73, 30.80, 30.85, 31.53, 31.94, 36.75, 36.92, 38.02, 38.17, 38.46, 45.34, 54.51, 54.56, 55.91, 57.53, 69.06, 70.78, 71.64, 73.17, 127.43, 127.55, 128.80, 128.92, 128.98, 129.85, 135.40, 135.57, 169.96, 170.36, 170.50, 170.63, 171.18, 171.37, 171.42, 171.77. MS (ES) *m/z* 997.5 [M+Na]. HRMS (FAB) *m/z* calcd for $C_{54}H_{78}N_4O_{12}$+H_1 975.5694, found 975.5711. Infrared (mull, cm^{-1}): ester C=O 1744; amide C=O 1666. UV (MeOH), λ_{max} (E): 250 nm (455), 263 nm (351). Anal. Calcd for $C_{54}H_{78}N_4O_{12}$: C, 66.51; H, 8.06; N, 5.74. Found: C, 66.23; H, 8.13; N, 5.75.
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7. TDP **24** was prepared by coupling tridepsipeptide **13** and D-lactic acid benzyl ester (DCC, DMAP, CH_2Cl_2, 53%) followed by removal of the benzyl protecting group (H_2, 10% Pd on C, EtOH, 91%).
8. HRMS (FAB) *m/z* calcd for $C_{48}H_{74}N_4O_{12}$+Na_1 921.5201, found 921.5222. HPLC R_t = 12.45 min (RP-8 column, gradient: 50 to 90% acetonitrile/water + 0.1% TFA over 30 min).