# Enantiodivergent Biosynthesis of the Dimeric Sphingolipid Oceanapiside from the Marine Sponge *Oceanapia phillipensis*. Determination of Remote Stereochemistry

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**Abstract:** The absolute stereochemistry of oceanapiside, an antifungal α,ω-bis-aminohydroxylipid with four stereogenic centers from the marine sponge *Oceanapia phillipensis* Dendy, 1895, has been obtained as 2*S*,3*R*,-26*R*,27*R* from development and application of a general CD method based on superposition of additive exciton couplings in perbenzoyl derivatives of bis-amino alcohols. The method allows simultaneous determination of the local relative configuration at each of the termini of the long chain bis-aminolipid and also relates the absolute configuration of the two remote termini. Oceanapiside contains *erythro* and *threo* relative configurations at C1,2 and C26,27, respectively, but *opposite* absolute configurations at the amino substituted carbons C2 and C27 which implies an enantiodivergent biogenesis formally derived from both D- and L-amino acids.

## Introduction

Oceanapiside (**1**) is an antifungal glycosidic amino alcohol lipid isolated[1] from a temperate water marine sponge, *Oceanapia phillipensis* Dendy, 1895 (Haplosclerida, Phloeodictyidae) that belongs to a recently discovered class of $C_{28}-C_{30}$ bipolar sphingolipids, each member of which is functionalized *at both ends* of the long chain as vicinal amino alcohols. In the case of **1**, the two termini are not symmetrical; C-1 (α-terminus) is substituted with an additional primary hydroxyl group, but C-28 (ω-terminus) is a methyl group. Other sponge-derived dimeric amino alcohol lipids include leucettamols A (**2a**) and B (**2b**) from *Leucetta* sp.,[2] rhizochalin (**3**), from *Rhizochalina incrustata*,[3] compound BRS1 from an unidentified sponge,[4] and related compounds, coriacenins from the Mediterranean *Clathrina coriacea*,[5] and rhapsamine from the Antarctic *Leucetta leptorhapsis*.[6] The structures of the latter compounds represent the products of a remarkable biosynthesis, suggestive of D-sphingosine (*erythro*-D-*E*-2-amino-4-octadecene-1,3-diol) and fumonisin $B_1$ (**5b**), but involving a double functionalization of an as yet unidentified α,ω-difunctional lipid precusor. The *erythro*-2-amino-1,3-diol chain terminus of D-sphinganine (**4**)—the immediate biosynthetic precursor to D-sphingosine—is derived from L-serine and the 2-amino-3-ol terminus of **5b** derives from L-alanine.[7,8] D-Sphinganine has the *erythro* relative configuration and fumonisin $B_1$ is *threo*, but both retain the (2*S*)-configurations of their L-amino acid precursors. The biosynthesis of **1** appears to differ radically from that of **3** by the involvement of *both* serine and alanine for the α and ω termini, respectively. The identity of the long-chain acyl precursor to bipolar lipids such as **1**, or the steps involved in condensation with amino acid precursors, are as yet unknown.

Stereochemical analysis of **1** and other members of this class of lipids presents an interesting case-problem of remote stereochemistry. Although NMR and other methods can be applied for determination of local relative stereochemistry (*threo* or *erythro*) at each terminus, how can the two remote pairs of vicinal stereocenters be related to each other? A similar problem presented itself with fumonisin $B_2$ (**5a**) and related AAL mycotoxins where remote stereocenters are separated by linear chains containing of up to six $CH_2$ groups ($C_6$ segment). In the case of fumonisin $B_2$ (**5a**)[9] and AAL toxin $T_A$,[10] the assignment was successfully made by Kishi and co-workers through total synthesis of stereoisomers of each isolated segment, coupling of stereodefined segments—in all combinations—to generate stereoisomers and matching the correct stereoisomer with the natural product by relating the remote centers through small, mutual lanthanide-induced NMR shifts.[9]

The stereogenic elements in compound **1** and its analogues are α,ω-stereodiads that are effectively insulated by relatively large distances ($C_{22}$ segment, ∼25 Å), too great to take advantage of mutual lanthanide induced interactions. We now present a solution to this problem that is independent of transmitted or relayed intramolecular effects and circumvents the requirement for total synthesis. The method is sensitive and relies, instead, on the superposition of exciton coupling in circular dichroism (CD) spectra that arise from local effects, dependent on vicinal stereochemistry at each terminus, but independent from the other terminus. The additivity of exciton

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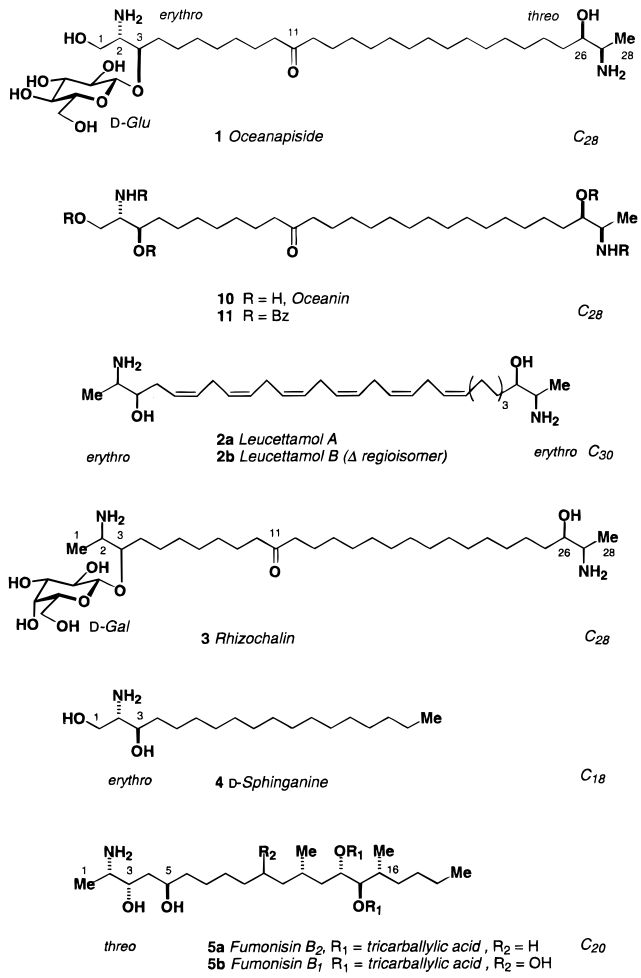
**Chart 1**




coupling has been exploited for characterizing configuration at multiple *local* stereocenters of many compounds, including polyols,[11−13] 1-aminopolyols.[14−16] Other chiroptical methods have been explored for stereochemical correlation of remote stereoelements based on van't Hoff's principle of optical superposition[17] and, more recently, ab initio computational methods for determining atomic contributions to optical rotation.[18−21] To the best of our knowledge, *superposition of excition coupled CD* has not been used in assigning the relationships between *very remote* stereoelements in acyclic molecules. In this report, we apply a novel CD analysis of derivatives of **1** to show that not only do the termini have different local stereochemistry (*erythro* and *threo* at C2,3 and C26,27, respectively), but the $NH_2$-substituted carbons at each end have *opposite absolute configurations* and, therefore, relate to amino acids of opposite absolute configuration. The stereochemical findings presented here suggest that **1** arises from enantiodivergent biogenesis that formally correlates with amino acids from antipodal series—L-serine at the hydroxymethylene terminus and D-alanine at the methyl terminus.[22]

Local exciton coupling effects in CD have been correlated with relative and absolute configuration of sphingolipids after derivatization of the natural product with aromatic chromophores. Nagai and co-workers[23a] showed that the diastereomers of optically pure *N*,*O*-bis-*p*-bromobenzoyl 2-amino-1-propanol are distinguishable by CD and provided a conformational analysis of contributions to exicton coupling from predominant gauche rotamers which determine the sign of the bisignate (split) CD spectrum. More recently, we extended this analysis to assignment of configuration of a marine-derived 1-amino-alken-2-ol.[23b] Kázmierczak et al.[24] made use of stronger bichromophoric interactions of *N*-phthalimido-*O*-benzoates of 2-amino-1-propanol. *N*-Phthalimides also confer the advantage of aligning the electronic transition dipole moment of the chromophore collinearly with the C−N bond, removing amide bond conformational dependence of the dipole vector. Suga and co-workers[25] exploited *N*,*O*,*O*′-tribenzoyl derivatives to confirm the configuration of D-sphingosine obtained from amphibian ceramides.[26] Nakanishi and co-investigators characterized all stereoisomers of sphingosine and sphinganine using an exceptionally sensitive CD method based on two-step conversion to fluorescent *N*-naphthimido-*O*,*O*′-dinaphthoates.[27,28] Unfortunately, for reasons outlined below, the two-step bichromophoric derivitization was not suitable for stereochemical analysis of **1**, and we chose a novel approach based on comparison of hybrid spectra constructed from the CD spectra of stereodefined *N*,*O*-perbenzoyl model amino alcohols.

## Results and Discussion

At the outset of this work, we recognized several criteria that must be met for CD stereochemical analysis of **1** and related compounds. First, we required that the amino alcohols be completely derivatized with only one aromatic reagent delivering a chromophore that would lend a sufficiently strong charge-transfer band to induce CD exciton coupling. The CD spectra of the derivatives should preferably show minimum fine structure which would compromise the fidelity of hybrid CD spectra obtained by linear combinations of CD spectra due to

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attendant errors in their measurement (typically ~±5%). We recognized, as have others,[27,28] that suitable derivatives should distinguish *erythro* and *threo* stereoisomers of aminoalkanols and aminoalkanediols while at the same time indicating absolute configuration. It was most important that derivatization of the OH and $NH_2$ groups should proceed with a one-reagent, one-step conversion to provide a penta-*O*,*N*-chromophoric derivative to avoid the expected difficulty of chromatographic separation of partially derivatized termini and the ambiguity associated with structural assignments of heterogeneous mixtures. After initial experimentation we found that simple conversion of amino alcohols to benzoate−benzamide chromophores was necessary and sufficient to fulfill all criteria.

There are 16 possible stereoisomers of **1** that comprise eight enantiomeric pairs of diastereomers. CD is a molar quantity that is equal and opposite for enantiomers; therefore, characteristic CD reference spectra would be required for only eight diastereomers. CD exciton coupling diminishes greatly with distance: the 22 carbons separating the termini eliminate intramolecular exciton coupling, and intramolecular effects will be negligible due to the high dilution of samples ($10^{-4}$−$10^{-5}$ M). The molar property of CD allows one to predict that the observed CD spectrum of **1** will be a sum of the expected local CD spectra at each terminus. Thus, the CD contributions at each terminus can be analyzed separately by measuring CD spectra of model compounds. Pairwise summation of all possible stereochemical permutations of termini would then generate eight hybrid CD spectra, representing the eight possible diastereomers of **1**. Because four distereomers of **1** have one end group enantiomeric to the other, the corresponding model CD spectra could be obtained simply by inverting the model spectra prior to combination into hybrid spectra. Therefore, it is possible to generate all eight required hybrid CD spectra by measuring CD of only four stereochemically defined model compounds—perbenzoyl derivatives of (2*S*,3*R*)-*erythro* and (2*S*,3*S*)-*threo* 2-amino-3-alkanols and 2-amino-1,3-alkanediols—that correspond to the ω- and α-termini, respectively. The natural product configuration would then emerge as the configuration of the single diastereomer whose hybrid spectrum uniquely matches the measured CD spectrum of a perbenzoyl derivative of **1** or to its mirror image.

It was necessary to remove the D-glucosyl group of **1** prior to derivatization. Oceanin (**10**), the aglycone of **1**, was obtained by acid-catalyzed methanolysis (MeOH, HCl, 60 °C, 16 h)[1] and converted to the *N*,*O*-pentabenzoyl derivative **11** (BzCl, py, DMAP, 80 °C, 31%). CD spectra of **11** measured in either MeOH (Figure 3) or $CH_3CN$ showed a characteristic bisignate CD curve due to the summation of all *local* pairwise exciton couplings between benzamide and benzoate chromophores, but as expected, resolution of individual CD contributions were not apparent. We describe below how the CD spectrum of **1** is deconvoluted into unique contributions from the terminal stereochemical diads by comparison with hybrid spectra of all possible diastereomers of **11**.

The model aminohexanols **6a**−**9a** were selected based on the expectation that both *erythro* and *threo* diasteromers could be synthesized from common intermediates and that the truncated side chains would faithfully reproduce the dominant local influences of exciton coupling in the CD spectrum of perbenzoyl derivative of **1**. Syntheses of the model compounds were straightforward, beginning with the amino acids L-alanine and L-serine. The known aldehyde **12**, prepared from L-alanine in three steps,[29,30] was treated with *n*-PrMgCl ($Et_2O$, 0 °C) according to Reetz et al.[30] to give a mixture of two diastereomeric alcohols (dr 1:30) from which the predominant *erythro* isomer **13** was isolated by silica chromatography. Pure *threo* stereoisomer **14** was more conveniently prepared from **12** by Lewis-acid-catalyzed chelate-controlled addition of allyltri-

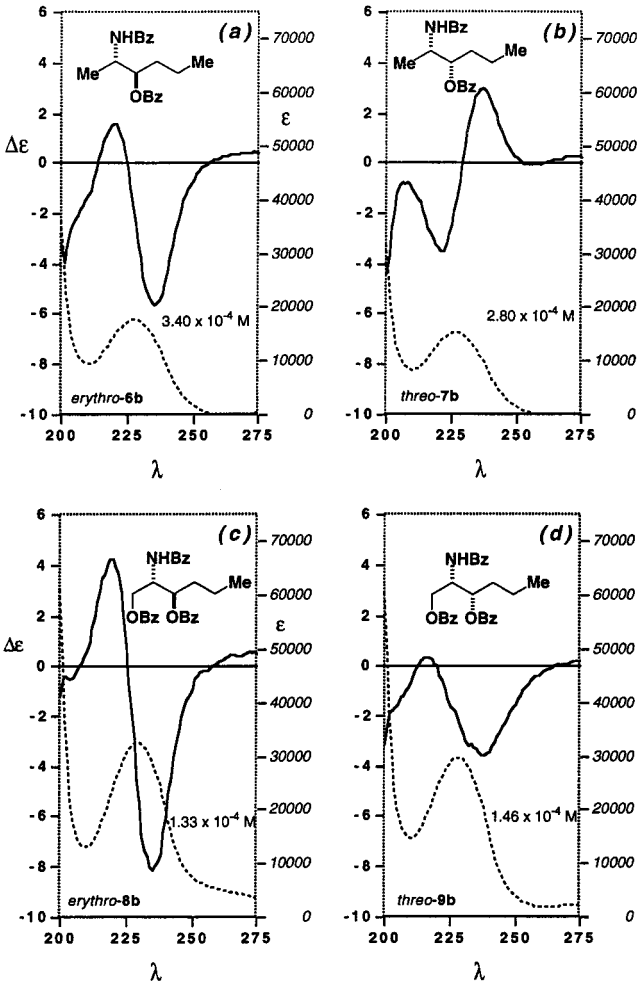



**Figure 1.** CD and UV spectra of model compounds **6b**−**9b** (MeOH, 25 °C).

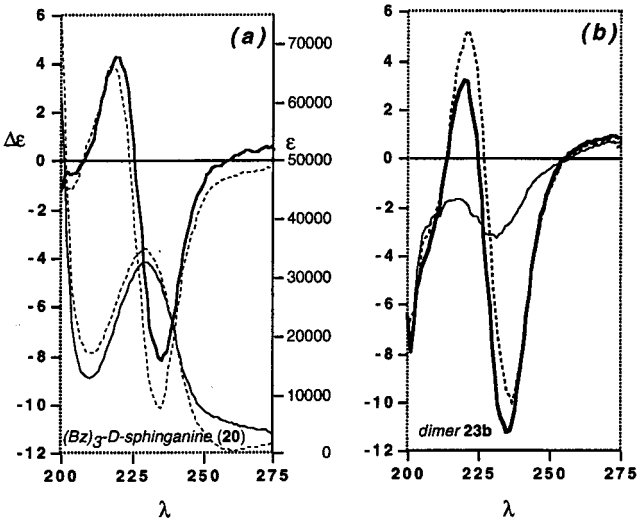
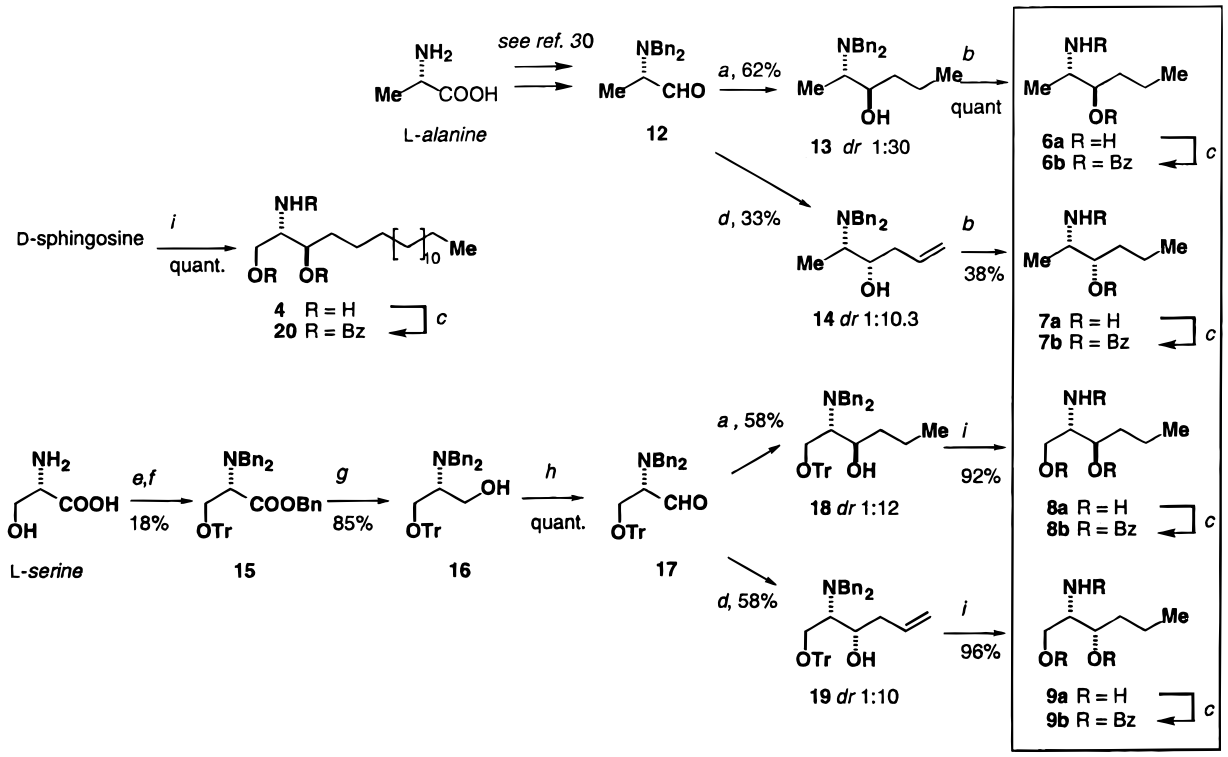



**Figure 2.** (a) CD and UV spectra (MeOH, 25 °C) of *N*,*O*,*O*′-tribenzoyl D-sphinganine (**20**, dashed line) overlayed with spectrum of *erythro*-**8b** (solid line). (b) CD spectrum of dimer **23b** (dashed line) overlayed with hybrid spectrum *erythro*-**6b**+*erythro*-**6b** (solid, heavy) and *erythro*-**6b**+*threo*-**7b** (solid, light). See Supporting Information for complete set of hybrid spectra corresponding to the six diastereomers of **23b**.

**Scheme 1**[a]



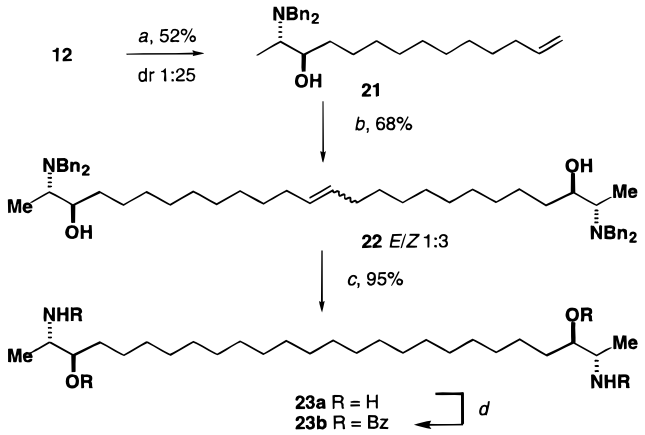

[a] (a) *n*-Propylmagnesium bromide, $Et_2O$, 0 °C; (b) $H_2$, Pd−C, MeOH; (c) BzCl, DMAP, py; (d) allyltrimethylsilane, $SnCl_4$, $CH_2Cl_2$, −78 °C; (e) BnBr, $K_2CO_3$, KOH aq, 100 °C; (f) TrCl, py, 100 °C; (g) $LiAlH_4$, $Et_2O$; (h) DMSO, $(COCl)_2$, $Et_3N$, $CH_2Cl_2$; (i) $H_2$, 10% Pd−C, MeOH, HCl aq.

methylsilane ($SnCl_4$, −78 °C, $CH_2Cl_2$, 33%, dr 1:10.3). The two diastereomers were separately hydrogenolyzed ($H_2$, Pd−C, MeOH)[30] to give amino alcohols **6a** and **7a**, respectively, which were converted (BzCl, pyridine, 60 °C) to their *N*,*O*-dibenzoyl derivatives **6b** and **7b**. Final purification of **6b**, **7b**, and all model compounds described below, was carried out using silica HPLC (>95% pure).

The *N*,*O*,*O*-tribenzoyl derivatives **8b** and **9b** were prepared in an analagous manner. L-Serine was transformed into the *N*,*O*,*O*-tribenzyl derivative[29] which was then protected (TrCl, pyridine, DMAP, 90 °C) as trityl ether **15**. Reduction of **15** (LAH, THF) to alcohol **16** followed by Swern oxidation[31] gave L-serinal derivative **17** and set the stage for repetition of the above-described organometallic addition reactions to provide **18** (58%) and **19** (58%) with high diastereoselectivity (ds 1:12 and 1:10, respectively). $^1$H NMR analysis of the *S* Mosher's esters[32] of secondary alcohols **18** and **19** confirmed the optical purity of each as >95% ee. Deprotection−hydrogenation of **18** and **19** ($H_2$, Pd−C, MeOH, HCl) gave aminodiols **8a** and **9a**, respectively, and the latter were converted into the corresponding tribenzoyl derivatives **8b** and **9b** as before.

The lipid side chain in **10** was expected to exert some influence on gauche conformer populations at the functionalized termini that in turn govern the appearance of the split-Cotton effects in the CD spectrum of **11**. The effects were expected to be negligible beyond about 3 × $CH_2$ groups (1,5-pentane interaction). Nevertheless, to provide comparisons with the shorter chain models **6**−**9** and validate the choice of truncated side chains, a long-chain model was prepared (Scheme 1). Hydrogenation of D-sphingosine ($H_2$, 1 atm, MeOH, 10% Pd−C, quantitative) gave **4** which was subjected to exhaustive benzoylation (BzCl, pyridine, 60 °C) and purification by silica HPLC to provide the known derivative *N*,*O*,*O*′-tribenzoylsphinganine (**20**).[25,33] A dimeric bipolar α,ω-bis-amino alcohol **23a** (Scheme 2) was also prepared. Addition of 10-undecenylmagnesium bromide (prepared from 11-bromo-1-undecene and Mg turnings in THF) to **12** (THF, 0 °C) gave **21** with high diastereoselectivity (52%, ds 1:25). The purified *erythro* amino alcohol **21** was dimerized by olefin metathesis coupling (Grubbs's catalyst: bis(tricyclohexylphosphine)benzylidene-

**Scheme 2**[a]




[a] (a) 11-Undecenylmagnesium bromide, THF, 0 °C; (b) dichlorobis(tricyclohexylphosphine)benzylideneruthenium (IV) dichloride (Grubbs's catalyst[34]), $CH_2Cl_2$ 42 °C; (*c*) $H_2$, $Pd(OH)_2$, MeOH/EtOAc (1 M HCl); (*d*) BzCl, DMAP, py, 25 °C.

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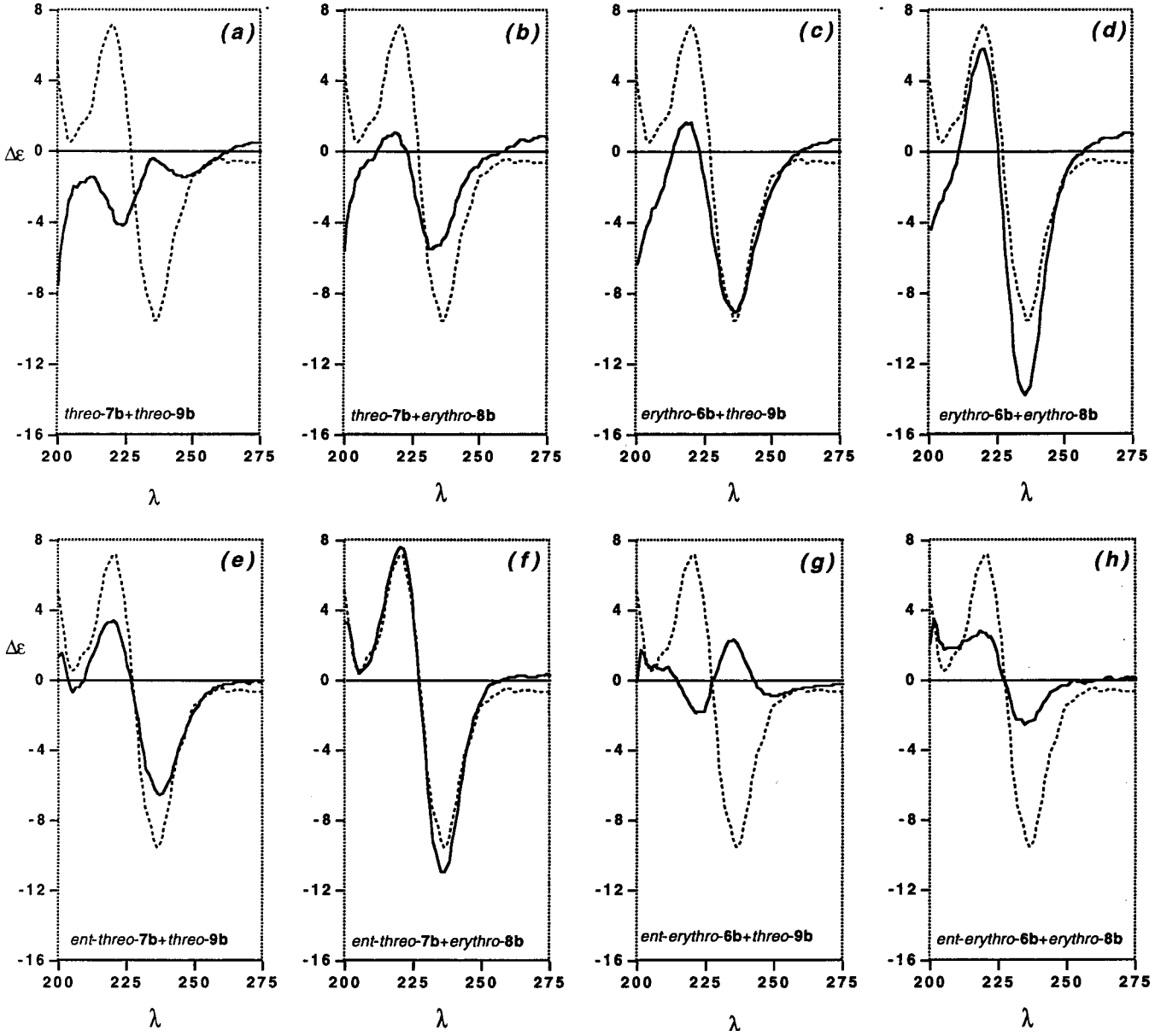


**Figure 3.** Hybrid CD spectra generated by linear combinations of model compound spectra (MeOH, 25 °C). Overlayed spectrum (dashed line) is CD of *N*,*N*′,*O*,*O*′,*O*″-pentabenzoyloceanin (**11**) (MeOH, 25 °C).

ruthenium(IV) dichloride,[34] $CH_2Cl_2$, [**21**] = 56 mM) to give the $C_{26}$ olefin **22** (68%) as a 1:3 *E*/*Z* mixture. Hydrogenation of **22** ($H_2$, $Pd(OH)_2$, MeOH/EtOAc, HCl) gave the $C_2$ symmetrical bis-amino alcohol **23a** (95%) which was converted to the perbenzoyl derivative **23b**.

The CD spectra of model compounds **6b**−**9b**, recorded in MeOH at 25 °C, are shown in Figure 1. We were pleased to find that the perbenzoyl derivatives **6b**−**9b** of amino alcohols and aminodiols exhibited characteristic bisignate CD spectra with Cotton effects (CE's) that distinguished both relative and absolute stereochemistry within the respective *threo* and *erythro* series. Spectra recorded in MeOH and $CH_3CN$ showed some qualitative and quantitatitve differences. The magnitudes of CD split-Cotton effects were slightly larger in $CH_3CN$ (see Supporting Information) for most compounds, but the diastereomers of sphinganine-like derivatives **8b** and **9b** were more readily distinguished in MeOH. In MeOH, *erythro*-**6b** showed a negative split Cotton effect ($\lambda$ 235 nm, $\Delta\epsilon$ −5.63; 220 nm, $\Delta\epsilon$ 1.59). The CE's were reversed in sign for the *threo* isomer **7b** ($\lambda$ 237 nm, $\Delta\epsilon$ +3.00; 221 nm, $\Delta\epsilon$ −3.53) and diminished in intensity. The *A* values—defined as the amplitude range of the negative and positive components of the split CE[26]—were larger for the *erythro* isomer **6b** ($A = 7.2$) than the *threo* isomer ($A = 6.5$). The same qualitative trend was observed for **6b** and **7b** in $CH_3CN$.

The 2-amino-1,3-alkanediol tribenzoyl derivatives **8b** and **9b** showed stronger CD effects due to additional exciton coupling contributions from the primary *O*-benzoyl chromophore, with the sign of the long wavelength CE dominated by the configuration at C2. In contrast to the amino alcohol series, the CD spectra (MeOH) of **8b** and **9b** were difficult to distinguish on sign alone as each spectrum showed a negative CE at $\lambda \sim 236$ nm with only a weak positive CE at $\lambda \sim 220$ nm, but the overall asymmetry of the two CD curves were clearly different. The *erythro* isomer **8b** showed a strong negative bisignate Cotton effect ($\lambda$ 235 nm, $\Delta\epsilon$ −8.13; 220 nm, $\Delta\epsilon$ +4.26) while the *threo* isomer **9b** also exhibited a negative long-wavelength CE, albeit with diminished intensity of the positive CE ($\lambda$ 237 nm, $\Delta\epsilon$

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−3.57; 216 nm, $\Delta\epsilon$ +0.34). Although the short-wavelength CE in **9b** appears to be blue-shifted ($\lambda_{max}$ 216 nm), this is an artifact due to band overlap with a weak CE below 200 nm. When the spectra of **6b**−**9b** were run in $CH_3CN$ the signs of the CD spectra were qualitatively and quantitatively similar with a small blue-shift ($\Delta\lambda_{max} \sim 2$ nm). The Cotton effects for *erythro* **8b** in $CH_3CN$ were strong [$\lambda$ 233 nm, $\Delta\epsilon$ −9.81; 218, $\Delta\epsilon$ +2.57, $A = 12.4$] while CE amplitudes for the *threo* **9b** were slightly diminished [$\lambda$ 235 nm ($\Delta\epsilon$ −2.86) and 217 ($\Delta\epsilon$ +0.2), $A = 3.1$] with respect to samples run in MeOH.

The CD spectrum (Figure 2a) of *erythro* D-sphinganine derivative **20** in MeOH [$\lambda$ 235 nm, $\Delta\epsilon$ −10.1; 218, $\Delta\epsilon$ +3.86, $A = 14.0$] was a good match with that of *erythro* **8b** showing that the short chain $C_6$ model faithfully reproduces the important chain-length influences on the split-CE effects of $C_{18}$ **20** with reasonable accuracy. The CD spectrum of dimeric bis-amino alcohol derivative **23b** (Figure 2b) was also found to be a good match for the homologous hybrid spectrum generated by doubling the CD spetrum of **6b** (2 × *erythro* **6b** shown in Figure 1a), but a poor match for *erythro* **6b**+*threo* **7b** or *threo*-**7b**+*threo*-**7b** (see Supporting Information for complete set of spectra). Note that the *ent-erythro* **6b**+*erythro* **6b** or *ent-threo* **7b**+*threo* **7b** combinations represent *meso* compounds that would be easily revealed by zero-line CD spectra.

The utility of the benzoyl derivatives in definining both relative and absolute configuration of 2-amino-3-alkanols and 2-amino-1,3-alkanediols were clearly established for the simple models **6b**−**9b**. Hybrid spectra were now constructed by linear combinations of spectra all *diastereomeric* combinations of *erythro*-**6b** and **8b** with *threo*-**7b** and **9b**. Stereochemical combinations involving *ent-threo*-**7b** and *ent-erythro*-**6b** were generated by first inverting the corresponding spectra. The eight unique hybrid spectra are shown in Figure 3 (the spectra of the enantiomeric series are not shown) overlayed against the CD spectrum of the natural product derivative **11**.

Like the model compounds, the eight hybrid CD spectra representing diastereomers of **11** are uniquely distinguished by shape, sign and magnitude of CE's as a result of cancellation or reinforcement of spectral features present in the component CD spectra (Figure 3). It is important to recognize that each of the hybrid spectra in Figure 3 have CE intensities asymmetrically skewed about either side of $\Delta\epsilon = 0$ line and allow clear discrimination of each of the eight diastereomers from their corresponding enantiomers. This is due in part to the fortuitous advantage that the two termini in **1** are substituted differentially by OH and $NH_2$ groups. The strongest intensity hybrid split-CE spectra (Figure 3d and 3f) are seen for combinations of strongly split-CE's of the same absolute configuration at the *O*-Bz-substituted position C3 ($A = 19.6$ and $A = 18.9$, respectively). The weakest *A* values are seen for the heterologous combinations of *threo*-**7b** + *threo*-**9b** (Figure 3a, $A = 3.8$) and *ent-erythro*-**7b**+*threo*-**9b** (Figure 3g, $A = 3.3$) where cancelation of stronger long-wavelength CE's ($\lambda \sim 233$ nm) are expected.

It is easily seen that the one excellent match for the CD spectrum of the oceanapiside derivative **11** is the spectrum of Figure 3f representing the chain termini heterologous combination of *ent-threo*-**7b**+*erythro*-**8b**. CD spectrum 3f is clearly distinguished from the other seven hybrid spectra by sign and intensity. The two closest mismatches for **11** are represented by spectra 3c and 3d. The relative configuration of *erythro*-**6b**+*erythro*-**8b** represented by the latter spectrum is ruled out by the higher intensity long-wavelength negative CE ($\lambda$ 233 nm, $\Delta\epsilon$ −13.8, cf. **11**, $\Delta\epsilon$ −9.6), while the relative configuration corresponding to spectrum 3c is eliminated by mismatch of the short-wavelength positive CE ($\lambda$ 220, $\Delta\epsilon$ +1.92, cf. **11**, $\Delta\epsilon$ +7.1) and strong negative slope near $\lambda$ 200 nm. A second CD comparison of oceanapiside derivative **11**, this time with spectra recorded in $CH_3CN$ (Figure 4−see also Table 2, Supporting Information) again gave the unique match of **11** with *ent-threo*-**7b** and *erythro*-**8b**. Moreover, assignment of *relative* configuration at each terminus in **11** is provided by examination of $^1$H NMR chemical shift and *J* values and comparison with those of model compounds **6b**−**9b**, **20**, **23b** (see Table 1). Coupling constants were obtained from extensive single-frequency homodecoupling experiments and $^1$H NMR shift assignments were confirmed by COSY experiments at 400 or 500 MHz. The relative stereochemistry of the 2-amino-3-alkanol terminus is correlated unambiguously with vicinal coupling of H2−H3 in the dibenzoyl derivatives **7b**, **11**, and **23b** (*threo* $J = 5.2$ Hz; *erythro* $J = 2.6$−$2.7$ Hz) and compound **11** clearly has the *threo*-$\omega$ terminus ($J = 5.2$ Hz). Assignment of coupling constants in the 2-amino-1,3-alkanediol series (**8b**, **9b**, and **20**) were more equivocal, but in this case the chemical shifts of the C2−NH signal were unmistakably correlated with stereochemistry. The *threo* isomers exhibit a downfield shift of C2−NH ($\Delta\delta$ 0.5−0.6 ppm) due to an intramolecular hydrogen bond between NH and the 3-*O*-benzoyloxy group that is favored in the dominant gauche conformation of these stereoisomers in $CDCl_3$. The characteristic downfield shift of the *threo* benzamido NH group is also seen in the 2-amino-3-alkanol series.

The NMR evidence provides independent assignment of terminal *local* stereochemistry of **11** which constrains the possible diastereomeric diad combinations to those represented by Figures 3b and 3f. Because $^1$H NMR shows that the stereochemistry of **11** is *erythro*-,*threo*- at the $\alpha$,$\omega$-termini, the CD shows with certainty that **11** can only have the absolute configuration depicted in Figure 3f. Thus it is concluded that **11** and (−)-oceanpiside (**1**) have the absolute configuration 2*S*,3*R*,26*R*,27*R*.

Studies of the biosynthesis of sphinganine (**4**)[35] and AAL-fumonisin mycotoxin family[36] reveal a conservative trait for incorporation of intact $\alpha$-and $\beta$-carbons from amino acid L-serine (in the case of AAL toxin TA and fumonisin $B_1$, it is L-alanine[7,8] and glycine,[36] respectively). The pyridoxal phosphate-dependent condensation of palmitoyl CoA with L-serine is catalyzed by 3-ketosphinganine synthase to give 3-ketosphinganine (dehydro-**4**) and represents the first committed step in biosynthesis of D-sphingosine and subsequently all normal animal, fungal sphingolipids and phytosphingolipids described to date.[35] Retention of configuration of the $\alpha$-carbon of L-serine is obeyed; however, the stereochemical outcome from subsequent ketone reduction, which is catalyzed by 3-ketosphinganine reductase and sets the C3 configuration, may vary and produces an *erythro* diastereomer in **4** (2*R*,3*S*), but a *threo* isomer in the fumonisins **5a**,**b**.[36] The two $C_{14}$ epimeric sphingolipids (2*S*,*S*) and (2*S*,3*R*)-aminotetradeca-5,7-dien-3-ol isolated from a marine sponge, *Xestospongia* sp. collected in Papua New Guinea, are a *threo*/*erythro* pair that represent diastereo-divergence of the keto-reductase step in the same organism, but again, retention of the 2*S* configuration is maintained. Oceanapiside (**1**), with a *threo*-2*R*,2*R*-motif (sphingosine numbering) at the $\omega$-terminus is a suprising departure from this convention. To our knowledge, no other examples of 2*R* sphingolipids have been reported. More remarkable is the finding that enantiomeric stereodiads **1** are present at opposing chain termini in the same molecule−one

(35) Kanfer, J. N.; Hakamori, S.-I. *Sphingolipid Biochemistry*; Plenum Press: New York, 1983.

(36) Caldas, E. D.; Sadilkova, K.; Ward, B. L.; Jones, A. D.; Winter, C. K.; Gilchrist, D. G. *J. Agric. Food Chem.* **1998**, *46*, 4734−4743.

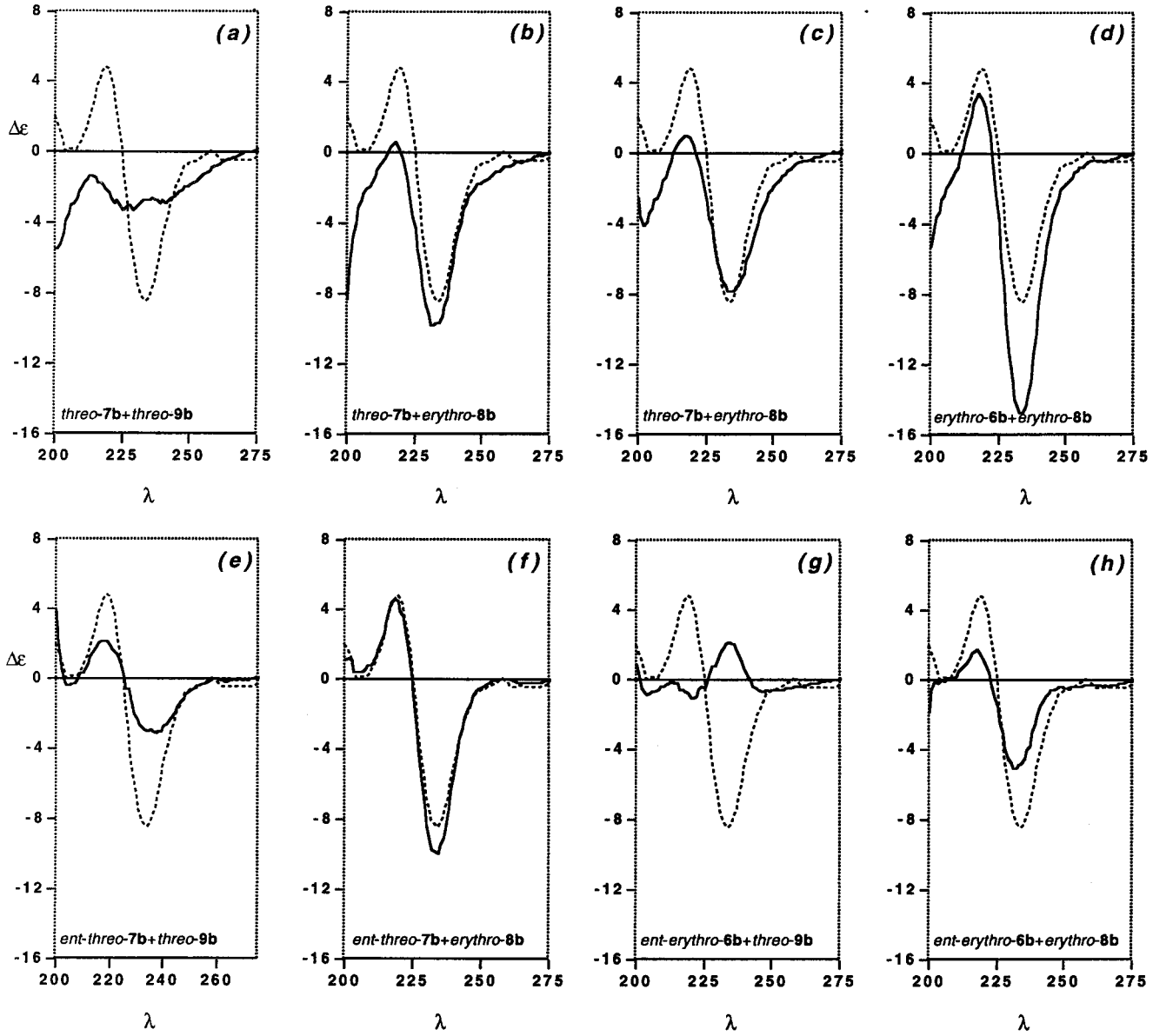



**Figure 4.** Hybrid CD spectra generated by linear combinations of model compound spectra ($CH_3CN$, 25 °C). Overlayed spectrum (dashed line) is CD of *N*,*N*′,*O*,*O*′,*O*″-pentabenzoyloceanin (**11**) ($CH_3CN$, 25 °C).

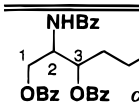
end formally derived from L-serine, the other from D-alanine—an observation that demonstrates enantiodivergent biogenesis for **1**.[37] The biogenesis of **1** is at present unknown, but its stereostructure would appear to require a novel enzyme-catalyzed reaction of an amino acid and fatty acyl CoA precursor, one that either uses D-alanine, or inverts the C2 configuration of (2*S*)-alanine during condensation or epimerizes C2 (C27 numbering for **1**) after condensation.

## Conclusions

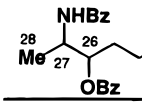
The CD method described here affords a simple method for determination of configuration in α,ω-bipolar aminohydroxylipids such as **1** that can be extended to generate hybrid spectra for configurational assignment in related compounds. Heterologous combinations of CD spectra obtained from **6b**, **7b** with **8b**, **9b** or *ent*-**6b**, *ent*-**7b** with **8b**, **9b** were used to generate eight hybrid spectra that allowed elucidation of the relative and absolute configuration of **1**. This finding underscores oceanapiside (**1**) as a remarkable example of a bipolar lipid in which stereostructure arises from enantiodivergent sphingolipid biosynthesis. The CD hybrid spectral method can easily be extended, in principle, to address stereochemical issues in other α,ω-symmetrical bipolar lipids including the aglycone of rhizochalin (**3**),[3] leucettamols A,B (**2a**,**b**),[2] and BSR1,[4] by homologous combinations of CD spectra of **6b** and **7b** and their respective *ent*-forms. Stereochemical analysis in the latter three compounds can be carried out after hydrogenation of the olefinic bonds prior to benzoylation. The method is simple and sufficiently sensitive for submilligram configurational assignments provided that accurate determinations of $\Delta\epsilon$ can be made. The latter is easily ensured by using HPLC-purified intermediates and weighings with a microbalance. Finally, because the method relies on exciton coupling, the degree of confidence remains high for stereochemical assignment of related lipids that contain midchain modifications (e.g., keto group, methyl branching) that do not obscure chromophoric interactions at the end groups.

(37) The current method makes the assumption that the molecule **1** and derivative **11** are diasteromerically *and optically* pure. We cannot rule out the remote possibility that each terminus is biosynthesized without complete enantioselective fidelity, giving rise to stereochemically heterogeneous **1.** This seems unlikely given the excellent match of hybrid spectral features with those of **11** and the superb enantioselectivity of enzymes, in general.

**Table 1.** Selected $^1$H NMR Chemical Shifts ($\delta$ ppm) and Coupling Constants, $J$ (Hz), for Pentabenzoyl Derivative **11** and Corresponding Values of Model Compounds **6b**−**9b**, **20**, and **23b** ($CDCl_3$, 300 MHz)




| | | $^2J_{NH\text{-}H2}$ | $^3J_{H2\text{-}H3}$ | $\delta_{C2\text{-}NH}$ | $\delta_{H3}$ | $\delta_{H2}$ | $\delta_{H1}$ |
|---|---|---|---|---|---|---|---|
| *α-terminus* | | (Hz) | (Hz) | ppm | ppm | ppm | ppm |
| *erythro* | **8b** | 8.7 | 4.1 | 7.10 | 5.41 | 4.87 | 4.61/4.65 |
| *erythro* | **11** | 8.6 | 3.8 | 7.08 | 5.38 | 4.88 | 4.61/4.64 |
| *erythro* | **20** | 8.7 | 3.9 | 7.08 | 5.38 | 4.87 | 4.61/4.64 |
| *threo* | **9b** | 9.2 | 4.8 | 6.63 | 5.56 | 4.89 | 4.48/4.57 |




| | | $^2J_{NH\text{-}H27}$ | $^3J_{H26\text{-}H27}$ | $\delta_{C27\text{-}NH}$ | $\delta_{H26}$ | $\delta_{H27}$ | $\delta_{H28}$ |
|---|---|---|---|---|---|---|---|
| *ω-terminus* | | (Hz) | (Hz) | ppm | ppm | ppm | ppm |
| *erythro* | **6b** | 7.8 | 2.6 | 6.97 | 5.24 | 4.46 | 0.97 |
| *erythro* | **23b** | 7.5 | 2.7 | 6.99 | 5.22 | 4.46 | 1.29 |
| *threo* | **7b** | 9.0 | 5.2 | 6.39 | 5.24 | 4.53 | 0.94 |
| *threo* | **11** | 8.9 | 5.2 | 6.38 | 5.21 | 4.53 | 1.28 |

For ease of comparison, the $\delta$ and $J$ values for model compounds are aligned in columns under the locants corresponding to atom positions for **11**.

## Experimental Section

**Pentabenzoyl Derivative of Oceanapiside Aglycone (11).** Oceanin (**10**), the aglycone of **1**, was prepared as previously described.[1] Benzoyl chloride (21 $\mu$L, 0.18 mmol) and DMAP (approximately 2 mg) were added to a sample of **2** (4.5 mg, 9.2 $\mu$mol) in dry pyridine (1.0 mL). The reaction was stirred at 25 °C for 9 h, at which time additional benzoyl chloride (50 $\mu$L, 0.4 mmol) was added and the mixture heated at 58 °C for 6 h. The mixture was treated with 1-(*N*,*N*-dimethylamino)-3-aminopropane (75 $\mu$L, 0.6 mmol), volatiles were removed under vacuum, and the residue was purified by chromatography (silica 25 × 55 mm, 1:3 EtOAc/$CHCl_3$) to give the *N*, *N*′,*O*,*O*′,*O*″-pentabenzoyl derivative **11** (2.9 mg, 31%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 8.03 (m, 4H), 7.95 (m, 2H), 7.77 (m, 2H), 7.12 (m, 2H), 7.34−7.56 (m, 15H), 7.08 (d, $J$ = 8.8 Hz, 1H, NH1′), 6.38 (d, $J$ = 8.8 Hz, 1H, NH2′), 5.38 (m, 1H, H3), 5.21 (m, 1H, H26), 4.88 (m, 1H, H2), 4.64 (m, 1H, H1a), 4.61 (m, 1H, H1b), 4.53 (m, 1H, H27), 2.33 (m, 4H), 1.93 (m, 1H), 1.87 (m, 1H), 1.75 (m, 2H), 1.53 (m), 1.28 (d, $J$ = 6.7 Hz, 3H, H28), 1.25 (m). DCI ($NH_3$) $m/z$ 1007.5781[M + H]$^+$, Calcd for $C_{63}H_{79}N_2O_9$ 1007.5786.

***erythro*-(2*S*,3*S*)-*N*,*O*,*O*-Tribenzoyl-dihydrosphingosine (20).** Palladium on carbon (4 mg, 10% Pd) was added to a solution of D-*erythro*-sphingosine (Sigma, 8 mg, 0.026 mmol) in MeOH (1 mL). The mixture was evacuated-purged with $H_2$ (×5) and left to stir under $H_2$ (1 atm) at 24 °C for 7.5 h. The catalyst was removed by filtration through Celite, and the evaporation of the solvent gave D-*erythro*-dihydrosphingosine (D-sphinganine, **4**, 8.1 mg, 100%). $^1$H NMR (300 MHz, $CD_3OD$) $\delta_H$ 3.71 (dd, $J$ = 4.2, 10.8 Hz, 1H), 3.49 (m, 1H), 3.45 (dd, $J$ = 7.5, 11.1 Hz, 1H), 2.70 (m, 1H), 1.2−1.6, 0.89 (t, $J$ = 6.3 Hz, 3H). $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta_C$ 74.1, 64.4, 58.1, 34.4, 33.0, 30.7, 30.4, 27.0, 23.6, 14.3. DCIMS ($NH_3$) found $m/z$ 302.3060 [M + H]$^+$, Calcd for $C_{18}H_{40}NO_2$ 302.3059.

Benzoyl chloride (30 $\mu$L, 0.26 mmol) was added to a solution of **4** (8.1 mg, 0.026 mmol) and DMAP (approximately 1 mg) in pyridine (1.5 mL). The reaction was heated at 50 °C for 5 h at which time the pyridine was removed under vacuum, and the residue purified by flash silica chromatography (10−20% EtOAc/*n*-hexane) followed by HPLC (silica, 25 × 300 mm, 1:4 EtOAc/*n*-hexane, 3 mL/min) to afford tribenzoyl derivative **20** (2.2 mg, 14%). $[\alpha]^{24}_D$ −26.0° (*c* 0.1, $CHCl_3$). $^1$H NMR data[25] and the optical rotation (lit.[33] −26°, $CHCl_3$) were found to be identical with those previously reported. $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 8.02 (m, 2H), 7.95 (m, 2H), 7.77 (m, 2H), 7.34−7.56 (m, 9H), 7.08 (d, $J$ = 8.6 Hz, 1H), 5.37 (m, 1H), 4.87 (m, 1H), 4.64 (m 1H), 4.61 (m 1H), 1.95 (m, 1H), 1.87 (m, 1H), 1.47 (m, 2H), 1.24, 0.87 (t, $J$ = 6.8 Hz, 3H). FABMS $m/z$ 614.3830 [M + H]$^+$, Calcd for $C_{39}H_{52}NO_5$ 614.3845.

**(2*S*,3*R*)-2-(*N*,*N*-Dibenzylamino)-13-tetradecen-3-ol (21).** 11-Bromo-1-undecene (Aldrich, 200 $\mu$L, 0.91 mmol) was added to dry magnesium turnings (135 mg, 5.5 mmol) in THF (500 $\mu$L) and heated. Additional bromide (800 $\mu$L, 3.64 mmol) in THF (5 mL) was added slowly at a rate to keep the mixture at reflux. After 30 min the Grignard reagent was allowed to cool, and a portion (approximately 1.5 mL, 0.7 M solution in THF, 1.0 mmol) was treated dropwise with a solution of aldehyde **12** (187 mg, 0.74 mmol) in THF (2 mL). After being stirred for 1 h, the mixture was treated with wet $Et_2O$ (2 mL) followed by sat. aqueous $NaHCO_3$ (5 mL) and extracted with EtOAc (×3). The combined organic phases were washed with $H_2O$ and brine and dried ($MgSO_4$) before concentration to give a yellow oil. Purification of the oil on silica gel (1:4 EtOAc/*n*-hexane) separated the minor (*2S*,*3S*)-*threo* isomer (6.0 mg, 2%) from the major (2*S*,*3R*)-*erythro* isomer **21** (152.0 mg, 50%) in a ratio of 1:25. UV (MeOH) $\lambda_{max}$ 210 nm ($\epsilon$ 20500). $[\alpha]^{26}_D$ +20.8° (*c* 0.34, $CHCl_3$). IR (NaCl plate, film) 3340 (br), 2924, 2852, 1452, 1367 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$ 7.20−7.40 (m, 10H), 5.01 (m, 1H), 4.95 (m, 1H), 3.79 (d, $J$ = 13.8 Hz, 2H), 3.61 (m, 1H), 3.49 (d, $J$ = 13.8 Hz, 2H), 2.73 (m, 1H), 2.06 (m, 2H), 1.70 (m, 2H), 1.38, 1.27, 0.87 (d, $J$ = 6.6 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta_C$ 140.0 (s), 139.0 (d), 128.6 (d), 128.1 (d), 126.7 (d), 114.0 (t), 73.6 (d), 57.2 (d), 54.8 (t), 34.3 (t), 33.8 (t), 29.7 (t), 29.6 (t), 29.6 (t), 29.5 (t), 29.2 (t), 29.0 (t), 25.9 (t), 8.7 (q). HRDCI ($NH_3$) $m/z$ 408.3268 [M + H]$^+$, Calcd for $C_{28}H_{42}NO$ 408.3266.

**(2*S*,3*R*,24*R*,25*S*)-2,25-Bis(*N*,*N*-dibenzylamino)-13-hexacosene-3,-24-diol (22).** Alkene **21** (70 mg, 0.17 mmol) in $CH_2Cl_2$ was added to a solution of dichlorobis(tricyclohexylphosphine)benzylideneruthenium-(IV) dichloride[34] (Grubbs's catalyst, 14 mg, 10 mol %) in $CH_2Cl_2$ (56 mM alkene). The solution initially appeared bright pink and turned yellow/orange after approximately 10 min. The reaction was heated at reflux for 10 h under $N_2$ after which time no starting material could be detected by TLC. The solvent was removed and the residue purified by silica chromatography (1:9 EtOAc/*n*-hexanes) to provide dimer **22** (45.3 mg, 68%) as a 3:1 mixture of *Z*:*E* isomers. $[\alpha]^{26}_D$ +21.8° (*c* 0.6, $CHCl_3$). UV (MeOH) $\lambda_{max}$ 209 nm ($\epsilon$ 33900), 258 nm ($\epsilon$ 1400). IR

(NaCl plate, film) 3360 (br), 2924, 1453, 1366 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.21−7.36 (m, 20H), 5.40 (m, 1.5H, (*Z*)-CH═), 5.36 (m, 0.5H, (*E*)-CH═), 3.77 (d, $J$ = 13.6 Hz, 4H), 3.60 (m, 2H), 3.48 (d, $J$ = 13.6 Hz, 4H), 2.72 (m,2H), 1.98 (m, 4H), 1.69 (m, 4H), 1.26 (m, 28H), 1.11 (d, $J$ = 6.8 Hz, 6H). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta_C$ 140.1 (s), 130.3 (d), 128.7 (d), 128.2 (d), 126.8 (d), 73.6 (d), 57.2 (d), 54.7 (t), 34.2 (t), 32.6 (t), 29.7 (t), 29.6 (t), 29.6 (t), 29.5 (t), 29.5 (t), 29.2 (t), 29.1 (t), 27.2 (t), 25.8 (t), 8.6 (q). HRDCI ($NH_3$) *m*/*z* 845.5450 $[M + H]^+$, Calcd for $C_{54}H_{73}N_2O6$ 845.5468.

**(2*S*,3*R*,24*R*,25*S*)-*N*,*N*′,*O*,*O*′-Tetrabenzoyl-2,25-diamino-3,24-hexacosanediol (23b).** A solution of the dimeric bis-amino alcohol **22** (45.3 mg, 0.057 mmol) in MeOH/1%HCl (2 mL) was added to presaturated 10% Pd on carbon (20 mg). The reaction was evacuated/purged with $H_2$ (×4) and stirred under $H_2$ (1 atm) for 27 h. The catalyst was removed by filtration and the solvent evaporated. This was repeated on another sample of compound **22** (31.2 mg, 0.039 mmol) with 5% Pd on carbon (15 mg). The combined crude products were purified by silica chromatography (9:4:1 $CHCl_3$/MeOH/$NH_4OH$) to provide the bis-*erythro* dimer (2*S*,3*R*,24*R*,25*S*)-2,25-diamino-3,24-hexacosanediol (**23a**) as a white solid (39.1 mg, 95%). $^1H$ NMR (400 MHz, $CD_3OD$) $\delta_H$ 3.69 (m, 2H), 3.26 (m, 2H), 1.51 (m, 2H), 1.42 (m, 5H), 1.20 (d, $J$ = 6.4 Hz, 6H). $^{13}C$ NMR 100 MHz ($CD_3OD$) (partial) $\delta_C$ 71.6 (d), 52.6 (d), 33.9 (t), 30.7 (t), 30.7 (t), 30.6 (t), 30.6 (t), 29.9 (t), 12.0 (q). HRFABMS found *m*/*z* 412.4432 $[M + H]^+$, Calcd for $C_{26}H_{56}N_2O_2$ 412.4393. Benzoyl chloride (45 $\mu$L, 0.39 mmol) was added to a solution of **23a** (30 mg, 0.049 mmol) and DMAP (approximately 1 mg) in pyridine (2 mL) and $CH_3CN$ (100 $\mu$L). The mixture was allowed to stir at 25 °C for 20 h at which time the reaction was quenched with 1-(*N*,*N*-dimethylamino)-3-aminopropane (50 $\mu$L, 0.4 mmol) and the volatiles removed under vacuum to give a yellow oil (91.0 mg). Purification of the residue by chromatography on silica (1:4 EtOAc/*n*-hexane) gave compound **23b** (16.8 mg, 40%). $[\alpha]^{25}_D$ −32.4° (*c* 0.17, $CHCl_3$). UV (MeOH) $\lambda_{max}$ 228 nm ($\epsilon$ 39900). IR (NaCl plate, film) 3320 (br), 2925, 1718 (C═O), 1639 (C═O), 1535, 1272 $cm^{-1}$. $^1H$ NMR (300 MHz, ($CDCl_3$) $\delta_H$ 8.09 (m, 4H), 7.77 (m, 4H), 7.60 (m, 2H), 7.40−7.50 (m, 10H), 6.99 (d, $J$ = 8.1 Hz, 2H, NH), 5.22 (m, 2H, C*H*OBz), 4.46 (m,2H, C*H*NBz), 1.83 (m, 2H), 1.71 (m, 2H), 1.42 (m, 4H), 1.29 (d, $J$ = 6.6 Hz, 6H). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta_C$ 167.1 (s), 166.3 (s), 134.3 (s), 133.2 (d), 131.2 (d), 129.7 (s), 129.6 (d), 128.4 (d), 126.8 (d), 78.1 (d), 48.8 (d), 32.1 (t), 29.8 (t), 29.7 (t), 29.7 (t), 29.6 (t), 29.5 (t), 29.4 (t), 25.8 (t), 14.7 (q). FABMS *m*/*z* 845.5450 $[M + H]^+$, Calcd for $C_{54}H_{73}N_2O_6$ 845.5469.

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**Supporting Information Available:** Complete tabulation of $\Delta\epsilon$, $\epsilon$, *A* values for all model compounds **6b**−**9b**, *N*,*O*,*O*′-tribenzoyl-D-sphinganine (**20**), dimeric compounds **11**, **23b**, and hybrid CD spectra. CD spectra of **23b** overlayed against corresponding hybrid CD spectra of dimeric amino alcohols (MeOH, 25 °C). Synthesis and characterization of **6ab**, **7ab**, **8ab**, **9ab**, $^1H$ and $^{13}C$ NMR spectra of **6b**−**9b**, **15**, **16**, **18**, **19**, **21**−**23a**,**b**. This material is available free of charge via the Internet at http://acs.pubs.org.

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