JOC The Journal of Organic Chemistry

ARTICLE

pubs.acs.org/joc

Benzotriazole-Mediated Syntheses of Depsipeptides and Oligoesters

Ilker Avan,[‡,§] Srinivasa R. Tala,[‡] Peter J. Steel,[∥] and Alan R. Katritzky*[,‡]

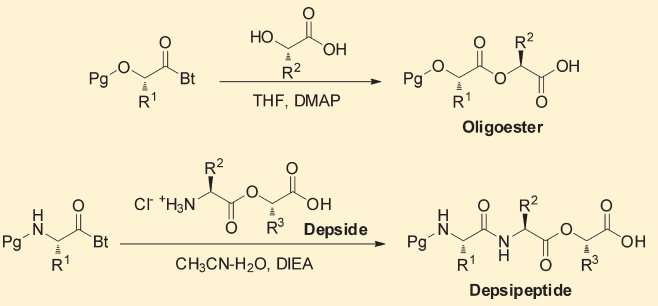
[‡]Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, Florida 32611-7200, United States

[§]Department of Chemistry, Anadolu University, 26470, Eskişehir, Turkey

[∥]Department of Chemistry, University of Canterbury, Christchurch, New Zealand

Supporting Information

ABSTRACT: Reactions of *O*-Pg(α-hydroxyacyl)benzotriazoles with (a) unprotected α-hydroxycarboxylic acids, (b) amino acids, and (c) amines afforded, respectively, chirally pure (a) oligoesters, (b) depsidipeptides, and (c) amide conjugates (yields 52−94%). *N*-Pg(α-Aminoacyl)benzotriazoles reacted with α-hydroxycarboxylic acids to yield depsidipeptides (47−87%). *N*-Pg(depsidipeptidoyl)benzotriazoles, obtained from depsidipeptides, gave depsitripeptides (yields 55−78%) on reaction with amino acids and α-hydroxycarboxylic acids. O-Acylation of α-hydroxycarboxylic acids with *N*-Pg(α-aminoacyl)benzotriazoles followed by deprotection produced unprotected depsides useful for the preparation of depsitripeptides.



INTRODUCTION

Depsipeptides, analogues of peptides, contain both amino acids and hydroxy acids linked by amide and ester bonds. Natural depsipeptides can exhibit significant biological activities (antimicrobial, antifungal, anti-inflammatory) and possess therapeutic properties including anticancer and anti-HIV activity.[1]

Cyclic depsipeptide romidepsin (FR228) is an antineoplastic antitumor agent as histone deacetylase inhibitor,[2] originally extracted from the bacterium *Chromobacterium violaceum*. Romidepsin (FK228) is an FDA-approved anticancer drug marketed under the trade name Istodax for treatment of cutaneous T-cell lymphoma.[3] Cytotoxic depsipeptides dolastine-10 and didemnin B were subjected to extensive phase II studies revealing their antitumor activities.[4] Callipeltins and papuamide A show promising inhibitory activity against HIV.[1,5] The cyclic depsipeptide valinomycin is a natural ionophore selective for potassium;[6a] nonactin is another natural ionophore.[6b]

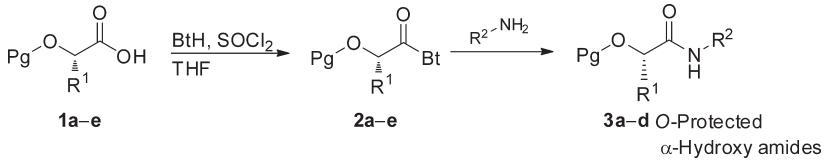
Depsipeptides contain at least one ester bond in place of an amide link in their structure. The isosteric replacement of the H-bond donor group (N−H) by the O atom of an ester causes depsipeptides to have poorer H-bonding. The decreased resonance of esters relative to amides leads to lower rotational barriers for cis−trans isomerization in depsipeptides than in native peptide conjugates and also induces more flexible structures.[7] Replacing an amino acid residue with an α-hydroxy acid causes minimal structural perturbation in α-helix[8] and β-sheet[9] peptide structures. Quantum mechanical calculations on the conformational properties of an alanine dipeptide show this depsidipeptide has a strong preference to have polyproline II (PPII) helical conformation by decreasing α-helix and β-sheet structures.[10]

Methods for the preparation of depsipeptides include the use, alone or in combination, of coupling reagents such as DIC/DMAP,[11] DCC/DMAP;[12] EDCl/DMAP,[13] or PyBrop/DIEA[14] or Yamaguchi conditions (TCBC, DIPEA, DMAP).[15] The study of several coupling reagents by Riguera et al.[11] showed variable yields (2−92%) and coupling times (2−20 h), with the best results (92%, 2 h) obtained by DIC in the presence of DMAP.

N-Acylbenzotriazoles are convenient intermediates to prepare longer peptide conjugates since they are stable, mostly crystalline compounds and easy to handle. *N*-Fmoc(α-aminoacyl)benzotriazoles were used to synthesize "difficult" peptide sequences on SPPS in good yields.[16] Recently, we were able to prepare *N*-Pg(tri- or tetrapeptidoyl)benzotriazoles as advantageous coupling reagents for synthesizing tetra-, penta-, and hexapeptides in solution phase.[17] These *N*-acylbenzotriazoles are also advantageous for N-, O-, C-, and S-acylation, especially while the corresponding acid chlorides are unstable or difficult to prepare.[18] Cysteine-containing *S*-Pg(α-aminoacyl)di- and tripeptides were prepared from *N*-Pg(α-aminoacyl)benzotriazoles via S-acylation without racemization and underwent chemical ligations to generate native peptides.[19] Moreover, we previously demonstrated the utility of *N*-Pg(α-aminoxyacyl)benzotriazoles for synthesizing aminoxy peptides in peptidomimetics.[20] We now describe a new and mild method for the efficient preparation of depsipeptides via both N- and O-acylation. In the present work, *O*-Pg(α-hydroxyacyl)-benzotriazoles were prepared and their synthetic utility was shown in the synthesis of both depsipeptides via N-acylation and chiral oligoesters via O-acylation without causing

Received: January 24, 2011
Published: March 31, 2011

Scheme 1. Synthesis of Depsiamides 3a−d



1a−e **2a−e** **3a−d** *O*-Protected α-Hydroxy amides

Table 1. *O*-Pg(α-Hydroxyacyl)benzotriazoles 2a−e

entry	Pg: protecting group	R^1	**2**, yield[a] (%)
a	Z	CH_2Ph (Phe)	**2a**, 76
b	Z	$CH_2CH(CH_3)_2$ (Leu)	**2b**, 86
c	Fmoc	$CH_2CH(CH_3)_2$ (Leu)	**2c**, 72
d	Fmoc	CH_2Ph (Phe)	**2d**, 80
e	THP	$CH(CH_3)_2$ (Val)	**2e**, 78

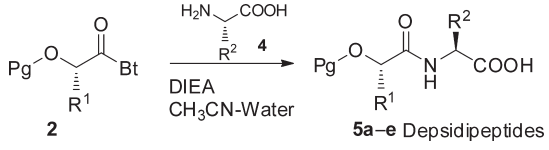
[a] Isolated yield.

Table 2. *O*-Pg(α-Hydroxyacyl)amides 3a−d

entry	**2**	amine	**3**, yield[a] (%)
a	Z-(*O*-Phe)-Bt, **2a**	L-α-methylbenzylamine	**3a**, 88
b	Z-(*O*-Phe)-Bt, **2a**	DL-α-methylbenzylamine	(**3a**+**3a′**), 76
c	Z-(*O*-Leu)-Bt, **2b**	L-α-methylbenzylamine	**3b**, 65
d	Z-(*O*-Leu)-Bt, **2b**	DL-α-methylbenzylamine	(**3b**+**3b′**), 56
e	Z-(*O*-Leu)-Bt, **2b**	*p*-methoxyaniline	**3c**, 71
f	F-(*O*-Leu)-Bt, **2c**	L-α-methylbenzylamine	**3d**, 67

[a] Isolated yield.

Scheme 2. Preparation of Depsipeptides 5a−e via N-Acylation



2 **5a−e** Depsidipeptides

racemization. Unprotected depsidipeptides (depsides) were readily obtained from *N*-Pg(α-aminoxyacyl)benzotriazoles and used for the preparation of longer depsipeptide conjugates.

RESULTS AND DISCUSSION

Preparation of Depsiamides 3a−d. *O*-Pg(α-Hydroxyacyl)benzotriazoles **2a−e** (72−86%) were prepared by treatment of the corresponding carboxylic acids **1a−e** with 4 equiv of 1*H*-benzotriazole and 1 equiv of $SOCl_2$ in THF at 10 °C for 4 h (Scheme 1, Table 1). Reaction of *O*-Pg(α-hydroxyacyl)-benzotriazoles **2a−d** with amines and amino acids affords the corresponding amide derivatives **3a−d** (56−88%) (Scheme 1 and Table 2). Retention of the original chirality in the products was confirmed by chiral HPLC analysis using a (*S*,*S*) Welk-O1 column (MeOH (100%), flow rate 1.0 mL/min, detection at 254 nm). The diastereomer **3a** showed a single retention-time peak in chiral HPLC at 5.93 min, while its corresponding diastereomeric mixture (**3a**+**3a′**) showed two peaks at 4.24 and 5.95 min. Compound **3b** has a single retention-time peak in chiral HPLC at 10.02 min, while its corresponding diastereomeric pair (**3b**+**3b′**) showed two peaks at 7.81 and 10.03 min (MeOH (100%), flow rate 0.5 mL/min, detection at 254 nm).

Table 3. Depsidipeptides 5a−e

entry	Pg	R^1	amino acid, **4**	**5**, yield (%)
a	Z	CH_2Ph (Phe), **2a**	L-Ala-OH, **4a**	**5a**, 86
b	Z	CH_2Ph (Phe), **2a**	DL-Ala-OH, (**4a**+**4a′**)	(**5a**+**5a′**), 80
c	Fmoc	CH_2Ph (Phe), **2c**	L-Met-OH, **4b**	**5b**, 74
d	Fmoc	CH_2Ph (Phe), **2c**	L-Glu-OH, **4c**	**5c**, 82
e	Fmoc	CH_2Ph (Phe), **2c**	L-Ala-OH, **4a**	**5d**, 87
f	Fmoc	CH_2Ph (Phe), **2c**	DL-Ala-OH, (**4a**+**4a′**)	(**5d**+**5d′**), 94
g	Fmoc	CH_2Ph (Phe), **2c**	L-Phe-OH, **4d**	**5e**, 86
h	Fmoc	CH_2Ph (Phe), **2c**	DL-Phe-OH, (**4d**+**4d′**)	(**5e**+**5e′**), 80

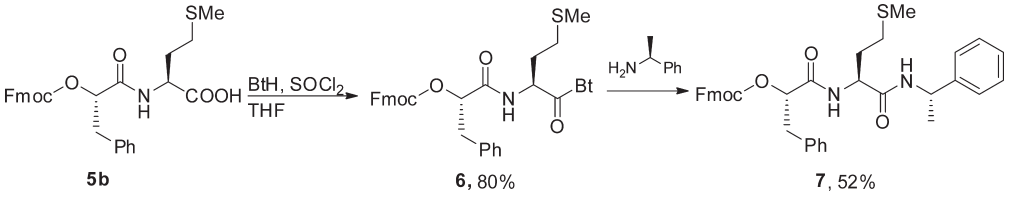
Preparation of Depsipeptides. Coupling of *O*-Pg(α-hydroxyacyl)benzotriazoles **2** with the appropriate natural amino acids in aqueous acetonitrile−diisopropylethylamine (DIEA) at 10 °C for 0.5−2 h yielded depsidipeptides **5a−e** (74−94%) (Scheme 2 and Table 3). In an attempt to show the retention of chirality, diastereoisomeric analogues of **5a**, **5d**, and **5e** were prepared from DL-amino acids, and chiral HPLC analyses were performed using Chirobiotic T, (*S*,*S*) Whelk-O1, and Chiracel OD-H. Diastereoisomeric separations for (**5a**+**5a′**), (**5d**+**5d′**), and (**5e**+**5e′**) were not observed on HPLC analysis using a variety of solvent system and flow rates; however, the absence of racemization in the depsidipeptide conjugates (**5a**+**5a′**) and (**5d**+**5d′**) was deduced from the ^1H NMR, where the methyl signal showed two separated doublets split in the DL-alanine moiety. While **5a** has a clear doublet at 1.27 ppm (J = 7.2 Hz), (**5a**+**5a′**) has two separated doublets at 1.24 and 1.33 ppm (J = 7.2 Hz). A similar result was observed for **5d** and (**5d**+**5d′**). Spectral data for **5a**, **5d**, and their diastereoisomers (**5a**+**5a′**) and (**5d**+**5d′**) are available in the Supporting Information. In previous studies, we showed retention of chirality on N-acylation with *N*-acylbenzotriazoles for aminoxy hybrid-peptides[20] and peptides.[18g]

Compound **5b** was treated with $SOCl_2$ and 1*H*-benzotriazole in THF to obtain benzotriazole-activated conjugate **6** (Scheme 3). *O*-Fmoc(depsidipeptidoyl)benzotriazole **6** was treated with L-methylbenzylamine to afford the corresponding amide derivative **7** in 52% yield (Scheme 3).

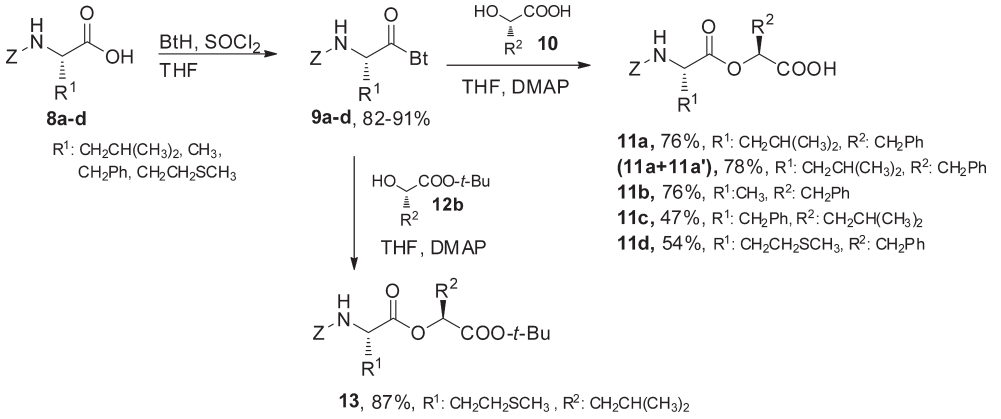
N-Pg(α-Aminoacyl)benzotriazoles **9a−d** on treatment with α-hydroxycarboxylic acids **10** in the presence of DMAP in THF afforded depsidipeptides **11a−d** (Scheme 4). The use of DMAP, which acts as a base and also activates the carboxyl group via the acyl pyridinium salt,[21] is advantageous for O-acylation. Moreover, in our preliminary results, when DBU, TEA, and DIEA were used for O-acylation, O-acylated products showed an increase in racemization since the coupling reaction needs a longer time.

dx.doi.org/10.1021/jo200174j |*J. Org. Chem.* 2011, 76, 4884–4893

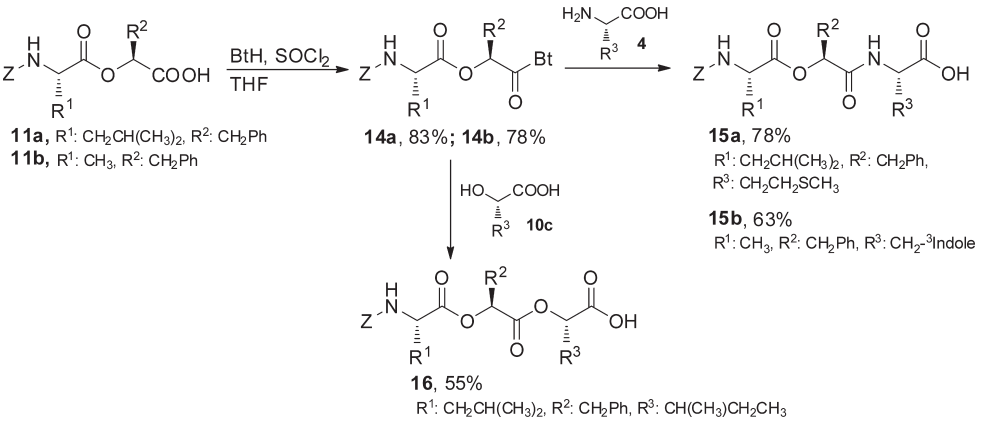
Scheme 3. Preparation of Amide Derivative 7



Scheme 4. Preparation of Depsidipeptides 11 and 13 via O-Acylation



Scheme 5. Preparation of Depsitripeptides 15a, 15b, and 16



The enantiopurity of product depsidipeptides **11a** and (**11a**+**11a**′) was supported by chiral HPLC analysis using a Chirobiotic T column (MeOH (100%), flow rate 0.5 mL/min, detection at 254 nm.). Compound **11a** showed a single retention-time peak in chiral HPLC analysis at 6.46 min, while the corresponding diastereomixture (**11a**+**11a**′) showed two peaks at 6.33 and 6.84 min. Similarly, compound **13** was derived from the *tert*-butyl ester of α-hydroxycarboxylate **12b** in 87% yield (Scheme 4). Compounds **11b** and **11c** were isolated as the dicyclohexylamine salts.

N-Cbz(Depsidipeptidoyl)benzotriazoles **14a** and **14b** were obtained by treatment of **11a** and **11b** with benzotriazole in the presence of $SOCl_2$ in THF. Reaction of **14a** and **14b** with amino acids **4a** and **4b** in CH_3CN−water in the presence of DIEA afforded depsitripeptides **15a** and **15b**, while treatment with α-

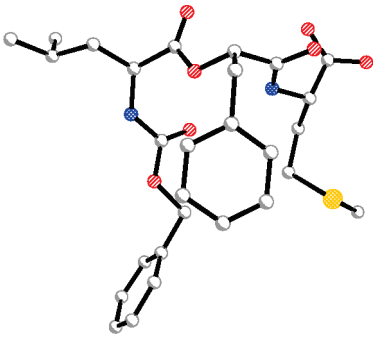
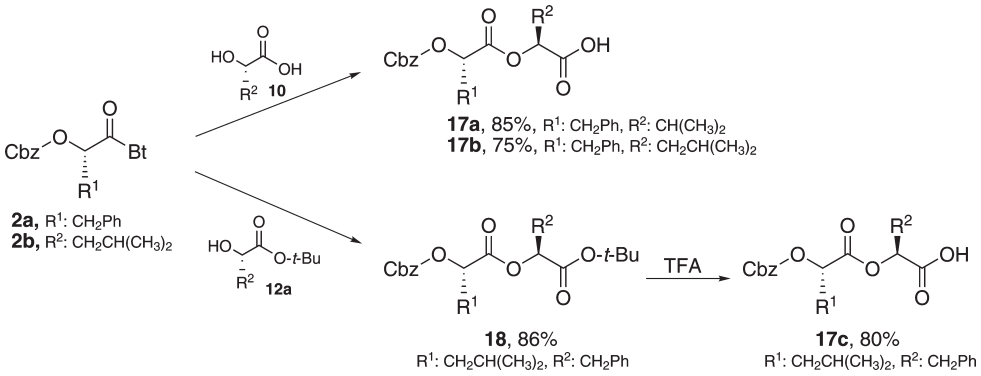


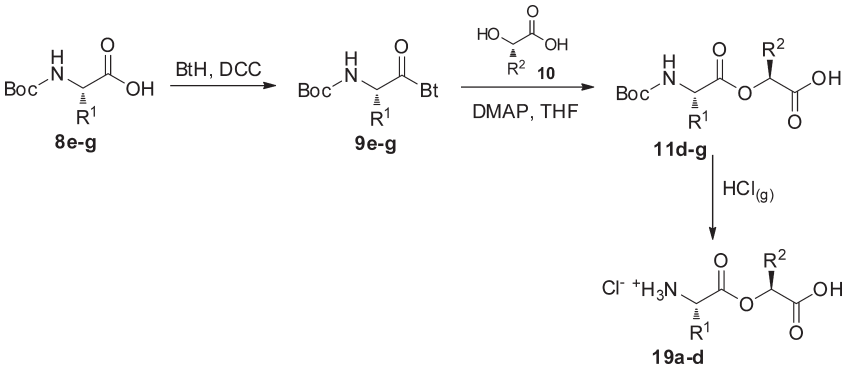
Figure 1. X-ray crystal structure of Z-Leu-(*O*-Phe)-Met-OH **15a**. Hydrogen atoms are not shown.

dx.doi.org/10.1021/jo200174j |*J. Org. Chem.* 2011, 76, 4884–4893

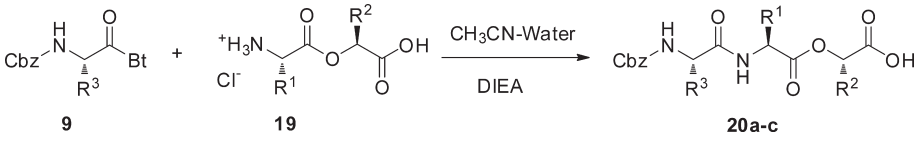
Scheme 6. Preparation of Oligoesters 17a−c via O-Acylation



Scheme 7. Synthesis of Unprotected Depsides 19a−d



Scheme 8. Preparation of Depsitripeptides 20a−c



hydroxycarboxylic acid **10c** in THF in the presence of DMAP gave depsitripeptide **16** by O-acylation (Scheme 5).

The structure and absolute configuration of **15a** was unambiguously established by X-ray crystallography (Figure 1).

Preparation of Chiral Oligoesters 17a−c. Oligoesters **17a** and **17b** were prepared by the reaction of Z-(*O*-Phe)-Bt **2a** with unprotected α-hydroxy acids **10b** and **10d** in THF in the presence of DMAP for 4−6 h (75−85%). In the case of Z-(*O*-Leu)-Bt **2b**, under the same conditions, the coupling reaction was completed in 10 h. Based on ^{1}H NMR studies, we observed some racemization due to the longer reaction time. To overcome this problem, the coupling reaction was carried out using the *tert*-butyl ester of α-hydroxy acid **12a**. Once **18** was formed, it was deprotected using a mixture of TFA/CH_2Cl_2 (1:1) to afford **17c** in 69% overall yield (Scheme 6).

Unprotected Depsides 19. L-α-Dipeptides (dipeptides) are useful intermediates to attain longer peptide analogues; nevertheless, because of the lack of an efficient process for dipeptide preparation, the functions and applications of dipeptides have been poorly examined compared with proteins or amino acids.[22] We now describe a new route to prepare unprotected depsidipeptides under mild conditions and a further manipulation to obtain depsitripeptides (Schemes 7 and 8). Boc-protected amino acids **8e−g** were treated with 1*H*-benzotriazole in DCC-coupling conditions to obtain *N*-Boc(α-aminoacyl)benzotriazoles **9e−g**, which were reacted with α-hydroxy acids **10a** and **10b** in THF in the presence of DMAP to obtain Boc-protected

Table 4. Unprotected Depsidipeptides 19a−d

entry	R^1	R^2	**19**, yield (%)
a	H	CH_2Ph	**19a**, 48
b	CH_3	$CH_2CH(CH_3)_2$	**19b**, 36
c	H	$CH_2CH(CH_3)_2$	**19c**, 62
d	CH_2Ph	$CH_2CH(CH_3)_2$	**19d**, 56

dx.doi.org/10.1021/jo200174j |*J. Org. Chem.* 2011, 76, 4884–4893

Table 5. Depsitripeptides 20a−c

entry	R^3	R^1	R^2	**20**, yield (%)
a	CH_2Ph	H	$CH_2CH(CH_3)_2$	**20a**, 71
b	$CH_2CH_2SCH_3$	CH_2Ph	$CH_2CH(CH_3)_2$	**20b**, 56
c	$CH_2CH_2SCH_3$	H	$CH_2CH(CH_3)_2$	**20c**, 68

depsidipeptides **11d−g**. Then, without isolation of **11d−g**, Boc-deprotection was conducted by $HCl_{(g)}$ in dry CH_2Cl_2 for 4−6 h to yield unprotected depsidipeptides **19a−d** as hydrochloride salts (Scheme 7, Table 4).

Unprotected depsidipeptides **19a** and **19d** were reacted with *N*-Pg(α-aminoacyl)benzotriazoles **9c** and **9d** in the presence of 2 equiv of DIEA in MeCN−H_2O (7:1) to afford *N*-Pg-depsitripeptides **20a−c** (Scheme 8, Table 5).

CONCLUSION

In conclusion, novel *O*-Pg(α-hydroxyacyl)benzotriazoles have been prepared and used for the synthesis of unprotected depsides, depsipeptides, depsitripeptides, and chiral oligoesters by *O*-acylation of unprotected α-hydroxy acids in dry THF solvent or *N*-acylation of unprotected amino acids in aqueous condition in good yields under mild conditions. The retention of chirality of depsipeptides in *O*-acylation and *N*-acylation reactions was examined by chiral HPLC, which revealed no racemization. In addition, novel unprotected depsides were prepared in good yields, and their synthetic utility for the preparation of longer depsipeptide analogues was demonstrated. These synthetic methodologies are expected to be useful for the syntheses of biologically active longer and cyclic depsipeptides.

EXPERIMENTAL SECTION

Melting points are uncorrected. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on 300 MHz apparatus in $CDCl_3$ or DMSO-d_6 with TMS as internal standard. The data are reported as follows: chemical shift in parts per million (ppm, δ units) and spin−spin coupling *J* (Hz). DMF was dried and distilled over CaH_2, whereas THF was used after distillation over Na/benzophenone. Unprotected amino acids **4** and *N*-(protected)-amino acids **8** were purchased from commercial sources. *N*-(Acylbenzotriazoles) **9a−d** were prepared by our previously reported methods.[18b,c] The elemental analysis of **2c** deviates from the calculated value. This compound was further characterized by the preparation of **3d**. L-α-Hydroxycarboxylic acids **10**,[23] THP-L-*O*-(Val)-OH **1e**,[24] and **12a,b**[25] were prepared using literature methods.

Syntheses of *O*-Cbz- and *O*-Fmoc-Protected α-Hydroxycarboxylic Acids Analogues 1a−e. *Syntheses of **1a** and **1b**.* Pyridine (18 mmol) was added to a stirred solution of α-hydroxycarboxylic acids **10** (18 mmol) in THF (30 mL) dropwise at 4 °C in 10 min. After the mixture was stirred 10 min in the cold, benzyl chloroformate (21.7 mmol) was added at same temperature over 30 min. Then the mixture was stirred overnight at room temperature. The solvent was removed and the residue taken into EtOAc (50 mL), washed with 2 N HCl (3 × 15 mL) and brine (15 mL), and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. The crude was purified with flash column chromatography (EtOAc−hexanes (15%)) to afford **1a,b** as a colorless oil.

*Z-(O-Phe)-OH (**1a**):* colorless oil (56%); $[\alpha]_D^{23}$ = −25.6 (*c* 1.5, CH_3OH) [lit.[26] $[\alpha]_D^{23}$ = −18.2 (*c* 1.2, $CHCl_3$)]; ^1H NMR ($CDCl_3$) δ 3.15 (dd, *J* = 14.3, 8.7 Hz, 1H), 3.26 (dd, *J* = 14.4, 4.2 Hz, 1H), 5.10−5.20 (m, 2H), 5.19 (dd, *J* = 8.4, 3.9 Hz, 1H), 5.40 (br s, 1H), 7.20−7.40 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 37.4, 70.4, 75.8, 127.4, 128.5, 128.8, 129.6, 134.9, 135.4, 154.7, 174.4. Anal. Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 67.71; H, 5.50.

*Z-(O-Leu)-OH (**1b**):* colorless oil (62%); $[\alpha]_D^{23}$ = −29.2 (*c* 1.5, CH_3OH); ^1H NMR ($CDCl_3$) δ 0.95 (dd, *J* = 6.0 Hz, 3.3 Hz, 6 H), 1.62−1.76 (m, 1H), 1.78−1.91 (m, 2H), 5.00 (dd, *J* = 9.6 Hz, 3.9 Hz, 1H), 5.20 (s, 2H), 7.30−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 21.6, 23.1, 24.7, 39.9, 70.9, 73.4, 128.5, 128.8, 135.0, 154.9, 176.2. Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 62.93; H, 7.14.

*Syntheses of **1c** and **1d**.* A solution of pyridine (8.2 mmol) in THF (8 mL) was added to a stirred solution of Fmoc-Cl (8.0 mmol) and α-hydroxycarboxylic acids **10** (8.2 mmol) at −10 °C in THF (30 mL). The reaction was allowed to reach room temperature and stirred overnight. The reaction was monitored by TLC [EtOAc−hexanes (1:4)]. The mixture was taken into a separation funnel and washed with 2 N HCl (3 × 20 mL) and brine (20 mL). After the mixture was dried over $MgSO_4$, the solvent was removed under reduced pressure. The crude was purified by column chromatography [EtOAc−hexanes (1:4)] to afford **1c,d** as white microcrystals.

*F-(O-Leu)-OH (**1c**).*[27] white microcrystals (1.76 g, 62%); mp 112−113 °C; $[\alpha]_D^{23}$ = −8.9 (*c* 1.5, CH_3OH); ^1H NMR ($CDCl_3$) δ 0.99 (dd, *J* = 7.2 Hz, 6.6 Hz, 6H), 1.66−1.78 (m, 1H), 1.80−1.98 (m, 2H), 4.26−4.40 (m, 2H), 4.53 (dd, *J* = 9.9 Hz, 6.9 Hz, 1H), 5.02 (dd, *J* = 9.6 Hz, 3.6 Hz, 1H), 7.28−7.36 (m, 2H), 7.36−7.44 (m, 2H), 7.62 (t, *J* = 6.6 Hz, 2H), 7.76 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.6, 23.2, 24.8, 39.8, 46.9, 70.6, 73.8, 120.3, 125.3, 125.4, 127.4, 128.1, 141.5, 143.2, 143.5, 154.9, 176.2. Anal. Calcd for $C_{21}H_{22}O_5$: C, 71.17; H, 6.26. Found: C, 71.26; H, 6.22.

*F-(O-Phe)-OH (**1d**):* white microcrystals (1.6 g, 51%); mp 101−103 °C; $[\alpha]_D^{23}$ = −12.4 (*c* 1.5, CH_3OH); ^1H NMR ($CDCl_3$) δ 3.18 (dd, *J* = 14.4 Hz, 9.0 Hz, 1H), 3.30 (dd, *J* = 14.4 Hz, 3.9 Hz, 1H), 4.20−4.34 (m, 2H), 4.38−4.46 (m, 1H), 5.21 (dd, *J* = 8.7 Hz, 4.1 Hz, 1H), 7.20−7.42 (m, 9H), 7.54 (dd, *J* = 7.5 Hz, 3.3 Hz, 2H), 7.73 (d, *J* = 7.5 Hz, 2H), 9.35 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 37.4, 46.7, 70.6, 75.8, 120.2, 125.3, 125.4, 127.4, 127.5, 128.1, 128.8, 129.6, 135.5, 141.4, 143.2, 143.6, 154.6, 175.1. Anal. Calcd for $C_{24}H_{20}O_5$: C, 74.21; H, 5.19. Found: C, 74.02; H, 5.42.

THP-(*O*-Val)-OH (**1e**) was prepared according to the literature method:[24] colorless oil (77%); $[\alpha]_D^{23}$ = −27.1 (*c* 1.5, $CHCl_3$).

General Preparation of *O*-Pg(α-hydroxyacyl)benzotriazole (2). Thionyl chloride (1.2 mmol) was added to a solution of benzotriazole (4.16 mmol) in freshly distilled CH_2Cl_2 (10 mL) at 5 °C and the reaction mixture stirred for 20 min at the same temperature. *O*-(Pg)Hydroxycarboxylic acid **1** (1.0 mmol) dissolved in CH_2Cl_2 (2 mL) was added dropwise to the mixture. After being stirred for 3 h at 10 °C, the reaction mixture was allowed to warm to room temperature. After 1 h, the white precipitate was filtered off and discarded. The solution was diluted with more CH_2Cl_2 (10 mL), washed with saturated Na_2CO_3 solution (3 × 10 mL) and then saturated brine solution, and finally dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford *O*-Pg(hydroxyacyl)benzotriazole **2**.

*Z-(O-Phe)-Bt (**2a**):* white microcrystals (76%); mp 97−98 °C; $[\alpha]_D^{23}$ = −4.3 (*c* 1.5, CH_3OH); ^1H NMR ($CDCl_3$) δ 3.34 (dd, *J* = 14.1 Hz, 9.0 Hz, 1H), 3.50 (dd, *J* = 14.1 Hz, 3.6 Hz, 1H), 5.15 (s, 2H), 6.49 (dd, *J* = 9.0 Hz, 3.6 Hz, 1H), 7.20−7.42 (m, 10H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.69 (t, *J* = 7.7 Hz, 1H), 8.15 (d, *J* = 8.1 Hz, 1H), 8.26 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 38.0, 70.6, 114.5, 120.6, 126.9, 127.6, 128.5, 128.8, 129.7, 131.1, 131.2, 134.8, 135.2, 146.1, 154.7, 168.4. Anal. Calcd for $C_{23}H_{19}N_3O_4$: C, 68.82; H, 4.77; N, 10.47. Found: C, 68.88; H, 4.77; N, 10.39.

*Z-(O-Leu)-Bt (**2b**):* colorless oil (86%); $[\alpha]_D^{23}$ = −61.6 (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.98 (d, *J* = 6.3 Hz, 3H), 1.08 (d, *J* = 6.3 Hz, 3H), 1.82−2.10 (m, 3H), 5.12 (s, 2H), 6.33 (dd, *J* = 10.2 Hz, 3.0 Hz, 1H), 7.30−7.42 (m, 5H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.69 (t, *J* = 6.9 Hz, 1H), 8.15 (d, *J* = 8.1 Hz, 1H), 8.27 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.5, 23.4, 25.2, 40.4, 70.6, 74.9, 114.6, 120.6, 126.8, 128.5, 128.8, 131.0, 131.3, 134.9, 146.1, 154.9, 169.6. Anal. Calcd

for $C_{20}H_{21}N_3O_4$: C, 65.38; H, 5.76; N, 11.44. Found: C, 65.24; H, 6.10; N, 11.07.

*F-(O-Leu)-Bt (**2c**):* colorless oil (72%); $[\alpha]_D^{23} = -79.2$ (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.03 (d, *J* = 5.1 Hz, 3H), 1.12 (d, *J* = 5.1 Hz, 3H), 1.86−2.28 (m, 3H), 4.28−4.42 (m, 2H), 4.50−4.58 (m, 1H), 6.33 (d, *J* = 10.8 Hz, 1H), 7.28−7.46 (m, 4H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.60−7.80 (m, 5H), 8.15 (d, *J* = 8.4 Hz, 1H), 8.27 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.5, 23.4, 25.3, 40.3, 46.9, 70.8, 75.0, 114.6, 120.3, 120.6, 125.4, 125.5, 126.8, 127.4, 128.2, 131.0, 131.3, 141.5, 143.2, 143.5, 146.2, 155.0, 169.6. Anal. Calcd for $C_{27}H_{25}N_3O_4$: C, 71.19; H, 5.53; N, 9.22. Found: C, 70.35; H, 5.58; N, 9.75.

*F-(O-Phe)-Bt (**2d**):* white microcrystals (80%); mp 132−134 °C; $[\alpha]_D^{23} = -12.4$ (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.37 (dd, *J* = 14.1 Hz, 9.3 Hz, 1H), 3.55 (dd, *J* = 14.1 Hz, 3.6 Hz, 1H), 4.20−4.36 (m, 2H), 4.38−4.50 (m, 1H), 6.49 (dd, *J* = 9.3 Hz, 3.6 Hz, 1H), 7.20−7.44 (m, 9H), 7.46−7.60 (m, 3H), 7.60−7.76 (m, 3H), 8.14 (d, *J* = 8.1 Hz, 1H), 8.25 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 38.0, 46.7, 70.8, 76.8, 114.5, 120.2, 120.6, 125.3, 125.5, 126.9, 127.4, 127.6, 128.1, 128.9, 129.7, 131.1, 131.2, 135.4, 141.4, 143.1, 143.4, 146.1, 154.6, 168.3. Anal. Calcd for $C_{30}H_{23}N_3O_4$: C, 73.61; H, 4.74; N, 8.58. Found: C, 73.47; H, 5.01; N, 8.40.

*THP-(O-Val)-Bt (**2e**):* Diastereisomeric pair, colorless oil (78%); $[\alpha]_D^{23} = -82.4$ (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.99 (d, *J* = 6.9 Hz, 1.5H), 1.05 (d, *J* = 6.9 Hz, 1.5H), 1.10 (d, *J* = 6.9 Hz, 1.5H), 1.18 (d, *J* = 6.9 Hz, 1.5H), 1.40−2.00 (m, 6H), 2.30−2.42 (m, 0.5 H), 2.44−2.54 (m, 0.5H), 3.16−3.26 (m, 0.5H), 3.50−3.60 (m, 0.5H), 3.68−3.78 (m, 0.5H), 3.86−3.96 (m, 0.5H), 4.72−4.80 (m, 1H), 5.30 (d, *J* = 6.9 Hz, 0.5 H), 5.67 (d, *J* = 4.5 Hz, 0.5 H), 7.48−7.58 (m, 1H), 7.63−7.72 (m, 1H), 8.10−8.18 (m, 1H), 8.30−8.38 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 17.2, 18.2, 18.8, 19.1, 19.8, 20.1, 25.2, 25.6, 30.5, 32.2, 62.4, 63.1, 77.9, 82.3, 96.8, 102.0, 114.6, 114.8, 120.3, 120.4, 126.4, 126.6, 130.5, 130.7, 131.3, 146.2, 172.2. Anal. Calcd for $C_{16}H_{21}N_3O_3$: C, 63.35; H, 6.98; N, 13.85. Found: C, 63.39; H, 7.20; N, 13.30.

General Preparation of *O*-Pg(α-hydroxyacyl) Amides (3a−d). Amine (1.2 equiv) and pyridine (1.2 molar equiv) in THF (2 mL) were added to a stirred solution of *O*-Pg(hydroxyacyl)benzotriazole **2** (1 molar equiv) in THF (4 mL) dropwise at 10 °C, and the mixture was stirred for 2 h at room temperature. After evaporation of THF, EtOAc (15 mL) was added to the solution, which was washed with 2 N HCl (2 × 10 mL), saturated Na_2CO_3 solution (3 × 10 mL), and brine (10 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave the crude amides **3a**−**d**.

Benzyl ((*S*)-1-Oxo-3-phenyl-1-(((*S*)-1-phenylethyl)amino)propan-2-yl)carbonate (3a). The crude product was recrystallized from diethyl ether−hexanes to give white microcrystals (88%): mp 121−122 °C; $[\alpha]_D^{23} = -12.9$ (*c* 1.5, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 1.28 (d, *J* = 6.9 Hz, 3H), 3.18 (dd, *J* = 14.4 Hz, 6.3 Hz, 1H), 3.28 (dd, *J* = 14.1 Hz, 4.5 Hz, 1H), 5.00−5.10 (m, 1H), 5.10 (d, *J* = 5.7 Hz, 2H), 5.29 (dd, *J* = 6.0 Hz, 4.8 Hz, 1H), 6.12 (d, *J* = 7.8 Hz, 1H), 7.12−7.40 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 21.5, 38.0, 48.5, 70.5, 77.9, 126.3, 127.2, 127.6, 128.6, 128.7, 128.8, 128.9, 129.0, 130.0, 134.8, 135.4, 142.5, 153.7, 167.6. Anal. Calcd for $C_{25}H_{25}N_1O_4$: C, 74.42; H, 6.25; N, 3.47. Found: C, 74.36; H, 6.44; N, 3.34.

Benzyl ((2*S*)-1-oxo-3-phenyl-1-((1-phenylethyl)amino)propan-2-yl) carbonate (3a+3a′): diastereoisomeric mixture; white microcrystals (76%); mp 88−92 °C; ^{1}H NMR ($CDCl_3$) δ 1.28 (d, *J* = 6.9 Hz, 2H), 1.37 (d, *J* = 6.9 Hz, 1H), 3.10−3.22 (m, 2H), 5.00−5.16 (m, 3H), 5.26−5.36 (m, 1H), 6.10−6.18 (m, 1H), 7.00−7.40 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 21.5, 21.6, 37.8, 38.0, 48.5, 70.5, 77.9, 126.3, 127.1, 127.2, 127.5, 127.6, 128.6, 128.7 (2C) 128.8, 128.9, 129.0, 130.0, 134.8, 135.4, 142.5, 153.7, 167.6. Anal. Calcd for $C_{25}H_{25}NO_4$: C, 74.42; H, 6.25; N, 3.47. Found: C, 74.25; H, 6.45; N, 3.35.

Benzyl ((*S*)-4-methyl-1-oxo-1-(((*S*)-1-phenylethyl)amino)pentan-2-yl)carbonate (3b): white microcrystals (65%); mp 66−67 °C; $[\alpha]_D^{23} = -66.0$ (*c* 1.5, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 0.93 (d, *J* = 6.3 Hz, 6H), 1.47 (d, *J* = 6.9 Hz, 3H), 1.72−1.82 (m, 3H), 5.10 (dd, *J* = 7.2 Hz, 5.4 Hz, 1H), 5.16 (s, 2H), 6.31 (d, *J* = 7.8 Hz, 1H), 7.20−7.44 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 21.8, 22.0, 23.3, 24.7, 41.1, 48.6, 70.5, 126.3, 127.6, 128.6, 128.9, 129.0, 134.9, 142.7, 154.2, 169.2. Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.15; H, 7.67; N, 3.54.

Benzyl ((2*S*)-4-methyl-1-oxo-1-((1-phenylethyl)amino)pentan-2-yl)carbonate (3b+3b′): diastereoisomeric mixture; white microcrystals (56%); mp 38−42 °C; ^{1}H NMR ($CDCl_3$) δ 0.84−0.98 (m, 6H), 1.38−1.52 (m, 3H), 1.66−1.82 (m, 3H), 5.04−5.26 (m, 4H), 6.24−6.36 (m, 1H), 7.20−7.42 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 21.8, 22.03, 23.3, 24.7, 41.1, 48.6, 70.5, 126.3, 127.6, 128.6, 128.7, 128.9, 134.9, 142.7, 154.2, 169.1. Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.20; H, 7.52; N, 3.60.

(S)-Benzyl (1-((4-methoxyphenyl)amino)-4-methyl-1-oxopentan-2-yl)carbonate (3c): white microcrystals (71%); mp 117−118 °C; $[\alpha]_D^{23} = -53.3$ (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.96 (dd, *J* = 6.0 Hz, 3.3 Hz, 6H), 1.72−1.86 (m, 3H), 3.79 (s, 3H), 5.20−5.28 (m, 3H), 6.85 (d, *J* = 6.9 Hz, 2H), 7.36−7.42 (m, 7H), 7.71 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.1, 23.2, 24.7, 41.3, 55.7, 70.7, 77.0, 114.4, 122.2, 128.7, 129.0, 129.1, 130.1, 134.8, 154.2, 157.0, 167.9. Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.78; N, 3.77. Found: C, 67.83; H, 6.98; N, 3.67.

(9*H*-Fluoren-9-yl)methyl ((2*S*)-4-methyl-1-oxo-1-((1-phenylethyl)amino)pentan-2-yl)carbonate (3d): white microcrystals (67%); mp 155−158 °C; $[\alpha]_D^{23} = -54.6$ (*c* 1.5, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 0.95 (dd, *J* = 6.3 Hz, 3.0 Hz, 6H), 1.51 (d, *J* = 6.9 Hz, 3H), 1.66−1.82 (m, 3H), 4.18−4.26 (m, 1H), 4.38−4.54 (m, 2H), 5.06−5.20 (m, 2H), 6.31 (d, *J* = 7.5 Hz, 1H), 7.22−7.34 (m, 7H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.52−7.58 (m, 2H), 7.77 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.8, 22.0, 23.4, 24.7, 41.2, 46.9, 48.7, 70.4, 120.3, 125.1, 126.3, 127.4, 127.7, 128.2, 128.9, 141.5, 143.2, 143.3, 154.3, 169.1. Anal. Calcd for $C_{29}H_{31}NO_4$: C, 76.12; H, 6.83; N, 3.06. Found: C, 76.13; H, 6.79; N, 2.71.

General Preparation of Depsidipeptides 5 and 15. The unprotected amino acids **4** (1.5 mmol) and DIEA (1.5 mmol) were dissolved in the minimum amount of water. Acetonitrile (3 mL) was added to the solution, which was cooled to 10 °C. A solution of *O*-Pg(hydroxyacyl)benzotriazole **2** or **14** (1 mmol) in acetonitrile (4 mL) was added dropwise over 10 min at 10 °C and stirred for 0.5−2 h at 10 °C. The reaction mixture was monitored by TLC [EtOAc−hexanes (1:2)]. After completion of reaction, the solvent was evaporated, EtOAc (20 mL) was added, and the mixture was washed with 4 N HCl solution (3 × 15 mL) and brine (15 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to give crude product **5** or **15**.

*Z-L-(O-Phe)-L-Ala-OH (**5a**).* The crude product was recrystallized from CH_2Cl_2−hexanes to give white microcrystals (86%): mp 137−139 °C; $[\alpha]_D^{23} = -17.6$ (*c* 1.5, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 1.27 (d, *J* = 7.2 Hz, 3H), 3.16 (dd, *J* = 14.4 Hz, 6.0 Hz, 1H), 3.26 (dd, *J* = 14.4 Hz, 4.2 Hz, 1H), 4.50−4.60 (m, 1H), 5.11 (d, *J* = 12.0 Hz, 1H), 5.17 (d, *J* = 12.0 Hz, 1H), 5.33 (t, *J* = 5.7 Hz, 1H), 6.48 (d, *J* = 7.5 Hz, 1H), 7.10−7.18 (m, 2H), 7.20−7.30 (m, 3H), 7.30−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 18.1, 37.9, 47.9, 70.6, 77.5, 127.3, 128.6, 128.7, 128.9, 129.0, 129.9, 134.8, 135.2, 153.7, 168.7, 176.4. Anal. Calcd for $C_{20}H_{21}N_1O_6$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.52; H, 5.82; N, 3.36.

*Z-L-(O-Phe)-DL-Ala-OH (**5a**+**5a′**).* The crude product was recrystallized from CH_2Cl_2−hexanes to give white microcrystals (80%): diastereoisomeric mixture; mp 135−137 °C; ^{1}H NMR ($CDCl_3$) δ 1.24 (d, *J* = 7.2 Hz, 1.5H), 1.33 (d, *J* = 7.2 Hz, 1.5H), 3.02−3.18 (m, 1H), 3.20−3.28 (m, 1H), 4.46−4.56 (m, 1H), 5.04−5.14 (m, 2H), 5.24−5.34 (m, 1H), 6.47 (d, *J* = 7.2 Hz, 1H), 7.08−7.16 (m, 2H), 7.17−7.24 (m, 3H), 7.26−7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 17.9, 18.1, 37.9, 38.1, 47.9,

48.0, 70.6, 127.3, 128.6, 128.9, 129.0, 129.8, 130.0, 134.8, 135.2, 135.3, 153.7, 168.6, 169.1, 176.5. Anal. Calcd for $C_{20}H_{21}N_1O_6$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.78; H, 5.80; N, 3.65.

*F-L-(O-Phe)-L-Met-OH (**5b**).* The crude product was recrystallized from CH_2Cl_2—hexanes to give white microcrystals (74%): mp 130—132 °C; $[\alpha]_D^{23}$ = −16.9 (*c* 1.0, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 1.84—1.96 (m, 1H), 1.98 (s, 3H), 2.00—2.12 (m, 1H), 2.15—2.28 (m, 2H), 3.19 (d, *J* = 4.8 Hz, 2H), 4.21 (t, *J* = 6.9 Hz, 1H), 4.40 (dd, *J* = 10.5 Hz, *J* = 6.9 Hz, 1H), 4.50 (dd, *J* = 10.8 Hz, 7.5 Hz, 1H), 4.64—4.80 (m, 1H), 5.34 (t, *J* = 4.8, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 7.08—7.14 (m, 2H), 7.20—7.36 (m, 5H), 7.36—7.44 (m, 2H), 7.56 (t, *J* = 7.2 Hz, 2H), 7.76 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 15.4, 29.7, 30.9, 37.7, 46.9, 51.4, 70.5, 77.5, 120.3, 125.2, 127.4, 128.2, 128.6, 130.1, 135.1, 141.5, 143.1, 143.4, 153.7, 168.8, 175.4. Anal. Calcd for $C_{29}H_{29}N_1O_6S$: C, 67.03; H, 5.63; N, 2.70. Found: C, 67.25; H, 5.93; N, 2.50.

*F-L-(O-Phe)-L-Glu-(OMe)-OH (**5c**).* The crude product was recrystallized from EtOAc—hexanes to give white microcrystals (82%): mp 155—157 °C; $[\alpha]_D^{23}$ = −23.8 (*c* 1.0, CH_3OH); ^{1}H NMR (DMSO-d_6) δ 1.76—1.90 (m, 1H), 1.98—2.10 (m, 1H), 2.28—2.38 (m, 2H), 2.94 (dd, *J* = 14.4 Hz, 9.6 Hz, 1H), 3.08 (dd, *J* = 14.7 Hz, 3.9 Hz, 1H), 3.55 (s, 3H), 4.20—4.32 (m, 2H), 4.34—4.48 (m, 2H), 5.07 (dd, *J* = 9.6 Hz, 3.6 Hz, 1H), 7.20—7.36 (m, 6H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.50—7.60 (m, 2H), 7.89 (d, *J* = 7.8 Hz, 2H), 8.51 (d, *J* = 8.1 Hz, 1H), 12.82 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 26.3, 29.7, 37.2, 46.2, 51.0, 51.4, 69.0, 76.9, 120.3, 125.1, 126.8, 127.2, 127.9, 128.4, 129.3, 136.6, 140.8, 143.1, 143.4, 153.8, 168.6, 172.7, 172.8. Anal. Calcd for $C_{30}H_{29}N_1O_8$: C, 67.79; H, 5.50; N, 2.63. Found: C, 67.43; H, 5.47; N, 2.57.

*F-L-(O-Phe)-L-Ala-OH (**5d**).* The crude product was recrystallized from EtOAc—hexanes to give white microcrystals (87%): mp 195—196 °C; $[\alpha]_D^{23}$ = −30.0 (*c* 1.5, CH_3OH); ^{1}H NMR (DMSO-d_6) δ 1.29 (d, *J* = 7.2 Hz, 3H), 3.92 (dd, *J* = 14.7 Hz, 9.9 Hz, 1H), 3.10 (dd, *J* = 14.4 Hz, 3.3 Hz, 1H), 4.20—4.30 (m, 2H), 4.32—4.44 (m, 2H), 5.05 (dd, *J* = 9.6 Hz, 3.3 Hz, 1H), 7.20—7.36 (m, 6H), 7.38—7.46 (m, 2H), 7.50—7.60 (m, 2H), 7.89 (d, *J* = 7.8 Hz, 2H), 8.52 (d, *J* = 7.5 Hz, 1H), 12.6 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 17.2, 37.3, 46.1, 47.5, 69.0, 76.8, 120.3, 125.0, 125.1, 126.7, 127.2, 127.8, 128.3, 129.3, 136.6, 140.8, 143.1, 143.3, 153.8, 168.2, 173.8. Anal. Calcd for $C_{27}H_{25}N_1O_6$: C, 70.58; H, 5.48; N, 3.05. Found: C, 70.20; H, 5.51; N, 2.86.

*F-L-(O-Phe)-DL-Ala-OH (**5d**+**5d′**).* The crude product was recrystallized from EtOAc—hexanes to give white microcrystals (94%): diastereoisomeric mixture; mp 203—205 °C; ^{1}H NMR (DMSO-d_6) δ 1.23 (d, *J* = 7.2 Hz, 1.5 H), 1.29 (d, *J* = 7.2 Hz, 1.5 H), 2.88—3.00 (m, 1H), 3.02—3.16 (m, 1H), 4.20—4.30 (m, 2H), 4.32—4.48 (m, 2H), 5.02—5.12 (m, 1H), 7.20—7.38 (m, 6H), 7.38—7.46 (m, 2H), 7.50—7.60 (m, 2H), 7.89 (d, *J* = 7.5 Hz, 2H), 8.52 (d, *J* = 7.5 Hz, 1H), 12.65 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 17.2, 17.4, 37.5, 46.2, 47.5, 69.0, 76.8, 76.9, 120.3, 125.0, 125.1, 126.7, 127.2, 127.9, 128.3, 129.3, 129.4, 136.5, 136.7, 140.8, 143.1, 143.4, 153.8, 168.0, 168.3, 173.8. Anal. Calcd for $C_{27}H_{25}N_1O_6$: C, 70.58; H, 5.48; N, 3.05. Found: C, 70.27; H, 5.55; N, 2.89.

*F-L-(O-Phe)-L-Phe-OH (**5e**).* The crude product was recrystallized from EtOAc—hexanes to give white microcrystals (86%): mp 165—167 °C; $[\alpha]_D^{23}$ = −13.4 (*c* 1.0, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 2.90 (dd, *J* = 13.8 Hz, 5.7 Hz, 1H), 3.04 (dd, *J* = 13.8 Hz, 5.4 Hz, 1H), 3.10—3.18 (m, 2H), 4.13 (t, *J* = 7.5 Hz, 1H), 4.28 (dd, *J* = 10.5 Hz, 6.9 Hz, 1H), 4.38 (dd, *J* = 10.5 Hz, 7.8 Hz, 1H), 4.82—4.90 (m, 1H), 5.22—5.30 (m, 1H), 6.46 (d, *J* = 7.2 Hz, 1H), 6.80 (dd, *J* = 5.7 Hz, 2.1 Hz, 2H), 7.08—7.50 (m, 15H), 7.73 (d, *J* = 7.8, 2H); ^{13}C NMR ($CDCl_3$) δ 37.6, 37.7, 46.8, 52.6, 70.4, 77.5, 120.3, 125.3, 127.4, 127.5 (2C), 128.2 (2C), 128.7, 128.8, 129.5, 130.1, 135.1, 135.3, 141.5, 143.1, 143.4, 153.7, 168.5, 175.0. Anal. Calcd for $C_{33}H_{29}N_1O_6$: C, 74.00; H, 5.46; N, 2.62. Found: C, 73.85; H, 5.51; N, 2.45.

*F-L-(O-Phe)-DL-Phe-OH (**5e**+**5e′**).* The crude product was recrystallized from EtOAc—hexanes to give white microcrystals (80%): diastereoisomeric mixture; mp 151—153 °C; ^{1}H NMR ($CDCl_3$) δ 2.90—3.30 (m, 4H), 4.10—4.46 (m, 3H), 4.82—4.94 (m, 1H), 5.22—5.32 (m, 1H), 6.46—6.52 (m, 1H), 6.84—6.88 (m, 1H), 7.00—7.04 (m, 1H), 7.12—7.34 (m, 11H), 7.38—7.44 (m, 2H), 7.46—7.54 (m 2H), 7.76 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 37.4, 37.6, 37.7, 38.1, 46.7, 46.8, 52.6, 52.9, 70.5, 70.6, 77.5, 77.9, 120.3, 125.3, 127.3, 127.4, 127.5, 128.2, 128.7 (2C), 128.9, 129.4, 129.5, 129.8, 130.1, 135.1, 135.3, 135.5, 141.5 (2C), 143.1, 143.2 (2C), 143.4, 153.7, 153.9, 168.6, 169.2, 175.2 (C). Anal. Calcd for $C_{33}H_{29}N_1O_6$: C, 74.00; H, 5.46; N, 2.62. Found: C, 73.66; H, 5.76; N, 2.31.

*F-L-(O-Phe)-L-Met-Bt (**6**).* Compound **6** was prepared according to the given procedure for **2**. The crude product was recrystallized from CH_2Cl_2—hexanes to give white microcrystals (80%): mp 160—162 °C; $[\alpha]_D^{23}$ = −56.9 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.96 (s, 3H), 2.02—2.18 (m, 1H), 2.22—2.40 (m, 3H), 3.25 (d, *J* = 5.1 Hz, 2H), 4.28 (t, *J* = 6.9 Hz, 1H), 4.47 (dd, *J* = 10.2 Hz, 6.9 Hz, 1H), 4.55 (dd, *J* = 10.5 Hz, 6.9 Hz, 1H), 5.39 (t, *J* = 4.8, 1H), 5.98—6.08 (m, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 7.14—7.46 (m, 9H), 7.52 (t, *J* = 6.9 Hz, 1H), 7.60—7.70 (m, 3H), 7.78 (d, *J* = 7.5 Hz, 2H), 8.13 (d, *J* = 8.1 Hz, 1H), 8.19 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 15.4, 29.9, 32.0, 37.7, 46.9, 52.5, 70.6, 77.7, 114.5, 120.3, 120.6, 125.3, 126.9, 127.4, 127.5, 128.2, 128.7, 130.1, 131.3, 131.2, 135.2, 141.6, 143.2, 143.4, 146.2, 153.8, 168.6, 170.5. Anal. Calcd for $C_{35}H_{32}N_4O_5S$: C, 67.72; H, 5.20; N, 9.03. Found: C, 67.48; H, 5.23; N, 8.85.

*(9H-Fluoren-9-yl)methyl ((S)-1-(((S)-4-(Methylthio)-1-oxo-1-(((S)-1-phenylethyl)amino)butan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)-carbonate Monohydrate (**7**).* Compound **7** was prepared according to the given procedure for **3**. The crude product was recrystallized from EtOAc—hexanes to give white microcrystals (52%): mp 176—178 °C; $[\alpha]_D^{23}$ = −60.0 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.45 (d, *J* = 6.9 Hz, 3H), 1.78—1.88 (m, 2H), 1.94 (s, 3H), 2.08—2.18 (m, 1H), 2.24—2.34 (m, 1H), 3.18—3.22 (m, 2H), 4.24 (t, *J* = 7.2 Hz, 1H), 4.38—4.56 (m, 3H), 5.00—5.10 (m, 1H), 5.29 (t, *J* = 5.4 Hz, 1H), 6.56 (d, *J* = 8.1 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 7.14—7.20 (m, 2H), 7.22—7.38 (m, 10H), 7.40—7.46 (m, 2H), 7.59 (t, *J* = 7.2 Hz, 2H), 7.78 (d, *J* = 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 15.1, 22.1, 30.0, 30.8, 37.9, 46.9, 49.4, 52.1, 70.6, 120.3, 125.3, 126.2, 127.5, 127.7, 128.2, 128.7, 128.9, 130.0, 135.3, 141.5, 143.1, 143.3 154.1, 168.6, 169.4. Anal. Calcd for $C_{37}H_{38}N_2O_5S.H_2O$: C, 69.35; H, 6.29; N, 4.37. Found: C, 69.09; H, 6.15; N, 4.25.

General Preparation of Depsidipeptides (11). DMAP (0.75 mmol) in dry THF (2 mL) was added to a stirred solution of *N*-Pg(α-aminoacyl)benzotriazole **9** (0.5 mmol) and α-hydroxycarboxylic acid (0.75 mmol) in dry THF (10 mL) at 4 °C. Then the reaction mixture was stirred for 4—6 h at room temperature until shown to be completed by TLC [EtOAc—hexanes (1:2)]. The solvent was evaporated under reduced pressure, and the residue was dissolved in diethyl ether (25 mL), washed with 3 N HCl (4 × 5 mL), water (3 × 10 mL), and brine (5 mL), and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to give crude product **11**.

*Z-L-Leu-L-(O-Phe)-OH (**11a**).* The residue was purified by column chromatograph [EtOAc—hexanes, (from 15 to 30%)] to obtain a sticky oil (76%): $[\alpha]_D^{23}$ = −21.0 (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.76—1.05 (m, 6H), 1.40—1.55 (m, 1H), 1.55—1.80 (m, 2H), 3.13 (dd, *J* = 13.8 Hz, 7.8 Hz, 1H), 3.26 (dd, *J* = 14.4 Hz, 4.2 Hz, 1H), 4.30—4.40 (m, 1H), 5.00—5.20 (m, 2H), 5.31 (dd, *J* = 8.4 Hz, 5.1 Hz, 1H), 7.18—7.52 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 21.9, 23.0, 24.8, 37.2, 41.6, 52.5, 67.3, 73.2, 127.3, 128.2, 128.4, 128.7, 129.5, 135.5, 136.3, 156.3, 172.5, 173.7. Anal. Calcd for $C_{23}H_{27}N_1O_6$: C, 66.81; H, 6.58; N, 3.39. Found: C, 66.54; H, 6.87; N, 3.29.

*Z-L-Leu-DL-(O-Phe)-OH (**11a**+**11a′**).* The crude was purified by column chromatography [EtOAc—hexanes, (from 15 to 30%)] to obtain a sticky oil (78%): diastereoisomeric mixture; ^{1}H NMR ($CDCl_3$) δ 0.76—1.00 (m, 6H), 1.30—1.53 (m, 2H), 1.56—1.76 (m, 1H), 3.04—3.20 (m, 1H), 3.20—3.36 (m, 1H), 3.34—3.44 (m, 1H), 5.02—5.18 (m, 3H), 5.33 (dd, *J* = 9.9 Hz, 3.6 Hz, 1H), 7.18—7.40

(m, 10H); ^{13}C NMR ($CDCl_3$) δ 21.9, 22.8, 23.0, 24.7, 24.8, 37.2, 41.4, 41.6, 52.5, 52.6, 67.4, 73.2, 73.4, 127.4, 128.3, 128.4, 128.7, 129.5, 129.6, 135.5, 135.8, 136.3, 156.2, 156.3, 172.5, 173.7. Anal. Calcd for $C_{23}H_{27}N_1O_6$: C, 66.81; H, 6.58; N, 3.39. Found: C, 66.40; H, 6.75; N, 3.60.

Z-L-Ala-L-(O-Phe)-N(Cy)$_2$ (***11b***). The crude was taken into in diethyl ether (6 mL) in a test tube, and dicyclohexylamine (110 mg, 0.60 mmol) was added dropwise. Hexane (2 mL) was added, and the mixture was kept at room temperature until it gave white crystals. Then the crystals were collected and washed with excess of hexanes to give pure Z-L-Ala-L-(OPhe)-N(Cy)$_2$ **11b** as white crystals (76%): mp 155−156 °C; $[\alpha]_D^{23}$ = −25.9 (*c* 1.2, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 1.00−1.25 (m, 7H), 1.30−1.45 (m, 6H), 1.59 (s, 2H), 1.73 (s, 4H), 1.91 (s, 4H), 2.80−2.95 (m, 2H), 3.04 (dd, *J* = 14.4 Hz, 9.9 Hz, 1H), 3.24 (dd, *J* = 14.4 Hz, 3.6 Hz, 1H), 4.20−4.40 (m, 1H), 4.95−5.10 (m, 3H), 5.30−5.41 (m, 1H), 7.10−7.40 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 25.0, 25.3, 29.0, 29.1, 38.2, 50.0, 52.7, 67.0, 77.0, 126.5, 128.5, 128.7, 129.4, 136.6, 138.4, 155.6, 172.2, 173.6. Anal. Calcd for $C_{32}H_{44}N_2O_6$: C, 69.54; H, 8.02; N, 5.07. Found: C, 69.25; H, 8.21; N, 4.90.

Z-L-Phe-L-(O-Leu)-N(Cy)$_2$ (***11c***). The crude was taken into diethyl ether (6 mL) in a test tube, and dicyclohexylamine (110 mg, 0.60 mmol) was added dropwise. Hexane (2 mL) was added, and the mixture was kept at room temperature until it gave white crystals. Then the crystals were collected and washed with excess of hexanes to give pure Z-L-Phe-L-(O-Leu)-N(Cy)$_2$ **11c** as white crystals (47%): mp 127−128 °C; $[\alpha]_D^{23}$ = −34.5 (*c* 1.2, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 0.90 (t, *J* = 6.2 Hz, 6H), 1.06−1.86 (m, 19H), 1.90−2.06 (m, 4H), 2.82−3.00 (m, 2H), 3.09 (dd, *J* = 14.4 Hz, 6.6 Hz, 1H), 3.31 (dd, *J* = 13.5 Hz, 5.7, 1H), 4.62−4.74 (m, 1H), 4.90−5.16 (m, 3H), 5.29 (d, *J* = 7.8 Hz, 1H), 7.18−7.40 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 21.9, 23.6, 25.0, 25.1, 25.3, 29.5, 38.4, 41.0, 52.8, 55.2, 67.0, 75.1, 127.0, 128.3, 128.5, 128.7, 129.9, 136.6, 155.8, 171.2, 175.0. Anal. Calcd for $C_{35}H_{50}N_2O_6$: C, 70.68; H, 8.47; N, 4.71. Found: C, 70.78; H, 8.92; N, 4.75.

Z-L-Met-L-(OPhe)-OH (***11d***). The crude was recrystallized from $CHCl_3$−hexanes to give white microcrystals (54%): mp 114−116 °C; $[\alpha]_D^{23}$ = −18.6 (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.88−2.00 (m, 1H), 2.03 (s, 3H), 2.06−2.20 (m, 1H), 2.44−2.58 (m, 2H), 3.14 (dd, *J* = 14.4 Hz, 7.8 Hz, 1H), 3.26 (dd, *J* = 14.7 Hz, 4.5 Hz, 1H), 4.50−4.60 (m, 1H), 5.09 (s, 2H), 5.32 (dd, *J* = 7.8 Hz, 3.9 Hz, 1H), 5.42 (d, *J* = 7.8 Hz, 1H), 7.18−7.40 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 15.4, 29.7, 31.9, 37.2, 53.1, 67.4, 73.4, 127.5, 128.3, 128.5, 128.7, 129.5, 135.3, 136.2, 156.1, 171.6, 173.7. Anal. Calcd for $C_{22}H_{25}N_1O_6S$: C, 61.24; H, 5.84; N, 3.25. Found: C, 60.98; H, 5.85; N, 3.08.

Synthesis of *tert*-Butyl L-α-Hydroxycarboxlates 12a and 12b. Compounds **12a** and **12b** were prepared using procedure reported by Yang et al.[4] (Scheme S1, Supporting Information).

Z-L-Met-L-(O-Leu)-OBu-t (***13***). DMAP (0.105 g, 0.85 mmol) was added to a stirred solution of Z-L-Met-Bt (0.32 g, 0.83 mmol) and H-(*O*-Leu)-OBu-*t* **12b** (0.16 g, 0.83 mmol) in THF (10 mL) at 4 °C. Then the reaction mixture was stirred for 5 h at room temperature until it was completed, which was monitored by TLC (EtOAc−hexanes (1:2)). Then the solvent was evaporated under reduced pressure. The residue was taken into EtOAc (25 mL) and washed with 3 N HCl (3 × 10 mL), saturated Na_2CO_3 (2 × 10 mL), and brine (10 mL). The mixture was dried over $MgSO_4$, and the solvent was evaporated to give Z-L-Met-L-(*O*-Leu)-OBu-*t* **13** as a colorless oil (87%): $[\alpha]_D^{23}$ = −15.3 (*c* 1.2, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 0.93 (dd, *J* = 8.4 Hz, 6.6 Hz, 6H), 1.44 (s, 9H), 1.54−1.84 (m, 3H), 1.92−2.32 (m, 4H), 2.28−2.30 (m, 1H), 2.54−2.70 (m, 2H), 4.57 (q, *J* = 5.1 Hz, 1H), 4.92 (dd, *J* = 8.4 Hz, 3.9 Hz, 1H), 5.10 (s, 2H), 5.46 (d, *J* = 8.1 Hz, 1H), 7.28−7.42 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.5, 21.9, 23.2, 24.8, 28.1, 30.0, 32.4, 39.8, 53.2, 67.3, 72.7, 82.4, 127.6, 128.3, 128.4, 128.7, 136.4, 156.1, 169.3, 171.9. Anal. Calcd for $C_{23}H_{35}N_1O_6S_1$: C, 60.90; H, 7.78; N, 3.09. Found: C, 60.99; H, 8.39; N, 3.23.

Z-L-Leu-L-(O-Phe)-Bt (***14a***). Compound **14a** was prepared according to the given procedure for **2**. The yellowish oil (83%) was used without purification.

Z-L-Ala-L-(O-Phe)-Bt (***14b***). Compound **14b** was prepared according to the given procedure for **2**. The yellowish oil (78%) was used without purification.

Z-L-Leu-L-(O-Phe)-L-Met-OH (***15a***). Compound **15a** was prepared according to the given procedure for **5**: white microcrystals (78%); mp 116−118 °C; $[\alpha]_D^{23}$ = −37.4 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.80−0.98 (m, 6H), 1.40−1.52 (m, 1H), 1.52−1.70 (m, 2H), 1.84−2.16 (m, 4H), 2.22 (q, *J* = 7.2 Hz, 2H), 3.08−3.25 (m, 2H), 4.25−4.30 (m, 1H), 4.50−4.62 (m, 1H), 4.90−5.04 (m, 1H), 5.05−5.20 (s, 2H), 5.40−5.50 (m, 1H), 6.40−6.65 (br s, 2H), 7.00−7.40 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 15.3, 21.7, 23.0, 24.9, 29.9, 30.7, 37.6, 40.5, 51.6, 53.0, 67.6, 74.9, 127.3, 128.2, 128.6, 128.8, 129.9, 135.6, 136.0, 156.9, 169.5, 171.3, 174.8. Anal. Calcd for $C_{28}H_{36}N_2O_7S$: C, 61.75; H, 6.66; N, 5.14. Found: C, 61.73; H, 6.62; N, 5.06.

Z-L-Ala-L-(O-Phe)-L-Trp-OH (***15b***). Compound **15b** was prepared according to the given procedure for **5**: white microcrystals (63%); mp 193−195 °C; $[\alpha]_D^{23}$ = −87.3 (*c* 1.5, CH_3OH); ^{1}H NMR (DMSO-d_6) δ 1.20 (d, *J* = 7.2 Hz, 3H), 2.85−3.20 (m, 4H), 4.00−4.15 (m, 1H), 4.51 (q, *J* = 7.2 Hz, 1H), 4.85−5.05 (m, 2H), 5.10−5.25 (m, 1H), 6.90−7.40 (m, 11H), 7.48 (d, *J* = 7.2 Hz, 1H), 7.23 (d, *J* = 6.9 Hz, 1H), 8.22 (d, *J* = 7.8 Hz, 1H), 10.87 (s, 1H), 12.71 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 16.7, 26.9, 37.2, 49.1, 52.6, 65.5, 74.0, 109.3, 111.3, 118.2, 118.4, 120.9, 123.6, 126.5, 127.2, 127.8, 127.8, 128.1, 128.3, 129.3, 136.0, 136.5, 136.8, 155.9, 168.3, 172.0, 172.8. Anal. Calcd for $C_{31}H_{31}N_3O_7$: C, 66.77; H, 5.60; N, 7.54. Found: C, 66.49; H, 5.48; N, 7.47.

Z-L-Leu-L-(O-Phe)-L-(O-Ile)-OH (***16***). Compound **16** was prepared according to the given procedure for **11**: colorless oil (55%); $[\alpha]_D^{23}$ = −24.2 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.80−1.00 (m, 12H), 1.20−1.40 (m, 1H), 1.40−1.60 (m, 2H), 1.60−1.78 (m, 2H), 1.94−2.08 (m, 1H), 3.14 (dd, *J* = 14.4 Hz, 8.1 Hz, 1H), 3.30 (dd, *J* = 14.7 Hz, 4.2 Hz, 1H), 4.36−4.48 (m, 1H), 5.00−5.12 (m, 3H), 5.14−5.40 (m, 2H), 7.10−7.40 (m, 10H), 8.56 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 11.7, 15.4, 21.8, 23.1, 24.5, 24.8, 36.7, 37.2, 41.8, 52.4, 67.3, 73.4, 127.3, 128.3, 128.4, 128.7 (2C), 129.5, 129.6, 135.6, 136.4, 156.2, 169.0, 172.7, 174.2. Anal. Calcd for $C_{29}H_{37}NO_8$: C, 66.02; H, 7.07; N, 2.65. Found: C, 65.79; H, 7.53; N, 2.42.

General Preparation of Oligoesters 17. *O*-Pg(α-Hydroxyacyl)benzotriazole **2** (0.5 mmol) in dry THF (2 mL) was added to a stirred solution of DMAP (0.6 mmol) and α-hydroxycarboxylic acid (0.6 mmol) in dry THF (10 mL) at 4 °C. Then the reaction mixture was stirred for 4−6 h at room temperature until it was completed, as indicated by monitoring with TLC [EtOAc−hexanes (1:2)]. The solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc (15 mL), washed with 3 N HCl (4 × 5 mL) and brine (5 mL), and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to give crude oily product **17a**,**b**. The solution of crude in CH_2Cl_2 (1 mL) was loaded onto a short silica column (1 cm diameter × 2 cm length) and eluted with EtOAc−hexanes (1:1). Evaporation of solvent gave pure **17a**,**b**.

Z-L-(O-Phe)-L-(O-Val)-OH (***17a***): colorless oil (85%); $[\alpha]_D^{23}$ = −30.0 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ ; 0.98 (t, *J* = 6.9 Hz, 6H), 2.24−2.36 (m, 1H), 3.14 (dd, *J* = 14.7 Hz, 9.0 Hz, 1H), 3.32 (dd, *J* = 14.7 Hz, 3.9 Hz, 1H), 5.00 (d, *J* = 4.2 Hz, 1H), 5.10 (d, *J* = 12.3 Hz, 1H), 5.16 (d, *J* = 12.3 Hz, 1H), 5.23 (dd, *J* = 9.0 Hz, 3.6 Hz, 1H), 7.20−7.38 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 17.1, 18.8, 30.3, 37.4, 70.3, 76.0, 77.1, 127.3, 128.5, 128.7, 128.8, 129.6, 135.0, 135.8, 154.7, 169.2, 174.5. Anal. Calcd for $C_{22}H_{24}O_7$·: C, 65.99; H, 6.04. Found: C, 65.61; H, 6.23.

Z-L-(O-Phe)-L-(O-Leu)-OH (***17b***): colorless oil (75%); $[\alpha]_D^{23}$ = −34.8 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.93 (dd, *J* = 8.1 Hz, 5.7 Hz, 6H), 1.64−1.86 (m, 3H), 3.12 (dd, *J* = 14.4, *J* = 9.3 Hz, 1H), 3.31 (dd, *J* = 14.7 Hz, 3.6 Hz, 1H), 5.04−5.22 (m, 4H), 7.20−7.38 (m, 10H); ^{13}C NMR

($CDCl_3$) δ 21.7, 23.1, 24.8, 37.3, 39.7, 70.3, 71.5, 76.1, 127.3, 128.5, 128.7, 128.8, 129.7, 135.0, 135.8, 154.7, 169.2, 175.3; HRMS (ESI) calcd for $C_{23}H_{26}O_7$ $[M + Na]^+$ 437.1571, found 437.1575.

Z-L-(O-Leu)-L-(O-Phe)-OBu-t (**18**). DMAP (0.05 g, 0.41 mmol) was added to a stirred solution of Z-(*O*-Leu)-Bt **2b** (0.15 g, 0.41 mmol) and H-(*O*-Phe)-OBu-*t* **12a** (0.091 g, 0.41 mmol) in THF (10 mL) at 4 °C. Then the reaction mixture was stirred for 5 h at room temperature until it was completed, as monitored by TLC (EtOAc−hexanes (1:2)). Then the solvent was evaporated under reduced pressure. The residue was taken into EtOAc (15 mL) and washed with saturated 3 N HCl (3 × 5 mL), saturated Na_2CO_3 (2 × 5 mL), and brine (5 mL). After dried over $MgSO_4$, the solvent was evaporated to give pure Z-L-(*O*-Leu)-L-(*O*-Phe)-OBu-*t* **18** as a colorless oil (86%): $[\alpha]_D^{23} = -39.0$ (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.93 (d, *J* = 6.3 Hz, 6H), 1.36 (s, 9H), 1.64−1.86 (m, 3H), 3.14 (d, *J* = 5.7 Hz, 2H), 5.00 (dd, *J* = 9.9, *J* = 4.2 Hz, 1H), 5.14−5.20 (m, 3H), 7.20−7.40 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 21.6, 23.2, 24.6, 28.1, 37.4, 39.9, 70.24, 74.1, 82.7, 127.2, 128.5 (2C), 128.8 (2C), 129.7, 135.2, 135.8, 154.8, 168.0, 169.9. Anal. Calcd for $C_{27}H_{34}O_7$: C, 68.92; H, 7.28. Found: C, 69.14; H, 7.62.

Z-L-(O-Leu)-L-(O-Phe)-OH (**17c**). The solution of Z-L-(*O*-Leu)-L-(*O*-Phe)-OBu-*t* **18** (0.10 g, 0.21 mmol) in CH_2Cl_2−TFA [6 mL, (1:1)] was stirred for 2 h at 4 °C. Then the volatile part was removed under reduced pressure. The residue oil which was taken into EtOAc (10 mL) was washed with 1 N HCl (3 × 5 mL) and brine (5 mL). After the mixture was dried over $MgSO_4$, the solvent was removed to give oily crude. The solution of crude in CH_2Cl_2 (1 mL) was loaded onto a short silica column (1 cm diameter × 2 cm length) and eluted with EtOAc−hexanes (1:1). Evaporation of solvent gave pure Z-L-(*O*-Leu)-L-(*O*-Phe)-OH **17c** as a colorless oil (80%): $[\alpha]_D^{23} = -38.9$ (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.90 (d, *J* = 6.3 Hz, 6H), 1.56−1.84 (m, 3H), 3.14 (dd, *J* = 14.4 Hz, 7.8 Hz, 1H), 3.25 (dd, *J* = 14.4 Hz, 4.5 Hz, 1H), 4.97 (dd, *J* = 9.3 Hz, 4.2 Hz, 1H), 5.16 (s, 2H), 5.36 (dd, *J* = 7.8 Hz, 4.5 Hz, 1H), 6.02 (s, 1H), 7.20−7.42 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 21.7, 23.1, 24.5, 37.2, 39.7, 70.3, 73.0, 74.1, 127.5, 128.5, 128.7, 128.8, 129.6, 135.1, 135.3, 154.9, 169.8, 173.8. Anal. Calcd for $C_{23}H_{24}O_7$: C, 66.65; H, 6.32. Found: C, 66.95; H, 6.54.

General Preparation of Unprotected Depsides (19). DMAP (6.0 mmol) was added to a stirred solution of *N*-Boc(α-aminoacyl)benzotriazole **9** (5.0 mmol) and α-hydroxycarboxylic acid **10** (0.6 mmol) in THF (10 mL) at 4 °C. The reaction mixture was stirred for 6 h at room temperature until the reaction was complete by TLC [EtOAc−hexanes (1:2)]. The solvent was evaporated under reduced pressure, and the residue was taken into EtOAc (25 mL), washed with saturated citric acid solution (3 × 15 mL) and brine (10 mL), and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to yield the crude product as an oil. The crude was dissolved in 5.0 N $HCl_{(g)}$ in dry EtOAc (20 mL), and the solution was stirred for 15 min at room temperature. A white precipitate was formed, filtered off, and discarded. The solvent was removed. The residue was dissolved in dry CH_2Cl_2 (25 mL). Dry HCl gas was bubbled into the flask for 4−6 h at room temperature while stirring. The precipitate which formed was collected and washed with dry CH_2Cl_2 to give pure unprotected depside as hydrochloride salt **19**.

Gly-L-(O-Phe)·HCl (**19a**): white microcrystals (48%); mp 150−155 °C; $[\alpha]_D^{23} = -31.4$ (*c* 1.5, CH_3OH); ^{1}H NMR (DMSO-d_6) δ 3.09 (dd, *J* = 14.4 Hz, 7.8 Hz, 1H), 3.20 (dd, *J* = 14.7 Hz, 4.5 Hz, 1H), 3.79 (s, 2H), 5.25 (dd, *J* = 7.5 Hz, 4.2 Hz, 1H), 7.20−7.40 (m, 5H), 8.57 (br s, 3H); ^{13}C NMR (DMSO-d_6) δ 36.4, 39.4, 74.0, 126.9, 128.5, 129.5, 136.1, 167.4, 169.8. Anal. Calcd for $C_{11}H_{14}ClNO_4$: C, 50.88; H, 5.43; N, 5.19. Found: C, 50.41; H, 5.93; N, 5.53.

L-Ala-L-(O-Leu)·HCl (**19b**): white microcrystals (36%); mp 165−168 °C; $[\alpha]_D^{23} = -25.8$ (*c* 1.5, CH_3OH); ^{1}H NMR (DMSO-d_6) δ 0.91 (t, *J* = 6.6 Hz, 6H), 1.48 (d, *J* = 7.2 Hz, 3H), 1.58−1.82 (m, 3H), 4.14 (q, *J* = 7.2 Hz, 1H), 4.98 (dd, *J* = 8.7 Hz, 3.6 Hz, 1H), 8.69 (br s, 3H); ^{13}C NMR (DMSO-d_6) δ 15.8, 21.5, 22.9, 24.1, 47.7, 71.8, 170.0, 170.8. Anal. Calcd for $C_9H_{18}ClNO_4$: C, 45.10; H, 7.57; N, 5.84. Found: C, 45.16; H, 7.84; N, 5.63.

Gly-L-(O-Leu)·HCl (**19c**): white hydroscopic microcrystals (62%); mp 65−70 °C; $[\alpha]_D^{23} = -37.5$ (*c* 1.5, CH_3OH); ^{1}H NMR (DMSO-d_6) δ 0.90 (t, *J* = 6.9 Hz, 6H), 1.52−1.82 (m, 3H), 3.87 (d, *J* = 9.0 Hz, 2H), 4.96 (dd, *J* = 9.6 Hz, 3.6 Hz, 1H), 8.58 (br s, 3H), 13.20 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.5, 22.9, 24.1, 39.1, 71.9, 167.5, 170.8. Anal. Calcd for $C_8H_{16}ClNO_4$: C, 42.58; H, 7.15; N, 6.21. Found: C, 42.96; H, 7.15; N, 6.15.

L-Phe-L-(O-Leu)·HCl (**19d**): white microcrystals (56%); mp 139−140 °C; $[\alpha]_D^{23} = -24.4$ (*c* 1.5, CH_3OH); ^{1}H NMR (DMSO-d_6) δ 0.84 (dd, *J* = 5.1 Hz, 5.1 Hz, 6H), 1.45−1.65 (m, 3H), 3.19 (d, *J* = 6.6 Hz, 2H), 4.35 (t, *J* = 6.3 Hz, 1H), 4.84−5.00 (m, 1H), 7.20−7.42 (m, 5H), 9.00 (br s, 3H); ^{13}C NMR (DMSO-d_6) δ 21.4, 22.8, 23.9, 35.6, 52.9, 72.1, 127.1, 128.4, 129.7, 135.1, 168.9, 170.8; HRMS (ESI) calcd for $C_{15}H_{22}ClNO_4$ $[M + H]^+$ 280.1543, found 280.1544.

General Procedure for the Preparation of Depsitripeptides (20). The HCl salt of depside **19** (0.40 mmol) and DIEA (0.80 mmol) were dissolved in the minimum amount of cold water. Acetonitrile (3 mL) was added and the solution cooled to 10 °C. A solution of *N*-Pg(α-aminoacyl)benzotriazoles **9** (0.20 mmol) in acetonitrile (3 mL) was added dropwise over 10 min at 10 °C and stirred for 0.5−2 h at 10 °C. The reaction mixture was monitored by TLC [EtOAc−hexanes (1:2)]. After completion of reaction, the solvent was evaporated. EtOAc (15 mL) was added, and the mixture was washed with 4 N HCl solution (3 × 10 mL) and brine (10 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to give crude product. The solution of crude in CH_2Cl_2 (1 mL) was loaded onto a short silica column (1 cm diameter × 2 cm length) and eluted with EtOAc. The solvent was removed under reduced pressure to give pure depsitripeptide **20a**−**c**.

Z-L-Phe-Gly-L-(O-Leu)-OH (**20a**): white hydroscopic microcrystals (71%); mp 52−55 °C; $[\alpha]_D^{23} = -15.7$ (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.91 (t, *J* = 6.9 Hz, 6H), 1.60−1.84 (m, 3H), 2.84−3.00 (m, 1H), 3.02−3.22 (m, 1H), 3.90−4.20 (m, 2H), 4.40−4.60 (m, 1H), 4.90−5.10 (m, 3H), 5.72 (d, *J* = 8.1 Hz, 1H), 6.93 (br s, 1H), 7.10−7.34 (m, 10H), 7.95 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.7, 23.2, 24.8, 38.6, 39.7, 41.3, 56.2, 67.4, 72.0, 127.2, 128.1, 128.4, 128.7, 128.8, 129.5, 136.2, 136.3, 156.5, 169.5, 172.1, 173.7. Anal. Calcd for $C_{25}H_{30}N_2O_7$: C, 63.82; H, 6.43; N, 5.95. Found: C, 63.76; H, 6.53; N, 5.90.

Z-L-Met-L-Phe-L-(O-Leu)-OH (**20b**): white microcrystals (56%); mp 140−142 °C; $[\alpha]_D^{23} = -36.3$ (*c* 1.2, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 0.93 (dd, *J* = 7.5 Hz, 6.3 Hz, 6H), 1.64−1.96 (m, 5H), 2.01 (s, 3H), 2.49 (t, *J* = 6.9 Hz, 2H), 3.05 (dd, *J* = 14.1 Hz, 7.5 Hz, 1H), 3.28 (dd, *J* = 14.1 Hz, 5.4 Hz, 1H), 4.34 (q, *J* = 7.2 Hz, 1H), 4.82−4.94 (m, 1H), 5.04−5.14 (m, 3H), 5.64 (d, *J* = 7.5 Hz, 1H), 6.77 (d, *J* = 7.2 Hz, 1H), 7.14−7.28 (m, 5H), 7.30−7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.2, 21.7, 23.2, 24.8, 30.0, 31.6, 37.7, 39.8, 53.3, 53.7, 67.4, 71.9, 127.4, 128.3, 128.5, 128.8 (2C), 129.6, 135.8, 136.2, 156.3, 171.1, 171.5, 174.1. Anal. Calcd for $C_{28}H_{36}N_2O_7S$: C, 61.75; H, 6.66; N, 5.14. Found: C, 61.53; H, 7.02; N, 5.35.

Z-L-Met-Gly-L-(O-Leu)-OH (**20c**): white microcrystals (68%); mp 113−115 °C; $[\alpha]_D^{23} = -22.5$ (*c* 1.5, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 0.94 (dd, *J* = 8.4 Hz, 6.3 Hz, 6H), 1.64−1.90 (m, 3H), 1.90−2.00 (m, 1H), 2.00−2.16 (m, 1H), 2.06 (s, 3H), 2.56 (t, *J* = 7.2 Hz, 2H), 3.95 (dd, *J* = 18.0 Hz, 3.9 Hz, 1H), 4.28 (dd, *J* = 17.4 Hz, 5.7 Hz, 1H), 4.40−4.50 (m, 1H), 5.00−5.20 (m, 3H), 5.92 (d, *J* = 8.4 Hz, 1H), 7.15 (br s, 1H), 7.30−7.40 (m, 5H), 8.20 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.4, 21.7, 23.2, 24.8, 30.0, 32.0, 39.7, 41.3, 53.9, 67.6, 72.0, 128.3, 128.5, 128.7, 136.1, 156.7, 169.6, 172.3, 173.5. Anal. Calcd for $C_{21}H_{30}N_2O_7S$: C, 55.49; H, 6.65; N, 6.16. Found: C, 55.71; H, 6.85; N, 5.95.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR spectra of compounds and chiral HPLC chromatograms; X-ray structure of

15a (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author
*E-mail: katritzky@chem.ufl.edu.

ACKNOWLEDGMENT

We thank Dr. C. D. Hall and Mr. Z. Wang for helpful discussions.

REFERENCES

(1) (a) Ballard, C. E.; Yu, H.; Wang, B. *Curr. Med. Chem.* **2002**, *9*, 471–498. (b) Sarabia, F.; Chammaa, S.; Ruiz, A. S.; Ortiz, L. M.; Herrera, F. J. L. *Curr. Med. Chem.* **2004**, *11*, 1309–1332.

(2) (a) Piekarz, R. L.; Frye, R.; Turner, M.; Wright, J. J.; Allen, S. L.; Kirschbaum, M. H.; Zain, J.; Prince, H. M.; Leonard, J. P.; Geskin, L. J.; Reeder, C.; Joske, D.; Figg, W. D.; Gardner, E. R.; Steinberg, S. M.; Jaffe, E. S.; Stetler-Stevenson, M.; Lade, S.; Fojo, A. T; Bates, S. *J. Clin. Oncol.* **2009**, *27*, 5410–5417. (b) Piekarz, R. L.; Frye, R.; Turner, M.; Wright, J. J.; Steinberg, S. M.; Liewehr, D. J.; Rosing, D. R.; Sachdev, V.; Fojo, T.; Bates, S. E. *Clin. Cancer Res.* **2006**, *12*, 3762–3773. (c) Chen, J.; Zhang, M.; Ju, W.; Waldmann, T. A *Blood* **2009**, *113*, 1287–1293.

(3) (a) http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm189466.htm, 01/19/2011. (b) http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022393lbl.pdf, 01/19/2011. (c) http://www.istodax.com/, 01/19/2011.

(4) (a) Vaishampayan, U.; Glode, M.; Du, W.; Kraft, A.; Hudes, G.; Wright, J.; Hussain, M. *Clin. Cancer Res.* **2000**, *6*, 4205–4208. (b) Mittelman, A.; Chun, H. G.; Puccio, C.; Coombe, N.; Lansen, T.; Ahmed, T. *Invest. New Drugs* **1999**, *17*, 179–182. (c) Shin, D. M.; Holoye, P. Y.; Forman, A.; Winn, R.; Perez-Soler, R.; Dakhil, S.; Rosenthal, J.; Raber, M. N.; Hong, W. K. *Invest. New Drugs* **1994**, *12*, 243–249.

(5) Andjelic, C. D.; Planelles, V.; Barrows, L. R. *Mar. Drugs* **2008**, *6*, 528–549.

(6) (a) Ovchinnikov, Y. A. *Eur. J. Biochem.* **1979**, *94*, 321–336. (b) Žižka, Z *Folia Microbiol.* **1998**, *43*, 7–14.

(7) (a) Liebman, J. F.; Greenberg, A. *Biophysic. Chem.* **1974**, *1*, 222–226. (b) Kang, Y. K.; Byun, B. J. *J. Phys. Chem. B* **2008**, *112*, 9126–9134.

(8) (a) Karle, I. L.; Das, C.; Balaram, P. *Biopolymers* **2001**, *59*, 276–289. (b) Oku, H.; Ohyama, T.; Hiroki, A.; Yamada, K.; Fukuyama, K.; Kawaguchi, H.; Katakai, R. *Biopolymers* **2004**, *75*, 242–254. (c) Cieplak, A. S.; Sürmeli, N. B. *J. Org. Chem.* **2004**, *69*, 3250–3261. (d) Scheike, J. A.; Baldauf, C.; Spengler, J.; Albericio, F.; Pisabarro, M. T.; Koksch, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 7766–7769.

(9) (a) Fu, Y.; Gao, J.; Bieschke, J.; Dendle, M. A.; Kelly, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 15948–15949. (b) Deechongkit, S.; Dawson, P. E.; Kelly, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 16762–16771. (c) Yang, X.; Wang, M.; Fitzgerald, M. C. *Bioorg. Chem.* **2004**, *32*, 438–449.

(10) Zhang, J; King, M; Suggs, L; Ren, P. *Biomacromolecules* **2007**, *8*, 3015–3024.

(11) Kuisle, O.; Quinoa, E.; Riguera, R. *J. Org. Chem.* **1999**, *64*, 8063–8075.

(12) Matkovic, M.; Veljkovic, J.; Majerski, K.; Molcanov, K.; Prodic, B. *J. Mol. Struct.* **2007**, *832*, 191–198.

(13) Ma, J.-Y.; Xu, L.-F.; Huang, W.-F.; Wei, B.-G.; Lin, G.-Q. *Synlett* **2009**, *8*, 1307–1310.

(14) Davies, J. S.; Howe, J.; Jayatilake, J.; Riley, T. *Lett. Pept. Sci.* **1997**, *4*, 441–445.

(15) Wang, Y.; Zhang, F.; Zhang, Y.; Liu, J. O.; Ma, D. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4385–4387.

(16) (a) Katritzky, A. R.; Haase, D. N.; Johnson, J. V.; Chung, A. *J. Org. Chem.* **2009**, *74*, 2028–2032. (b) Katritzky, A. R.; Yoshioka, M.; Narindoshvili, T.; Chung, A.; Khashab, N. M. *Chem. Biol. Drug Des.* **2008**, *72*, 182–188. (c) Katritzky, A. R.; Khashab, N. M.; Yoshioka, M.; Haase, D. N.; Wilson, K. R.; Johnson, J. V.; Chung, A.; Haskell-Luevano, C. *Chem. Biol. Drug Des.* **2007**, *70*, 465–468.

(17) Katritzky, A. R.; Abdelmajeid, A.; Tala, S. R.; Amine, M. S. *Unpublished results*

(18) (a) Katritzky, A. R.; Suzuki, K.; Wang, Z. *Synlett* **2005**, 1656–1665. (b) Katritzky, A. R.; Angrish, P.; Suzuki, K. *Synthesis* **2006**, 411–424. (c) Katritzky, A. R.; Angrish, P.; Hur, D.; Suzuki, K. *Synthesis* **2005**, 397–402. (d) Katritzky, A. R.; Todadze, E.; Angrish, P.; Draghici, B. *J. Org. Chem.* **2007**, *72*, 5794–5801. (e) Katritzky, A. R.; Angrish, P. *Steroids* **2006**, *71*, 660–669. (f) Katritzky, A. R.; Jishkariani, D.; Narindoshvili, T. *Chem. Biol. Drug Des.* **2009**, *73*, 618–626. (g) Katritzky, A. R.; Singh, A.; Haase, D. N.; Yoshioka, M. *Arkivoc* **2009**, *8*, 47–56.

(19) (a) Katritzky, A. R.; Abo-Dya, N. E.; Tala, S. R.; Ghazvini-Zadeh, E. H.; Bajaj, K.; El-Feky, S. A. *Synlett* **2010**, *9*, 1337–1340. (b) Katritzky, A. R.; Abo-Dya, N. E.; Tala, S. R.; Abdel-Samii, Z. K *Org. Biomol. Chem.* **2010**, *8*, 2316–2319. (c) Katritzky, A. R.; Tala, S. R.; Abo-Dya, N. E.; Gyanda, K.; El-Gendy, B. E-D. M.; Abdel-Samii, Z. K.; Steel, P. J. *J. Org. Chem.* **2009**, *74*, 7165–7167. (d) Katritzky, A. R.; Tala, S. R.; Abo-Dya, N. E.; Ibrahim, T. S.; El-Feky, S. A.; Gyanda, K.; Pandya, K. M. *J. Org. Chem.* **2011**, *76*, 85–96.

(20) Katritzky, A. R.; Avan, I.; Tala, S. R. *J. Org. Chem.* **2009**, *74*, 8690–8694.

(21) Davies, J. S.; Howe, J.; Le Breton, M. *J. Chem. Soc., Perkin Trans. 2.* **1995**, 2335–2339.

(22) Yagasaki, M; Hashimoto, S.-I. *Appl. Microbiol. Biotechnol.* **2008**, *81*, 13–22.

(23) Bauer, T.; Gajewiak, J. *Tetrahedron* **2004**, *60*, 9163–9170.

(24) Kim, H.-O.; Richard, K. O.; Choi, O.-S. *J. Org. Chem.* **1987**, *52*, 4531–4536.

(25) Yang, D.; Li, B.; Ng, F.-F.; Yan, Y.-L.; Qu, J.; Wu, Y.-D. *J. Org. Chem.* **2001**, *66*, 7303–73124.

(26) Lee, K. J.; Kim, D. H. *Bioorg. Med. Chem.* **1998**, *6*, 1613–1622.

(27) Seufert, W; Beck, Z. Q.; Sherman, D. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 9298–9300.