Antineoplastic Agents. 561. Total Synthesis of Respirantin[1a]

George R. Pettit,* Thomas H. Smith, Song Feng, John C. Knight, Rui Tan, Robin K. Pettit, and Peter A. Hinrichs

Cancer Research Institute and Department of Chemistry and Biochemistry, Arizona State University, P.O. Box 872404, Tempe, Arizona 85287-2404

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Total synthesis of the 18-membered ring cyclodepsipeptide believed to be respirantin (**1b**) has been achieved. The key step in the synthesis is an intramolecular transesterification of the β-ketoester alcohol **6** to afford the protected macrocycle **5**. The synthetic product was shown to be identical to a natural product presumed to be respirantin (**1b**), and the absolute stereochemistry of six of the seven asymmetric centers of cyclodepsipeptide **1b** was unequivocally established. Respirantin (**1b**) was found to be a remarkable inhibitor of cancer cell growth and related to the antimycin family of antibiotics.

In the preceding report, we summarized the isolation and structures of three exceptional cancer cell growth inhibitory cyclodepsipeptides from the bacterium *Kitasatospora* sp. found on the Beaufort Sea coast of the Alaska North Slope.[1a] One of these corresponded to a unique structure and was designated kitastatin 1 (**1a**) (Figure 1), while the other two cyclodepsipeptides on the basis of reported NMR assignments were presumed to be respirantin (**1b**) and a valeryl modification (**1c**).[1b]

Respirantin (**1b**) was first reported in 1993[1b] as an insecticidal antibiotic isolated from a *Streptomyces* species found in a soil sample from Japan and shown to have cyclodepsipeptide structure **1b** on the basis of analysis of its spectroscopic properties. The stereochemistry was not determined. Kitastatin 1 (**1a**) and respirantin (**1b**) contain a blastmycic acid unit also found in the antimycins[2] such as **2** and neoantimycin.[3] An unusual structural feature is the β-ketoester linkage (carbons 6−8) in the 18-membered depsipeptide macrocycle. In order to obtain sufficient material for more extensive biological evaluation as well as to determine the stereochemistry and absolute configuration of kitastatin 1 (**1a**) and respirantin (**1b**), we undertook research to develop a total synthesis of **1b** with flexibility to enable future SAR development. Herein we report the successful results.

Results and Discussion

Inspection of the kitastatin 1 (**1a**) and respirantin (**1b**) macrocycle revealed that they are composed of common amino acids, or α-hydroxycarboxylic acids derived from them, along with the β-ketoester unit. Since the absolute stereochemistry of **1a** and **1b** was undetermined at the onset of this study, our initial target **1b** was selected by assuming the most common *S*-configuration for the constituent amino acids and their presumed α-hydroxy derivatives. Fortunately, that proved to be the correct choice among the 256 possible optical isomers. A retrosynthetic analysis of the ultimately successful route to respirantin (**1b**) is presented in Scheme 1. Prior antimycin syntheses[2] offered good precedent for appending the protected benzoic acid **3** to amino-substituted macrocycles. However other issues that needed to be addressed in developing our approach to **1b** included introduction of the β-ketoester unit, selection of appropriate esterification and peptide bond forming methods, protecting-group strategy, and the method and site of its macrocyclic lactonization.

Our initial approach is outlined in Scheme 2, where β-ketoester **7**[4] represented a good starting material for incorporating carbons 6−9. Introduction of the *gem*-dimethyl groups was not trivial, but after some experimentation α,α-dimethyl ester **11** was obtained in reasonable yield. While β-ketoacids are well known to be susceptible to decarboxylation, carboxylic acid **12** was acquired via carefully controlled saponification. However all attempts to esterify **12** with alcohol **13**[5] were deflected by either decarboxylation to ketone **15** or intramolecular cyclization to the pyrrolidine-2,4-dione **16**. The method of choice for the preparation of complex β-ketoesters is via transesterification. However, as this reaction proceeds through a ketene intermediate,[6,7] ester **11** is not a suitable substrate. Nevertheless this approach was pursued in the belief that the introduction of the *gem*-dimethyl groups could be postponed until the needed β-ketoester linkage was formed. After extensive experimentation we were able to obtain ester **14** via reaction of ester **7** with excess alcohol **13** in refluxing cyclohexane[8] in the presence of a catalytic amount of activated zinc.[9] However the modest yield and the need for excess alcohol **13** limited this approach. A timely report[10] describing a high-yield intramolecular β-ketoester transesterification used to form a 15-membered macrocycle seemed to not only address the troublesome formation of the required β-ketoester linkage but also simplify projected functional group manipulations needed for macrocycle formation.

The initial approach designed to utilize the intramolecular β-ketoester transesterification method of macrocyclization is outlined in Scheme 3. The diester **20** was obtained via reaction of the acid chloride derived from silyl ester **18** under neutral conditions[11,12] with alcohol **19**.[5] Selective hydrolytic cleavage of methyl ester **20** could not be achieved, as extensive cleavage of the internal ester linkage occurred. The desired carboxylic acid **21** was obtained via nucleophilic alkyl cleavage with LiI in pyridine.[13] Formation of the amide linkage leading to amide **22** proved to be problematic. Reaction of carboxylic acid **21** with the amine derived from TFA deprotection of Boc-protected **7** under a variety of peptide coupling procedures (BOP,[14] PyBroP,[15] DEPC[16]) afforded at best low yields of amide **22** along with the pyrazine **24**. The formation of **24** can be explained by dimerization of the amine free base via Schiff base formation followed by oxidative aromatization. Subsequent experimentation revealed that while the trifluoroacetate salt of the parent amine from **7** could be isolated, we were not able to isolate the corresponding free base. In attempts to prepare amide **22**, dimerization of the free base occurred in preference to reaction with the activated carboxylic acid **21**. To avoid this problem a solution of the TFA salt in DCM was added to a solution of **21**, PyBroP, and 3 equiv of DIPEA in DCM. By this method, the free base was generated only in the presence of excess activated carboxylic acid, and a reasonable yield of amide **22** was reproducibly obtained.

Deprotection of amide **22** was also nontrivial. Standard TBAF treatment afforded a fairly complex mixture, of which the desired alcohol **23** was the major component. Better results were obtained using $BF_3 \cdot Et_2O$,[17] which provided alcohol **23** cleanly and in high yield. Condensation of **23** with carboxylic acid **25**[18] mediated with 2-methyl-6-nitrobenzoic anhydride (MNBA)[19] afforded ester **26** in

* To whom correspondence should be addressed. Tel: (480) 965-3461. Fax: (480) 965-2747. E-mail: bpettit@asu.edu.

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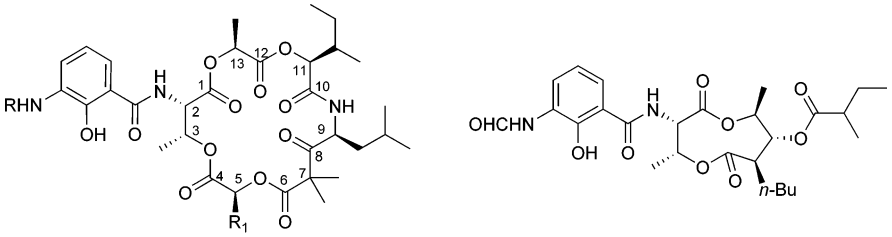
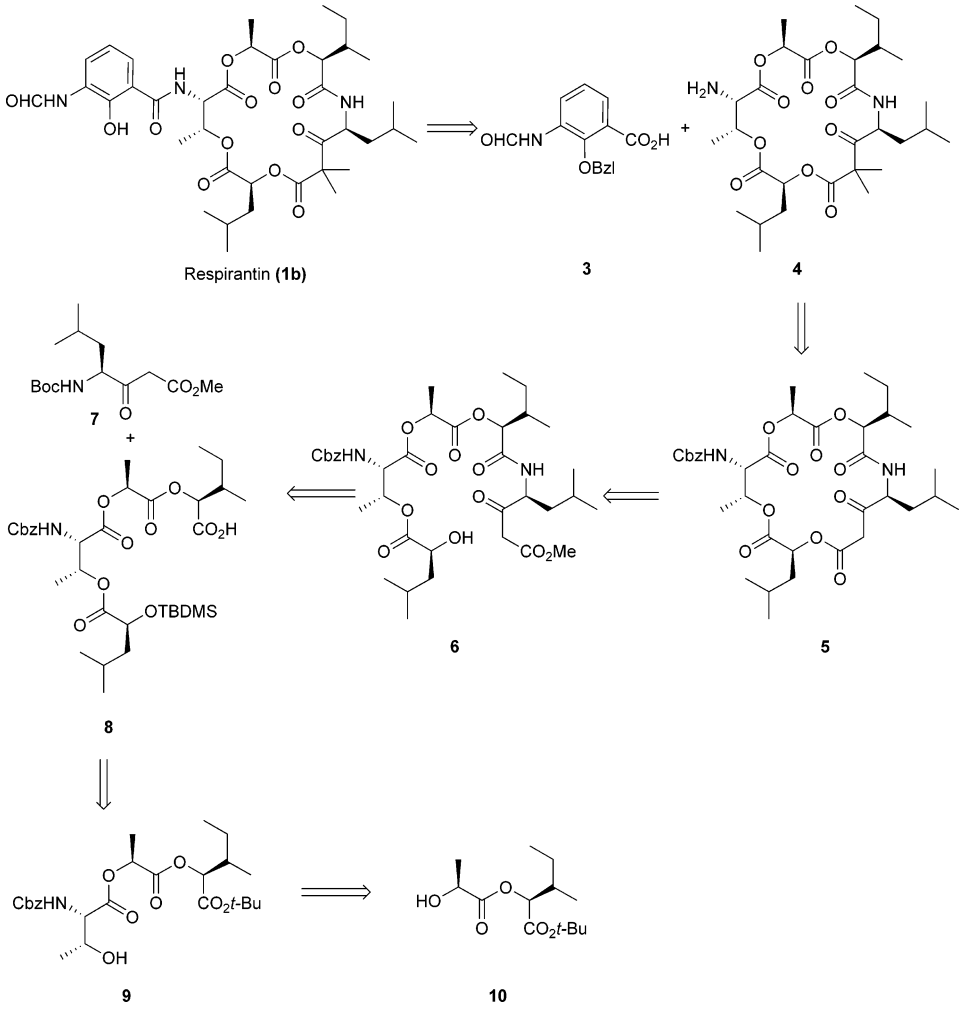


1a R = H, R_1 = $CH_2CH(Me)_2$
1b R = CHO, R_1 = $CH_2CH(Me)_2$
1c R = CHO, R_1 = $CH(Me)_2$

2

Figure 1. Kitastatin, respirantin, and valeryl modification and (+)-antimycin A_{3b}.

Scheme 1. Retrosynthetic Analysis of Respirantin

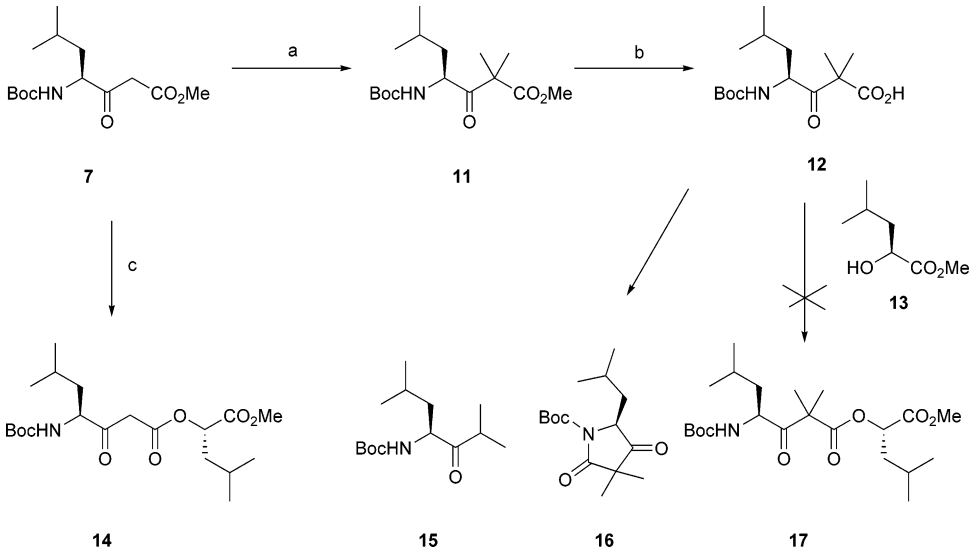


a reasonable yield. Desilylation of **26** using the $BF_3{\cdot}Et_2O$ procedure cleanly provided a 1:1 mixture of isomeric alcohols **27** and **28**. The spectroscopic and analytical properties of both were consistent with the expected product and characterized as **27**−**28**, a mixture of diastereomers arising from racemization of the carbon bearing the terminal hydroxyl.

An explanation for the epimerization evident during the deprotection of silyl ether **26** remains obscure. Model studies (Scheme 4) did not indicate evidence of any obvious problem. The epimerization problem and the somewhat variable results in the presence of the β-ketoester suggested that the presence of this potentially base labile moiety could be a problem and that delaying its introduction should be beneficial. Concurrently additional model studies indicated another area of concern. The C1−5 fragment **34** was prepared by condensation of the acid chloride derived from silyl ester **32**[20] and alcohol **33**[21] with a view toward increasing the convergency of the synthesis. However, efforts to deprotect either the carboxyl (mild base or LiI/pyridine) or the hydroxyl (TBAF) groups led to β-elimination of the leucic acid moiety, leading to olefin **36** as the major product (Scheme 5). These results introduced additional constraints upon the reagents available for this synthetic approach. The desired desilylated alcohol **35** was eventually obtained by $BF_3{\cdot}Et_2O$ deprotection.

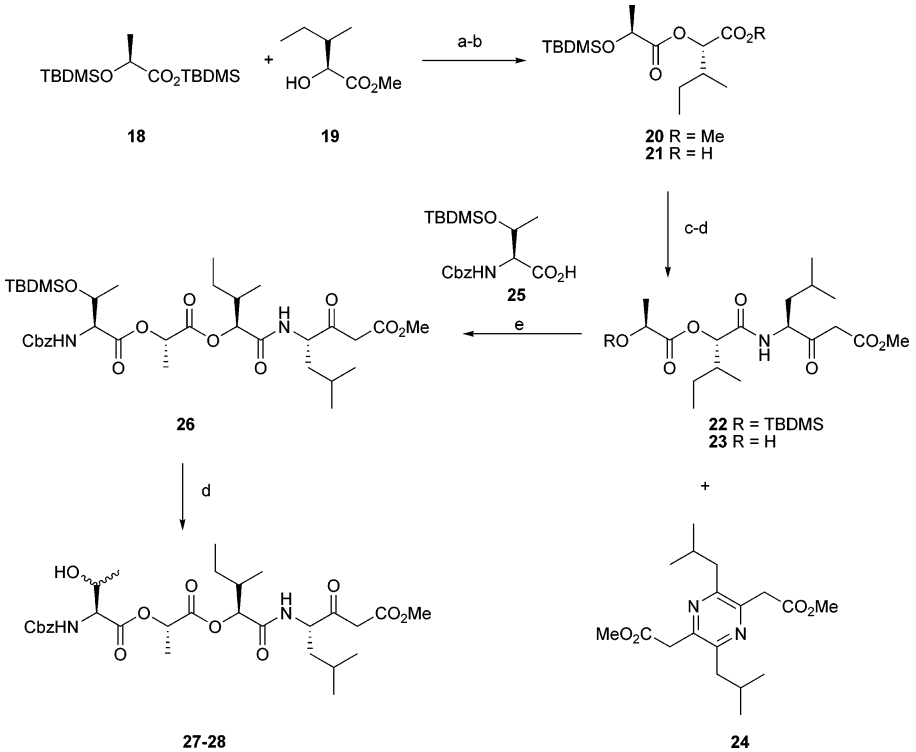
With these results in mind we embarked on the ultimately successful route to respirantin. Scheme 6 outlines our approach to the respirantin macrocyclic lactone **5**. Condensation of the acid chloride derived from **18** with alcohol **37**[22] provided ester **38**. The *tert*-butyl ester was chosen for carboxyl protection due to the lability of the leucic acid portion to the conditions required for methyl ester cleavage. Desilylation with TBAF followed by MNBA-mediated condensation of the resulting alcohol **10** with carboxylic acid **25** provided ester **39** and ultimately alcohol **9** following TBAF

Scheme 2[a]



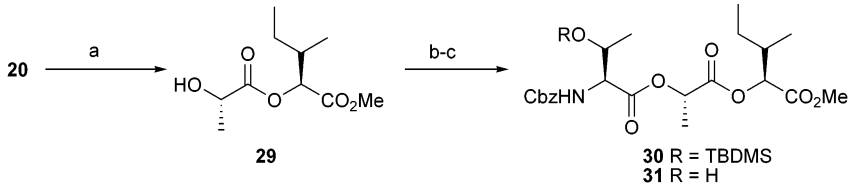
[a] Reagents and conditions: (a) K_2CO_3, MeI, DMSO, 23 °C, 48 h, 65%; (b) KOH, aq CH_3OH, 23 °C, 0.25 h, 81%; (c) **13**, Zn, cyclohexane, 80 °C, 33%.

Scheme 3[a]



[a] Reagents and conditions: (a) (i) Oxalyl chloride, catalytic DMF, DCM, 0−23 °C, 2 h; (ii) **19**, pyridine, 23 °C, 16 h, 75%; (b) LiI, pyridine, 110 °C, 40 h, 89%; (c) (i) **7**, 1:1 TFA−DCM, 0.5 h; (ii) PyBroP, DIPEA, DCM, product from (i), 4 h, 65%; (d) $BF_3{\cdot}Et_2O$, DCM, 0.5 h, 87% for **23,** 83% for **27**−**28**; (e) **25**, MNBA, DMAP, TEA, DCM, 23 °C, 16 h, 77%.

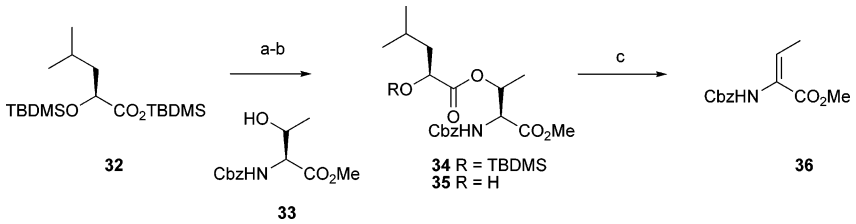
Scheme 4[a]



[a] Reagents and conditions: (a) TBAF, THF, 0 °C, 1 h, 85%; (b) **25**, MNBA, DMAP, TEA, DCM, 23 °C, 16 h, 75%; (c) $BF_3{\cdot}Et_2O$, DCM, 23 °C, 1.5 h, 92%.

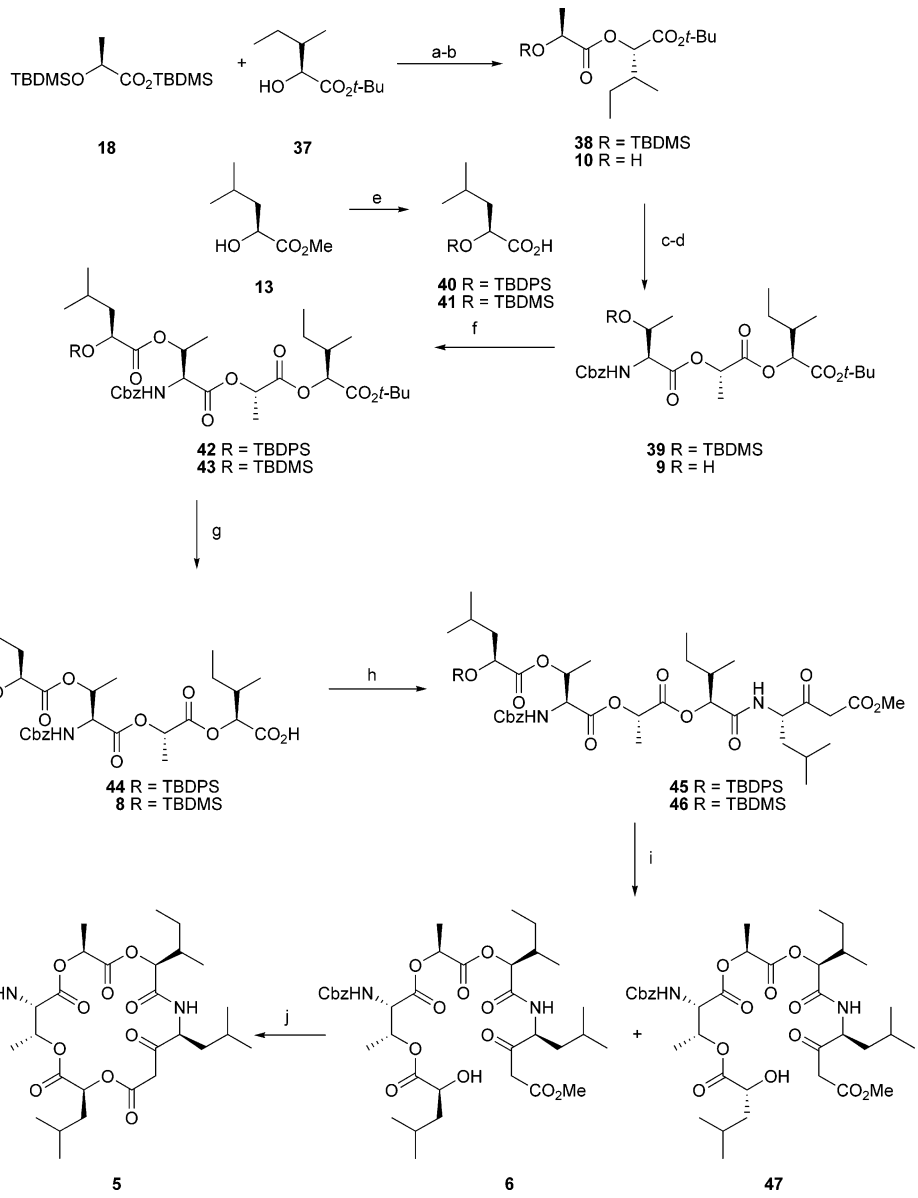
deprotection. Anticipating the need for acidic conditions to achieve deprotection of the *tert*-butyl ester, it was considered prudent to utilize the more stable TBDPS protecting group rather than the usual TBDMS group for the terminal hydroxyl protection. Condensation of carboxylic acid **40** (available from ester **13**)[5] with alcohol **9** using the MNBA procedure provided tetraester **42**. Cleavage of the *tert*-

Scheme 5[a]



[a] Reagents and conditions: (a) (i) oxalyl chloride, catalytic DMF, DCM, 0−23 °C, 2 h; (ii) **33**, pyridine, 23 °C, 16 h, 55%; (b) $BF_3{\cdot}Et_2O$, DCM, 23 °C, 1 h, 51%; (c) K_2CO_3, aqueous CH_3OH or TBAF.

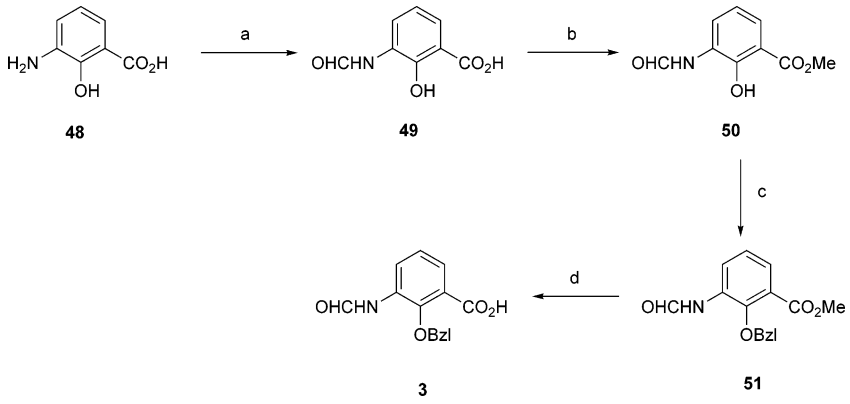
Scheme 6[a]



[a] Reagents and conditions: (a) (i) oxalyl chloride, catalytic DMF, DCM, 0−23 °C, 2 h; (ii) **37**, pyridine, 23 °C, 16 h, 81%; (b) TBAF, THF, 23 °C, 1 h, 100%; (c) **25**, MNBA, DMAP, TEA, DCM, 23 °C, 16 h, 87%; (d) TBAF, THF, 23 °C, 1 h, 100%; (e) (i) TBDPSCl or TBDMSCl, imidazole, DMF, 23 °C, 16 h; (ii) LiOH, aq THF/CH_3OH, 0−23 °C, 24 h, 80% for **40**, 85% for **41**; (f) **40** or **41**, MNBA, DMAP, TEA, DCM, 23 °C, 16 h, 85% for **42**, 83% for **43**; (g) $ZnBr_2$, DCM, 23 °C, 24 h, 80% for **44**; SiO_2, toluene, 110 °C, 4 h, 59% for **8**; (h) (i) **7**, 1:1 TFA−DCM, 0.5 h; (ii) PyBroP, DIPEA, DCM, product from (i), 4 h, 52% for **45**, 65% for **46**; (i) CH_3OH, AcCl, 0.5 h, 63%; (j) toluene, anhydrous $CuSO_4$, 125 °C, 4 h, 80%.

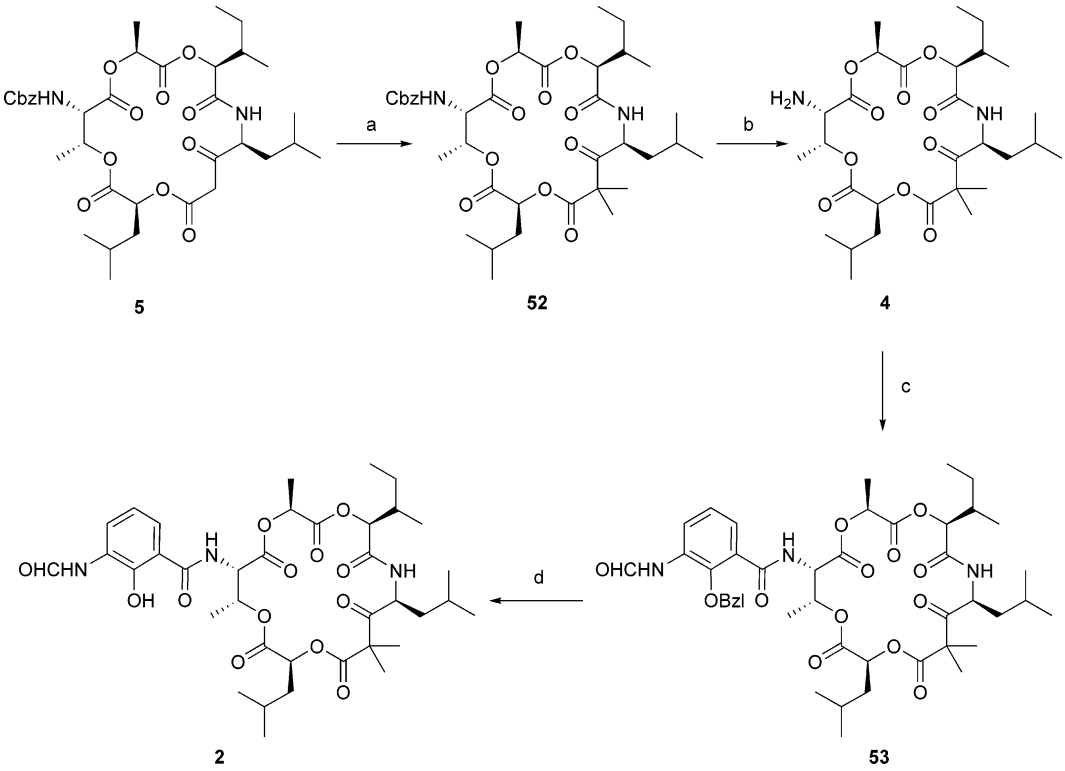
butyl group was achieved with $ZnBr_2$ in DCM,[23] providing carboxylic acid **44**, which was coupled with the amine derived from β-ketoester **7** employing the PyBroP coupling procedure previously described to afford amide **45**. At this point we were challenged by attempts to remove the TBDPS group, which resulted in eliminating the leucic acid unit. For example, amide **45** was inert to $BF_3{\cdot}Et_2O$ at ambient temperature, as well as several other acidic reagents, and TBAF caused the expected elimination of the leucic acid residue. Consequently, we chose to proceed with a MNBA-promoted coupling of alcohol **9** with carboxylic acid **41** to provide ester **43**. To achieve good results with this esterfication, it was necessary to use freshly prepared acid **41**. Apparently the acidity

Scheme 7[a]



[a] Reagents and conditions: (a) formamide, 150 °C, 0.5 h, 100%;[27] (b) MeI, $NaHCO_3$, DMF, 23 °C, 18 h, 83%;[28] (c) BzlBr, K_2CO_3, DMF, 60 °C, 18 h, 95%;[29] (d) LiOH, aq Thf/CH_3OH, 23 °C, 18 h, 79%.

Scheme 8[a]



[a] Reagents and conditions: (a) MeI, K_2CO_3, DMSO, 23 °C, 3 h, 28%; (b) H_2, Pd/C, EtOAc, 23 °C, 2 h, 73%; (c) **3**, EDCI, HOBt, NMM, DMF, 23 °C, 11 h, 61%; (d) H_2, Pd/C, EtOAc, 23 °C, 2 h, 82%.

of **41** is sufficient to cause decomposition to the corresponding α-hydroxy acid. As anticipated, cleavage of the *tert*-butyl ester in the presence of the TBDMS group proved to be problematic. The $ZnBr_2$ procedure successful with silyl ether **42** resulted in simultaneous cleavage of the TBDMS group and the *tert*-butyl ester. Selective carboxyl deprotection was achieved by treatment of *tert*-butyl ester **43** with flash silica gel[24] in refluxing toluene to afford **8**. PyBroP-promoted condensation of **8** with the amine derived from *β*-ketoester **7** provided the key intermediate ester **46**. Desilylation once again proved to be a nontrivial operation. Similar to the results observed with silyl ether **26**, reaction of silyl ether **46** with $BF_3 \cdot Et_2O$ afforded a 1:1 mixture of compounds with spectral and analytical properties consistent with epimeric alcohols **6** and **47**. Better results were obtained by effecting desilylation using acetyl chloride in CH_3OH,[25] which provided predominantly a single product. While we were unable to unequivocally distinguish between epimers **6** and **47** for the desilylation product, we tentatively assigned isomer **6** as the structure for the predominant product. The stage was now set for the key macrocyclization step. Gratifyingly, treatment of alcohol **6** in refluxing toluene[10] in the presence of catalytic anhydrous $CuSO_4$[26] smoothly afforded macrocyclic lactone **5**.

The synthesis of the aromatic synthon **3** was achieved in four steps from the commercially available intermediate **48** as outlined in Scheme 7. The completion of the synthesis is outlined in Scheme 8. Introduction of the *gem*-dimethyl groups at C7 (**5** → **52**) was problematic. Insertion of one methyl group occurred readily, while addition of the second methyl group to afford lactone **52** was more difficult and occurred in only a modest yield. Hydrogenolysis of the Cbz protecting group afforded amine **4**, which was condensed with benzoic acid **3** employing EDCI to provide amide **53**. Removal (hydrogenolysis) of the benzyl ether protecting group provided the cyclodepsipeptide presumed on the basis of spectroscopic data to be respirantin (**1b**). The synthetic specimen of cyclodepsipeptide (**1b**) was found to be identical with the natural product **1b**. The

Table 1. Comparison of the Cancer Cell Growth Inhibition (GI_{50}, μg/mL) of Kitastatin 1 (**1a**), Respirantin (**1b**), and the Valeryl Analogue **1c** against a Panel of Murine (P388, Lymphocytic Leukemia) and Human Cancer Cell Lines

compound	leukemia P388	pancreas BXPC-3	breast MCF-7	CNS SF268	lung-NSC NCI-H460	colon KM20L2	prostate DU-145
1a	0.045	0.0066	0.004	0.0035	<0.001	0.0024	0.0026
1b	0.0037	0.47	0.0006	0.0016	0.0006	0.0006	0.00018
1c	0.033	1.2	0.00062	0.016	0.00063	0.00058	<0.0001

spectral properties (^{1}H, ^{13}C NMR, IR, HRMS) of **1b** matched perfectly with the published values for respirantin.[1b]

The absolute stereochemistry of depsipeptide **1b** at carbons 2, 3, 9, 11, and 13 follows from the chirality of the starting materials. Presumably, the 2(*S*),3(*R*)-stereochemistry of natural threonine and the 2(*S*),3(*S*)-stereochemistry of natural isoleucine have been retained in the biosynthesis of kitastatin 1 (**1a**) and respirantin (**1b**). In accord with that assumption, C-5 was tentatively assigned the *R*-configuration (cf. **1b**), as the synthetic and natural specimens were identical. The modular nature of this approach should offer ready access to the scale-up synthesis of respirantin, kitastatin, and a variety of structural modifications to develop structure−activity relationships in this interesting class of powerful cancer cell growth inhibitors.

Kitastatin 1 (**1a**), respirantin (**1b**), and the valeryl analogue **1c** were evaluated as inhibitors of cancer cell growth versus the murine P388 leukemia cell line[30] and a panel of human cancer cell lines.[31] The data are reported in Table 1. All three compounds displayed an impressive spectrum of activity. An interesting observation was the substantially better activity of kitastatin 1 (**1a**) against the pancreas BXPC-3 human cancer cell line relative to the other panel members. Whether this indicates a special selectivity against this cancer is a question that must be explored. Pancreatic cancer is one of the most deadly types and is notoriously refractory to current modes of treatment. In addition to the human cancer cell line activity cyclodepsipeptide **1b** had activity against the pathogenic fungus *Cryptococcus neoformans* (minimum inhibitory activity, MIC = 2).[1a]

Experimental Section

General Experimental Procedures. Solvents were redistilled prior to use. Reagents were used as received. MNBA was obtained from TCI America. Thin-layer chromatography (TLC) was carried out with Analtech 250 μm thick silica gel GHLF plates and visualized with H_2SO_4, phosphomolybdic acid, iodine, or UV. Organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure using a rotary evaporator. The crude products were separated by flash column chromatography on flash (230−400 mesh ASTM) silica from E. Merck.

Melting points are uncorrected and were determined employing an Electrothermal Mel-Temp apparatus. Optical rotations were measured using a Perkin-Elmer 241 polarimeter. The $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. IR spectra were obtained with a Thermo Nicolet Avatar 360 FT-IR instrument equipped with a single reflection horizontal ATR sampling device from PIKE Technologies. HRMS data were recorded with a JEOL LCmate mass spectrometer. The ^{1}H and ^{13}C spectra were recorded employing Varian Gemini 300, Varian Unity 400, or Varian Unity 500 instruments in $CDCl_3$ unless otherwise noted and were referenced to either TMS or the solvent. Elemental analyses were determined by Galbraith Laboratories, Inc., Knoxville, TN.

Methyl 4-(*tert*-Butoxycarbonyl)amino-2,2,6-trimethyl-3-oxoheptanoate (11). Ketone **7** (0.47 g, 1.63 mmol), K_2CO_3 (2.26 g, 16.3 mmol), and MeI (0.31 mL, 0.71 g, 4.98 mmol) were placed in DMSO (7 mL) under N_2 and stirred at ambient temperature for 48 h. The reaction mixture was diluted with H_2O (30 mL) and extracted with Et_2O (3 × 20 mL). The extracts were combined, washed with H_2O (10 mL) and 5 M NaCl (5 mL), dried, and evaporated. The residue was flash chromatographed (15 g, SiO_2, 95:5 hexane−EtOAc) to afford 0.34 g (65%) of ketone **11** as a colorless oil: TLC R_f 0.63 (4:1 hexane−EtOAc); IR 3377, 1705 cm^{-1}; ^{1}H NMR δ (4.78 1H, br d), 4.65 (1H, m), 3.73 (3H, s), 1.70 (1H, m), 1.43 (17H, m), 0.95 and 0.92 (6H, 2 d, J = 6.6 Hz); ^{13}C NMR δ 208.7, 173.5, 155.0, 79.7, 54.7, 53.8, 52.5, 41.8, 28.3, 24.6, 23.5, 22.2, 22.0, 21.33.

4-(*tert*-Butoxycarbonyl)amino-2,2,6-trimethyl-3-oxoheptanoic Acid (12). To ester **11** (65.7 mg, 0.21 mmol) in CH_3OH (0.35 mL) under N_2 was added 3.5 N KOH (0.25 mL, 0.88 mmol) and the solution stirred at ambient temperature for 15 min. The reaction mixture was diluted with H_2O (15 mL) and washed with Et_2O (2 × 15 mL). The aqueous layer was acidified (pH 2) with 1 N H_2SO_4 and extracted with Et_2O (3 × 15 mL). The combined extract was washed with H_2O (5 mL) and 5 M NaCl (5 mL), dried, and evaporated to afford 50.8 mg (81%) of **12** as a viscous oil, which solidified on standing: mp 121 °C; TLC R_f 0.52 (95:5:1 DCM−CH_3OH−HOAc); IR 3268, 1714, 1655 cm^{-1}; ^{1}H NMR (d_6-DMSO) δ 7.05 (1H, d, J = 9 Hz), 4.51 (1H, td, J = 9, 7 Hz), 1.87 (1H, m), 1.38 (9H, s), 1.34 (3H, s), 1.26 (4H, s and m), 0.99 (1H, dd, J = 9, 7 Hz), 0.87 (6H, d); ^{13}C NMR (d_6-DMSO) δ 214.1, 155.5, 78.0, 56.8, 38.3, 35.3, 28.1, 23.0, 21.1, 18.7, 18.2; *anal.* C 60.12%, H 9.27%, N 4.68%, calcd for $C_{15}H_{27}NO_5$, C 59.78%, H 9.03%, N 4.65%.

1-Methoxycarbonyl-3-methylbutyl 4-*tert*-Butoxycarbonylamino-6-methyl-3-oxoheptanoate (14). Ketone **7** (0.274 g, 0.95 mmol), alcohol **13** (0.17 g, 1.13 mmol), and activated Zn (30 mg, 0.46 mmol) were placed in cyclohexane (4 mL) under N_2 and heated at reflux for 16 h with a Dean−Stark separator. Additional **13** (0.17 g, 1.13 mmol) in cyclohexane (1 mL) was added, and heating at reflux continued for 24 h. The solution was diluted with EtOAc (40 mL), filtered through Celite, washed with 6% $NaHCO_3$ (3 × 10 mL), H_2O (10 mL), and 5 M NaCl (10 mL), dried, and evaporated to give 0.38 g of a pale yellow oil. This was flash chromatographed (10 g, SiO_2, 93:7 hexane−EtOAc) to afford 0.127 g (33%) of ester **14** as a colorless oil: TLC R_f 0.50 (4:1 hexane−EtOAc); IR 3368, 1751, 1712 cm^{-1}; ^{1}H NMR δ 5.48 (1H, br d), 5.08 (1H, m), 4.28 (1H, br t), 3.77 and 3.46−3.80 (5H, s and m), 1.56−1.82 (6H, m), 1.45 (9H, s), 0.95 (12H, m); ^{13}C NMR δ 203.3, 171.1, 166.2, 155.8, 79.8, 71.6, 58.5, 52.4, 46.1, 39.7, 39.6, 28.2, 24.7, 24.4, 23.2, 22.8, 21.4, 21.3; *anal.* C 59.88%, H 9.02%, N 3.49%, calcd for $C_{20}H_{35}NO_7$, C 59.83%, H 8.79%, N 3.49%.

Methyl 2-[2-(*tert*-Butyldimethylsilyl)oxypropionyloxy]-3-methylpentanoate (20). Silyl ether **18** (3.23 g, 10.16 mmol) was dissolved in CH_2Cl_2 (10 mL) containing DMF (280 μL, 0.26 g, 3.62 mmol) under N_2 and cooled to 0 °C. Oxalyl chloride (5.6 mL of a 2 M solution in CH_2Cl_2, 11.2 mmol) was added dropwise over 5 min. The solution was stirred at 0 °C for 1.5 h and at ambient temperature for 0.5 h. The solvent was evaporated. To the residue was added dropwise a solution of alcohol **19** (1.27 g, 8.71 mmol) in pyridine (5 mL). The solution was stirred under N_2 for 16 h, diluted with THF (100 mL), and filtered through Celite. The filtrate was evaporated, and the residue was partitioned between EtOAc (200 mL) and H_2O (20 mL). The organic phase was separated, washed with H_2O (20 mL), 6% $NaHCO_3$ (2 × 30 mL), H_2O (20 mL), and 5 M NaCl (10 mL), dried, and evaporated. The residue was flash chromatographed (90 g, SiO_2, 96:4 hexane−EtOAc) to yield 2.16 g (75%) of ester **20**: TLC R_f 0.37 (95:5 hexane−EtOAc); IR 1757 cm^{-1}; ^{1}H NMR δ 4.93 (1H, d, J = 4.8 Hz), 4.41 (1H, q, J = 6.6 Hz), 3.72 (3H, s), 2.01 (1H, m), 1.45 (3H, d), 1.33 (2H, m), 0.97 (3H, d), 0.92 (3H, t), 0.91 (9H, s), 0.11 and 0.09 (6H, 2s); ^{13}C NMR δ 179.1, 175.2, 81.7, 73.4, 57.3, 41.9, 31.0, 29.9, 26.7, 23.6, 20.6, 16.8, 0.4, 0.0; *anal.* C 58.07%, H 9.87%, calcd for $C_{16}H_{32}O_5Si$, C 57.79%, H 9.70%.

2-[2-(*tert*-Butyldimethylsilanyloxy)propionyloxy]-3-methylpentanoic Acid (21). Ester **20** (1.01 g, 3.04 mmol) and LiI (1.24 g, 9.25 mmol) were placed in pyridine (8.0 mL) under N_2 and stirred at 105 °C for 40 h. The reaction mixture was allowed to cool, diluted with toluene (30 mL), evaporated, and coevaporated with toluene (20 mL). The residue was diluted with H_2O (50 mL), acidified (pH 4) with $KHSO_4$, and extracted with EtOAc (3 × 30 mL). The extracts were combined, washed with 10% $Na_2S_2O_3$ (10 mL), H_2O (10 mL), and 5 M NaCl (10 mL), dried, and evaporated. The residue was flash chromatographed (30 g, SiO_2, 99:1:0.5 DCM−CH_3OH−HOAc) to provide 0.86 g (89%) of carboxylic acid **21** as a pale yellow oil: TLC

R_f 0.58 (95:5:1 DCM−CH_3OH−HOAc); IR 1726 cm^{-1}; ^1H NMR δ 4.98 (1H, d, $J = 4.4$ Hz), 4.42 (1H, q, $J = 7.6$ Hz), 2.04 (1H, m), 1.56 (1H, m), 1.45 (3H, d, $J = 6.6$ Hz), 1.37 (1H, m), 1.01 (3H, d, $J = 7.2$ Hz), 0.94 (3H, t, $J = 7.1$ Hz), 0.91 (9H, s), 0.11 and 0.08 (6H, 2s); ^{13}C NMR δ 175.3, 173.8, 75.9, 68.1, 36.5, 25.7, 24.4, 21.3, 18.2, 15.3, 11.5, −5.0, −5.4.

Methyl 4-{2-[2-(*tert*-Butyldimethylsilyloxy)propionyloxy]-3-methylpentanoylamino}-6-methyl-3-oxoheptanoate (22). Ketone **7** (0.88 g, 3.05 mmol) was placed in 1:1 TFA−DCM (12.0 mL) under N_2 and stirred at ambient temperature for 1 h. The solvent was removed and the residue coevaporated with toluene (2 × 10 mL). Carboxylic acid **21** (0.88 g, 2.76 mmol) and PyBroP (1.29 g, 2.76 mmol) in DCM (6.0 mL) under N_2 was cooled to 0 °C. Diisopropylethylamine (1.07 g, 1.4 mL, 8.28 mmol) was added over 5 min. The residue from the TFA cleavage reaction was dissolved in DCM (10 mL) and added over 15 min. The solution was stirred at 0 °C for 4.5 h. The reaction mixture was diluted with EtOAc (100 mL), washed with 5% citric acid (2 × 10 mL), H_2O (10 mL), 6% $NaHCO_3$ (2 × 10 mL), H_2O (10 mL), and 5 M NaCl (10 mL), dried, and evaporated. The residue was flash chromatographed (60 g, SiO_2, 90:10 → 80:20 hexane−EtOAc) to afford 0.88 g (65%) of amide **22** as a yellow oil: TLC R_f 0.39 (4:1 hexane−EtOAc); IR 3341, 1750, 1665 cm^{-1}; ^1H NMR δ 11.98 (0.1H, s), 6.46 (1H, d, $J = 7.5$ Hz), 5.14 (1H, d, $J = 4.5$ Hz), 4.72 (1H, m), 4.43 (1H, q), 3.86 (0.5H, s), 3.72 (3H, s), 3.57 (1H, d, $J = 16.5$ Hz), 3.49 (1H, d, $J = 15.3$ Hz), 2.04 (1H, m), 1.65 (2H, m), 1.46 (6H, m and d), 1.26 (1H, m), 0.91 (21H, m), 0.12 and 0.10 (6H, 2 d); ^{13}C NMR δ 201.5, 172.8, 169.1, 167.2, 89.5, 77.6, 68.3, 56.3, 52.4, 46.1, 39.7, 37.0, 25.7, 24.8, 24.2, 23.2, 22.4, 21.4, 21.3, 18.1, 14.9, 11.4, −4.9, −5.2; MS APCI$^+$ 488.30444 $[M + H]^+$, calcd 488.3044; *anal.* C 58.94%, H 9.54%, N 2.94%, calcd for $C_{24}H_{45}NO_7Si$, C 59.11%, H 9.30%, N 2.87%.

Methyl 4-[2-(2-Hydroxypropionyloxy)-3-methylpentanoylamino]-6-methyl-3-oxoheptanoate (23). To amide **22** (0.51 g, 1.04 mmol) in DCM (30 mL) under N_2 was added $BF_3{\cdot}Et_2O$ (1.42 g, 1.27 mL, 10 mmol) and the solution stirred at ambient temperature for 2 h. The solution was poured into 6% $NaHCO_3$−ice (100 mL). The organic phase was separated and the aqueous phase extracted with DCM (40 mL). The combined organic extract was washed with 6% $NaHCO_3$ (30 mL), H_2O (20 mL), and 5 M NaCl (20 mL), dried, and evaporated. The residue was flash chromatographed (15 g, SiO_2, 60:40 hexane−EtOAc) to give 0.34 g (87%) of carboxylic acid **23** as a colorless oil: TLC R_f 0.34 (50:50 hexane−EtOAc); ^1H NMR δ 12.02 (0.1H, enolic H, s), 6.53 (1H, d, $J = 8.2$ Hz), 5.14 (1H, d, $J = 4.9$ Hz), 4.72 (1H, m), 4.40 (1H, m), 3.74 (3H, s), 3.60 (1H, d, $J = 16$ Hz), 3.50 (1H, d, $J = 16$ Hz), 2.95 (1H, d, $J = 5.5$ Hz), 2.05 (1H, m), 1.61 (2H, m), 1.50 (4H, d and m, $J = 7.1$ Hz), 1.28 (1H, m), 0.95 (12H, m); ^{13}C NMR δ 201.6, 174.4, 168.7, 167.4, 78.5, 67.1, 56.5, 52.6, 46.2, 40.0, 37.0, 25.0, 24.3, 23.7, 21.5, 20.2, 15.0, 11.4; FABMS 374.2189 $[M + H]^+$, calcd 374.2179; *anal.* C 57.16%, H 8.56%, N 3.70%, calcd for $C_{18}H_{31}NO_7{\cdot}0.2H_2O$, C 57.33%, H 8.41%, N 3.71%.

Methyl (3,6-Diisobutyl-5-methoxycarbonylmethylpyrazin-2-yl)-acetate (24). Ketone **7** (0.28 g, 0.97 mmol) was placed in 1:1 TFA−DCM (4.0 mL) under N_2 and stirred at ambient temperature for 45 min. The solvent was evaporated and the residue coevaporated with toluene (2 × 10 mL). The residue was dissolved in DCM (3.0 mL) and cooled to 0 °C. TEA (0.41 mL, 293.3 mg, 2.91 mmol) was added dropwise and the solution stirred at 0 °C for 4 h. The reaction mixture was diluted with EtOAc (50 mL), washed with 5% citric acid (2 × 10 mL), H_2O (10 mL), 6% $NaHCO_3$ (2 × 10 mL), H_2O (10 mL), and 5 M NaCl (10 mL), dried, and evaporated. The residue was flash chromatographed (10 g, SiO_2^-, 95:5 → 90:10 hexane−EtOAc) to afford 78.2 mg (49%) of **24** as a pale yellow solid, which was recrystallyzed from hexane (1 mL): TLC R_f 0.34 (4:1 hexane−EtOAc); mp 72−74 °C; IR 1734 cm^{-1}; ^1H NMR δ 3.87 (4H, s), 3.70 (6H, s), 2.61 (4H, d, $J = 7.1$ Hz), 2.14 (2H, m), 0.92 (12H, d); ^{13}C NMR δ 170.6, 151.7, 146.2, 52.1, 42.6, 40.6, 28.2, 22.4; *anal.* C 63.82%, H 8.52%, N 8.20%, calcd for $C_{18}H_{28}N_2O_4$, C 64.26%, H 8.39%, N 8.33%.

Methyl 4-(2-{2-[2-Benyloxycarbonylamino-3-(*tert*-butyldimethylsilyloxy)butyryloxy]propionyloxy}-3-methylpentanoylamino)-6-methyl-3-oxoheptanoate (26). Carboxylic acid **25** (0.26 g, 0.72 mmol), alcohol **23** (241.2 mg, 0.65 mmol), MNBA (0.25 g, 0.73 mmol), DMAP (20.0 mg, 0.16 mmol), and TEA (0.30 mL, 0.22 g, 2.13 mmol) were placed in DCM (3.5 mL) under N_2 and stirred at ambient for 16 h. The reaction mixture was diluted with EtOAc (50 mL), washed with H_2O (10 mL), 6% $NaHCO_3$ (2 × 10 mL), H_2O (10 mL), 5% citric acid (2 × 10 mL), H_2O (10 mL), and 5 M NaCl (10 mL), dried, and evaporated. The residue was flash chromatographed (15 g, SiO_2, 85:15 hexane−EtOAc) to yield 0.36 g (77%) of ester **26** as a colorless oil, which crystallized on standing: mp 84−86 °C; TLC R_f 0.22 (4:1 hexane−EtOAc); ^1H NMR δ 7.37 (5H, m), 6.94 (1H, d, $J = 8.3$ Hz), 5.47 (1H, d, $J = 9.4$ Hz), 5.16 (4H, m), 4.67 (1H, m), 4.48 (1H, q), 4.27 (1H, m), 3.72 (3H, s), 3.52−3.62 (2H, m), 2.00 (1H, m), 1.63 (2H, m), 1.53 (4H, d and m, $J = 7.1$ Hz), 1.25 (5H, m), 0.93 (12H, m), 0.84 (9H, s), 0.06 and −0.01 (6H, 2 s); ^{13}C NMR δ 202.0, 171.7, 168.9, 168.8, 167.5, 156.7, 136.2, 128.6, 128.3, 128.0, 78.5, 70.0, 68.7, 67.1, 60.2, 56.4, 52.3, 45.9, 38.8, 37.1, 25.6, 24.7, 24.2, 23.3, 21.2, 21.1, 17.8, 16.9, 14.8, 11.4, −4.4, −5.4; MSFAB$^+$ 723.3890 (M + H), calcd 723.3889; *anal.* C 59.95%, H 8.44%, N 3.91%, calcd for $C_{36}H_{58}N_2O_{11}Si$, C 59.81%, H 8.09%, N 3.87%.

Methyl 4-{2-[2-(2-Benzyloxycarbonylamino-3-hydroxybutyryloxy)propionyloxy]-3-methylpentanoylamino}-6-methyl-3-oxoheptanoate (27, 28). To silyl ether **26** (0.73 g, 1.02 mmol) in DCM (30 mL) under N_2 was added $BF_3{\cdot}Et_2O$ (1.44 g, 1.3 mL, 10.2 mmol) and the solution stirred at ambient temperature for 1.5 h. The solution was poured into 6% $NaHCO_3$−ice (100 mL). The organic phase was separated and the aqueous phase extracted with DCM (50 mL). The combined extract was washed with 6% $NaHCO_3$ (30 mL), H_2O (20 mL), and 5 M NaCl (20 mL), dried, and evaporated. The residue was flash chromatographed (20 g, SiO_2, 70:30 hexane−EtOAc) to afford 0.155 g (25%) of alcohol **27** as a single isomer: TLC R_f 0.62 (50:50 hexane−EtOAc); ^1H NMR δ 12.11 (0.1H, enolic H, s), 7.35 (5H, m), 6.72 (1H, d, $J = 8.2$ Hz), 5.60 (1H, d, 9.9 Hz), 5.18 and 5.14 (4H, m and s), 4.67 (1H, m), 4.53 (1H, m), 4.39 (1H, d, $J = 9.3$ Hz), 3.72 (3H, s), 3.64 (1H, d, $J = 16.2$ Hz), 3.50 (1H, d, $J = 16.5$ Hz), 3.13 (1H, d, $J = 5.8$ Hz), 2.05 (1H, m), 1.59 and 1.46−1.64 (7H, d and m), 1.32 (5H, m), 0.92 (12H, m); ^{13}C NMR δ 202.5, 171.5, 169.9, 168.9, 167.9, 156.9, 136.2, 128.5, 128.2, 128.0, 78.5, 69.9, 67.6, 67.2, 58.8, 56.4, 52.6, 46.2, 38.8, 37.1, 24.7, 24.0, 23.2, 21.3, 20.1, 17.2, 15.0, 11.4; *anal.* C 59.09%, H 7.45%, N 4.49%, calcd for $C_{30}H_{44}N_2O_{11}$, C 59.20%, H 7.29%, N 4.60%. Continued elution led to 0.16 g (31%) of alcohols **27** and **28** as a mixture of isomers. Further elution provided 0.20 g (39%) of alcohol **28** as a single isomer: TLC R_f 0.58 (50:50 hexane−EtOAc); ^1H NMR δ 12.04 (0.1H, enolic H, s), 7.35 (5H, m), 6.50 (1H, d, $J = 8.3$ Hz), 5.65 (1H, d, $J = 9.3$ Hz), 5.18 and 5.14 (3H, m and s), 5.03 (1H, m), 4.72 (1H, m), 4.53 (1H, m), 4.42 (1H, d, $J = 9.4$ Hz), 3.72 (3H, s), 3.55 (2H, m), 3.03 (1H, d, $J = 5.5$ Hz), 1.99 (1H, m), 1.61 (6H, d and m, $J = 7.2$ Hz), 1.29 (5H, m and d, $J = 6.6$ Hz), 0.93 (12 H, m); ^{13}C NMR δ 201.7, 171.1, 170.2, 168.5, 167.3, 156.8, 136.2, 128.5, 128.2, 128.0, 78.8, 69.7, 67.8, 67.1, 59.2, 56.5, 52.5, 46.2, 39.6, 36.9, 24.9, 24.4, 23.2, 21.6, 21.3, 19.7, 16.8, 14.8, 11.2; *anal.* C 59.28%, H 7.58%, N 4.24%, calcd for $C_{30}H_{44}N_2O_{11}$, C 59.20%, H 7.29%, N 4.60%.

Methyl 2-(2-Hydroxypropionyloxy)-3-methylpentanoate (29). To a solution cooled to 0 °C of silyl ether **20** (0.52 g, 1.56 mmol) in THF (10 mL) under N_2 was added a 1 M THF solution (3.2 mL) of TBAF dropwise and the resulting solution stirred at 0 °C for 20 min. The solution was poured into H_2O and extracted with EtOAc (3 × 25 mL). The combined extract was washed with H_2O (10 mL) and 5 M NaCl (10 mL), dried, and evaporated. The residue was flash chromatographed (15 g, SiO_2, 85:15 hexane−EtOAc) to afford 0.29 g (85%) of alcohol **29** as a colorless oil: TLC R_f 0.29 (80:20 hexane−EtOAc); IR 3488, 1744 cm^{-1}; ^1H NMR δ 5.00 (1H, d, $J = 4.4$ Hz), 4.37 (1H, q, $J = 6.6$ Hz), 3.75 (3H, s), 2.82 (1H, d, $J = 6.0$ Hz), 2.04 (1H, m), 1.50 (4H, d and m, $J = 6.0$ Hz), 1.33 (1H, m), 0.98 (3H, d, $J = 7.1$ Hz), 0.93 (3H, t, $J = 7.7$ Hz); ^{13}C NMR δ 175.44, 169.58, 66.66, 52.13, 36.51, 24.41, 20.50, 15.31, 11.49.

Methyl 2-{2-[2-Benyloxycarbonylamino-3-(*tert*-butyldimethylsilyloxy)butyryloxy]propionyloxy}-3-methylpentanoate (30). Alcohol **29** (0.115 g, 0.53 mmol) and carboxylic acid **25** (0.213 g, 0.58 mmol) were allowed to react using the MNBA esterification procedure described for **26** to afford 0.23 g (75%) of ester **30** as a colorless oil: TLC R_f 0.43 (80:20 hexane−EtOAc); ^1H NMR δ 7.37 (5H, m), 5.47 (1H, d, $J = 9.3$ Hz), 5.24 (1H, q, $J = 7.1$ Hz), 5.14 (2H, s), 4.98 (1H, d, $J = 4.4$ Hz), 4.47 (1H, m), 4.30 (1H, dd, $J = 9.3$, 1.6 Hz), 3.73 (3H, s), 2.01 (1H, m), 1.57 (3H, d, $J = 6.6$ Hz), 1.50 (1H, m), 1.30 (1H, m), 1.26 (3H, d, $J = 6.0$ Hz), 0.97 (3H, d, $J = 6.5$ Hz), 0.91 (3H, t, $J = 7.7$ Hz), 0.83 (9H, s), 0.05 and 0.00 (6H, 2 s); ^{13}C NMR δ 170.35, 169.85, 169.63, 159.61, 136.32, 128.56, 128.19, 68.91, 68.63, 67.13, 60.39, 59.71, 52.10, 36.52, 25.70, 24.43, 21.25, 17.88, 17.10, 15.31, 11.50, −4.31, −5.34.

Methyl 2-{2-[2-Benyloxycarbonylamino-3-hydroxybutyryloxy]-propionyloxy}-3-methylpentanoate (31). Ester **30** (0.60 g, 1.05 mmol) was converted employing the BF_3·Et_2O desilylation procedure described for **23** to provide 0.44 g (92%) of alcohol **31** as a colorless oil: TLC R_f 0.13 (80:20 hexane−EtOAc); ^{1}H NMR δ 7.35 (5H, m), 5.56 (1H, d, J = 9.9 Hz) 5.27 (1H, q, J = 7.1 Hz), 5.13 (2H, s), 5.02 (1H, d, J = 4.4 Hz), 4.58 (1H, m), 4.43 (1H, dd, J = 9.0, 1.6 Hz), 3.74 (3H, s), 3.17 (1H, d, J = 4.4 Hz), 2.02 (1H, m), 1.63 (3H, d), 1.47 (1H, m), 1.32 (1H, m), 1.26 (3H, d, J = 6.0 Hz), 0.98 (3H, d, J = 6.5 Hz), 0.92 (3H, t, J = 7.7 Hz); ^{13}C NMR δ 171.14, 170.88, 169.59, 156.78, 136.25, 128.49, 128.08, 127.91, 77.07, 69.14, 67.73, 67.05, 59.38, 52.31, 36.59, 24.41, 18.97, 16.58, 15.20, 11.46.

2-Benzyloxycarbonylamino-2-methoxycarbonyl-1-methylethyl 2-(*tert*-Butyldimethylsilyloxy)-4-methylpentanoate (34). Silyl ester **32** (4.5 g, 12.5 mmol) and DMF (300 μL, 3.7 mmol) were placed in DCM (20 mL) under N_2 and cooled to 0 °C. Oxalyl chloride (12.5 mL of a 2 M solution in DCM, 25 mmol) was added dropwise. The mixture was warmed to ambient temperature and stirred for 4.5 h, and the solvent was evaporated. To the residue under N_2 was added a solution of alcohol **33** (2.02 g, 8 mmol), DMAP (2.9 g, 24 mmol), and TEA (2.3 mL, 20 mmol) in DCM (15 mL) at 0 °C. The mixture was stirred at ambient temperature for 2 h, and the reaction was terminated with 6% $NaHCO_3$ (50 mL) and extracted with Et_2O (3 × 50 mL). The extracts were combined, dried, and evaporated. The residue was flash chromatographed (100 g, SiO_2, 6:1 hexane−EtOAc) to afford 2.17 g (56%) of ester **34** as a colorless oil: TLC R_f 0.33 (80:20 hexane−EtOAc); ^{1}H NMR δ 7.37 (5H, m), 5.44 (2H, m), 5.15 (2H, s), 4.56 (1H, d, J = 8.1 Hz), 4.15 (1H, dd, J = 4.2, 8.1 Hz), 3.72 (3H, s), 1.78 (1H, m), 1.59 (1H, m), 1.40 (1H, m), 1.32 (3H, d, J = 6.6 Hz), 0.87 (18H, m), 0.22 (6H, m); FABMS $[M + H]^+$ 496.2735, calcd for $C_{25}H_{42}NO_7Si$, 496.2731.

2-Benzyloxycarbonyl-2-methoxycarbonyl-1-methylethyl 2-Hydroxy-4-methylpentanoate (35). The BF_3·Et_2O desilylation procedure described for **23** was applied to silyl ester **34** (265.3 mg, 0.54 mmol) to provide 0.11 g (51%) of alcohol **35** as a colorless oil: TLC R_f 0.18 (80:20 hexane−EtOAc); ^{1}H NMR δ 7.37 (5H, m), 5.56 (1H, d, J = 9.3 Hz), 5.49 (1H, qd, J = 6.6, 2.2 Hz), 5.14 (2H, s), 4.55 (1H, dd, J = 9.3, 2.5 Hz), 4.12 (1H, q, J = 6.6 Hz), 3.73 (3H, s), 2.71 (1H, d, J = 6.1 Hz), 1.83 (1H, hept, J = 6.6 Hz), 1.49 (2H, t, J = 6.6 Hz), 1.33 (3H, d, J = 6.6 Hz), 0.94 and 0.92 (6H, 2 d); ^{13}C NMR δ 174.5, 170.2, 156.5, 128.6, 128.3, 128.2, 71.6, 69.0, 67.4, 57.4, 52.8, 43.2, 24.3, 23.1, 21.5, 16.8.

***tert*-Butyl 2-[2-(*tert*-Butyldimethylsilyloxy)propionyloxy]-3-methylpentanoate (38).** The acid chloride derivative of silyl ester **18** (8.73 g, 27.4 mmol) and alcohol **37** (3.90 g, 20.7 mmol) were allowed to react using the catalytic DMF, oxalyl chloride esterification procedure described for ester **20** to give 6.24 g (81%) of ester **38** as a colorless oil: TLC R_f 0.60 (4:1 hexane−EtOAc); IR 1738, 1651 cm^{-1}; ^{1}H NMR δ 4.78 (1H, d, J = 4.5 Hz), 4.38 (1H, dd, J = 13.8, 6.6 Hz), 1.95 (1H, m), 1.24−1.54 (15H, m), 0.84−0.97 (15H, m), 0.10 (6H, m); MS APCI$^+$ 375.2567 $[M + H]^+$, calcd for $C_{19}H_{38}O_5Si$, 375.2567; *anal.* C 61.42%, H 10.36%, calcd for $C_{19}H_{38}O_5Si$, C 60.92%, H 10.23%.

***tert*-Butyl 2-(2-Hydroxypropionyloxy)-3-methylpentanoate (10).** Ester **38** (0.77 g, 2.05 mmol) was transformed employing the TBAF desilylation procedure described for alcohol **29** to provide 0.54 g (100%) of alcohol **10** as a colorless oil: TLC R_f 0.41 (80:20 hexane−EtOAc); IR 1745 cm^{-1}; ^{1}H NMR δ 4.85 (1H, d, J = 4.5 Hz), 4.35 (1H, dd, J = 13.8, 6.6 Hz), 2.72 (1H, m), 2.01 (1H, m), 1.23−1.68 (15H, m), 0.95 (6H, m); *anal.* C 59.93%, H 9.35%, calcd for $C_{13}H_{24}O_5$, C 59.98%, H 9.29%.

***tert*-Butyl 2-{2-[2-Benzyloxycarbonylamino-3-(*tert*-butyldimethylsilyloxy)butyryloxy] propionyloxy}-3-methylpentanoate (39).** Alcohol **10** (0.50 g, 1.92 mmol) was esterfied with carboxylic acid **25** (768 mg, 2.09 mmol) by means of the MNBA procedure described for ester **26** to yield 1.02 g (87%) of ester **39** as a colorless oil: TLC R_f 0.55 (80:20 hexane−EtOAc); IR 3453, 1745, 1625 cm^{-1}; ^{1}H NMR δ 7.36 (5H, m), 5.46 (1H, m), 5.24 (1H, m), 5.13 (2H, s), 4.81 (1H, d, J = 4.2 Hz), 4.46 (1H, d, J = 6.0 Hz), 1.96 (1H, m), 1.22−1.55 (18H, m), 0.95 (6H, m), 0.82 (9H, s), 0.02 (6H, m); MS APCI$^+$ 610.3456 $[M + H]^+$, calcd for $C_{31}H_{52}NO_9Si$, 610.3411.

***tert*-Butyl 2-[2-(2-Benzyloxycarbonylamino-3-hydroxybutyryloxy)propionyloxy]-3-methylpentanoate (9).** Ester **39** (1.02 g, 1.68 mmol) was converted using the TBAF desilylation procedure described for alcohol **29** to afford 0.83 g (100%) of alcohol **9** as a colorless oil: TLC R_f 0.46 (6:1 hexane−EtOAc); IR 1745 cm^{-1}; ^{1}H NMR δ 7.32 (5H, m), 5.54 (1H, d, J = 9.9 Hz), 5.16−5.23 (2H, m), 5.12 (2H, s), 4.86 (1H, d, J = 4.5 Hz), 4.58 (1H, m), 4.41 (1H, dd, J = 9.3, 3.0), 3.29 (1H, d, J = 4.2 Hz), 1.98 (1H, m), 1.21−1.60 (18H, m), 0.84−0.99 (9H, m); MS APCI$^+$ 496.2541 $[M + H]^+$, calcd for $C_{25}H_{38}NO_9$, 496.2547; *anal.* C 60.50%, H 7.67%, N 2.66%, calcd for $C_{25}H_{37}NO_9$, C 60.59%, H 7.53%, N 2.83%.

2-(*tert*-Butyldiphenylsilyloxy)-4-methylpentanoic Acid (40). Alcohol **13** (3.00 g, 20.5 mmol), imidazole (2.79 g, 41.0 mmol), and TBDPSCl (7.93 g, 28.8 mmol) were dissolved in DMF (30 mL under N_2), and the solution was stirred at ambient temperature for 18 h. The reaction was terminated with 5 M NaCl (100 mL) and extracted with EtOAc (2 × 100 mL). The extracts were combined, washed with cold 5% citric acid (50 mL), H_2O (20 mL), and 5 M NaCl (20 mL), dried, and evaporated, and the residue coevaporated with toluene (2 × 75 mL). The residue was flash chromatographed (270 g, SiO_2, 95:5 hexane−EtOAc) to afford 6.92 g (88%) of the methyl ester: TLC R_f 0.37 (95:5 hexane−EtOAc); IR 1750, 1649 cm^{-1}; ^{1}H NMR δ 7.67 (4H, m), 7.40 (6H, m), 4.23 (1H, dd, J = 4.2, 7.2 Hz), 3.44 (3H, s), 1.43−1.76 (3H, m), 1.09 (9H, s), 0.81 (6H, dd, J = 6.0, 16.5 Hz); ^{13}C NMR δ 174.0, 136.0, 135.9, 133.9, 133.3, 129.73, 129.66, 127.6, 127.4, 71.5, 51.3, 44.3, 26.9, 24.1, 22.9, 22.2, 19.4.

A portion of this material (1.76 g, 4.58 mmol) was placed in 1:1 THF−CH_3OH (40 mL) at 0 °C under N_2, and LiOH (14 mL of 0.5 M cold solution, 7.0 mmol) was added over 20 min. The mixture was stirred at ambient temperature for 28 h, cooled to 0 °C, acidified (pH 3) with 1 M $KHSO_4$, and extracted with EtOAc (2 × 50 mL). The combined extract was washed with H_2O (20 mL) and 5 M NaCl (20 mL) and dried, and the solvent was evaporated. The residue was flash chromatographed (60 g, SiO_2, 8:1 hexane−EtOAc) to provide 1.73 g (98%) of carboxylic acid **40** as a colorless oil: TLC R_f 0.67 (95:5:1 DCM−CH_3OH−HOAc); IR 1721 cm^{-1}; ^{1}H NMR δ 7.64 (4H, m), 7.41 (6H, m), 4.26 (1H, t, J = 6.0 Hz), 1.48−1.74 (3H, m), 1.08 (9H, s), 0.69 (6H, dd, J = 6.6, 9.3 Hz).

2-(*tert*-Butyldimethylsilyloxy)-4-methylpentanoic Acid (41). Alcohol **13** (1.06 g, 6.84 mmol) was treated with TBDMSCl (1.61 g, 10.26 mmol) according to the procedure described for obtaining **40** and silyl ester, which led to 1.74 g (98%) of the TBDMS ether as a colorless oil: IR 1761 cm^{-1}; ^{1}H NMR δ 4.22 (1H, dd, J = 3.9, 8.4 Hz), 3.70 (3H, s), 1.76 (1H, m), 1.55 (2H, m), 0.93−0.98 (15H, m), 0.04 (6H, dd, J = 4.2, 18.6). A portion of this methyl ester (1.30 g, 5.0 mmol) was hydrolyzed as described for carboxylic acid **40**, which led to 1.07 g (87%) of carboxylic acid **41** as a somewhat unstable colorless oil: ^{1}H NMR δ 4.27 (1H, dd, J = 4.2, 7.2 Hz), 1.84 (1H, m), 1.62 (2H, m), 0.82−0.95 (15H, m), 0.06−0.12 (6H, m).

2-Benzyloxycarbonylamino-2-[1-(1-*tert*-butoxycarbonyl-2-methylbutoxycarbonyl)ethoxycarbonyl]-1-methylethyl 2-(*tert*-Butyldiphenylsilyloxy)-4-methylpentanoate (42). Alcohol **9** (0.83 g, 1.68 mmol) was esterified with carboxylic acid **40** (0.78 g, 2.1 mmol) employing the MNBA procedure described for diester **26** to afford 1.21 g (85%) of ester **42** as a colorless oil: IR 1745 cm^{-1}; ^{1}H NMR δ 7.61 (4H, m), 7.35 (11H, m), 5.22 (2H, m), 5.09 (3H, m), 4.80 (1H, d, J = 4.5 Hz), 4.43 (1H, dd, J = 3.3, 9.3 Hz), 4.30 (1H, t, J = 6.1 Hz), 1.94 (1H, m), 1.24−1.69 (16H, m), 1.05 (9H, s), 0.94 (6H, m), 0.74 (6H, dd, J = 4.2, 15.3 Hz); MS APCI$^+$ 848.4402 $[M + H]^+$, calcd for $C_{47}H_{66}NO_{11}Si$, 848.4406.

2-Benzyloxycarbonylamino-2-[1-(1-*tert*-butoxycarbonyl-2-methylbutoxycarbonyl)ethoxycarbonyl]-1-methylethyl 2-(*tert*-Butyldimethylsilyloxy)-4-methylpentanoate (43). By applying the preceding method (cf. **26** and **42**) alcohol **9** (3.17 g, 6.40 mmol) was esterified with carboxylic acid **41** (1.84 g, 7.60 mmol) using MNBA, and that reaction led to 3.85 g (83%) of ester **43** as a colorless oil: TLC R_f 0.38 (6:1 hexane−EtOAc); IR 3446, 3336, 1747 cm^{-1}; ^{1}H NMR δ 7.35 (5H, m), 5.43 (2H, m), 5.11 (3H, m), 4.82 (1H, d, J = 4.5 Hz), 4.55 (1H, m), 4.22 (1H, m), 1.94 (1H, m), 1.24−1.59 (21H, m), 0.85−0.98 (21H, m), 0.11 (6H, m); ^{13}C NMR δ 173.0, 169.2, 169.1, 128.5, 128.2, 128.1, 82.2, 76.9, 70.5, 69.5, 67.3, 57.6, 43.9, 36.6, 28.0, 25.7, 24.5, 23.4, 16.9, 15.3, 11.6, −4.8, −0.5.5; *anal.* C 61.57%, H 8.62%, N 1.87%, calcd for $C_{37}H_{61}NO_{11}Si$, C 61.38%, H 8.49%, N 1.93%.

2-Benzyloxycarbonylamino-2-[1-(1-carboxy-2-methylbutoxycarbonyl)ethoxycarbonyl]-1-methylethyl 2-(*tert*-Butyldiphenylsilyloxy)-4-methylpentanoate (44). To *tert*-butyl ester **42** (1.09 g, 1.29 mmol) in DCM (5 mL) was added $ZnBr_2$ (1.45 g, 6.43 mmol), the solution was stirred for 48 h, H_2O (20 mL) was added, and stirring continued for 2 h. The organic phase was separated and the aqueous phase extracted with DCM (2 × 20 mL). The organic solutions were

combined, dried, and evaporated to furnish 0.82 g (80%) of carboxylic acid **44** as a colorless oil: TLC R_f 0.50 (50:1 DCM−CH_3OH); IR 1752 cm^{-1}; ^1H NMR δ 7.62 (4H, s), 7.30 (11H, m), 4.91−5.21 (5H, m), 4.44 (1H, m), 4.30 (2H, m), 1.98 (1H, m), 0.73−1.66 (33H, m); FABMS 792.3786 $[M + H]^+$, calcd for $C_{43}H_{58}NO_{11}Si$, 792.3780.

2-Benzyloxycarbonylamino-2-[1-(1-carboxy-2-methylbutoxycarbonyl)ethoxycarbonyl]-1-methylethyl 2-(*tert*-Butyldimethylsilyloxy)-4-methylpentanoate (8). To *tert*-butyl ester **43** (2.52 g, 3.10 mmol) in toluene (70 mL) was added 230−400 mesh silica gel (5 g). The mixture was heated at reflux under N_2 for 6 h, allowed to cool, and diluted with 4:1 DCM−CH_3OH (200 mL). The solution was filtered and the solid phase washed with 4:1 DCM−CH_3OH (50 mL). The combined DCM filtrate and washings were evaporated to dryness. The residue was flash chromatographed (60 g, SiO_2, 50:1 DCM−CH_3OH) to afford 1.54 g (66%) of carboxylic acid **8** as a colorless oil: TLC R_f 0.51 (50:1 DCM−CH_3OH); $[\alpha]^{26}_D$ −33.9 (*c* 1.1, $CHCl_3$); IR 3319, 1755 cm^{-1}; ^1H NMR δ 7.34 (5H, m), 5.31 (2H, m), 4.98−5.13 (5H, m), 4.57 (1H, dd, J = 3.3, 9.9 Hz), 4.20 (2H, dd, J = 3.6, 8.7 Hz), 2.01 (1H, m), 1.33−1.76 (9H, m), 0.81−1.24 (22H, m), 0.01−0.05 (6H, m); ^{13}C NMR δ 173.1, 169.3, 156.5, 136.0, 128.6, 128.3, 128.1, 76.2, 70.7, 70.5, 69.5, 67.4, 57.6, 43.9, 36.5, 25.7, 24.4, 24.0, 23.4, 21.5, 18.1, 16.9, 16.7, 15.3, 11.5, −4.8, −5.5; *anal.* C 59.49%, H 8.32%, N 1.97%, calcd for $C_{33}H_{53}NO_{11}Si$, C 59.35%, H 8.00%, N 2.10%.

Methyl 4-[2-(2-{2-Benzyloxycarbonylamino-3-[2-(*tert*-butyldiphenylsilyloxy)-4-methylpentanoyloxy]butyryloxy}propionyloxy)-3-methylpentanoylamino]-6-methyl-3-oxoheptanoate (45). Boc-protected ketone **7** (0.287 g, 1.0 mmol) was deprotected (TFA-DCM) and allowed to react with carboxylic acid **44** (0.640 g, 0.81 mmol) employing the PyBroP-mediated amide formation procedure described for **22** to afford 0.375 g (52%) of amide **45** as a colorless oil: TLC R_f 0.45 (80:20 hexane−EtOAc); IR 3367, 1755, 1682 cm^{-1}; ^1H NMR δ 7.59 (4H, m), 7.33 (11H, m), 6.70 (1H, d, J = 7.8 Hz), 5.00−5.13 (6H, m), 4.70 (1H, m), 4.41 (1H, m), 4.27 (1H, m), 3.69 (3H, d, J = 3.0 Hz), 3.52 (2H, d, J = 2.7 Hz); ^{13}C NMR δ 201.7, 172.4, 169.7, 168.7, 167.3, 156.3, 136.0, 135.7, 133.1, 129.9, 128.6, 128.3, 128.1, 127.7, 78.6, 71.7, 70.7, 70.1, 67.3, 57.9, 56.4, 52.4, 46.0, 44.5, 39.2, 37.0, 29.7, 26.8, 24.8, 24.2, 24.1, 23.3, 22.9, 22.3, 21.4, 19.4, 16.9, 14.9, 11.4; FABMS 961.4854 $[M + H]^+$, calcd for $C_{52}H_{73}N_2O_{13}Si$, 961.4882; *anal.* C 64.76%, H 7.77%, N 2.72%, calcd for $C_{52}H_{72}N_2O_{13}Si$, C 64.98%, H 7.55%, N 2.91%.

Methyl 4-[2-(2-{2-Benzyloxycarbonylamino-3-[2-(*tert*-butylmethylsilyloxy)-4-methylpentanoyloxy]butyryloxy}propionyloxy)-3-methylpentanoylamino]-6-methyl-3-oxoheptanoate (46). Ketone **7** (1.16 g, 4.00 mmol), following cleavage of the Boc group, and carboxylic acid **8** (2.25 g, 3.37 mmol) were coupled by PyBroP-promoted amide formation as described for amide **22** to supply 1.83 g (65%) of amide **46** as a colorless oil: TLC R_f 0.46 (80:20 hexane−EtOAc); $[\alpha]^{25}_D$ −38.5 (*c* 0.98, $CHCl_3$); IR 3359, 1753, 1682 cm^{-1}; ^1H NMR δ 7.35 (5H, m), 6.70 (1H, d, J = 7.8 Hz), 5.43 (2H, d, J = 9.3 Hz), 5.13 (4H, m), 4.68 (1H, m), 4.54 (1H, m), 4.18 (1H, dd, J = 3.6, 9.3 Hz), 3.70 (3H, t, J = 3.0 Hz), 3.52 (2H, s), 2.00 (1H, s), 1.27−1.74 (18H, m), 0.88−0.94 (24H, m), 0.02 (6H, m); *anal.* C 60.40%, H 8.52%, N 3.31%, calcd for $C_{42}H_{68}N_2O_{13}Si$, C 60.26%, H 8.19%, N 3.35%.

Methyl 4-(2-{2-[2-Benzyloxycarbonylamino-3-(2-hydroxy-4-methylpentanoyloxy)butyryloxy]propionyloxy}-3-methylpentanoylamino)-6-methyl-3-oxoheptanoate (6). To amide **46** (0.367 g, 0.44 mmol) in CH_3OH (5 mL) under N_2 at 0 °C was added acetyl chloride (50 μL, 69.5 mg, 0.88 mmol). The solution was stirred at ambient temperature for 30 min, diluted with DCM (40 mL), washed with 6% $NaHCO_3$ (20 mL) and H_2O (10 mL), dried, and evaporated. The residue was flash chromatographed (10 g, SiO_2, 2:1 hexane−EtOAc) to afford 0.198 g (63%) of epimer **6** as a colorless oil: TLC R_f 0.40 (50:50 hexane−EtOAc); $[\alpha]^{25}_D$ −30.4 (*c* 0.92, $CHCl_3$); ^1H NMR δ 7.37 (5H, m), 6.63 (1H, d, J = 8.4 Hz), 5.45 (2H, m), 5.53 (2H, s), 5.03 (1H, d, J = 4.8 Hz), 4.65 (2H, m), 4.10 (1H, m), 3.72 (3H, d, J = 2.7 Hz), 3.50 (2H, m), 1.86−2.02 (2H, m), 0.68−1.83 (33H, m); ^{13}C NMR δ 201.7, 174.8, 169.3, 169.2, 168.6, 135.8, 128.6, 128.4, 128.2, 79.0, 78.8, 71.2, 69.9, 69.0, 68.9, 67.5, 57.5, 56.5, 56.4, 46.1, 42.8, 39.7, 36.8, 29.7, 24.9, 24.3, 24.3, 23.2, 21.5, 16.7, 14.8, 11.2; FABMS 723.3735 $[M + H]^+$, calcd for $C_{36}H_{55}N_2O_{13}$, 723.3704; *anal.* C 59.64%, H 7.81%, N 3.79%, calcd for $C_{36}H_{54}N_2O_{13}$, C 59.82%, H 7.53%, N 3.88%.

Benzyl (5-*s*-Butyl-8,13-diisobutyl-2,16-dimethyl-3,6,9,11,14,18-hexaoxo-1,4,12,15-tetraoxa-7-azacyclooctadec-17-yl)carbamate (5). A mixture of alcohol **6** (0.12 g, 0.17 mmol) and anhydrous $CuSO_4$ (0.60 g, 3.75 mmol) in toluene (150 mL, under N_2) was stirred at 120 °C for 12 h. The mixture was allowed to cool, the mixture filtered, and the solvent evaporated. The residue was flash chromatographed (10 g, SiO_2) to afford 92 mg (80%) of lactone **5** as a colorless solid: TLC R_f 0.61 (75:25 hexane−EtOAc); $[\alpha]^{25}_D$ +13.5 (*c* 0.68, $CHCl_3$); IR 3336, 1735, 1717, 1684 cm^{-1}; ^1H NMR δ 7.46 (1H, d, J = 8.7 Hz), 7.38 (5H, m), 5.91 (1H, m), 5.70 (1H, dd, J = 7.2, 13.8 Hz), 5.54 (1H, d, J = 9.6 Hz), 5.20 (3H, m), 4.82 (1H, d, J = 9.0 Hz), 4.71 (3H, m), 3.45 (1H, d, J = 15.9 Hz), 3.23 (1H, d, J = 15.6 Hz), 2.03 (1H, m), 1.42−1.86 (10H, m), 1.36 (6H, d, J = 6.9 Hz), 0.87−1.02 (15H, m); ^{13}C NMR δ 204.5, 171.7, 170.1, 169.8, 167.7, 166.4, 156.7, 135.8, 128.6, 128.4, 128.2, 81.2, 72.4, 72.2, 71.3, 67.6, 57.8, 57.2, 47.0, 41.2, 39.2, 36.7, 25.3, 24.9, 24.4, 23.5, 22.8, 21.8, 20.8, 18.5, 16.4, 14.4, 10.6; FABMS 691.3450 $[M + H]^+$, calcd for $C_{35}H_{51}N_2O_{12}$, 691.3442; *anal.* C 61.23%, H 7.30%, N 4.06%, calcd for $C_{35}H_{50}N_2O_{12}$, C 60.86%, H 7.30%, N 4.06%.

2-Hydroxy-3-formylaminobenzoic acid (49). Aniline **48** (0.51 g, 3.31 mmol) was suspended in formamide (3.0 mL under N_2) and the mixture stirred at 150 °C for 0.5 h. The resulting solution was allowed to cool, dissolved in 6% $NaHCO_3$ (50 mL), acidified with 1 M $KHSO_4$, and extracted with EtOAc (3 × 50 mL). The combined extract was washed with 5 M NaCl (10 mL), dried, and evaporated, and the residue was coevaporated with toluene (10 mL) to furnish 90% of phenol **49** as a greenish-gray solid: mp 168−169 °C; TLC R_f 0.20 (95:5:1 DCM−MeOH−HOAc); ^1H NMR (d_6-DMSO) δ 9.82 (1H, s), 8.38 (1H, d, J = 9.3 Hz), 7.55 (1H, d, J = 7.7 Hz), 6.92 (1H, t, J = 7.7 Hz); ^{13}C NMR (d_6-DMSO) δ 172.3, 160.3, 151.2, 126.5, 125.7, 124.5, 118.6, 112.6.

Methyl 2-Hydroxy-3-formylaminobenzoate (50). Benzoic acid derivative **49** (1.37 g, 7.57 mmol) and $NaHCO_3$ (1.40 g, 16.65 mmol) were placed in DMF (20 mL) under N_2. MeI (5.37 g, 2.36 mL, 37.85 mmol) in DMF (20 mL) was added and the mixture stirred at ambient temperature for 15 h. The mixture was diluted with EtOAc (250 mL), washed with H_2O (50 mL), 6% $NaHCO_3$ (50 mL), H_2O (20 mL), and 5 M NaCl (20 mL), and dried, the solvent was evaporated, and the residue was coevaporated with toluene (50 mL). The residue was flash chromatographed (36 g, SiO_2, 70:30 hexane−EtOAc) to supply 1.17 g (79%) of ester **50** as an off-white solid: mp 99 °C; TLC R_f 0.66 (95:5 DCM−MeOH); IR 3248, 1693, 1651 cm^{-1}; ^1H NMR δ 11.29 and 11.18 (1H, 2 s), 8.76 and 8.56 (1H, 2 dd, J = 7.9, 1.7 Hz), 8.51 (1H, d, J = 1.7 Hz), 7.97 (1H, br s), 7.65 and 7.57 (1H, 2 dd, J = 8.2, 1.6 Hz), 6.90 and 6.88 (1, 2 t, J = 8.2 Hz), 3.97 (3H, s); ^{13}C NMR δ 170.8, 170.4, 161.2, 158.9, 151.2, 150.3, 126.5, 125.8, 125.4, 124.3, 121.7, 119.2, 113.1, 111.9, 52.7, 52.6.

Methyl 2-Benzyloxy-3-formylaminobenzoate (51). To methyl ester **50** (1.01 g, 5.20 mmol) and benzyl bromide (1.44 g, 1 mL, 8.42 mmol) in DMF (20 mL under N_2) was added K_2CO_3 (1.44 g, 10.40 mmol) and the mixture stirred at 60 °C for 15 h. The mixture was diluted with EtOAc (100 mL), washed with H_2O (2 × 20 mL) and 5 M NaCl (10 mL), and dried, the solvent was evaporated, and the residue was coevaporated with toluene (20 mL). The residue was separated by flash chromatography (50 g, SiO_2, 80:20 hexane−EtOAc) to afford 1.41 g (95%) of benzyl ester **51** as a pinkish oil, which solidified on standing. A portion was recrystallized from toluene−hexane: mp 52−53 °C; TLC R_f 0.59 (50:50 hexane−EtOAc); IR 3284, 1720, 1674 cm^{-1}; ^1H NMR δ 8.53 (1H, dd, J = 8.3, 1.6 Hz), 8.19 (1H, d, J = 1.7 Hz), 7.65 (2H, dd, J = 8.2, 1.6 Hz), 7.41 (5H, m), 7.18 (1H, t, J = 8.3 Hz), 5.03 (2H, s), 3.93 (3H, s); ^{13}C NMR δ 165.7, 158.7, 147.7, 136.4, 132.0, 128.9, 128.9, 128.5, 126.7, 124.9, 124.4, 77.8, 52.4; *anal.* C 67.51%, H 5.42%, N 4.88%, calcd for $C_{16}H_{15}NO_4$, C 67.36%, H 5.30%, N 4.91%.

2-Benzyloxy-3-formylaminobenzoic Acid (3). To methyl ester **51** (1.28 g, 4.48 mmol) in 3:1 THF−MeOH (20 mL) under N_2 was added LiOH (11.6 mL of 0.5 M aqueous solution, 5.8 mmol) and the mixture stirred at ambient temperature for 18 h. The reaction mixture was acidified (pH 3) with 1 M $KHSO_4$, diluted with H_2O (200 mL), and extracted with EtOAc (3 × 65 mL). The combined extract was washed with H_2O (10 mL), and 5 M NaCl (20 mL), dried, and evaporated. The residue was crystallized from EtOAc−hexane to afford 0.96 g (79%) of benzoic acid **3** as an off-white solid: mp 133 °C; TLC R_f 0.51 (95:5:1 DCM−CH_3OH−HOAc); IR 3343, 1697, 1636 cm^{-1}; ^1H NMR (d_6-DMSO) δ 13.09 (1H, s), 9.76 (1H, s), 8.34 (1H, s), 8.30 (1H, d, J = 8.2 Hz), 7.25−7.60 (6H, m), 7.18 (1H, t, J = 7.7 Hz), 4.95 (2H, s); ^{13}C NMR (d_6-DMSO) δ 167.0, 160.5, 147.3, 136.8, 132.3,

128.4, 128.0, 127.9, 126.4, 125.6, 124.7, 124.0, 75.7; *anal.* C 65.84%, H 4.91%, N 5.06%, calcd for $C_{15}H_{13}NO_4 \cdot 0.1H_2O$, C 65.97%, H 4.88%, N 5.12%.

Benzyl (5-*s*-Butyl-8,13-diisobutyl-2,10,10,16-tetramethyl-3,6,9,-11,14,18-hexaoxo-1,4,12,15-tetraoxa-7-azacyclooctadec-17-yl)carbamate (52). To a stirred solution of lactone **5** (76 mg, 0.11 mmol) in DMSO (3 mL) under N_2 were added K_2CO_3 (153 mg, 1.01 mmol) and MeI (20 μL, 0.33 mmol). The mixture was stirred at ambient temperature for 3 h, diluted with H_2O (12 mL), and extracted with EtOAc (3 × 20 mL). The extracts were combined, washed with H_2O (10 mL) and 5 M NaCl (5 mL), dried, and evaporated. The residue was flash chromatographed (10 g, SiO_2, 3:1 hexane−EtOAc) to afford 22 mg (28%) of Cbz-protected lactone **52** as an oil: TLC R_f 0.55 (75:25 hexane−EtOAc); $[\alpha]^{25}_D$ −17.7 (*c* 0.90, $CHCl_3$); IR 3330, 1738, 1718 cm^{-1}; ^1H NMR δ 7.50 (1H, d, J = 9.3 Hz), 7.37 (5H, m), 5.91 (1H, m), 5.80 (1H, dd, J = 6.6, 13.8 Hz), 5.56 (1H, d, J = 9.0 Hz), 5.18 (2H, dd, J = 12.0, 17.1 Hz), 4.86 (2H, m), 4.72 (1H, d, J = 9.0 Hz), 4.59 (1H, dd, J = 4.2, 10.2 Hz), 2.06 (1H, m), 1.13−1.83 (20H, m), 0.77−0.98 (19H, m); ^{13}C NMR δ 208.3, 173.1, 171.8, 170.0, 169.7, 167.8, 156.6, 135.8, 128.7, 128.5, 128.2, 80.8, 72.3, 71.9, 71.1, 67.6, 57.7, 56.4, 53.0, 43.0, 39.4, 36.6, 31.9; MS APCI$^+$ 719.3767 [M + H]$^+$, calcd for $C_{37}H_{55}N_2O_{12}$, 719.3755.

17-Amino-5-*s*-butyl-8,13-diisobutyl-2,10,10,16-tetramethyl-1,4,-12,15-tetraoxa-7-azacyclooctadecane-3,6,9,11,14,18-hexaone (4). Benzyl carbamate **52** (16 mg, 0.022 mmol) and 10% Pd/C (15 mg) in EtOAc (3 mL) were stirred under a H_2 atmosphere at ambient temperature for 2 h. The solution phase was filtered through Celite and the solid phase washed with CH_3OH (20 mL). The combined solvent filtrate and washings were evaporated, and the residue was flash chromatographed (10 g, SiO_2, 3:1 hexane−EtOAc) to furnish 9.5 mg (73%) of amine **4** as a colorless oil: TLC R_f 0.40 (75:25 EtOAc−hexane); $[\alpha]^{27}_D$ −55.1 (*c* 0.67, $CHCl_3$); IR 3222, 1749, 1712, 1686 cm^{-1}; ^1H NMR δ 7.60 (1H, d, J = 9.3 Hz), 5.90 (1H, d, J = 6.6 Hz), 5.78 (1H, dd, J = 6.3, 13.5 Hz), 4.86 (2H, m), 4.63 (1H, dd, J = 4.2, 9.9 Hz), 3.62 (1H, br s), 2.08 (1H, m), 1.26−1.82 (22H, m), 0.86−1.18 (18H, m); ^{13}C NMR δ 208.5, 173.1, 172.1, 171.7, 170.2, 170.1, 80.7, 72.8, 72.1, 70.6, 58.3, 56.5, 53.1, 43.0, 39.5, 36.6, 29.7, 25.3, 24.7, 24.5, 24.0, 23.6, 22.9, 21.4, 21.1, 19.8, 18.2, 16.5, 14.5, 10.5; FABMS 585.3360 [M + H]$^+$, calcd for $C_{29}H_{49}N_2O_{10}$, 585.3387.

2-Benzyloxy-*N*-(5-*s*-butyl-8,13-diisobutyl-2,10,10,16-tetramethyl-3,6,9,11,14,18-hexaoxo-1,4,12,15-tetraoxa-7-azacyclooctadec-17-yl)-3-formylaminobenzamide (53). Benzoic acid **3** (14.0 mg, 0.051 mmol), 1-hydroxybenzotriazole (7.0 mg, 0.051 mmol), EDCI (7.4 mg, 0.038 mmol), and *N*-methylmorpholine (20 μL, 0.18 mmol) were added successively to a solution of amine **4** (15.0 mg, 0.026 mmol) in DMF (1.5 mL) under N_2. The reaction mixture was stirred at ambient temperature for 11 h, and the reaction was terminated by addition of saturated $NaHSO_4$ (20 mL) and extracted with EtOAc (30 mL). The extract was dried and evaporated, and the residue was flash chromatographed (10 g, SiO_2, 2.2:1 hexane−EtOAc) to provide 13 mg (61%) of amide **53** as a colorless oil: TLC R_f 0.42 (2:1 hexane−EtOAc); $[\alpha]^{25}_D$ −45.7 (*c* 0.65, $CHCl_3$); IR 3321, 1745, 1678 cm^{-1}; ^1H NMR δ 8.45 (1H, d, J = 8.1 Hz), 8.20 (1H, d, J = 9.3 Hz), 8.10 (1H, s), 7.79 (1H, d, J = 6.0 Hz), 7.52 (1H, d, J = 9.3 Hz), 7.26−7.38 (7H, m), 6.05 (1H, d, J = 6.6 Hz), 5.86 (1H, dd, J = 8.2, 13.8 Hz), 5.45 (1H, d, J = 11.7), 5.36 (1H, m), 4.88 (3H, m), 4.56 (1H, d, J = 9.9 Hz), 2.10 (1H, m), 1.47−1.85 (8H, m), 1.13−1.42 (12H, m), 0.75−1.02 (18H, m); ^{13}C NMR δ 208.2, 173.3, 171.8, 170.0, 169.8, 167.9, 165.8, 146.0, 135.3, 131.5, 129.5, 129.2, 129.1, 126.5, 126.2, 125.5, 124.9, 80.9, 79.1, 72.6, 72.0, 71.2, 56.4, 55.9, 53.1, 43.1, 39.5, 36.6, 25.3, 24.6, 24.4, 24.1, 21.0, 19.8, 18.3, 16.6, 14.5, 10.4; MS APCI$^+$ 838.4131 [M + H]$^+$, calcd for $C_{44}H_{60}N_3O_{13}$, 838.4126.

***N*-(5-*s*-Butyl-8,13-diisobutyl-2,10,10,16-tetramethyl-3,6,9,11,14,-18-hexaoxo-1,4,12,15-tetraoxa-7-azacyclooctadec-17-yl)-3-formylamino-2-hydroxybenzamide (Respirantin 1b).** Amide **53** (15 mg, 0.018 mmol) and 10% Pd/C (17 mg) in EtOAc (3 mL) were stirred under a H_2 atmosphere at ambient temperature for 2 h. The solution phase was filtered through Celite and the solid phase washed with 1:1 EtOAc−CH_3OH (20 mL). The combined solvent filtrate and washings was evaporated and the residue flash chromatographed (10 g, SiO_2, 1:1 hexane−EtOAc) to afford 11 mg (82%) of **1b** as a glassy solid: TLC R_f 0.38 (50:50 hexane−EtOAc); $[\alpha]^{25}_D$ −6.0 (*c* 0.53, CH_3OH); IR 3325, 1749, 1708, 1687 cm^{-1}; ^1H NMR δ 12.51 (1H, br), 8.58 (1H, d, J = 8.0 Hz), 8.52 (1H, d, J = 1.5 Hz), 7.94 (1H, s), 7.47 (1H, d, J = 9.5 Hz), 7.36 (1H, d, J = 9.5 Hz), 7.15 (1H, d, J = 9.0 Hz), 6.97 (1H, t, J = 8.0 Hz), 6.03 (1H, dd, J = 2.7, 6.6 Hz), 5.86 (1H, q, J = 6.8 Hz), 5.21 (1H, dd, J = 2.7, 8.7 Hz), 4.94 (1H, ddd, J = 3.8, 9.9, 11.0 Hz), 4.86 (1H, d, J = 9.6 Hz), 4.68 (1H, dd, J = 4.5, 9.9 Hz), 2.12 (1H, m), 1.50−1.90 (10H, m), 1.24−1.44 (12H, m), 0.90−1.02 (16H, m); ^{13}C NMR δ 208.1, 173.4, 171.8, 170.4, 169.9, 169.5, 167.5, 159.0, 150.6, 127.5, 125.0, 120.3, 119.1, 112.8, 80.9, 72.3, 72.0, 71.5, 56.4, 55.6, 53.0, 43.1, 39.4, 36.5, 25.3, 24.7, 24.5, 24.1, 23.6, 22.8, 21.4, 21.0, 19.8, 18.2, 16.6, 14.4, 10.4; MS APCI$^+$ 748.3631 [M + H]$^+$, calcd for $C_{37}H_{54}N_3O_{13}$, 748.3657.

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