Hz); ^{31}P NMR 6.29 ppm (t); ^{1}H NMR (360 MHz) 1.390 (t, CH_3, $^{3}J_{H,H}$ = 7.5 Hz), 2.702-2.824 (m, CF_2CH_2), 4.283 (dq, 5 lines, CH_2O, $^{3}J_{H,H} \sim {}^{3}J_{H,P}$ = 7.3 Hz), 4.344 ppm (vinyl H, partially overlapped by resonance at 4.283 ppm); ^{13}C NMR (100 MHz) 15.79 (d, CH_3, $^{3}J_{C,P}$ = 5.6 Hz), 28.02 (tdd, CF_2CH_2, J = 30.7, 11.4, 5.2 Hz), 64.12 (d, CH_2O, $^{2}J_{C,P}$ = 7.0 Hz), 68.51-69.11 (m CH=C), 118.47 (td, CF_2CH_2, $^{1}J_{C,F}$ = 260.7 Hz, $^{1}J_{C,P}$ = 216.2 Hz), 157 ppm (t, C=CF_2, $^{1}J_{C,F}$ = 288.4 Hz); IR (neat) 2995 (m), 2965 (w), 1765 (vs, C=CF_2), 1485 (w), 1455 (w), 1410 (w), 1385 (w), 1290 (s, P=O), 1220 (m), 1180 (s), 1050 (vs, POR), 1000 (m), 880 (w), 815 cm^{-1} (m).

Anal. Calcd for $C_8H_{13}F_4O_3P$: C, 36.38; H, 4.96; F, 28.77. Found: C, 36.44; H, 5.08; F, 28.21.

Reaction of [(Diethoxyphosphinyl)difluoromethyl]zinc Bromide with CuBr and 3-Chloro-3,3-d_2-propene. A hot, oven-dried NMR tube was flushed with dry nitrogen until cool and charged with 0.33 mL (0.3703 g, ~0.0007 mol) of a Schlenk funnel filtered (medium frit) solution of [(diethoxyphosphinyl)difluoromethyl]zinc bromide which had been prepared from diethyl bromodifluoromethanephosphonate (2.67 g, 0.01 mol), acid-washed zinc powder (0.7 g, 0.01 g-atom), and 5 mL of dry monoglyme. To the NMR tube were also added 3-chloro-3,3-d_2-propene[26] (0.0206 g, 0.0003 mol) and CuBr (0.0155 g, 0.0001 mol). The NMR tube was capped and shaken vigorously. An exothermic reaction resulted which lasted for only 5 min. After $2^1/_2$ h, benzotrifluoride was added to the reaction mixture, and the yields of allylated products were determined by ^{19}F NMR spectroscopy to be 69% $(EtO)_2P(O)CF_2CH_2CH{=}CD_2$ and 28% $(EtO)_2P(O)CF_2CD_2CH{=}CH_2$. ^{2}H NMR spectral integration revealed the ratio of products to be 65%/35%, respectively.

Diethyl 1,1-difluoro-4,4-d_2-butenephosphonate (14): ^{19}F NMR (MG) -111.08 ppm (dt, $^{2}J_{F,P}$ = 114.9 Hz, $^{3}J_{F,H}$ = 19.8 Hz); ^{31}P NMR 5.30 ppm (t); ^{2}H NMR (MG) 4.67 ppm (br s).

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Diethyl 1,1-difluoro-2,2-d_2-butenephosphonate (15): ^{19}F NMR (MG) -111.10 ppm (br d, $^{2}J_{F,P}$ = 115.3 Hz); ^{31}P NMR 5.30 ppm (t); ^{2}H NMR (MG) 2.85 ppm (br s).

Reaction of [(Diethoxyphosphinyl)difluoromethyl]zinc Bromide with 3-Chloro-1-propyne (Propargyl Chloride). A round-bottomed flask was connected to a nitrogen bubbler and was equipped with a Teflon-coated spin bar. To the flask was added a Schlenk-filtered (medium frit) solution of [(diethoxyphosphinyl)difluoromethyl]zinc bromide which had been prepared from diethyl bromodifluoromethanephosphonate (53.4 g, 0.20 mol), acid-washed zinc powder (13.1 g, 0.20 g-atom), and 100 mL of dry monoglyme. To this solution were added 3-chloro-1-propyne (14.5 mL, 15 g, 0.20 mol, Aldrich Chemical Co., and CuBr (1.1 g, 0.01 mol). The reaction mixture was stirred for 24 h at room temperature. Analysis by ^{19}F NMR spectroscopy indicated that the mixture consisted of 86% (normalized) diethyl 1,1-difluoro-2,3-butadienephosphonate, 6% diethyl 1,1-difluoro-3-propynephosphonate, and 8% diethyl difluoromethanephosphonate. The inorganic salts were removed by filtration through a fritted-glass funnel (medium frit) under aspirator vacuum; $3^1/_2$ mL of water was added to the filtrate, and the solution was concentrated by rotary evaporation. The attempted flash distillation of the mixture did not yield any distillate, but violently converted the contents of the flask into a black dry solid.

Diethyl 1,1-difluoro-2,3-butadienephosphonate (4): ^{19}F NMR (MG) -105.3 ppm (ddt, $^{2}J_{F,P}$ = 121 Hz, $^{3}J_{F,H}$ = 12 Hz, $^{5}J_{F,H}$ = 7 Hz); ^{31}P NMR 4.20 ppm (t).

Diethyl 1,1-difluoro-3-propynephosphonate (5): ^{19}F NMR (MG) -110.0 ppm (dt, $^{2}J_{F,P}$ = 120 Hz, $^{3}J_{F,H}$ = 18 Hz); ^{31}P NMR 4.60 ppm (t).

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Synthesis of the Cyclodepsipeptide Nordidemnin B, a Cytotoxic Minor Product Isolated from the Sea Tunicate *Tridemnum cyanophorum*[1]

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Nordidemnin B (3), a cyclodepsipeptide isolated from a sea tunicate, was prepared by following a segment strategy which will permit further structural modifications. The non-proteinogenic D-Val-ψ(CHOH)-Gly-HIP subunit was elaborated sequentially by using a β-keto ester preparation via lithium enolate condensation with 2-acyl-3,5-dioxo-4-methyl-1,2,4-oxadiazolidine (acyl-MODD) derivatives. Isopropenyl chlorocarbonate activation was employed for depsipeptide bond formation. Coupling of this subunit with the tetradepsipeptide Z-Thr-(Leu-Pro-MeTyr(Me))-OAll made use of the CuI-promoted *tert*-butyl thioester activation. Macro ring closure was carried out by using BOP reagent and sodium bicarbonate. The total synthesis of nordidemnin B was achieved by coupling the dipeptidyl unit Lac-Pro-D-MeLeu (25) to the cyclic fragment 21 by using BOP methodology. The synthetic compound was identical in every respect with the natural nordidemnin B (3).

Numerous cyclopeptides and linear peptides of natural origin that contain non-proteinogenic amino acids exhibit various important biological activities.[2,3] Didemnins are a family of cyclodepsipeptides first extracted from a Caribbean tunicate during a systematic study of marine natural products to identify antimicrobial and antiviral activity.[4]

(1) Abbreviations and symbols follow the recommendations of IUPAC-IUB Joint Commission on Biochemical Nomenclature (*Eur. J. Biochem.* **1984**, *138*, 9.) In addition, the following abbreviations are used: All, allyl; BOP, (1*H*-1,2,3-benzotriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate; BOP-Cl, *N,N'*-bis(2-oxo-3-oxazolidinyl)phosphonic chloride; COMODD, 2,2'-carbonylbis(3,5-dioxo-4-methyl-1,2,4-oxadiazolidine; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCC, *N,N*-dicyclohexylcarbodiimide; DIEA, diisopropylethylamine; DMAP, 4-(dimethylamino)pyridine; DPPA, diphenyl phosphorazidate; EDCI, 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride; HIP, (2*S*,4*S*)-2,5-dimethyl-3-oxo-4-hydroxyhexanoic acid; Hyv, L-α-isovaleric acid; IPCC, isopropenyl chlorocarbonate; Lac, L-lactic acid; MODD, 3,5-dioxo-4-methyl-1,2,4-oxadiazolidine; TEA, triethylamine; TFA, trifluoroacetic acid.

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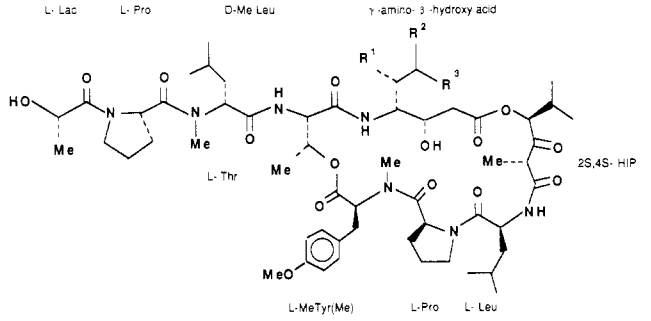
Didemnin B (1), the more active compound of this class, has been shown to be markedly active against P388 leukemia and B16 melanoma as well as a variety of human tumors.[5] This cyclic peptide also possesses potent antiviral activity[6] and a potential but as yet unclear immunomodulatory activity both in vitro and in vivo.[7] The



	R^1	R^2	R^3	
1	Me	H	Me	Didemnin B
2	H	Me	Me	"uncorrect" Didemnin B
3	Me	H	H	nor-Didemnin B

incorrect structure **2** was originally assigned in 1981 to didemnin B, isolated from *Tridemnum solidum*.[8] The structure **1** was recently proposed after X-ray crystallographic study[9] and total synthesis.[10] Didemnin B (**1**) proved to be identical with the major component isodidemnin B discovered in the Guadaloupean sea collections of *Tridemnum cyanophorum*.[11,12] A minor component of this class, nordidemnin B (**3**), was isolated and structurally identified by GC/MS analysis of derivatized hydrolysates[13] and 2D NMR spectroscopy.[14] The stereochemistry of the residues present in nordidemnin B (**3**) was presumed to be the same as in their parental counterparts **1**, but this has not been completely established.

The structure–activity relationship studies were limited due to the restricted number of available modifications of the extracted natural compounds.[13] Because of these limitations, the synthesis of analogues is a target of considerable interest. The total synthesis of the erroneous structure **2** which contained the (3*S*,4*R*)-4-amino-3-hydroxy-6-methylheptanoic acid (D-Leu-ψ(CHOH)-Gly: statine) residue instead of the (3*S*,4*R*,5*S*)-4-amino-3-hydroxy-5-methylheptanoic acid (D-*allo*-Ile-ψ(CHOH)-Gly) was completed by two different laboratories.[10,15] The synthesis of didemnin B (**1**) has also been published recently[10,16] and is now under investigation by others.[17] In order to evaluate the mechanisms of action of the didemnins, we chose to develop a general, versatile approach that would provide structural modifications of the parent compound didemnin B (**1**).

We discuss here a new approach to the didemnin skeleton and relate this to the total synthesis of nordidemnin B (**3**).

Results and Discussion

Synthetic Strategy. We carried out a retrosynthetic analysis of nordidemnin of which three subunits are defined for sequential construction. First, biological activities already reported for different didemnins seemed to be closely related to the length of the chain A, but no data were given on variations in the chemical nature and stereodependence of the residues.[13] Secondly, the significance of γ-amino β-hydroxy acids and γ-hydroxy β-keto esters in anticancer drug design has to be explained,[3] and the investigation of structural modifications in the subunit B represents an important part of our program. Finally, it is expected that modifications are possible in the last subunit C for synthetic simplifications which could maintain the tertiary structure of this cyclic molecule.

The major prerequisite for the nordidemnin B (**3**) synthesis is the availability of a strategy for assembling the three subunits A, B, and C.

When considering the coupling between subunits B and C, we took into account the conflicting results published on the instability of free β-keto acids.[10,15,18,19] Despite some claims presented in the literature,[10,15] preparation of the (2*S*,4*S*)-2,5-dimethyl-3-oxo-4-hydroxyhexanoyl acid (HIP) residue and related β-keto acids was unsuccessful in other laboratories.[18,19] This drawback was overcome by using β-keto thioesters as potentially reactive units for β-keto amide preparation.[20] The method recently was illustrated for preparing HIP-Leu by Kim et al.[19]

Several sites are available for cyclization, but only two were involved in our strategy. Owing to the limited number of possible orthogonal protections in the tetradepsipeptide C, X^1-Thr(X^2-Leu-Pro-MeTyr(Me))-OX^3, and the X^4-D-[*N*,*O*-isopropylidene]Val-ψ(CHO)-Gly-HIP-StBu subunit B, we decided to first condense these two segments between HIP and Leu and then achieve the cyclization by coupling the threonyl carboxylate with the amine of the (3*S*,4*R*)-4-amino-3-hydroxy-5-methylhexanoic acid residue (D-Val-ψ(CHOH)-Gly).

The final segment coupling between the dipeptidyl chain Lac-Pro-MeLeu (A) and the cyclic skeleton was thought to be more favorable than a stepwise elongation because of the difficult bond formation between a prolyl residue and an *N*-methyl amino acid. The main question to be addressed was whether or not this fragment coupling would suffer from epimerization at the D-*N*-methylleucyl level.

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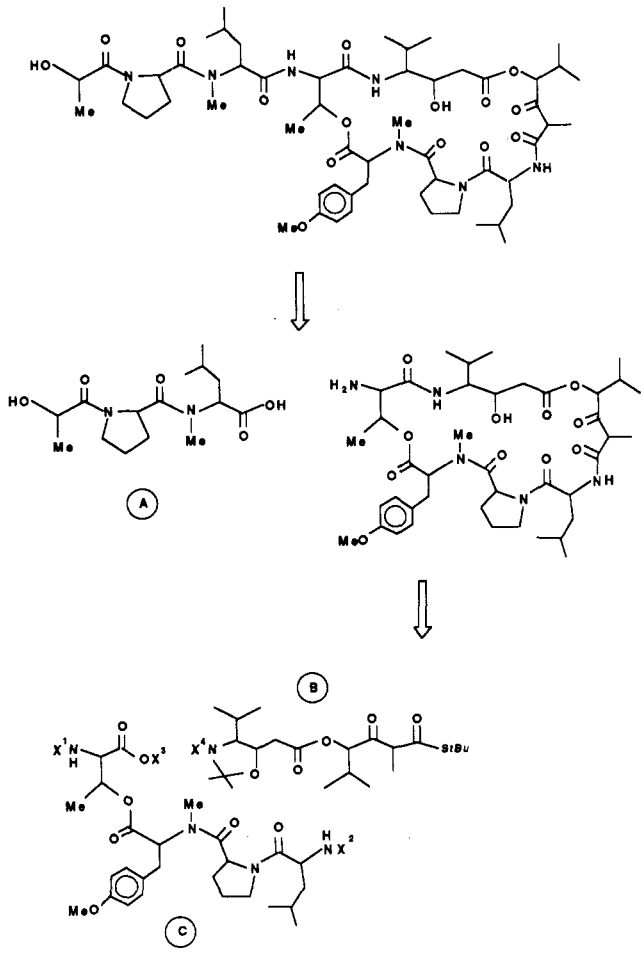
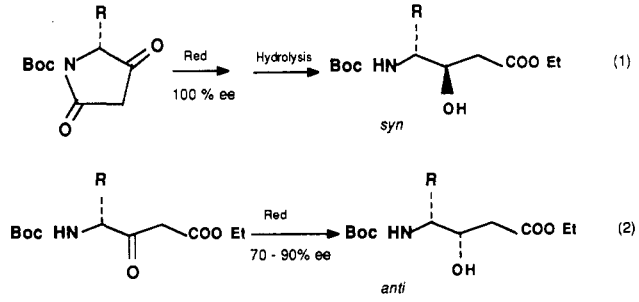
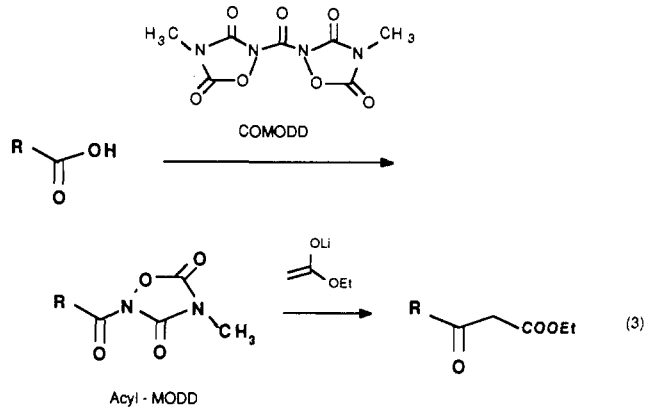


We stress that epimerization could be minimized by using the BOP reagent developed by Castro et al.,[21] and as depicted in several fragment coupling experiments.[22]

Synthesis of the Non-Proteinogenic Subunit B. The preparation of the non-proteinogenic depsipeptide subunit D-Val-ψ(CHOH)-Gly-HIP is shown in Scheme I. Among the non-proteinogenic amino acids, γ-amino β-hydroxy acids remain a challenging problem.[23-25] It has been shown that the reduction of the cyclic amide proceeded exclusively with syn selectivity (eq 1),[24] although the anti isomer found in the didemnin structure could be favorably obtained from reduction of the linear β-keto ester (eq 2).[23] Furthermore, substantial improvements on the synthesis of β-keto esters from N-protected amino acids have been reported recently.[23b,c,25] Methods based on the condensation of the activated amino acid with metalated acetic acid derivatives[19,23b] or with nucleophilic magnesium enolate[23c] suffer from the tedious manipulation of the unstable activated amino acids employed and are reported to cause epimerization in some cases. In a recent study, advantage was taken of the stability of the newly activated



2-acyl-3,5-dioxo-4-methyl-1,2,4-oxadiazolidines (acyl-MODD) species, and their reactivity through lithium enolate condensation, to prepare a series of β-keto esters in high yields (eq 3).[25]



In the present instance, Boc-D-Val-MODD (4) was prepared in 98% yield from 2,2′-carbonylbis(3,5-dioxo-4-methyl-1,2,4-oxadiazolidine) (COMODD) activation of Boc-D-Val-OH. This activated acid was allowed to react with the lithium enolate of ethyl acetate at −78°C in THF to give the β-keto ester **5** in 94% yield. When the method we have previously described[24] was followed, sodium borohydride reduction of **5** in an acidic dichloromethane/acetic acid medium furnished the Boc-D-Val-ψ(CHOH)-Gly-OEt as a mixture of 3*R*,4*R* and 3*S*,4*R* diastereomers **6**; the diastereomeric ratio, evaluated from NMR, was 5:95.[26] The potential reactivity of the statine hydroxyl required protection during the depsipeptide bond formation. The hydroxy and Boc-amino functions were protected in the form of a dimethyloxazolidine derivative **7**.[27] This isopropylidene protecting group was readily introduced by refluxing Boc-D-Val-ψ(CHOH)-Gly-OEt (**6**) in dimethoxypropane with a catalytic amount of *p*-toluenesulfonic acid (PTSA). This protection offered an additional advantage in preventing the formation of an intramolecular cyclization at the D-Val-ψ(CHOH)-Gly-HIP activation step for the next coupling. At this stage, the diastereoisomerically and enantiomerically pure 3*S*,4*R* isomer **7a** was easily isolated after silica gel column chromatography in 65% yield, calculated from the β-keto ester **5**.

We planned to introduce the potentially reactive thioester function preferably toward the end of the subunit B stepwise synthesis as shown in Scheme I, to circumvent the possibility of tetronic acid formation by lactonization[28] of the HIP thioester bearing a free hydroxyl group, which could occur during the alternative depsipeptide bond formation between Boc-D-[*N*,*O*-isopropylidene]Val-ψ-(CHO)-Gly and HIP-StBu.

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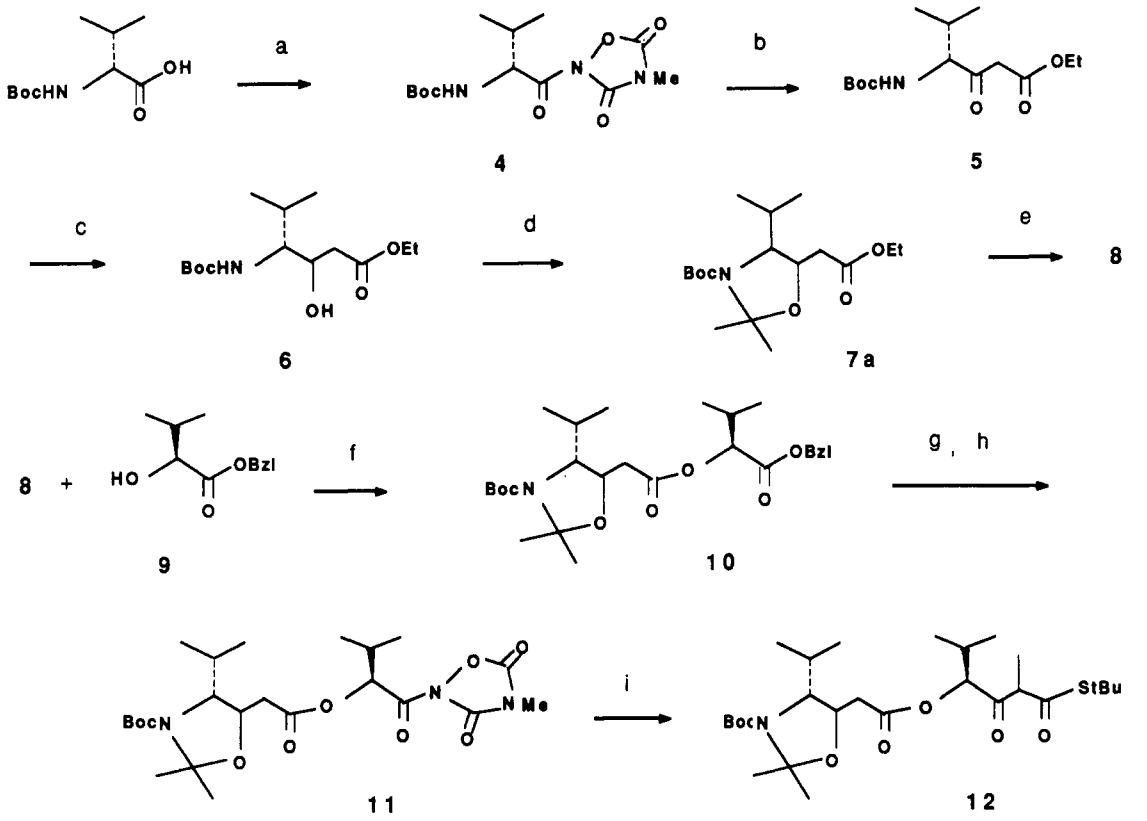
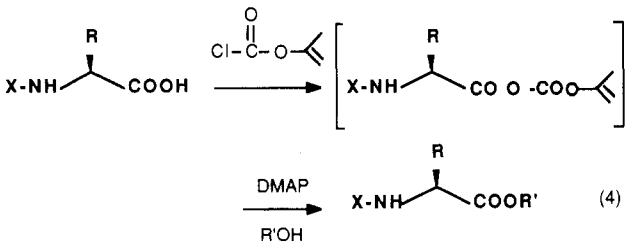
Scheme I. Synthesis of Boc-D-[*N*,*O*-isopropylidene]Val-ψ(CHO)-Gly-HIP-StBu. Subunit B



[a] (a) COMODD (1.1 equiv), 0.1 equiv of TEA, THF, 0 °C, 2 h, 98%; (b) 2.1 equiv of lithium ethyl acetate, THF, −78 °C; then HCl (1 M) 94%; (c) 2 equiv of $NaBH_4$, CH_2Cl_2/AcOH (4:1), 5 °C; (d) APTS catalytic, dimethoxypropane, reflux, 18 h, 62% (from **5**); (e) 1.1 equiv of NaOH (2 M), MeOH, 98%; (f) 1.1 equiv of TEA, 0.1 equiv of DMAP, 1.1 equiv of IPCC, CH_2Cl_2, −5 °C, 0.5 h, 92%; (g) Pd/C, 2-propanol, quantitative; (h) 1.1 equiv of COMODD, 0.1 equiv of TEA, THF, 0 °C, 2 h, 97%; (i) 2.1 equiv of lithium *tert*-butyl thiopropionate,[19] THF, −78 °C; then HCl (1 M), 98%.

The synthesis of Boc-D-[*N*,*O*-isopropylidene]Val-ψ-(CHO)-Gly-Hyv-OBzl **10** was carried out by taking advantage of a preceding development of an efficient ester synthesis that employs isopropenyl chlorocarbonate (IPCC) for acid activation (eq 4).[29] In this process, the N-protected amino acid was activated in situ as the mixed anhydride, which in turn, under the catalytic action of DMAP, was condensed with the alcohol already present in the reaction mixture.



Thus, the hydroxyl part, L-α-isovaleric benzyl ester (Hyv-OBzl, **9**), was obtained from standard nitrosation of the L-valine[30] and protected at its carboxylic function as the benzyl ester by alkylation with benzyl bromide and DBU.[31] For the depsipeptide bond construction, IPCC is slowly added at 0 °C to a dichloromethane solution of the saponified derivative **8**, Hyv-OBzl (**9**), TEA, and a catalytic amount of DMAP; after a half-hour, the depsipeptide was isolated in 92% yield.[32] The depsipeptide ester **10** was quantitatively converted into the corresponding acid by catalytic hydrogenation, and the HIP unit was built up by following a route similar to that used for the construction of the β-keto ester **5** (vide supra). Acylation of lithium *tert*-butyl thiopropionate with the purified acyl-MODD **11** gave the β-keto ester **12** in 98% yield as an expected mixture of epimers at carbon C-2 of the HIP residue. At this stage it did not appear reasonable to undertake the separation of the epimers, since we assumed that a rigorous control of the stereochemistry at this position would not be retained in the following steps. Moreover, it was emphasized that the correct isomer would emerge from a thermodynamically favorable equilibration within the cyclization (vide infra).

Preparation of the Tetradepsipeptide Z-Thr(Boc-Leu-Pro-MeTyr(Me))-OAll (18). In the strategy planned for the synthesis of the targeted cyclic part of nordidemnin B, a fully protected linear peptide had to be prepared with the following requirements:

(1) The N-protection of the threonyl residue must be acid resistant with respect to the Boc-D-[*N*,*O*-isopropylidene]Val-ψ(CHO)-Gly deprotection of the linear peptide previous to cyclization. (2) Deprotection reactions have to be compatible with the presence of depsipeptide

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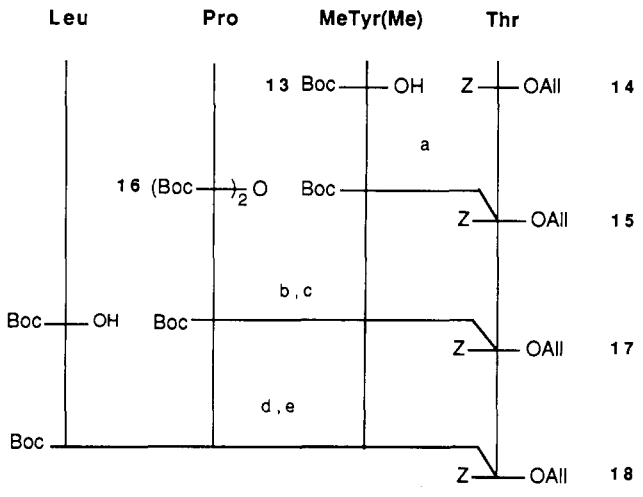
(32) The depsipeptide **14** was alternatively obtained in 76% yield by using the *N*,*N*-dicyclohexylcarbodiimide with DMAP method described by Gilon et al.: Gilon, C.; Klausner, Y.; Hassner, A. *Tetrahedron Lett.* **1979**, 3811.

Table I. Comparative Study of Pro-MeTyr(Me) Coupling

TFA•HMeTyr(Me)—O / Z—Thr—OAll +	reagent	temp, °C	time, h	yield, %	meth ref
Boc-Leu-Pro	BOP-Cl	rt[a]	16	65	35
	DCC	0	72	63	22b
	EDCI	0	24	23	36
	BOP	rt	24	16	22
	IPCC	0	1	0[b]	37
Boc-Pro	DCC	0	24	60	
	EDCI	0	24	29	

[a] Room temperature. [b] The isopropenyl ester of Boc-Leu-Pro was the only characterized compound.

Scheme II. Preparation of the Tetradepsipeptide Z-Thr(Boc-Leu-Pro-MeTyr(Me))-OAll



[a] (a) TEA (1.1 equiv), 0.2 equiv of DMAP, 1.1 equiv of IPCC, −5 °C, 0.5 h, 98%; (b) TFA, 0.5 h, 90%; then 5% $NaHCO_3$; (c) heating, 130 °C, 5 min, 89%; (d) TFA, 0.5 h; (e) 3 equiv of DIEA, 1 equiv of BOP, CH_2Cl_2, 2 h, 94%.

bonds. For this purpose, we chose the hydrogenolysis-labile benzyloxycarbonyl group for N-terminal protection of threonine, and the acid-stable and palladium-cleavable allylic ester developed by Kunz, as temporary protection for the threonyl carboxylate.[33]

Thus, alkylation of Z-Thr with allyl bromide and cesium carbonate provided Z-Thr-OAll (**14**) in 98% yield. The tetradepsipeptide was prepared stepwise, as depicted in Scheme II. Boc-MeTyr(Me) (**13**) was prepared in a four-step synthesis from the commercially available Boc-Tyr(Bzl). Methylation of the amine with minimal epimerization was accomplished according to the method of Cheung and Benoiton.[34] The requisite *O*-methyl substitution of the phenyl ring was introduced, after catalytic hydrogenolysis removed the benzyl protecting group, by treatment with dimethyl sulfate and potassium carbonate. Boc-MeTyr(Me) (**13**) was isolated in 80% overall yield after saponification of the methyl ester. Coupling of **13** with Z-Thr-OAll (**14**) by means of the IPCC activation procedure afforded the depsipeptide **15** in 98% yield. As expected from the presence of the *N*-methyl amino acid in this sequence, two conformers were visible in the NMR spectrum although high diastereomeric purity was ascertained from HPLC analysis. The Boc group in depsipeptide **15** was removed with trifluoroacetic acid at room temperature under our usual conditions. The trifluoroacetate salt obtained after ether precipitation was isolated as a white powder in 90% yield.

In the first set of experiments, segment coupling between the N-deprotected depsipeptide derived from **15** and the dipeptide Boc-Leu-Pro was undertaken under various conditions, assuming that the C-terminal proline gave no epimerization. Boc-Leu-Pro was obtained by saponification of the dipeptide Boc-Leu-Pro-OMe, which had been prepared in 95% yield with the BOP peptide synthesis method. The use of *N,N'*-bis(2-oxo-3-oxazolidinyl)-phosphonic chloride (BOP-Cl) has usually been recommended for the critical *N*-methyl amino acid coupling.[35] However, in addition to the moderate yields obtained following other methods, BOP-Cl also gave a disappointing result for this sequence (65% yield), as summarized in Table I. This nonexhaustive study was extended to the coupling of the Boc-Pro with the depsipeptide without improvement, as Table I shows. This difficult coupling was successfully carried out only by the unconventional solvent-free condensation, in which a poorly reactive amine and a carboxylic anhydride are heated together, as suggested by Rodriguez and Goodman.[38] An excess of the syrupy $(Boc\text{-}Pro)_2O$ symmetrical anhydride **16** was mixed with the free secondary amine derived from **15**, and the mixture was heated at 130 °C for 5 min, giving the depsipeptide **17** in 84% yield. Boc removal, followed by BOP coupling with Boc-Leu, gave Z-Thr(Boc-Leu-Pro-MeTyr-(Me))-OAll (**18**) in 94% yield.

Synthesis of the Cyclodepsipeptide 21 Subtarget. A crucial step in our sequence, showed in Scheme III, was the promoted thiophilic metal cation coupling process that joined the two subunits A and B preceding cyclization.[19,20] Unfortunately, when the conditions described for use of either the Ag(II) or Cu(I) cations were followed, the condensation progressed very slowly and significant decomposition was observed during the course of the reaction, as indicated by HPLC monitoring. However, considerable improvements were achieved with addition of base. An equimolar composition of the amine free tetradepsipeptide issued from **18** and the thioester **12** was vigorously stirred in a dichloromethane solution in the presence of a 2-fold excess of CuI and 1 equiv of TEA for a half-hour. After filtration through Celite, the linear depsipeptide **19** was purified by flash column chromatography (85% yield). The allyl deprotection of the C-terminal of **19** was performed in THF solution under an inert atmosphere with the use of the soluble $Pd(Ph_3P)_4$ catalyst.[33] The catalyst was then removed by chromatography and the peptide submitted to the trifluoroacetic acid deprotection of the N-terminus. The trifluoroacetate salt **20** was precipitated with ether in 67% yield (calculated from the protected linear depsipeptide **19**) with an HPLC purity greater than

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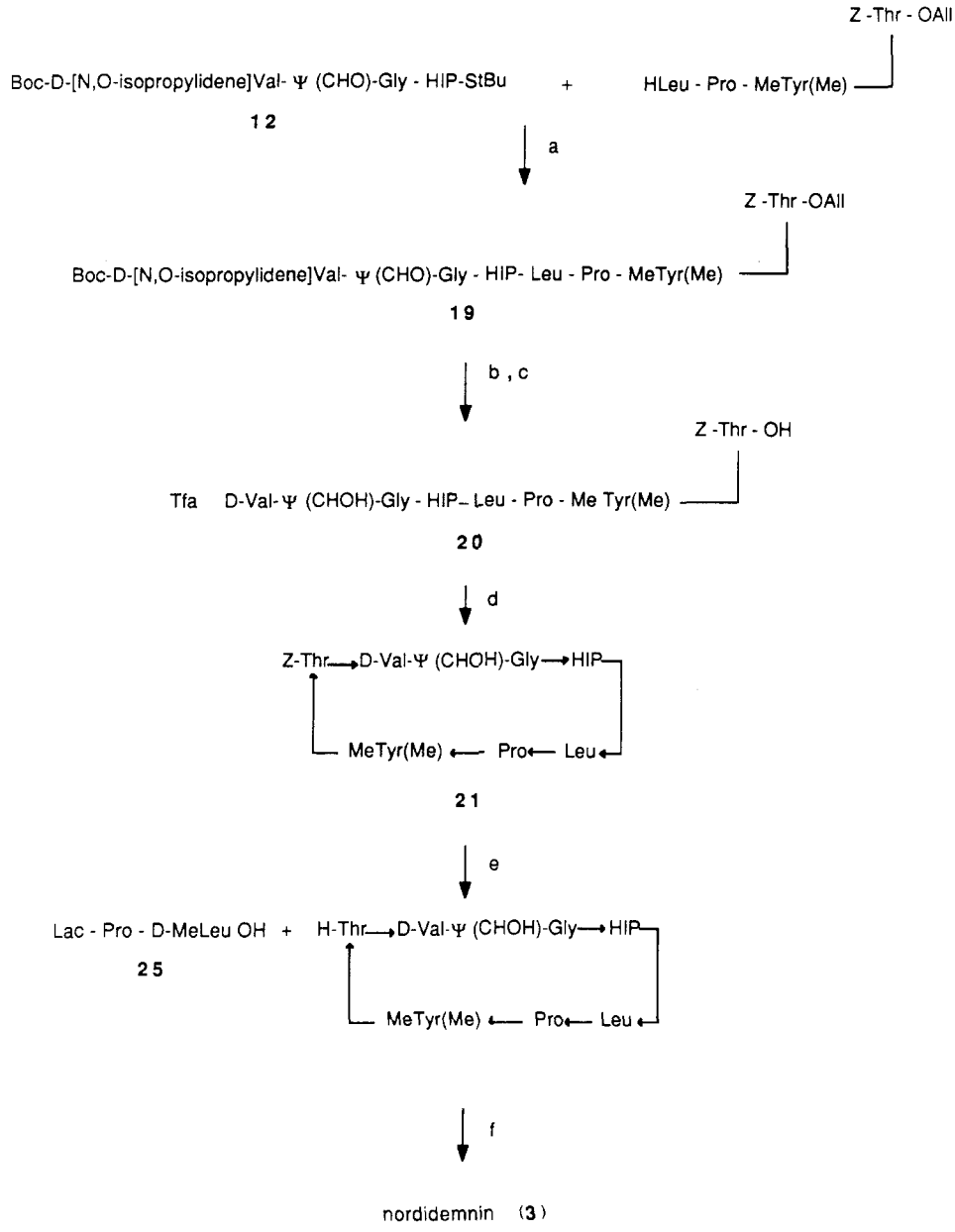
Scheme III. Synthesis of Nordidemnin B from A, B, and C Subunits



[a] (a) TEA (1 equiv), 2 equiv of CuI, CH_2Cl_2, 0.5 h, 85%; (b) $Pd(Ph_3P)_4$ catalytic, 1.2 equiv of morpholine, THF, 10 min; (c) TFA, 0.5 h, 67% (from **19**); (d) 1.1 equiv of BOP, 5 equiv of $NaHCO_3$, DMF, 24 h, 54%; (e) Pd/C catalytic, MeOH, 2 h; (f) 2 equiv of NMM, 1 equiv of BOP, CH_2Cl_2, 3 h, 57%.

98%. As mentioned before, the presence of slowly interconverted rotamers prevented a complete analysis of the materials by NMR. The purity of the isolated compound was efficiently determined by HPLC.

In the light of the abundant literature devoted to the cyclization problem in the cyclopeptide synthesis,[39] we deliberately did not plan an exhaustive comparative study, but followed an improved mild cyclization technique described by Brady et al.,[39c] with the slight modification of using BOP for carboxyl activation instead of DPPA. The cyclization was performed for 24 h in a 10^{-2} M solution of **20** in DMF, at room temperature, with sodium bicarbonate as the insoluble base. Although the conversion of the linear peptide **20** into the cyclo monomer **21** occurred in 66% yield, as estimated from HPLC analysis, the yield in purified product **21** was only 54% after flash chromatography. Analytical data were in agreement with the structure proposed. As expected, the NMR spectrum, run in deuteriated benzene, showed dramatic simplifications as compared to the linear molecule. The most satisfactory feature arising from these data was the presence of only one epimer at the C-2 position of the HIP residue.

Preparation of the Dipeptidyl Extra Chain Lac-Pro-D-MeLeu (25). Given our main subtarget, we prepared the external chain as outlined in Scheme IV. On the basis of our previous results related to the coupling of the Lac-Pro unit with D-MeLeu secondary amine,[12] we decided to follow the stepwise route that had proved convenient for the tetradepsipeptide unit synthesis. Thus, D-MeLeu-OMe, obtained after methylation and hydrogenolysis of the Z-D-Leu, was coupled with $(Boc\text{-}Pro)_2O$ symmetrical anhydride by heating the mixture without solvent. The crystalline dipeptide **23** was isolated in 97%

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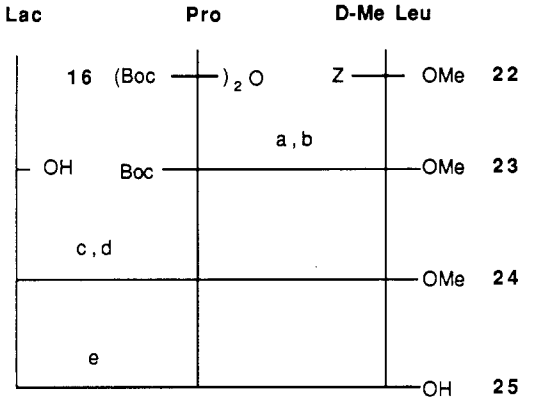
Table II. ^{1}H NMR Spectral Data for Nordidemnin B (3)[a]

residue	NMR data					
lactic acid	C2–H	$C2CH_3$				
δ	q, 4.11	d, 1.26				
J	6.5–7.2	6.5				
proline		α C–H	β C–H_2	γ C–H_2	δ C–H_2	
δ		q, 4.13	m, 1.48–1.34	m, 1.44–1.1	m, 2.86–2.7	
J		7.1–7.2				
N-methylleucine	N–CH_3	α C–H	β C–H_2	γ C–H	γ C–CH_3	
δ	2.87	q, 5.62	m, 2.02–1.6	m, 1.36	dd, 0.97–0.85	
J		11.7–4.0				
threonine	N–H	α C–H	β C–H	β C–CH_3		
δ	d, 8.02	q, 4.9	m, 5.89	d, 1.89		
J	5.0	5.0–2.3		6.3		
Valψ(CHOH)Gly	N–H	C2–H	C3–H	C4–H	C5–H	C5–CH_3
δ	d, 7.51	qd, 3.92–2.85	m, 4.45	q, 4.48	m, 2.43	dd, 1.04–1.17
J	9.5	17.2 (gem)		9.1–3.4		6.8
HIP		C2–H	C2–CH_3	C4–H	C5–H	C5–CH_3
δ		q, 4.66	d, 1.74	d, 5.64	m, 2.48	d, 0.88
J		6.8	6.8	3.3		6.8
leucine	NH	α C–H	β C–H_2	γ C–H	γ C–CH_3	
δ	d, 8.17	m, 5.1	m, 1.58–1.45	m, 1.8	0.99	
J	9.3					
proline		α C–H	β C–H_2	γ C–H_2	δ C–H_2	
δ		q, 4.34	m, 1.24	m, 1.45–1.17	m, 3.31–3.09	
J		4.65–8.15				
N,O-dimethyltyrosine	N–CH_3	α C–H	β C–H_2	aromatic	O–CH_3	
δ	s, 2.16	m, 3.38	m, 3.38–3.16	dd, 6.77–6.68	s, 3.34	
J				8.6		

[a] Spectra recorded in C_6D_6 at 370 MHz. Coupling constants are given in hertz and δ values in parts per million. Assignments were obtained by correlation analysis (COSY).

Scheme IV. Preparation of the Dipeptide Lac-Pro-D-MeLeu



[a] (a) H_2, Pd/C catalytic, MeOH, 2 h; (b) heating, 130 °C, 5 min, 97%; (c) TFA, 0.5 h; (d) 5 equiv of $NaHCO_3$, 1.5 equiv of BOP, DMF, 18 h, 77%; (e) 3 equiv of NaOH (2 M), MeOH, 90%.

yield by trituration of the crude product obtained after repeated washings. After trifluoroacetic acid Boc deblocking, the peptide was acylated with an excess of the free lactic acid in DMF, using BOP reagent as coupling agent and an excess of sodium bicarbonate as base. Pure Lac-Pro-D-MeLeu-OMe (**24**) was isolated in 77% yield after flash column chromatography. As shown for other fragments containing *N*-methyl amino acid and prolyl residues, the NMR spectra indicated several rotamers. However, HPLC and mass spectrometry analysis demonstrated the purity of this peptide **24** which was saponified in **25** (90%).

Completion of the Nordidemnin B (3) Synthesis. The final BOP-promoted coupling between **25** and the N-free cyclic depsipeptide obtained from the Z-protected macrocyclic compound **21** by hydrogenolysis provided nordidemnin B (**3**, 57% yield) in pure form with no observable epimerization in the purified compound, after flash column silica gel chromatography.

The synthetic product was identical in every respect with the natural nordidemnin B (**3**) that had been extracted and purified from *Tridemnum cyanophorum* by Guyot.[14] This identity was established by HPLC, mass spectrometry fragmentation, circular dichroism (Figure 1), and 2D NMR COSY analysis (Table II). Taking into account the strong concentration dependence of the chemical shifts in didemnin B and nordidemnin B, the NMR spectrum of the synthetic and natural nordidemnin mixture furnished additional evidence of their identity.

Further information obtained from 2D NMR ROESY measurements from both didemnin B and nordidemnin

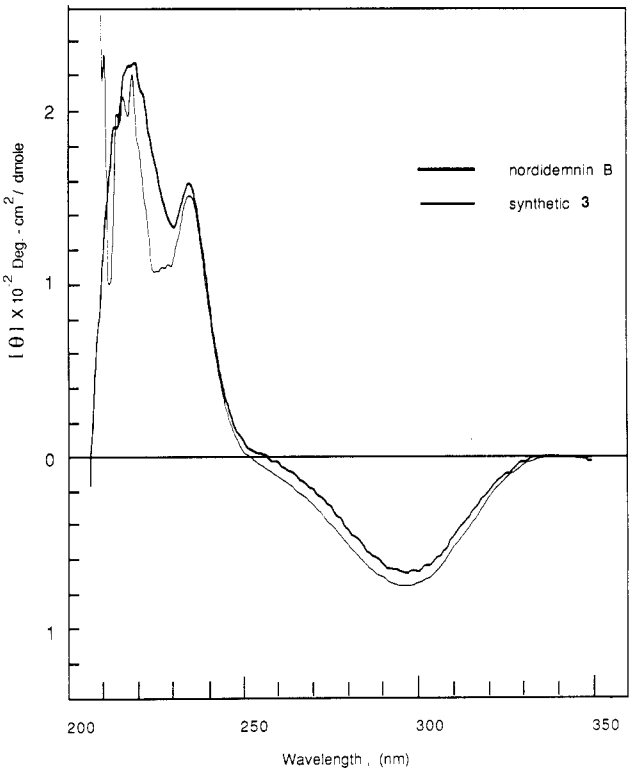


Figure 1. CD spectra of natural and synthetic nordidemnin B (**3**), in methanol.

B are currently being used in a predictive tertiary structure study by distance-geometry molecular modeling calculations.[40]

Experimental Section

Melting points were determined by using a Büchi melting point apparatus. NMR data were obtained at 360 MHz on a Bruker WM-360 instrument; chemical shifts (parts per million) were reported relative to internal tetramethylsilane. Specific optical rotations were measured on a Schmidt and Haensch Polartronic D apparatus and are at ±1°. Circular dichroism spectra were obtained on a Jobin et Yvon Autodichrograph Mark V instrument; λ_{max} values are expressed in nanometers and θ values in deg $cm^2/dmol$. HPLC analyses were performed on a Beckman apparatus (System Gold) using Ultrasphere ODS (4.6 × 150 mm) (column A) or Hypersyl C8 (4.6 × 250 mm) (column B) columns and mixtures of 1‰ trifluoroacetic acid (TFA) in water (solvent A) and 1‰ TFA in methanol (solvent B) as eluent. Mass spectrometry was obtained at the Centre de Recherche de Biochimie et de Génétique Cellulaire (Toulouse). Elemental analyses were obtained from the Service de microanalyses du CNRS, Ecole Nationale Supérieure de Chimie de Montpellier. Analytical TLC were performed on silica gel F254 aluminum sheets (0.2 mm thick; Merck). Column chromatographies were performed by using silica gel (70–200 mm, Amicon). BOP reagent [(benzotriazolyloxy)-tris(dimethylamino)phosphonium hexafluorophosphate] was a gift from Sempa-Chimie. IPCC and COMODD were obtained, as a gift, from SNPE (France). Amino acid derivatives were purchased from Bachem or Novabiochem.

2-[*N*-(*tert*-Butyloxycarbonyl)-D-valyl]-3,5-dioxo-4-methyl-1,2,4-oxadiazolidine (4). This compound was prepared from Boc-D-Val according to Jouin et al.[25] To a cooled (0–5 °C) solution of Boc-D-Val (15.2 g, 70 mmol) in tetrahydrofuran (150 mL) were added COMODD reagent (19.9 g, 77 mmol) and triethylamine (0.97 mL, 7 mmol). After 2 h of stirring at this temperature, the reaction mixture was diluted with ethyl acetate (300 mL) and washed successively with 5% $KHSO_4$ (50 mL), water (50 mL), 5% $NaHCO_3$ (2 × 50 mL), and saturated brine (50 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to furnish **4** as a thick oil (21.6 g, 98%): R_f 0.49 (ethyl acetate/hexane, 30:70); $[\alpha]^{20}_D$ −42° (*c* 1, MeOH); ^1H NMR (DMSO-d_6) δ 0.85 (d, J = 6.8 Hz, 3 H), 0.93 (d, J = 6.8 Hz, 3 H), 1.38 (s, 9 H), 2.04–2.21 (m, 1 H), 3.01 (s, 3 H), 4.86 (dd, J_1 = 4.9 Hz, J_2 = 8.3 Hz, 1 H), 7.25 (d, J = 8.3 Hz, 1 H).

Ethyl (4*R*)-4-[(*tert*-Butyloxycarbonyl)amino]-3-oxo-5-methylhexanoate (5). This compound was prepared according to Jouin et al.[25] To a cooled (−78 °C) solution of lithium diisopropylamide in dry tetrahydrofuran (150 mL), prepared from *n*-BuLi, 1.5 M in hexane (93.3 mL, 140 mmol), and diisopropylamine (19.6 mL, 140 mmol), was added a solution of ethyl acetate (13.6 mL, 140 mmol) in dry tetrahydrofuran (50 mL), at such a rate as to maintain the temperature below −75 °C. Immediately after the end of the addition, a solution of **4** (21.6 g, 68.6 mmol) in dry tetrahydrofuran (50 mL) was added dropwise so as to keep the temperature below −70 °C. Stirring was continued for 15 min more, and the reaction was quenched by rapid addition of 1 M HCl (150 mL). The reaction mixture was diluted with ethyl acetate (200 mL). The organic layer was decanted and washed successively with water (50 mL), 5% $NaHCO_3$ (2 × 50 mL), and saturated brine (50 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to furnish **5** as an oil (18.5 g, 94%): R_f 0.64 (ethyl acetate/hexane, 30:70); $[\alpha]^{20}_D$ +34° (*c* 1, MeOH); ^1H NMR (DMSO-d_6; keto form/enol form, 83:17) keto form δ 0.80 (d, J = 6.8 Hz, 3 H), 0.85 (d, J = 6.8 Hz, 3 H), 1.17 (t, J = 6.8 Hz, 3 H), 1.39 (s, 9 H), 2.02–2.15 (m, 1 H), 3.56 (s, 2 H), 3.88 (dd, J_1 = 6.8 Hz, J_2 = 8.3 Hz, 1 H), 4.07 (q, J = 6.8 Hz, 2 H), 7.23 (d, J = 8.3 Hz, 1 H), enol form δ 1.21 (t, J = 6.8 Hz, 3 H), 4.15 (q, J = 6.8 Hz, 2 H), 5.16 (s, 1 H), 11.95 (s, 1 H).

Ethyl (3*S*,4*R*)-N^4,O^3-Isopropylidene-4-[(*tert*-butyloxycarbonyl)amino]-3-hydroxy-5-methylhexanoate (7). To a stirred and cooled (0–5 °C) solution of **5** (17.2 g, 60.0 mmol) in a mixture of acetic acid (28 mL) and methylene chloride (120 mL) was added $NaBH_4$ (4.6 g, 120 mmol) by batches, so that temperature did not exceed 5 °C. Stirring was continued for 1 h more at 0–5 °C at the end of the addition. The reaction mixture was then diluted with ethyl acetate (250 mL) and water (50 mL). The two phases were decanted, and the organic one was washed one more time with water (50 mL) and then cautiously with 5% $NaHCO_3$ to pH 8. The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to furnish **6** as a mixture of epimers at the C-3 position (*S*/*R*, 95:5, ^1H NMR evaluation).[26] This compound was used without further purification for the following step.

A solution of **6** and *p*-toluenesulfonic acid (100 mg) in 2,2-dimethoxypropane was refluxed for 3 h and then stirred, overnight, at room temperature. The solvent was eliminated under reduced pressure and the residue solubilized in ethyl acetate (300 mL). After washing (5% $NaHCO_3$, 50 mL) and drying (Na_2SO_4), the solvent was removed under vacuum to give **7** as a mixture of epimers, which were separated by silica gel chromatography. The good diastereomer **7a** was obtained with an overall yield of 62% from the β-keto ester **5** (12.3 g, oil): R_f 0.78 (ethyl acetate/hexane, 20:80); $[\alpha]^{20}_D$ +19° (*c* 1, MeOH); ^1H NMR (DMSO-d_6) δ 0.82–0.92 (m, 6 H), 1.19 (t, J = 6.6 Hz, 3 H), 1.41 (s, 9 H), 1.46 (s, 6 H), 1.71–1.87 (m, 1 H), 2.58 (dd, J_1 = 8.1 Hz, J_2 = 16.2 Hz, 1 H), 2.76 (dd, J_1 = 5.9 Hz, J_2 = 16.2 Hz, 1 H), 3.66–3.83 (m, 1 H), 4.09 (q, J = 6.6 Hz, 2 H), 4.34–4.42 (m, 1 H).

Benzyl (2*S*)-2-[[(3*S*,4*R*)-N^4,O^3-Isopropylidene-4-((*tert*-butyloxycarbonyl)amino)-3-hydroxy-5-methylhexanoyl]-oxy]-3-methylbutanoate (10). To an ice-cooled and stirred solution of **7a** (6.09 g, 18.5 mmol) in methanol (15 mL) was added 2 M NaOH (18 mL) at such a rate that the temperature did not exceed 5 °C. The reaction was monitored by TLC analysis. When all the ester had disappeared, the pH was adjusted to pH 2 with 5% $KHSO_4$ and the aqueous phase was extracted with ethyl acetate (2 × 100 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to furnish **8** as a colorless oil (5.46 g, 98%).

To a cooled (−5 °C) solution of **8** (5.46 g, 18.1 mmol) and **9**, prepared in two steps from L-valine by using conventional procedures (3.73 g, 17.9 mmol),[30,31] in ethanol-free methylene chloride (50 mL), were added triethylamine (2.75 mL, 19.9 mmol), 4-(dimethylamino)pyridine (0.44 g, 3.6 mmol), and, dropwise, isopropenyl chlorocarbonate (IPCC) (2.4 mL, 19.9 mmol) over a 15-min period.[29] After an additional 15 min at −5 °C, the solvent was removed under vacuum, and the residue was taken up with ethyl acetate (150 mL). The organic phase was washed with 5% $KHSO_4$ (2 × 20 mL), water (20 mL), 5% $NaHCO_3$ (2 × 20 mL), and saturated brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to furnish **10** as a colorless oil (8.10 g, 92%), homogeneous by TLC analysis: R_f 0.63 (ethyl acetate/hexane, 20:80); $[\alpha]^{20}_D$ −8° (*c* 1, MeOH); ^1H NMR (DMSO-d_6) δ 0.80–0.95 (m, 12 H), 1.41 (s, 9 H), 1.44 (s, 3 H), 1.46 (s, 3 H), 1.75–1.87 (m, 1 H), 2.10–2.22 (m, 1 H), 2.71 (dd, J_1 = 4.9 Hz, J_2 = 16.6 Hz, 1 H), 2.84 (dd, J_1 = 5.9 Hz, J_2 = 16.6 Hz, 1 H), 3.68–3.86 (m, 1 H), 4.33–4.41 (m, 1 H), 4.87 (d, J = 4.4 Hz, 1 H), 5.17 (s, 2 H), 7.36 (m, 5 H).

3,5-Dioxo-2-[(2*S*)-2-[[(3*S*,4*R*)-N^4,O^3-isopropylidene-4-[(*tert*-butyloxycarbonyl)amino]-3-hydroxy-5-methylhexanoyl]oxy]-3-methylbutanoyl]-4-methyl-1,2,4-oxadiazolidine (11). **10** (8.00 g, 16.3 mmol) was hydrogenated at atmospheric pressure, in 2-propanol (100 mL), over 10% palladium on charcoal (2 g) to give, after filtration and concentration, the free acid (6.54 g, quantitative yield), which was immediately transformed into **11** (7.90 g, 97%) by using COMODD reagent as described for **4**: R_f 0.49 (ethyl acetate/hexane, 30:70); ^1H NMR (DMSO-d_6) δ 0.84–0.94 (m, 9 H), 1.02 (d, J = 6.8 Hz, 3 H), 1.46 (s, 9 H), 1.47 (s, 3 H), 1.46 (s, 3 H), 1.74–1.89 (m, 1 H), 2.24–2.37 (m, 1 H), 2.65–2.83 (m, 1 H), 2.86–2.95 (m, 1 H), 3.02 (s, 3 H), 3.72–3.86 (m, 1 H), 4.35–4.42 (m, 1 H), 5.52 (d, J = 3.4 Hz, 1 H).

***tert*-Butyl (4*S*)-4-[[(3*S*,4*R*)-N^4,O^3-Isopropylidene-4-[(*tert*-butyloxycarbonyl)amino]-3-hydroxy-5-methylhexanoyl]oxy]-3-oxo-2,5-dimethylthiohexanoate (12).** This compound was prepared from **11** (7.90 g, 15.8 mmol) and *tert*-butyl propionic acid thioester (31.6 mmol) by using the procedure described for **5** (8.20 g, 98%). The two epimers obtained were not separated: R_f 0.88 (ethyl acetate/hexane, 10:90); ^1H NMR

(40) Havel, T. F.; Wütrich, K. *J. Mol. Biol.* **1985**, *182*, 281.

(DMSO-d_6) δ 0.78–0.99 (m, 12 H), 1.17 (d, J = 7.0 Hz, 3 H), 1.39 (s, 18 H), 1.41 (s, 6 H), 1.75–1.87 (m, 1 H), 2.29–2.42 (m, 1 H), 2.53–2.94 (m, 2 H), 3.73–3.86 (m, 1 H), 4.07 (q, J = 7.0 Hz, 1 H), 4.34–4.44 (m, 1 H), 5.13 (m, 1 H); distinguishable signals of the second epimer δ 1.23 (d, J = 7.0 Hz, 3 H), 4.19 (q, J = 7.0 Hz, 1 H).

N-(*tert*-Butyloxycarbonyl)-N,O-dimethyl-L-tyrosine (13). N-(*tert*-Butyloxycarbonyl)-N-methyl-O-benzyl-L-tyrosine was prepared in 87% yield from Boc-Tyr(Bzl) according to Cheung et al.;[34] $[\alpha]^{20}_D$ –67° (*c* 1, MeOH); mp 130–134 °C (lit.:[41] $[\alpha]^{20}_D$ –69.4° (*c* 1, MeOH); mp 131–134 °C). This last compound (20.0 g, 51.9 mmol) was hydrogenated at atmospheric pressure and room temperature, over 10% palladium on charcoal in methanol (100 mL). The reaction was monitored by TLC (ethyl acetate/hexane/acetic acid, 50:50:1). After filtration and evaporation of the solvent under reduced pressure, Boc-MeTyr was obtained as a colorless oil (15.3 g, 100%).

To a solution of Boc-MeTyr and dimethyl sulfate (10 mL) in acetone (250 mL) was added K_2CO_3 (14.3 g, 103.8 mmol); the suspension was then refluxed for 5 h. The resulting precipitate was eliminated by filtration, and the filtrate was concentrated under vacuum. The residue was solubilized in ethyl acetate (250 mL) and washed with water (50 mL) and 5% $NaHCO_3$ (2 × 30 mL). After drying over Na_2SO_4 and filtering, the solvent was removed under reduced pressure to give Boc-MeTyr(Me)-OMe as a colorless oil (15.6 g, 93%).

This last compound was immediately dissolved in methanol (30 mL). To this stirred and cooled solution (0–5 °C) was added dropwise 2 N NaOH (48 mL). At the end of the addition, stirring was continued at 0–5 °C and the reaction was monitored by TLC (ethyl acetate/hexane/acetic acid, 50:50:1) until no more ester could be detected. The pH was then adjusted to pH 2 with 5% $KHSO_4$, and the aqueous phase was extracted with ethyl acetate (2 × 100 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to furnish **13** as a colorless oil (14.8 g, 99%), homogeneous by TLC analysis (ethyl acetate/hexane/acetic acid, 50:50:1; R_f 0.33); $[\alpha]^{20}_D$ –16° (*c* 1, MeOH).

Allyl N-(Benzyloxycarbonyl)-L-threoninate (14). To a stirred solution of Z-Thr (12.7 g, 50 mmol) and allyl bromide (4.5 mL, 52 mmol) in dimethylformamide (50 mL) was added Cs_2CO_3 (8.50 g, 26 mmol). The reaction is slightly exothermic. After 2 h of stirring, the precipitate was filtered off, and the solvent was removed under vacuum. The oily residue was diluted in diethyl ether (200 mL) and washed with water (3 × 30 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give **14** as an oil (14.4 g, 98%), homogeneous by TLC analysis (ethyl acetate/hexane, 50:50; R_f 0.68): $[\alpha]^{20}_D$ –23° (*c* 1, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.12 (d, J = 6.4 Hz, 3 H), 4.06–4.14 (m, 2 H), 4.55–4.65 (m, 2 H), 4.78 (d, J = 6.8 Hz, 1 H), 5.07 (s, 2 H), 5.20 (dd, J_1 = 1.5 Hz, J_2 = 10.7 Hz, 1 H), 5.34 (dd, J_1 = 1.5 Hz, J_2 = 17.1 Hz, 1 H), 5.84–5.95 (m, 1 H), 7.19 (d, J = 8.4 Hz, 1 H), 7.27–7.39 (m, 5 H).

Allyl N-(Benzyloxycarbonyl)-O-[N-(*tert*-butyloxycarbonyl)-N,O-dimethyl-L-tyrosyl]-L-threoninate (15). Following the procedure used for the preparation of **10**, we prepared **15** from **13** (11.4 g, 35.9 mmol) and **14** (10.4 g, 35.5 mmol) as a colorless oil (20.3 g, 98%), homogeneous by TLC analysis (ethyl acetate/hexane, 30:70; R_f 0.39): $[\alpha]^{20}_D$ –23° (*c* 1, MeOH); ^{1}H NMR (DMSO-d_6) major conformer δ 1.25 (s, 12 H), 2.60 (s, 3 H), 2.87 (dd, J_1 = 12.7 Hz, J_2 = 14.7 Hz, 1 H), 3.21 (dd, J_1 = 4.9 Hz, J_2 = 14.7 Hz, 1 H), 3.60 (s, 3 H), 4.42–4.52 (m, 1 H), 4.52–4.67 (m, 2 H), 4.75–4.86 (m, 1 H), 5.09 (AB, J = 12.2 Hz, 2 H), 5.17–5.37 (m, 3 H), 5.81–5.95 (m, 1 H), 6.85 (d, J = 7.1 Hz, 2 H), 7.09 (d, J = 7.1 Hz, 2 H), 7.28–7.40 (m, 5 H), 7.84 (d, J = 8.8 Hz, 1 H), minor conformer (distinguishable signals) δ 1.30 (s, 3 H), 7.75 (d, J = 8.3 Hz, 1 H).

Allyl N-(Benzyloxycarbonyl)-O-[[N-(*tert*-butyloxycarbonyl)-L-prolyl]-(N,O-dimethyl-L-tyrosyl)]-L-threoninate (17). Compound **15** (20.0 g, 34.2 mmol) was treated with trifluoroacetic acid (30 mL) over a 30-min period. The mixture was diluted with diethyl ether/hexane (1:1, 1000 mL), and the TFA salt of the resulting amino free depsipeptide was crystallized upon trituration (18.4 g, 90%). Treatment of a solution of the preceding salt (2.40 g, 4.01 mmol) in ethyl acetate (30 mL) by 5% $NaHCO_3$ and the usual workup furnished the amino free depsipeptide as an oil (quantitative yield).

We followed, then, the procedure described by Rodriguez and Goodman.[38] To this compound was added the symmetrical anhydride **16** (2.48 g, 6.00 mmol) (prepared from Boc-Pro according to Chen et al.[42]), and the resulting thick oil was heated at 130 °C for 5 min. The reaction mixture was rapidly cooled, diluted with diethyl ether (50 mL), transferred to a separatory funnel, and washed with water to neutral pH. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was then chromatographed on silica gel (eluent: ethyl acetate/hexane, 50:50) to give **17** as a thick oil (2.30 g, 84%), homogeneous by TLC analysis (ethyl acetate/hexane, 50:50; R_f 0.53): HPLC, column A (A/B, 25:75), t_R = 5.96 min; $[\alpha]^{20}_D$ –48° (*c* 1, MeOH); ^{1}H NMR (DMSO-d_6) major conformer δ 1.11 (s, 9 H), 1.20 (d, J = 6.3 Hz, 3 H), 1.59–1.88 (m, 4 H), 2.79 (s, 3 H), 2.92 (dd, J_1 = 11.2 Hz, J_2 = 15.1 Hz, 1 H), 3.20 (dd, J_1 = 4.4 Hz, J_2 = 15.1 Hz, 1 H), 3.23–3.34 (m, 2 H), 3.69 (s, 3 H), 4.38–4.55 (m, 1 H), 4.55–4.62 (m, 2 H), 5.08 (s, 3 H), 5.13 (dd, J_1 = 4.4 Hz, J_2 = 11.2 Hz, 1 H), 5.17–5.36 (m, 3 H), 5.80–5.96 (m, 1 H), 6.81 (d, J = 8.8 Hz, 2 H), 7.12 (d, J = 8.8 Hz, 2 H), 7.28–7.40 (m, 5 H), 7.84 (d, J = 8.8 Hz, 1 H), minor conformer (distinguishable signals) δ 2.81 (s, 3 H), 7.70 (d, J = 8.8 Hz, 1 H).

Allyl N-(Benzyloxycarbonyl)-O-[[N-(*tert*-butyloxycarbonyl)-L-leucyl]-L-prolyl-(N,O-dimethyl-L-tyrosyl)]-L-threoninate (18). Compound **17** (2.20 g, 3.23 mmol) was treated with trifluoroacetic acid for 30 min. The corresponding trifluoroacetic acid salt could not be crystallized; thus, it was dried in high vacuum and over KOH until the weight was constant. To a stirred solution of this salt and Boc-Leu·H_2O (0.92 g, 3.69 mmol) in methylene chloride (5 mL) were added, successively, diisopropylethylamine (1.8 mL, 10.6 mmol) and BOP reagent (1.63 g, 3.69 mmol). Stirring was continued for 2 h. The reaction mixture was then diluted with ethyl acetate (30 mL) and transferred to a separatory funnel, where the organic phase was washed with 5% $KHSO_4$ (2 × 10 mL), water (10 mL), 5% $NaHCO_3$ (2 × 10 mL), and saturated brine. The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to furnish a yellow residue, which was chromatographed on silica gel (ethyl acetate/hexane, 70:30). After evaporation of the solvent, **18** was obtained as a foam (2.42 g, 94%): R_f 0.58 (ethyl acetate/hexane, 70:30); HPLC, column B (A/B, 20:80), t_R = 5.83 min; $[\alpha]^{20}_D$ –89° (*c* 1, MeOH); ^{1}H NMR (DMSO-d_6) (two conformers in equimolar quantities which were not distinguished δ 0.42–0.51 (m, 0.5 H), 0.74 (d, J = 7.2 Hz, 1.5 H), 0.84 (d, J = 7.2 Hz, 1.5 H), 0.86 (d, J = 7.3 Hz, 1.5 H), 0.87 (d, J = 6.4 Hz, 1.5 H), 1.10–1.49 (m, 3 H), 1.17 (d, J = 6.3 Hz, 1.5 H), 1.26 (d, J = 6.4 Hz, 1.5 H), 1.32 (s, 4.5 H), 1.35 (s, 4.5 H), 1.59–1.72 (m, 2 H), 1.84–1.99 (m, 1 H), 2.02–2.13 (m, 0.5 H), 2.57 (s, 1.5 H), 2.84 (s, 1.5 H), 2.89 (t, J = 14.2 Hz, 0.5 H), 2.91 (dd, J_1 = 12.7 Hz, J_2 = 14.6 Hz, 1 H), 3.13 (dd, J_1 = 3.7 Hz, J_2 = 14.4 Hz, 0.5 H), 3.18 (dd, J_1 = 6.0 Hz, J_2 = 15.0 Hz, 0.5 H), 3.30–3.37 (m, 0.5 H), 3.40–3.48 (m, 0.5 H), 3.49–3.50 (m, 0.5 H), 3.61–3.68 (m, 0.5 H), 3.70 (s, 1.5 H), 3.71 (s, 1.5 H), 4.17–4.23 (m, 0.5 H), 4.26–4.32 (m, 0.5 H), 4.43 (dd, J_1 = 3.9 Hz, J_2 = 8.9 Hz, 0.5 H), 4.38–4.55 (m, 1 H), 4.56–4.60 (m, 2.5 H), 4.64 (dd, J_1 = 4.4 Hz, J_2 = 8.9 Hz, 0.5 H), 4.72 (dd, J_1 = 3.4 Hz, J_2 = 7.9 Hz, 0.5 H), 4.95–5.05 (m, 1 H), 5.08 (s, 3 H), 5.12–5.34 (m, 2.5 H), 5.42 (qd, J_1 = 2.9 Hz, J_2 = 6.3 Hz, 1 H), 5.80–5.93 (m, 1 H), 5.88 (d, J = 10.3 Hz, 0.5 H), 6.78 (d, J = 7.8 Hz, 0.5 H), 6.81 (d, J = 8.3 Hz, 1 H), 6.85 (d, J = 8.9 Hz, 1 H), 7.09 (d, J = 8.3 Hz, 1 H), 7.16 (d, J = 8.9 Hz, 1 H), 7.28–7.40 (m, 5 H), 7.71 (d, J = 8.9 Hz, 0.5 H), 8.17 (d, J = 9.8 Hz, 0.5 H).

Anal. Calcd for $C_{42}H_{58}N_4O_{11}$: C, 63.46; H, 7.35; N, 7.05. Found: C, 63.00; H, 7.33; N, 7.03.

Allyl N-(Benzyloxycarbonyl)-O-[[N-[(4S)-4-[(3S,4R)-N^4,O^3-isopropylidene-4-[(*tert*-butyloxycarbonyl)amino]-3-hydroxy-5-methylhexanoyl]oxy-3-oxo-2,5-dimethylhexanoyl]-L-leucyl]-L-prolyl-[N,O-dimethyl-L-tyrosyl]]-L-

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threoninate (19). We used a modification of the procedure described by Kim et al.[19]

Compound **18** (1.00 g, 1.26 mmol) was treated with trifluoroacetic acid for 30 min. The solvent was then evaporated, and the residue was solubilized in methylene chloride (20 mL) and washed with 5% $NaHCO_3$ (10 mL). The organic layer was dried (Na_2SO_4) and concentrated under vacuum to give the amino free tetradepsipeptide.

To a solution of the preceding crude material and **12** (0.66 g, 1.25 mmol) in methylene chloride (5 mL) were added triethylamine (173 μL, 1.25 mmol) and CuI (476 mg, 2.50 mmol). The reaction mixture was stirred at room temperature for 30 min. Methylene chloride and acetic acid (1 mL) were added, and the mixture was filtered. The filtrate was washed with water (2 × 10 mL), 5% $NaHCO_3$ (2 × 10 mL), and brine. After drying (Na_2SO_4), concentration of the solvent provided **19** as a mixture of diastereomers, which were crystallized upon trituration in hexane (1.21 g, 85%).

***N*-(Benzyloxycarbonyl)-*O*-[[*N*-[(4*S*)-4-[(3*S*,4*R*)-4-amino-3-hydroxyl-5-methylhexanoyl]oxy-3-oxo-2,5-dimethylhexanoyl]-L-leucyl]-L-prolyl-[*N*,*O*-dimethyl-L-tyrosyl]]-L-threonine (20).** Following the procedure described by Kunz et al.[33] and using tetrakis(triphenylphosphine)palladium(0) as catalyst, **19** (1.00 g, 0.88 mmol) provided the free acid, which was purified by column chromatography (methanol/methylene chloride, 8:92). This slightly yellow material was immediately treated with trifluoroacetic acid for 30 min. After evaporation of the solvent under reduced pressure, **20** was crystallized from diethyl ether (0.65 g) in a 67% overall yield from **19**: R_f 0.36 (methanol/methylene chloride, 10:90); HPLC, column B (A/B, 30:70), t_R = 3.54 and 3.62 min.

***cyclo*-[*N*-(Benzyloxycarbonyl)-*O*-[[*N*-[(4*S*)-4-[(3*S*,4*R*)-4-amino-3-hydroxy-5-methylhexanoyl]oxy-3-oxo-2,5-dimethylhexanoyl]-L-leucyl]-L-prolyl-[*N*,*O*-dimethyl-L-tyrosyl]]-L-threonyl] (21).** To a solution of **20** (0.42 g, 0.39 mmol) in dimethylformamide (40 mL) were added BOP reagent (0.18 g, 0.41 mmol) and $NaHCO_3$ (0.16 g, 2 mmol), and the mixture was stirred for 24 h, at room temperature and in the dark. The reaction mixture was concentrated under vacuum, solubilized in ethyl acetate (40 mL), and washed with 5% $KHSO_4$ (2 × 5 mL), water (5 mL), 5% $NaHCO_3$ (2 × 5 mL), and saturated brine. The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to furnish a solid residue, which was chromatographed on silica gel (methanol/methylene chloride, 5:95). Compound **21** was crystallized upon trituration in hexane (0.19 g, 54%): R_f 0.17 (acetone/hexane, 30:70); HPLC, column B (gradient from A/B, 30:70), to B in 15 min), t_R = 7.41 min; ^{1}H NMR (DMSO-d_6) δ 0.80 (d, J = 6.8 Hz, 3 H), 0.84 (d, J = 6.8 Hz, 3 H), 0.88 (d, J = 6.4 Hz, 3 H), 1.00 (d, J = 6.3 Hz, 3 H), 1.17 (d, J = 6.8 Hz, 3 H), 1.26 (d, J = 6.8 Hz, 3 H), 1.23–1.38 (m, 2 H), 1.52 (d, J = 6.8 Hz, 3 H), 1.46–1.52 (m, 1 H), 1.74–1.83 (m, 2 H), 2.12 (s, 3 H), 2.38–2.47 (m, 2 H), 2.68 (dd, J_1 = 10.0 Hz, J_2 = 18.6 Hz, 1 H), 3.12–3.19 (m, 2 H), 3.29–3.41 (m, 2 H), 3.34 (s, 3 H), 3.56 (d, J = 18.6 Hz. 1 H), 4.06 (q, J = 6.8 Hz, 1 H), 4.29–4.41 (m, 4 H), 4.87 (d, J = 6.8 Hz, 1 H), 4.96 (m, 1 H), 5.00 (m, 1 H), 5.03 (q, J = 9.7 Hz, 1 H), 5.23 (qd, J_1 = 3.4 Hz, J_2 = 6.3 Hz, 1 H), 5.58 (d, J = 9.8 Hz, 1 H), 5.66 (d, J = 3.4 Hz, 1 H), 6.68 (d, J = 8.8 Hz, 2 H), 6.80 (d, J = 8.3 Hz, 2 H), 7.00–7.16 (m, 5 H), 7.50 (d, J = 8.8 Hz, 1 H), 7.63 (d, J = 8.8 Hz, 1 H); FABMS, m/e (relative intensity) 936 (M^+ + H, 30), 802 (MH^+ – Z, 5), 685 (MH^+ – HIPLeu, 9), 70 (base).

***N*-(Benzyloxycarbonyl)-*N*-methyl-D-leucine Methyl Ester (22).** To a solution of Z-D-MeLeu prepared on a 50-mmol scale according to McDermott et al.[43] [82%; $[\alpha]^{20}_D$ +23° (c 1 in MeOH) (lit.[43] $[\alpha]^{20}_D$ –23.0° for the L isomer)] (5.58 g, 20 mmol) in dimethylformamide (40 mL) were added ICH_3 (1.6 mL, 20 mmol) and K_2CO_3 (2.7 g, 20 mmol), and the mixture was stirred for 24 h at room temperature. The reaction mixture was filtered, and the filtrate was concentrated under vacuum, solubilized in ethyl acetate (40 mL), and washed with 5% $KHSO_4$ (2 × 5 mL), water (5 mL), 5% $NaHCO_3$ (2 × 5 mL), and saturated brine. The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure, providing **22** as an oil (5.7 g, 98%): R_f 0.45 (ethyl acetate/hexane, 20:80); $[\alpha]^{20}_D$ +35° (c 1, MeOH); ^{1}H NMR (DMSO-d_6) major conformer δ 0.89 (dd, J = 6.34 Hz, 3 H), 1.38–1.53 (m, 1 H), 1.53–1.68 (m, 1 H), 1.68–1.82 (m, 1 H), 2.82 (s, 3 H), 3.64 (s, 3 H), 4.77 (dd, J_1 = 4.9 Hz, J_2 = 10.7 Hz, 1 H), 5.13 (s, 2 H), 7.34–7.37 (m, 5 H), minor conformer (distinguishable signals) δ 0.82 (dd, J = 5.9 Hz, 3 H), 2.80 (s, 3 H), 3.61 (s, 3 H), 4.64 (dd, J_1 = 4.3 Hz, J_2 = 10.4 Hz, 1 H).

[*N*-(*tert*-Butyloxycarbonyl)-L-prolyl]-*N*-methyl-D-leucine Methyl Ester (23). Compound **22** (3.18 g, 20 mmol) was hydrogenated at atmospheric pressure, in methanol (100 mL), over 10% palladium on charcoal (2 g) to give, after filtration and concentration, the free amine in quantitative yield. We followed, then, the procedure described by Rodriguez and Goodman.[38] To this compound was added the symmetrical anhydride **16** (8.2 g, 20 mmol) (prepared from Boc-Pro according to Chen et al.[42]), and the resulting thick oil was heated at 130 °C for 5 min. The reaction mixture was rapidly cooled, diluted with diethyl ether (50 mL), transferred to a separatory funnel, and washed with water to neutral pH. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was crystallized in diethyl ether (6.4 g, 90%): R_f 0.42 (ethyl acetate/hexane, 50:50); $[\alpha]^{20}_D$ 0° (c 1, MeOH); ^{1}H NMR (DMSO-d_6) major conformer δ 0.83 (dd, J = 6.34 Hz, 3 H), 0.90 (dd, J = 6.8 Hz, 3 H), 1.32 (s, 9 H), 1.39–1.45 (m, 1 H), 1.50–1.69 (m, 3 H), 1.70–1.85 (m, 2 H), 2.10–2.32 (m, 1 H), 2.94 (s, 3 H), 3.24–3.38 (m, 2 H), 3.60 (s, 3 H), 4.26–4.33 (m, 1 H), 4.68 (d, J = 6.8 Hz, 1 H), 4.62 (dd, J_1 = 3.4 Hz, J_2 = 8.3 Hz, 1 H), 4.93 (dd, J_1 = 4.4 Hz, J_2 = 11.2 Hz, 1 H), minor conformer (distinguishable signals) δ 1.38 (s, 9 H), 2.96 (s, 3 H), 3.62 (s, 3 H).

Anal. Calcd for $C_{18}H_{32}N_2O_5$: C, 60.65; H, 9.05; N, 7.86. Found: C, 60.50; H, 9.15; N, 7.80.

L-Lactyl-L-prolyl-*N*-methyl-D-leucine Methyl Ester (24). Compound **23** (1.78 g, 5 mmol) was treated with trifluoroacetic acid for 30 min. The corresponding trifluoroacetate salt could not be crystallized; it was dried under vacuum and over KOH until the weight was constant. To a stirred solution of this salt in dimethylformamide (10 mL) were added L-lactic acid (0.90 g, 10 mmol) and $NaHCO_3$ (2 g, 25 mmol), BOP reagent (2.2 g, 5 mmol) was added after 5 min, and the mixture was stirred for 24 h, at room temperature. The reaction mixture was concentrated under vacuum, solubilized in ethyl acetate (40 mL), and washed with 5% $KHSO_4$ (2 × 5 mL), water (5 mL), 5% $NaHCO_3$ (2 × 5 mL), and saturated brine. The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. **24** was chromatographed on silica gel (hexane/acetone, 60:40) (1.2 g, 77%): mp 118 °C; R_f 0.36 (hexane/acetone, 50:50).

Anal. Calcd for $C_{16}H_{28}N_2O_5$: C, 58.52; H, 8.59; N, 8.53. Found: C, 58.35; H, 8.50; N, 8.50.

L-Lactyl-L-prolyl-*N*-methyl-D-leucine (25). To an ice-cooled solution of **24** (0.70 g, 2.13 mmol) in methanol (3 mL) was added dropwise 2 N NaOH (3 mL), over a 5-min period. Stirring was then continued for 2 h at room temperature. After acidification (pH 2) with 5% $KHSO_4$, the aqueous mixture was saturated with NaCl and extracted with methylene chloride (3 × 30 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure, providing **25** as an oil, which was crystallized from diethyl ether/hexane (0.60 g, 90%): mp 213 °C; ^{1}H NMR (DMSO-d_6) major conformer δ 0.82 (dd, J = 6.8 Hz, 3 H), 0.89 (dd, J = 6.8 Hz, 3 H), 1.17 (dd, J = 6.4 Hz, 3 H), 1.34–1.44 (m, 1 H), 1.52–1.64 (m, 1 H), 1.59–1.68 (m, 1 H), 1.69–1.78 (m, 1 H), 1.83–1.91 (m, 2 H), 2.14–2.24 (m, 1 H), 2.97 (s, 3 H), 3.40–3.47 (m, 1 H), 3.65–3.72 (m, 1 H), 4.26–4.33 (m, 1 H), 4.68 (d, J = 6.8 Hz, 1 H), 4.82 (dd, J_1 = 4.4 Hz, J_2 = 8.3 Hz, 1 H), 4.90 (dd, J_1 = 4.7 Hz, J_2 = 10.9 Hz, 1 H), minor conformer (distinguishable signals) δ 0.94 (dd, J = 6.4 Hz, 3 H), 0.98 (dd, J = 6.4 Hz, 3 H), 2.96 (s, 3 H), 3.89–3.96 (m, 1 H); FABMS, m/e (relative intensity), 337 (M^+ + Na, 10), 315 (M^+ + H, 35), 70 (base).

Nordidemnin B (3). Compound **21** (120 mg, 128 μmol) in methanol solution (5 mL) was hydrogenated for 2 h at atmospheric pressure and room temperature over 10% palladium on charcoal to provide the free amino cycle (quantitative yield) after filtration and evaporation of the solvent.

To a solution of this last product and **25** (63 mg, 200 μmol) in methylene chloride (1 mL) were added BOP reagent (88 mg, 200 μmol) and *N*-methylmorpholine (20 μL). After 3 h of stirring at room temperature, the usual workup provided a residue, which was chromatographed on a Lobar (Merck) column (acetone/

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methylene chloride). After concentration of the solvent, **3** was crystallized from diethyl ether/hexane (80 mg, 57%): HPLC, column A (A/B, 25:75), t_R = 5.96 min (coelution with the natural nordidemnin B); HRFABMS, *m/e* (M^+ + H) 1098.61 ($C_{56}H_{88}N_7O_{15}$ requires 1098.63); CD (methanol) $[\theta]_{218}$ +212, $[\theta]_{234}$ +145, $[\theta]_{295}$ −72 (natural nordidemnin B, $[\theta]_{219}$ +221, $[\theta]_{234}$ +153 $[\theta]_{296}$ −67.

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Registry No. **3**, 117710-03-9; **4**, 117710-04-0; **5**, 117710-05-1; (3*S*)-**6**, 117710-06-2; **7a**, 117710-07-3; **8**, 117710-08-4; **9**, 65138-05-8; **10**, 117710-09-5; **10** (free acid), 117710-20-0; **11**, 117710-10-8; (2*S*)-**12**, 117710-11-9; (2*R*)-**12**, 117773-51-0; **13**, 73584-84-6; **14**, 117710-12-0; **15**, 117710-13-1; **15** (BOC-deprotected)·TFA, 117710-23-3; **15** (BOC-deprotected), 117710-22-2; **16**, 33294-56-3; **17**, 117710-14-2; **17** (BOC-deprotected)·TFA, 117710-25-5; **18**, 117710-15-3; **18** (BOC-deprotected)·TFA, 117710-27-7; **18** (BOC-deprotected), 117710-26-6; **19** (2*S*-HIP epimer), 117710-16-4; **19** (2*R*-HIP epimer), 117773-52-1; **19** (free acid, 2*S*-HIP epimer), 117710-34-6; **19** (free acid, 2*R*-HIP epimer), 117773-55-4; **20** (2*S*-HIP epimer), 117710-29-9; **20** (2*R*-HIP epimer), 117773-54-3; **21**, 117710-17-5; **21** (*N*-deprotected), 117733-99-0; **22**, 117710-30-2; **22** (*N*-deprotected), 117710-31-3; **23**, 67971-34-0; **23** (*N*-deprotected)·TFA, 117710-33-5; **24**, 117710-18-6; **25**, 117710-19-7; COMODD, 115491-90-2; BOC-D-Val-OH, 22838-58-0; AcOEt, 141-78-6; BOC-MeTyr(CH_2Ph)-OH, 64263-81-6; BOC-MeTyr-OH, 82038-34-4; BOC-MeTyr(Me)-OMe, 117710-21-1; Cbz-Thr-OH, 19728-63-3; BOC-Leu-OH, 13139-15-6; $CH_3CH_2C(O)SBu$-*t*, 61540-13-4; Cbz-D-MeLeu-OH, 65635-85-0; (*S*)-$CH_3CH(OH)CO$-OH, 79-33-4.

Synthesis of Phosphonates from α-Hydroxy Carbonyl Compounds and Dialkyl Phosphorochloridites

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In the presence of a Lewis acid, dialkyl phosphorochloridites react with α-hydroxy ketones to afford β-keto phosphonates and with α-hydroxy esters to afford phosphonic acid diesters. These reactions provide convenient access to a variety of structures, including β-keto phosphonates that are fully substituted at the α-carbon.

In recent years, interest in phosphonate chemistry has expanded dramatically for a variety of reasons. Phosphonates bearing α-hydrogen can be readily ionized and the resulting anions used in a number of carbon–carbon bond forming reactions. For example, the Wadsworth–Horner–Emmons condensation,[2] in which a stabilized phosphonate anion reacts with an aldehyde or ketone, has become a very popular method for the synthesis of α,β-unsaturated ketones and esters.[3] Phosphonates fully substituted at the α-carbon do not find such frequent use as synthetic intermediates, but because the geometry and spatial demands of pentavalent phosphorus are comparable to those of quaternary carbon, the isosteric replacement of carbon with phosphorus has been studied in biologically active molecules.[4] Phosphonate analogues of a number of biologically active phosphates also have been prepared[5] and studied for their biological activity. Finally, the hypothesis that phosphonates model the transition states of a variety of biologically important carboxylate reactions has culminated in the synthesis of antibodies to specific phosphonates, with the objective of obtaining synthetic enzymes.[6]

In marked contrast to the number of investigations that incorporate phosphonate reagents or focus on the biological activities of phosphonates, relatively little work has appeared describing general new syntheses of this functionality. The most commonly used methods for preparing phosphonates remain the classical Arbuzov reaction[7] and the elaboration of simpler alkyl phosphonate anions.[8]

Our research has focused on developing new, potentially general routes to β-keto phosphonates, and we recently have reported two different approaches. The first route relies on formation of a vinyllithium reagent from an α-bromo ketone enolate and reaction of this intermediate with a phosphorochloridate.[9] More recently we have discovered a 1,3-phosphorus migration, which provides access to β-keto phosphonate derivatives of cyclic ketones via rearrangement of vinyl phosphates.[10] In this paper, we describe a preparation of β-keto phosphonates from α-hydroxy ketones, and a parallel reaction which affords phosphonic acid diesters from α-hydroxy esters.

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