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A Straightforward Protocol for the Solution-Phase Parallel Synthesis of Ceramide Analogues

Santiago Grijalvo,[a,b] Xavier Matabosch,[a] Amadeu Llebaria,[a] and Antonio Delgado*[a,b]

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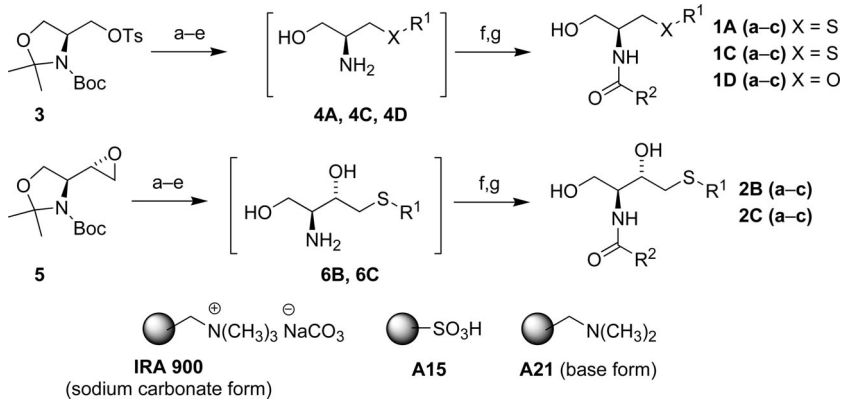
A simple solution-phase protocol for the synthesis of ceramide analogues from easily accessible enantiopure scaffolds is disclosed. The method relies on the use of nucleophilic thiolates or phenoxides and appropriate supported reagents or scavengers to give the target compounds in good overall yields. The method is easily adaptable to combinatorial protocols and also amenable to automated processes for the generation of small-to-medium-sized libraries for further screening.

Introduction

Sphingolipids are an important group of biomolecules that play important functions in the regulation of many cell functions and also as cell membrane components.[1] From a structural standpoint, they all share a sphingoid base consisting of a 2-amino-1,3-diol core and an unsaturated hydrocarbon chain.[2] *N*-Acylation of the sphingoid base leads to ceramide, which plays a pivotal role in sphingolipid biosynthesis and metabolism. In order to better understand the biological and biophysical roles of sphingolipids, many efforts have been made to design analogues to enable a detailed study of the structure–activity relationships.[3] Very recently, we reported on a new class of sphingosine-1-phosphate and ceramide analogues that incorporate a bioisosteric sulfur atom as part of the sphingoid backbone.[4,5] On the basis of these precedents, we became interested in "second generation" analogues containing both a sulfur atom and the 3-hydroxy motif present in natural sphingolipids. In addition, the possibility to gain access to oxygen analogues seemed also promising for structure–activity studies.



Scheme 1. Reagents and conditions: (a) R^1SH (**A**–**C**) or R^1OH (**D**), NaH, DMF, 60–90 °C; (b) 20% TFA/DCM, r.t.; (c) IRA900 ($NaCO_3^-$ form), EtOAc, r.t.; (d) Amberlyst A15, DCM, r.t.; (e) $MeOH/NH_3$, r.t.; (f) PS-EDC, R^2COOH (**a**–**c**), solvent, r.t.; (g) Amberlyst A21, DCM, r.t.

Combinatorial chemistry has become a useful tool for the discovery and development of new bioactive compounds. An efficient combinatorial approach for library generation and high-throughput screening requires minimal methodological complexity with maximal synthetic effi-

[a] Research Unit on BioActive Molecules (RUBAM), Departament de Química Orgànica Biològica, Institut d'Investigacions Químiques i Ambientals de Barcelona (IIQAB-C.S.I.C), Jordi Girona 18–26, 08034 Barcelona, Spain
Fax: +34-932-045-904
E-mail: adelgado@cid.csic.es
[b] Universitat de Barcelona, Facultat de Farmàcia, Unitat de Química Farmacèutica (Unitat Associada al CSIC), Avgda. Juan XXIII, s/n, 08028 Barcelona, Spain

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ciency. In this context, the use of classical solution-phase methods has gained new impetus with the use of solid-supported reagents and scavengers.[6] In this context, we have developed a fast and reliable methodology, amenable to combinatorial protocols, to gain access to the new families of ceramide analogues **1** and **2** (Scheme 1). Interestingly, despite the fact that we[7] and others[8,9] have recently reported on combinatorial approaches to the synthesis of these kinds of analogues, examples in the literature on this topic are still scarce.

Results and Discussion

The methodology here reported starts from enantiopure scaffolds **3**[5] and **5**,[10] which are easily available from Garner aldehyde following described methods. To exemplify the versatility of our synthetic protocol, the above scaffolds were treated with thiols **A**–**C** and carboxylic acids **a**–**c** to afford a small test library in excellent purities and good overall yields (Table 1, Scheme 1).

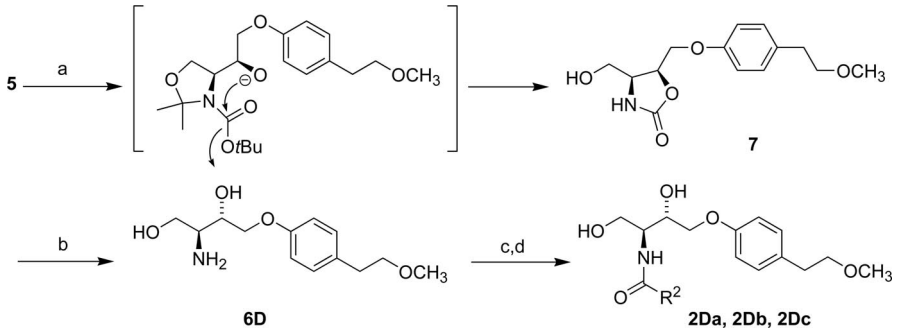
It is worth mentioning that the overall three-step process can be carried out without isolation of any of the synthetic intermediates leading ultimately to the target compounds in high purities and acceptable yields. Workup protocols are reduced to a minimum with the help of supported scavengers and reagents (Scheme 1).

The reaction took place both with aliphatic and aromatic thiols **A**–**C** and carboxylic acids **a**–**c** with different steric and/or electronic demands. Nucleophilic displacement of the tosyloxy group in **3** or epoxide opening in **5** was carried out by the corresponding thiolates, which were generated in situ under basic conditions.[5] Acetonide hydrolysis and *N*-Boc removal was carried out simultaneously in acidic medium (TFA/DCM) to afford corresponding amines **4** and **6** (trifluoroacetate salts), together with the excess thiol of the previous step. Purification at this stage was carried out by amine deprotonation with Amberlyst A21 resin (sodium carbonate form) and subsequent capture of the free amine with the sulfonic acid resin A15.[11,17] Amines **4** and **6** were finally released by treatment with 2 M NH_3 in MeOH, fil-

Table 1. Solution-phase synthesis of Cer analogues by using solid-supported reagents and scavengers.

Entry	Scaffold	R^1SH	R^2COOH	Compound	Yield [%]
1			$CH_3(CH_2)_5COOH$ (**a**)	**1Aa**	80
2		$CH_3(CH_2)_{13}SH$ (**A**)	$(CH_3)_3CCOOH$ (**b**)	**1Ab**	75
3			*p*-*t*BuPhCOOH (**c**)	**1Ac**	83
4			$CH_3(CH_2)_5COOH$ (**a**)	**1Ca**	75
5	**3**	2-naphthyl-SH (**C**)	$(CH_3)_3CCOOH$ (**b**)	**1Cb**	90
6			*p*-*t*BuPhCOOH (**c**)	**1Cc**	68
7			$CH_3(CH_2)_5COOH$ (**a**)	**1Da**	65
8		*p*-$(CH_3O(CH_2)_2$Ph-OH (**D**)	$(CH_3)_3CCOOH$ (**b**)	**1Db**	72
9			*p*-*t*BuPhCOOH (**c**)	**1Dc**	63
10			$CH_3(CH_2)_5COOH$ (**a**)	**2Ba**	69
11		$CH_3(CH_2)_{12}SH$ (**B**)	$(CH_3)_3CCOOH$ (**b**)	**2Bb**	79
12			*p*-*t*BuPhCOOH (**c**)	**2Bc**	69
13			$CH_3(CH_2)_5COOH$ (**a**)	**2Ca**	62
14	**5**	2-naphthyl-SH (**C**)	$(CH_3)_3CCOOH$ (**b**)	**2Cb**	88
15			*p*-*t*BuPhCOOH (**c**)	**2Cc**	52
16			$CH_3(CH_2)_5COOH$ (**a**)	**2Da**	65[a]
17		*p*-$[CH_3O(CH_2)_2]$Ph-OH (**D**)	$(CH_3)_3CCOOH$ (**b**)	**2Db**	72[a]
18			*p*-*t*BuPhCOOH (**c**)	**2Dc**	63[a]

[a] Overall yield including hydrolysis of **7** to give **6** (see Scheme 2).



Scheme 2. Reagents and conditions: (a) NaH, *p*-$[CH_3O(CH_2)_2]$Ph-OH (**D**), DMF, followed by steps b–e (Scheme 1); (b) 2 N NaOH/EtOH, 80 °C; (c) PS-EDC, R^2COOH (**a**–**c**), $CHCl_3$/*t*BuOH, r.t.; (d) Amberlyst A21, DCM, r.t.

tration, and concentration.[12] Acylations were carried out by coupling the product with the corresponding carboxylic acid in the presence of polymer-supported EDC (PS-EDC) in DCM at room temperature.[13] Only *N*-acylation compounds were observed by ^{1}H NMR spectroscopic analysis of the crude mixtures, and no trace amounts of *O*-acylated compounds were observed. Excess carboxylic acid was removed with the help of amino resin A21.[14]

Attempts to widen the reaction scope to phenoxides by taking phenol **D** as a model were also successful from tosylate **3**, which led to corresponding analogues **1D(a–d)** in good yields (Table 1). However, application of the above protocol to epoxide **5** led to oxazolidinone **7**,[15] which required a subsequent hydrolytic cleavage to **6D** for further amidation under the above conditions (Scheme 2). Nevertheless, although this additional step did not substantially affect the overall reaction yields (Table 1, Entries 16–18), the required isolation of **7** precludes the applicability of the above one-pot protocol.

Conclusions

A simple solution-phase protocol for the synthesis of ceramide analogues **1** and **2** from scaffolds **3** and **5** is disclosed. The method relies on the use of nucleophilic thiolates or phenoxides and the appropriate supported reagents or scavengers to obtain the target compounds in good overall yields. The method here reported is easily adaptable to combinatorial protocols and also amenable to automated processes for the generation of small-to-medium-sized libraries for further screening.

Experimental Section

General Methods: Unless otherwise specified, all moisture-sensitive reactions were handled under an argon atmosphere. All the materials were obtained commercially and used without further purification. Solvents were distilled prior to use and dried by standard methods.[16] Analytical samples were homogeneous as confirmed by TLC and afforded spectroscopic results consistent with the assigned structures. Melting points were determined with a SMP10 melting point apparatus and are uncorrected. Chemical shifts are reported in parts per million (ppm) relative to the singlet at δ = 7.24 ppm of $CHCl_3$ and 3.31 ppm of MeOH for ^{1}H NMR and to the centre line of the triplet at δ = 77.0 ppm of $CDCl_3$ and 49.0 ppm of MeOD for ^{13}C NMR. IR spectra were measured in film and were recorded with a BOMEM MB-120. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1} and were measured with a Perkin–Elmer 341 polarimeter. Thin-layer chromatography (TLC) was performed on silica gel (Alugram Sil G/UV). The following resins were used in this study: IRA900 (Fluka, ref 21850, 3.5 mmol g^{-1} $NaCO_3^-$ loading), Amberlyst A15 (Fluka, ref 06423, 4.7 meq g^{-1}), and PS-EDC (Fluka, ref 09657, 1.4 mmol g^{-1}). Amberlyst A21 (Aldrich, ref 216410, alkylamine, 4.7 meq mL^{-1}). Amberlite IR120 (Aldrich, ref 216534, 4.4 meq g^{-1}) was cleaned by washing several times with aqueous 1 M HCl and rinsed with water until neutral pH, followed by drying in vacuo for 15 h. Amberlyst A15 resin was conditioned as described in the literature.[17] Amberlyst A21, IRA900, and PS-EDC resins were used as received.

General Method for the Synthesis of Libraries 1 and 2: A solution of the corresponding thiol or phenol (0.25 mmol) in DMF (0.5 mL) was added dropwise to a suspension of NaH (ca. 60% dispersion in mineral oil, 12 mg, equivalent to 7 mg, 0.25 mmol) in DMF (0.5 mL) at room temperature. After 10 min, the resulting mixture was transferred by cannula to a solution of tosylate **3** (65 mg, 0.17 mmol) or epoxide **5** (45 mg, 0.18 mmol) in DMF (0.5 mL). The reaction mixture was stirred at 60–80 °C for 2 h, cooled to room temperature, and the solvents evaporated to dryness. The resulting residue was taken up in DCM (0.5 mL), treated with TFA in DCM (20% solution, 1.0 mL), and stirred at room temperature for 10 min. The solvent was next removed under vacuum to afford crude amino alcohols as the corresponding trifluoroacetate salts. The residue was taken up in EtOAc (1 mL) and treated with IRA 900 resin (sodium carbonate form, 600 mg, equivalent to 2.0 mmol, based on resin loading). After 1 h stirring, the resin was filtered off and washed thoroughly with EtOAc (3 × 5.0 mL). The combined filtrates were concentrated under vacuum, and the residue was taken up in DCM (3 mL). Amberlyst A15 resin (400 mg, equivalent to 2.0 mmol based on resin loading) was next added to the solution, and the mixture was stirred until disappearance of the amino alcohol (checked by TLC). The reaction mixture was filtered; the resin was suspended in a solution of NH_3 (2 M in MeOH, 5 mL) and agitated overnight. The resin was filtered off and washed thoroughly with additional NH_3 (2 M in MeOH, 3 × 2.0 mL). The filtrates were collected, and the solvents were evaporated to dryness to give amino alcohols **4(A,C,D)**, **6(B,D)** (see Scheme 1) or **7** (see Scheme 2).

Acylation step: A suspension of PS-EDC (250 mg, 0.35 mmol based on resin loading, previously swollen in 1 mL of $CHCl_3$ for 20 min) and the corresponding carboxylic acid (0.3 mmol) in $CHCl_3$ (0.5 mL) was stirred for 20 min. A solution of the above amino alcohols in DCM (1 mL, for amino alcohols **4**) or *t*BuOH (for amino alcohols **6**) was next added over the above suspension. After stirring for 16 h at room temperature, PS-EDC was filtered off and washed thoroughly with DCM (3 × 2.0 mL). The combined filtrates and washings were next treated with Amberlyst A21 (400 mg, equivalent to 2.0 mmol based on resin loading) and stirred until disappearance of the carboxylic acid (checked by TLC). The resin was filtered off and washed with additional DCM (3 × 2.0 mL). The combined filtrates were evaporated to dryness to afford the corresponding ceramide analogues **1(A,C,D)(a–c)** and **2(B,C,D)(a–c)**.

(*S*)-*N*-[1-Hydroxy-3-(tetradecylthio)propan-2-yl]heptanamide (1Aa): Yield: 56 mg, 80%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.07 (br. d, 1 H), 4.03 (m, 1 H), 3.78 (dd, J = 4.9 Hz, J' = 11.1 Hz, 1 H), 3.69 (dd, J = 3.7 Hz, J' = 11.1 Hz, 1 H), 2.71 (m, 2 H), 2.52 (m, 2 H), 2.21 (t, J = J' = 7.4 Hz, 2 H), 1.62 (m, 2 H), 1.56 (m, 2 H), 1.27 (m, 26 H), 0.87 (m, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.3, 64.6, 50.9, 37.0, 33.3, 32.7, 32.1, 31.7, 29.9, 29.9, 29.8, 29.8, 29.7, 29.5, 29.4, 29.1, 29.0, 25.8, 22.9, 22.7, 14.3, 14.2 ppm. IR (film): $\tilde{\nu}$ = 3230, 2954, 2923, 2856, 1705, 1592, 1459, 1182, 808, 745, 719 cm^{-1}. HRMS: calcd. for $C_{24}H_{50}NO_2S$ 416.3562; found 416.3565. $[\alpha]_D$ = +15.4 (c = 1.0, $CHCl_3$).

(*S*)-*N*-[1-Hydroxy-3-(tetradecylthio)propan-2-yl]pivaloylamide (1Ab): Yield: 49 mg, 75%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.32 (br. d, 1 H), 3.98 (m, 1 H), 3.77 (dd, J = 11.1 Hz, J' = 5.0 Hz, 1 H), 3.68 (dd, J = 11.1 Hz, J' = 3.3 Hz, 1 H), 2.72 (m, 2 H), 2.52 (m, 2 H), 1.56 (m, 2 H), 1.24 (m, 20 H), 1.21 (s, 9 H), 0.86 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.8, 65.0, 50.9, 39.1, 33.2, 32.5, 32.1, 29.9, 29.9, 29.8, 29.8, 29.7, 29.5, 29.4, 29.0, 27.7, 22.9, 14.3 ppm. IR (film): $\tilde{\nu}$ = 3376, 2926, 2854, 1641, 1509,

1461 cm^{-1}. HRMS: calcd. for $C_{22}H_{46}NO_2S$ 388.3249; found 388.3240. $[\alpha]_D$ = +8.38 (*c* = 1.0, $CHCl_3$).

(*S*)-4-*tert*-Butyl-*N*-[1-hydroxy-3-(tetradecylthio)propan-2-yl]benzamide (1Ac): Yield: 65.5 mg, 83%. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 8.39 Hz, 2 H), 7.45 (d, *J* = 8.35 Hz, 2 H), 6.81 (br. d, 1 H), 4.23 (m, 1 H), 3.91 (dd, *J* = 11.2 Hz, *J′* = 4.9 Hz, 1 H), 3.80 (dd, *J* = 11.2 Hz, *J′* = 3.7 Hz, 1 H), 2.83 (m, 2 H), 2.56 (t, *J* = *J′* = 7.4 Hz, 2 H), 1.58 (m, 2 H), 1.32 (s, 9 H), 1.24 (m, 22 H), 0.87 (t, *J* = *J′* = 7.4 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.2, 155.5, 131.3, 127.1, 125.7, 64.8, 51.3, 35.1, 33.4, 32.7, 32.1, 31.3, 30.0, 29.9, 29.8, 29.8, 29.8, 29.7, 29.5, 29.4, 29.0, 22.9, 14.3 ppm. IR (film): $\tilde{\nu}$ = 3423, 2961, 2870, 1718, 1640, 1532, 1499, 1463, 1211, 1071, 851, 813, 756 cm^{-1}. HRMS: calcd. for $C_{28}H_{50}NO_2S$ 464.3562; found 464.3552. $[\alpha]_D$ = +47.3 (*c* = 1.0, $CHCl_3$).

(*S*)-*N*-[1-Hydroxy-3-(2-naphthylthio)propan-2-yl]heptanamide (1Ca): Yield: 44 mg, 75%. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 1.5 Hz, 1 H), 7.77 (m, 3 H), 7.45 (m, 3 H), 6.08 (br. d, 1 H), 4.12 (m, 1 H), 3.88 (dd, *J* = 11.2 Hz, *J′* = 4.5 Hz, 1 H), 3.70 (dd, *J* = 11.2 Hz, *J′* = 3.8 Hz, 1 H), 3.28 (dd, *J* = 13.9 Hz, *J′* = 6.2 Hz, 1 H), 3.23 (dd, *J* = 13.9 Hz, *J′* = 6.8 Hz, 1 H), 2.10 (t, *J* = *J′* = 8.1 Hz, 2 H), 1.53 (m, 2 H), 1.24 (m, 6 H), 0.86 (t, *J* = *J′* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.2, 133.9, 132.8, 132.1, 128.9, 127.9, 127.5, 127.4, 127.3, 126.9, 126.1, 63.7, 51.1, 36.9, 34.4, 31.6, 29.0, 25.8, 22.7, 14.2 ppm. IR (film): $\tilde{\nu}$ = 3269, 2957, 2928, 2858, 2360, 1646, 1538, 1459, 1069, 1036, 812, 741 cm^{-1}. HRMS: calcd. for $C_{20}H_{28}NO_2S$ 346.1841; found 346.1835. $[\alpha]_D$ = +15.9 (*c* = 1.0, $CHCl_3$).

(*S*)-*N*-[1-Hydroxy-3-(2-naphthylthio)propan-2-yl]pivaloylamide (1Cb): Yield: 48.5 mg, 90%. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.88 (m, 1 H), 7.78 (m, 3 H), 7.47 (m, 3 H), 6.29 (br. d, 1 H), 4.11 (m, 1 H), 3.88 (dd, *J* = 11.1 Hz, *J′* = 4.6 Hz, 1 H), 3.72 (dd, *J* = 4.0 Hz, *J′* = 11.1 Hz, 1 H), 3.28 (m, 2 H), 1.15 (s, 9 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.6, 133.9, 132.8, 132.1, 129.0, 127.9, 127.7, 127.4, 126.9, 126.2, 64.0, 51.1, 39.0, 34.6, 27.6 ppm. IR (film): $\tilde{\nu}$ = 3327, 2965, 2933, 2364, 1636, 1510, 1202, 1071, 812, 738 cm^{-1}. HRMS: calcd. for $C_{18}H_{24}NO_2S$ 318.1528; found 318.1537. $[\alpha]_D$ = +26.1 (*c* = 1.0, $CHCl_3$).

(*S*)-4-*tert*-Butyl-*N*-[1-hydroxy-3-(2-naphthylthio)propan-2-yl]benzamide (1Cc): Yield: 45.5 mg, 68%. M.p. 120 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.90 (m, 1 H), 7.75 (m, 4 H), 7.49 (d, *J* = 8.60 Hz, 2 H), 7.45 (m, 2 H), 7.25 (d, *J* = 8.60 Hz, 2 H), 6.75 (br., 1 H), 4.34 (m, 1 H), 3.93–3.80 (m, 2 H), 3.34 (m, 2 H), 1.27 (s, 9 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.8, 155.2, 133.6, 132.6, 131.9, 130.7, 128.7, 127.5, 127.1, 126.7, 125.9, 125.2, 63.3, 51.5, 34.7, 31.6, 30.9 ppm. IR (film): $\tilde{\nu}$ = 3423, 2961, 2870, 1718, 1640, 1532, 1499, 1463, 1211, 1071, 851, 813, 756 cm^{-1}. MS (ESI): *m*/*z* = 416.5 $[M + 23]^+$. HRMS: calcd. for $C_{24}H_{28}NO_2S$ 394.1841; found 394.1838. $[\alpha]_D$ = +47.38 (*c* = 1.0, $CHCl_3$).

(*S*)-*N*-{1-Hydroxy-3-[4-(2-methoxyethyl)phenoxy]propan-2-yl}heptanamide (1Da): Yield: 37 mg, 65%. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.14 (d, *J* = 8.7 Hz, 2 H), 6.84 (d, *J* = 8.7 Hz, 2 H), 6.18 (br., 1 H), 4.27 (m, 1 H), 4.12 (dd, *J* = 9.5 Hz, *J′* = 4.1 Hz, 1 H), 4.05 (dd, *J* = 9.5 Hz, *J′* = 4.7 Hz, 1 H), 3.92 (dd, *J* = 11.2 Hz, *J′* = 4.5 Hz, 1 H), 3.77 (dd, *J* = 11.2 Hz, *J′* = 4.7 Hz, 1 H), 3.55 (t, *J* = *J′* = 7.0 Hz, 2 H), 3.34 (s, 3 H), 2.81 (t, *J* = *J′* = 7.0 Hz, 2 H), 2.21 (t, *J* = *J′* = 7.4 Hz, 2 H), 1.62 (m, 2 H), 1.27 (m, 6 H), 0.86 (t, *J* = *J′* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.1, 156.8, 132.1, 130.1, 114.6, 73.9, 67.6, 63.2, 58.8, 50.6, 36.9, 35.4, 31.7, 29.1, 25.8, 22.7, 14.2 ppm. IR (film): $\tilde{\nu}$ = 3293, 2924, 2857, 2365, 2332, 1637, 1536, 1511, 1462, 1238, 1047 cm^{-1}. HRMS: calcd. for $C_{19}H_{32}NO_4$ 338.2331; found 338.2336. $[\alpha]_D$ = –16.8 (*c* = 1.0, $CHCl_3$).

(*S*)-*N*-{1-Hydroxy-3-[4-(2-methoxyethyl)phenoxy]propan-2-yl}pivaloylamide (1Db): Yield: 38 mg, 72%. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.14 (d, *J* = 8.6 Hz, 2 H), 6.84 (d, *J* = 8.6 Hz, 2 H), 6.36 (br., 1 H), 4.23 (m, 1 H), 4.13 (dd, *J* = 9.6 Hz, *J′* = 4.1 Hz, 1 H), 4.06 (dd, *J* = 9.6 Hz, *J′* = 4.9 Hz, 1 H), 3.91 (dd, *J* = 11.2 Hz, *J′* = 4.5 Hz, 1 H), 3.76 (dd, *J* = 11.2 Hz, *J′* = 4.7 Hz, 1 H), 3.55 (t, *J* = *J′* = 7.0 Hz, 2 H), 3.34 (s, 3 H), 2.81 (t, *J* = *J′* = 7.0 Hz, 2 H), 1.20 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.2, 156.6, 131.8, 129.8, 114.4, 73.6, 67.2, 62.8, 58.5, 50.3, 38.7, 35.1, 27.4 ppm. IR (film): $\tilde{\nu}$ = 3376, 2964, 2934, 2869, 2358, 1647, 1509, 1465, 1240, 1110, 1045, 824 cm^{-1}. HRMS: calcd. for $C_{17}H_{28}NO_4$ 310.2018; found 310.2011. $[\alpha]_D$ = –14.5 (*c* = 1.0, $CHCl_3$).

(*S*)-4-*tert*-Butyl-*N*-{1-hydroxy-3-[4-(2-methoxyethyl)phenoxy]propan-2-yl}benzamide (1Dc): Yield: 41 mg, 63%. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 8.5 Hz, 2 H), 7.45 (d, *J* = 8.5 Hz, 2 H), 7.15 (d, *J* = 8.6 Hz, 2 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 6.82 (br., 1 H), 4.49 (m, 1 H), 4.22 (dd, *J* = 9.5 Hz, *J′* = 4.0 Hz, 2 H), 4.04 (dd, *J* = 11.2 Hz, *J′* = 4.4 Hz, 1 H), 3.88 (dd, *J* = 11.5 Hz, *J′* = 4.9 Hz, 1 H), 3.55 (t, *J* = *J′* = 7.0 Hz, 2 H), 3.34 (s, 3 H), 2.82 (t, *J* = *J′* = 7.0 Hz, 2 H), 1.65 (br., 1 H), 1.32 (s, 9 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.7, 156.6, 155.2, 131.9, 131.0, 129.8, 126.8, 125.4, 114.3, 73.6, 67.4, 62.9, 58.5, 50.7, 35.1, 34.8, 31.0, 29.6 ppm. IR (film): $\tilde{\nu}$ = 3389, 2967, 2934, 2872, 1641, 1611, 1536, 1510, 1461, 1235, 1107, 1039, 750 cm^{-1}. MS (ESI): *m*/*z* = 404 [M + 23]$^+$. HRMS: calcd. for $C_{23}H_{32}NO_4$ 386.2331; found 386.2332. $[\alpha]_D$ = –19.3 (*c* = 1.0, $CHCl_3$).

(2′*S*,3′*S*)-*N*-[1,3-Dihydroxy-4-(tridecylthio)-2-butyl]heptanamide (2Ba): Yield: 53.5 mg, 69%. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.37 (br., 1 H), 4.00 (dd, *J* = 11.5 Hz, *J′* = 3.0 Hz, 1 H), 3.94 (m, 1 H), 3.82 (m, 1 H), 3.68 (dd, *J* = 11.5 Hz, *J′* = 3.5 Hz, 1 H), 2.79 (m, 1 H), 2.59 (m, 1 H), 2.51 (m, 2 H), 2.22 (t, *J* = *J′* = 7.4 Hz, 2 H), 1.63 (m, 2 H), 1.56 (m, 2 H), 1.24 (m, 26 H), 0.87 (t, *J* = *J′* = 6.8 Hz, 3 H), 0.86 (t, *J* = *J′* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.8, 71.5, 62.2, 53.3, 37.1, 37.0, 32.2, 32.1, 31.7, 29.9, 29.8, 29.8, 29.7, 29.5, 29.4, 29.1, 29.0, 25.9, 22.9, 22.7, 14.3, 14.2 ppm. IR (film): $\tilde{\nu}$ = 3674, 3295, 2920, 2851, 2360, 1747, 1635, 1536, 1433, 1359 cm^{-1}. HRMS: calcd. for $C_{24}H_{50}NO_3S$ 432.3511; found 432.3498. $[\alpha]_D$ = +2.2 (*c* = 1.0, $CHCl_3$).

(2′*S*,3′*S*)-*N*-[1,3-Dihydroxy-4-(tridecylthio)-2-butyl]pivaloylamide (2Bb): Yield: 57 mg, 79%. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.55 (br., 1 H), 4.00 (dd, *J* = 11.5 Hz, *J′* = 3.1 Hz, 1 H), 3.91 (m, 1 H), 3.82 (m, 1 H), 3.68 (dd, *J* = 11.5 Hz, *J′* = 3.6 Hz, 1 H), 2.76 (m, 1 H), 2.60 (m, 1 H), 2.52 (m, 2 H), 1.56 (m, 2 H), 1.24 (m, 20 H), 1.22 (s, 9 H), 0.87 (t, *J* = *J′* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.2, 71.5, 62.3, 53.6, 39.0, 37.1, 37.0, 32.2, 32.1, 30.0, 29.9, 29.8, 29.8, 29.7, 29.7, 29.5, 29.4, 29.0, 27.7, 22.9, 14.3 ppm. IR (film): $\tilde{\nu}$ = 3233, 3134, 2923, 2853, 2360, 1637, 1586, 1537, 1456, 1371, 1082 cm^{-1}. HRMS: calcd. for $C_{22}H_{46}NO_3S$ 404.3198; found 404.3183. $[\alpha]_D$ = +2.6 (*c* = 1.0, $CHCl_3$).

(2′*S*,3′*S*)-4-*tert*-Butyl-*N*-[1,3-dihydroxy-4-(tridecylthio)-2-butyl]benzamide (2Bc): Yield: 59.5 mg, 69%. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.5 Hz, 2 H), 7.45 (d, *J* = 8.5 Hz, 2 H), 7.07 (br., 1 H), 4.15 (m, 1 H), 4.11 (m, 1 H), 3.96 (m, 1 H), 3.81 (dd, *J* = 11.5 Hz, *J′* = 3.5 Hz, 1 H), 2.79 (m, 2 H), 2.54 (m, 2 H), 1.56 (m, 2 H), 1.33 (s, 9 H), 1.24 (m, 20 H), 0.87 (t, *J* = *J′* = 6.7 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 400 MHz): δ = 167.7, 155.6, 131.2, 127.1, 125.7, 71.6, 62.3, 53.9, 35.1, 32.1, 31.4, 31.3, 29.9, 29.8, 29.8, 29.7, 29.7, 29.5, 29.4, 29.0, 22.9, 14.3 ppm. IR (film): $\tilde{\nu}$ = 3668, 2922, 2851, 2359, 1716, 1608, 1538, 1425, 1360 cm^{-1}. HRMS: calcd.

for $C_{28}H_{50}NO_3S$ 480.3511; found 480.3507. $[a]_D$ = +4.2 (*c* = 1.0, $CHCl_3$).

(2′*S*,3′*S*)-*N*-[1,3-Dihydroxy-4-(2-naphthylthio)-2-butyl]heptanamide (2Ca): Yield: 42 mg, 62%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.37 (br., 1 H), 4.00 (dd, *J* = 11.5 Hz, *J*′ = 3.0 Hz, 1 H), 3.94 (m, 1 H), 3.82 (m, 1 H), 3.68 (dd, *J* = 11.5 Hz, *J*′ = 3.5 Hz, 1 H), 2.79 (m, 1 H), 2.59 (m, 1 H), 2.51 (m, 2 H), 2.22 (t, *J* = *J*′ = 7.4 Hz, 2 H), 1.63 (m, 2 H), 1.56 (m, 2 H), 1.24 (m, 26 H), 0.87 (t, *J* = *J*′ = 6.8 Hz, 3 H), 0.86 (t, *J* = *J*′ = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.8, 71.5, 62.2, 53.3, 37.1, 37.0, 32.2, 32.1, 31.7, 29.9, 29.8, 29.8, 29.7, 29.5, 29.4, 29.1, 29.0, 25.9, 22.9, 22.7, 14.3, 14.2 ppm. IR (film): $\tilde{\nu}$ = 3674, 3295, 2920, 2851, 2360, 1747, 1635, 1536, 1433, 1359 cm^{-1}. HRMS: calcd. for $C_{21}H_{30}NO_3S$ 376.1946; found 376.1942. $[a]_D$ = +2.2 (*c* = 1.0, $CHCl_3$).

(2′*S*,3′*S*)-*N*-[1,3-Dihydroxy-4-(2-naphthylthio)-2-butyl]pivaloylamide (2Cb): Yield: 55 mg, 88%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.55 (br. d, 1 H), 4.00 (dd, *J* = 11.5 Hz, *J*′ = 3.1 Hz, 1 H), 3.91 (m, 1 H), 3.82 (m, 1 H), 3.68 (dd, *J* = 11.5 Hz, *J*′ = 3.6 Hz, 1 H), 2.76 (m, 1 H), 2.60 (m, 1 H), 2.52 (m, 2 H), 1.56 (m, 2 H), 1.24 (m, 20 H), 1.22 (s, 9 H), 0.87 (t, *J* = *J*′ = 6.6 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.2, 71.5, 62.3, 53.6, 39.0, 37.1, 37.0, 32.2, 32.1, 30.0, 29.9, 29.8, 29.8, 29.7, 29.7, 29.5, 29.4, 29.0, 27.7, 22.9, 14.3 ppm. IR (film): $\tilde{\nu}$ = 3233, 3134, 2923, 2853, 2360, 1637, 1586, 1537, 1456, 1371, 1082 cm^{-1}. HRMS: calcd. for $C_{19}H_{46}NO_3S$ 348.1633; found 348.1616. $[a]_D$ = +2.6 (*c* = 1.0, $CHCl_3$).

(2′*S*,3′*S*)-*N*-[1,3-Dihydroxy-4-(2-naphthylthio)-2-butyl]benzamide (2Cc): Yield: 39.5 mg, 52%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.5 Hz, 2 H), 7.45 (d, *J* = 8.5 Hz, 2 H), 7.07 (br., 1 H), 4.15 (m, 1 H), 4.11 (m, 1 H), 3.96 (m, 1 H), 3.81 (dd, *J* = 11.5 Hz, *J*′ = 3.5 Hz, 1 H), 2.79 (m, 2 H), 2.54 (m, 2 H), 1.56 (m, 2 H), 1.33 (s, 9 H), 1.24 (m, 20 H), 0.87 (t, *J* = *J*′ = 6.7 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.7, 155.6, 131.2, 127.1, 125.7, 71.6, 62.3, 53.9, 35.1, 32.1, 31.4, 31.3, 29.9, 29.8, 29.8, 29.7, 29.7, 29.5, 29.4, 29.0, 22.9, 14.3 ppm. IR (film): $\tilde{\nu}$ = 3668, 2922, 2851, 2359, 1716, 1608, 1538, 1425, 1360 cm^{-1}. HRMS: calcd. for $C_{25}H_{30}NO_3S$ 424.1947; found 424.1953. $[a]_D$ = +4.2 (*c* = 1.0, $CHCl_3$).

(2′*S*,3′*S*)-*N*-{1,3-Dihydroxy-4-[4-(2-methoxyethyl)phenoxy]-2-butyl}heptanamide (2Da): Yield: 43.6 mg, 66%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 (d, *J* = 8.5 Hz, 2 H), 6.84 (d, *J* = 8.5 Hz, 2 H), 6.36 (br., 1 H), 4.13 (m, 2 H), 4.02 (m, 3 H), 3.75 (m, 1 H), 3.56 (t, *J* = *J*′ = 7.0 Hz, 2 H), 3.34 (s, 3 H), 2.82 (t, *J* = *J*′ = 6.9 Hz, 2 H), 2.24 (t, *J* = *J*′ = 7.0 Hz, 2 H), 1.63 (m, 2 H), 1.28 (m, 6 H), 0.87 (t, *J* = *J*′ = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.6, 156.6, 132.3, 130.1, 114.7, 73.9, 72.1, 69.3, 62.6, 58.8, 53.1, 36.9, 35.4, 31.7, 29.1, 25.9, 22.7, 14.2 ppm. IR (film): $\tilde{\nu}$ = 3301, 2933, 2857, 1642, 1550, 1514, 1242, 1114, 802 cm^{-1}. HRMS: calcd. for $C_{20}H_{34}NO_5$ 368.2437; found 368.2432. $[a]_D$ = +3.3 (*c* = 1.0, $CHCl_3$).

(2′*S*,3′*S*)-*N*-{1,3-Dihydroxy-4-[4-(2-methoxyethyl)phenoxy]-2-butyl}pivaloylamide (2Db): Yield: 31.2 mg, 56%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15 (d, *J* = 7.9 Hz, 2 H), 6.84 (d, *J* = 7.4 Hz, 2 H), 6.56 (br., 1 H), 4.15 (m, 1 H), 4.10 (m, 1 H), 4.01 (m, 3 H), 3.75 (m, 1 H), 3.56 (t, *J* = *J*′ = 7.0 Hz, 2 H), 3.34 (s, 3 H), 2.82 (t, *J* = *J*′ = 7.0 Hz, 2 H), 1.22 (s, 9 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 180.1, 156.6, 132.3, 130.1, 114.6, 73.9, 72.0, 69.4, 62.6, 58.9, 53.3, 39.0, 35.4, 27.7 ppm. IR (film): $\tilde{\nu}$ = 3386, 2932, 2360, 1640, 1512, 1242, 1109 cm^{-1}. HRMS: calcd. for $C_{17}H_{28}NO_4$ 310.2018; found 310.2011. $[a]_D$ = +2.2 (*c* = 1.0, $CHCl_3$).

(2′*S*,3′*S*)-4-*tert*-Butyl-*N*-{1,3-dihydroxy-4-[4-(2-methoxyethyl)phenoxy]-2-butyl}benzamide (2Dc): Yield: 39 mg, 52%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 7.6 Hz, 2 H), 7.46 (d, *J* = 8.2 Hz, 2 H), 7.14 (d, *J* = 8.2 Hz, 2 H), 7.09 (br., 1 H), 6.85 (d, *J* = 8.1 Hz, 2 H), 4.31 (m, 1 H), 4.27 (m, 1 H), 4.13 (m, 1 H), 4.09 (m, 2 H), 3.85 (m, 1 H), 3.55 (t, *J* = *J*′ = 6.9 Hz, 2 H), 3.34 (s, 3 H), 2.81 (t, *J* = *J*′ = 6.9 Hz, 2 H), 1.32 (s, 9 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.4, 156.6, 155.8, 132.3, 130.2, 130.1, 127.1, 125.8, 114.7, 73.9, 71.9, 69.4, 62.5, 58.8, 53.4, 35.4, 31.4, 31.3 ppm. IR (film): $\tilde{\nu}$ = 3384, 2966, 1643, 1509, 1242, 1116 cm^{-1}. HRMS: calcd. for $C_{24}H_{34}NO_5$ 416.2437; found 416.2446. $[a]_D$ = –2.1 (*c* = 1.0, $CHCl_3$).

(4*S*,5*S*)-4-(Hydroxymethyl)-5-{[4-(2-methoxyethyl)phenoxy]methyl}-oxazolidin-2-one (7): Yield: 48 mg, 95%. ^{1}H NMR (400 MHz, MeOD): δ = 7.14 (d, *J* = 8.69 Hz, 2 H), 6.87 (d, *J* = 8.69 Hz, 2 H), 4.99 (m, 1 H), 4.31 (dd, *J* = 10.7 Hz, *J*′ = 4.3 Hz, 1 H), 4.29 (dd, *J* = 10.7 Hz, *J*′ = 6.2 Hz, 1 H), 4.03 (m, 1 H), 3.70 (m, 2 H), 3.55 (t, *J* = *J*′ = 7.0 Hz, 2 H), 3.31 (s, 3 H), 2.78 (t, *J* = *J*′ = 7.0 Hz, 2 H), 2.78 (t, *J* = *J*′ = 7.0 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, MeOD): δ = 160.4, 157.0, 131.8, 129.7, 114.3, 77.2, 73.7, 66.0, 60.2, 57.5, 55.9, 34.9 ppm. IR (KBr): $\tilde{\nu}$ = 3321, 2632, 2543, 1735, 1515, 1321, 855 cm^{-1}. $[a]_D$ = +3.3 (*c* = 1.0, MeOH).

Basic Hydrolysis of 7: A mixture of oxazolidinone **7** (114 mg, 0.405 mmol), aqueous NaOH (2 N, 12 mL) and EtOH (12 mL) was heated at 80 °C for 3 h. The mixture was cooled to room temperature, the solvent was removed under vacuum, and the residue was taken up in Et_2O. The organic layer was washed with brine and dried, and the solvent was evaporated to give 98.3 mg (0.385 mmol, 95%) of amino alcohol **6D**, which was used in the acylation step without further purification.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR copies of all library members and compound **7**.

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[1] A. Morales, J. C. Fernandez-Checa, *Mini-Rev. Med. Chem.* **2007**, *7*, 371–382.
[2] J. Y. Liao, J. H. Tao, G. Q. Lin, D. G. Liu, *Tetrahedron* **2005**, *61*, 4715–4733.
[3] A. Delgado, J. Casas, A. Llebaria, J. L. Abad, G. Fabrias, *ChemMedChem* **2007**, *2*, 580–606.
[4] S. Grijalvo, A. Llebaria, A. Delgado, *Synth. Commun.* **2007**, *37*, 2737–2751.
[5] S. Grijalvo, C. Bedia, G. Triola, J. Casas, A. Llebaria, J. Teixido, O. Rabal, T. Levade, A. Delgado, G. Fabrias, *Chem. Phys. Lipids* **2006**, *144*, 69–84.
[6] S. V. Ley, I. R. Baxendale, *Nat. Rev. Drug Discovery* **2002**, *1*, 573–586.
[7] G. Villorbina, D. Canals, L. Carde, S. Grijalvo, R. Pascual, O. Rabal, J. Teixido, G. Fabrias, A. Llebaria, J. Casas, A. Delgado, *Bioorg. Med. Chem.* **2007**, *15*, 50–62.
[8] Y. T. Chang, J. Choi, S. Ding, E. E. Prieschl, T. Baumruker, J. M. Lee, S. K. Chung, P. G. Schultz, *J. Am. Chem. Soc.* **2002**, *124*, 1856–1857.
[9] J. Park, Q. Li, Y. T. Chang, T. S. Kim, *Bioorg. Med. Chem.* **2005**, *13*, 2589–2595.

[10] W. J. Moore, F. A. Luzzio, *Tetrahedron Lett.* **1995**, *36*, 6599–6602.
[11] I. R. Baxendale, G. Brusotti, M. Matsuoka, S. V. Ley, *J. Chem. Soc. Perkin Trans. 1* **2002**, 143–154.
[12] Some of the intermediate amines were checked by ^{1}H NMR spectroscopy and were consistently pure enough for the next step.
[13] M. C. Desai, L. M. S. Stramiello, *Tetrahedron Lett.* **1993**, *34*, 7685–7688.
[14] When required, traces of unreacted starting amine were removed with the acidic resin Amberlyte IR120 hydrogen form (Aldrich, ref 216534) as follows: A solution of the corresponding ceramide analogue in MeOH (2.0 mL) was treated with Amberlyte IR120 (100 mg, equivalent to 0.4 mmol based on resin loading) and stirred overnight at room temperature. The resin was filtered out, and the solution was evaporated to dryness to afford the required ceramide analogues.
[15] Formation of **7** can be interpreted as a result of an intramolecular displacement of the *tert*-butoxide group by a transient alkoxide. This process seems sensitive to the electronic effects of the aromatic ring, as the reaction from *p*-chloro-3-methylphenol led to an approximately 1:1 mixture of the intermediate oxazolidinone and the corresponding ceramide analogue. For a related example of this intramolecular cyclization, see: G. Triola, G. Fabrias, J. Casas, A. Llebaria, *J. Org. Chem.* **2003**, *68*, 9924–9932.
[16] D. D. Perrin, W. L. F. Armarego, *Purification of Laboratory Chemicals*, 3rd ed., Pergamon Press, Oxford, **1988**.
[17] Y. S. Liu, C. X. Zhao, D. E. Bergbreiter, D. Romo, *J. Org. Chem.* **1998**, *63*, 3471–3473.

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