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SYNTHETIC STUDIES OF DIDEMNINS. IV. SYNTHESIS OF THE MACROCYCLE

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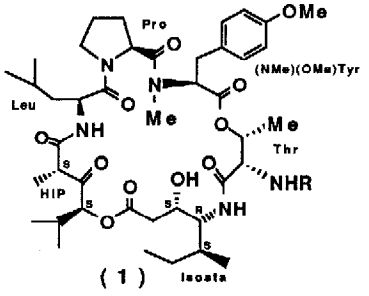
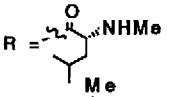
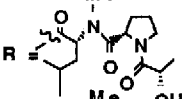
Abstract: *A stereocontrolled route to the 23-membered macrocycle found in the didemnins is described.*

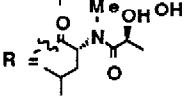
As a continuation of our synthetic studies of the didemnins,[2] we now wish to report our synthesis of the didemnins' macrocycle. The didemnins (**1**) are a new class of depsipeptides originally isolated from a Caribbean



(1)

(1a) didemnin A, R = 

(1b) didemnin B, R = 

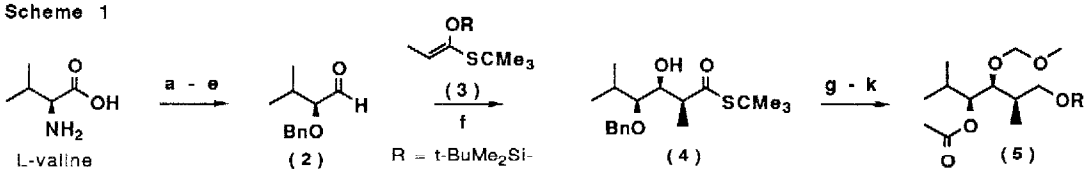
(1c) didemnin C, R = 

(1d) R = H · HCl

tunicate of the *Didemnidae* family (*Trididemnum genus*).[3a] All didemnins contain the same parent macrocycle which is attached at the threonine nitrogen to N-methyl-D-leucine. This moiety, in turn, is found to be attached to lactic acid (didemnin C), lactylproline (didemnin B), or hydrogen (didemnin A). The interesting and varied biological activity of didemnins A and B has been the subject of many investigations.[3] Antiviral, antitumor and immunosuppressive activities have been reported for these compounds. The crystal structure has been determined by X-ray analysis.[4] Total syntheses[5] and other synthetic studies have also been reported.[6] Since the differences in biological activity and potency of didemnins A, B and C are due to the variations in the side chains, a synthesis of the macrocycle would be useful for structural modifications. The didemnins pose a number of synthetic challenges. Maintaining the chiral integrity of the 2-methyl group found in the hydroxy isovaleryl propionyl (HIP) unit is among the most difficult. The 2-methyl group of the HIP unit is situated between a keto group and an amide group. This center is prone to racemization in synthetic linear precursors used to form the macrocycle. In order to avoid carrying on diastereomers at this center throughout the synthesis, and to circumvent the formation of the unwanted epimer after cyclization, we chose to work with the 3-keto group as a protected hydroxyl functionality. Oxidation of this center could then be carried out after macrocyclization.

Our retrosynthetic analysis led us to make bond disconnections between L-leucine and the HIP unit, and between L-threonine and isostatine. The synthesis of the HIP-isostatine unit was accomplished using methodology previously developed in our laboratories.[2c] A suitably activated alloisoleucine was condensed with the enolate of HIP acetate (Scheme 2). Preparation of the HIP acetate is shown in Scheme 1.

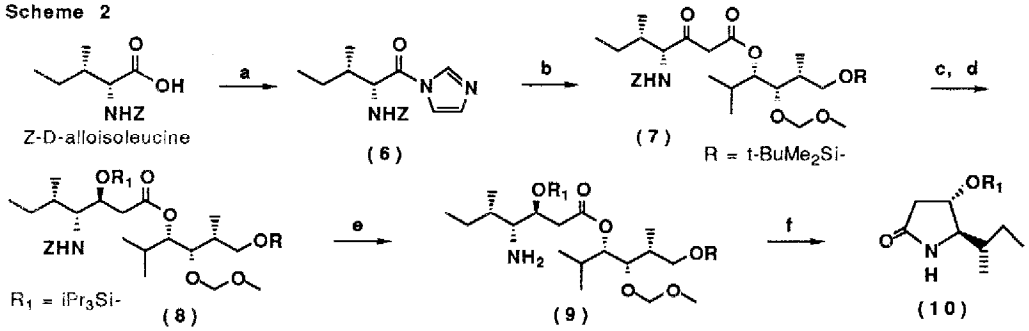
Scheme 1



a. 1N H_2SO_4, 1N $NaNO_2$, 57%; b. MeOH, cat. H_2SO_4, 87%; c. benzyl 2,2,2-trichloroacetimidate, TfOH, 80%; d. LAH, 89%; e. SO_3.pyridine, DMSO, Et_3N, 70%; f. $SnCl_4$, CH_2Cl_2, -78°C, 74%; g. LAH, 92%; h. TBDMS-Cl, DMAP, Et_3N, 100%; i. CH_3OCH_2Cl, iPrNEt, 96%; j. Na, NH_3, THF, 82%; k. $(MeCO)_2O$, DMAP, CH_2Cl_2, 90%.

The protected aldehyde (**2**) was synthesized from L-valine by a known series of reactions.[7] Benzylation was accomplished by acid-catalyzed addition to benzyl 2,2,2-trichloroacetimidate,[8] after which a reduction-oxidation sequence afforded **2**. The remaining stereochemistry was set by a chelation-controlled aldol condensation.[9] Compound **2** was treated with the silylketene thioacetal **3**, prepared by literature procedure,[9] to afford a 74% yield of the all *syn* diastereomer as the only product. Reduction of the thioester gave a crystalline diol (94% ee, ^{19}F NMR on Mosher's ester), which could be recrystallized to > 99%ee. Selective protection of the primary hydroxyl group with t-butyldimethylsilyl chloride was followed by protection of the secondary hydroxyl group as its MOM ether. The resulting compound was then debenzylated using sodium in liquid ammonia, followed by conversion to its corresponding acetate (**5**).

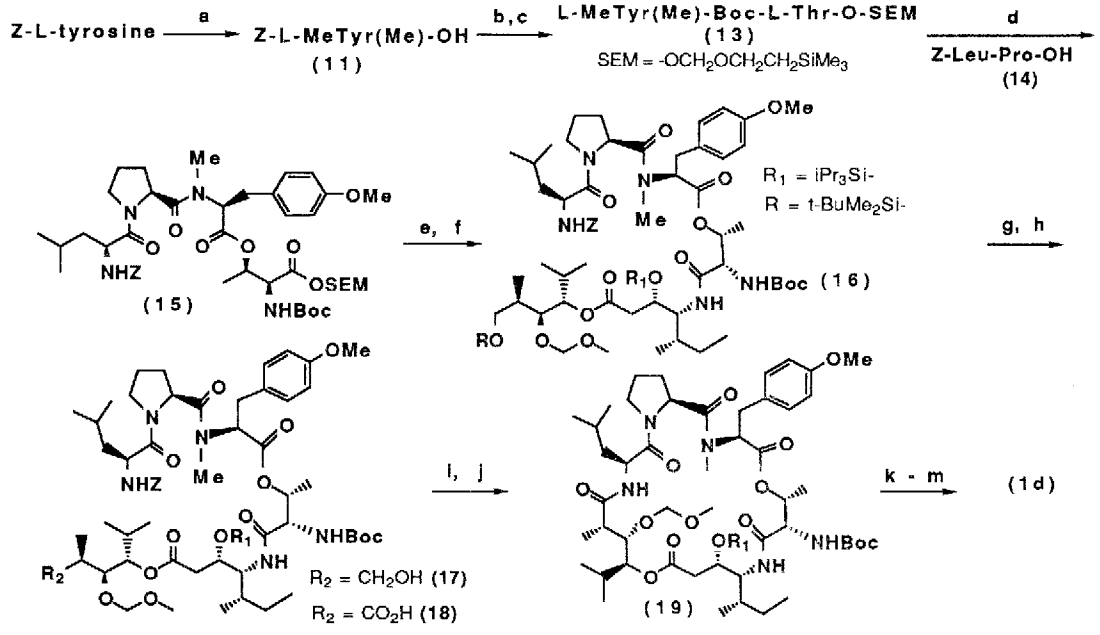
Scheme 2



a. CDI; b. LDA, THF, (**5**), a - b = 76%; c. KBH_4, EtOH, 83%; d. iPr_3SiOTf, 2,6-lutidine, 93%; e. H_2, Pd/C, 100%; f. imidazole, MeOH, 100%.

Z-D-Alloisoleucine (Scheme 2) was converted to imidazolide **6**, which was then directly condensed with the lithium enolate of compound **5**, to afford the corresponding b-keto ester (**7**) in 76% overall yield from Z-D-alloisoleucine. Treatment of this compound with potassium borohydride in ethanol,[2c] followed by treatment of the resulting diastereomeric mixture with triisopropylsilyl triflate gave a separable (column chromatography) mixture of two silyl ethers. The ratio of these two diastereomers was found to be 12.6:1 by HPLC analysis. The carbobenzyloxy group of the *anti* diastereomer (**8**) was removed by catalytic hydrogenation. Confirmation of the assigned stereochemistry was accomplished by converting the amino derivative **9** to a protected pyrrolidinone (**10**) which was then subjected to ^1H NMR decoupling experiments. The synthesis of the macrocycle is shown in Scheme 3.

Scheme 3



a. 1. Me_2SO_4, KOH, $nBu_4N^+HSO_4^-$, THF; 2. H_2O, 82%; b. isopropenyl chloroformate, N-Boc-L-Thr-O-SEM, DMAP, 87%; c. H_2, Pd/C, 99%; d. 1. BOP-Cl, Et_3N, -15°C, 2. **(13)**, Et_3N, 85%; e. HF, CH_3CN, 88%; f. **(9)**, isopropenyl chloroformate, N-methylmorpholine, THF, -15°C - 0°C, 60%; g. AcOH, THF, H_2O,12 h, 83%; h. 1. TFAA, DMSO, CH_2Cl_2, Et_3N, 2. $KMnO_4$, 5% NaH_2PO_4, t-BuOH; i. H_2, Pd/C; j. diphenyl phosphoryl azide, DMF, $NaHCO_3$, 0°C, 3 days, h - j = 40%; k. Me_2BBr, CH_2Cl_2, 93%; l. TFAA, DMSO, Et_3N, 92%; m. HCl, EtOAc, -30 - 0°C, 90%.

Z-L-Tyrosine was converted to its N,O-dimethyl derivative (**11**) using catalytic phase transfer conditions (82% yield). The free carboxylic acid was esterified with N-Boc-L-Thr-O-SEM to give Z-L-MeTyr(Me)-Boc-L-Thr-O-SEM (**12**) (87% yield, 1h) as described by Castro.[10] The Z group of **12** was removed by catalytic hydrogenation to afford the amine (**13**). Treatment of Z-Leu-Pro-OH (**14**) with N,N'-bis(2-oxo-3-oxazolidinyl) phosphinic chloride (BOP-Cl),[11] followed by addition of the amine gave the fully protected tetrapeptide (**15**). The carboxyl protecting group of L-threonine was removed, followed by coupling to the amino group of the HIP-isostatine unit (**9**) using isopropenyl chloroformate. This gave compound **16** in 60% yield. In order to form the macrocycle, the primary hydroxyl of the HIP unit in **16** was oxidized to the corresponding carboxylic acid (**18**). The carbobenzyloxy protecting group on leucine was removed and cyclization was accomplished using diphenylphosphoryl azide (DPPA) in the presence of sodium bicarbonate[12]. The protected macrocycle (**19**) was obtained in 40% overall yield from **17**. Selective deprotection of the HIP alcohol was accomplished with dimethylboron bromide (93% yield), and Swern oxidation afforded the ketone in 92% yield. No epimerization at the 2-methyl center was observed. Unexpectedly, the Boc group on L-threonine proved to be quite stable to acidic conditions, due to the steric environment. Both the triisopropyl group and the Boc group, however, were removed with hydrogen chloride in ethyl acetate to afford the corresponding hydrochloride salt of the macrocycle.[13] We are currently exploring the coupling of this macrocycle with the side chains found in didemnins A, B, and C.

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13. All yields refer to isolated, chromatographically pure materials that were fully characterized by IR, NMR, MS, and HRMS data. All new compounds gave satisfactory analytical data or HRMS data.

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