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The Configuration of Distaminolyne A is *S*: Quantitative Evaluation of Exciton Coupling Circular Dichroism of *N,O*- Bis-arenoyl-1-amino-2-alkanols

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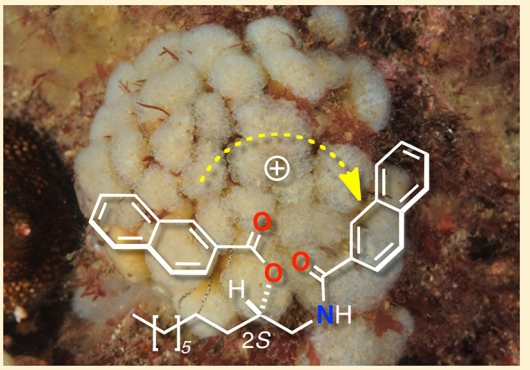
Supporting Information

ABSTRACT: The 2*S* configuration of the marine natural product distaminolyne A was recently disputed based upon total synthesis, yet paradoxically supported by a second independent total synthesis from a different research group. We now verify the 2*S* configuration of distaminolyne A by extensive chiroptical studies and support the veracity of the EC ECD method originally used to prove it. The origin of the apparent paradox appears to lie in the limits of precision of polarimetry in the context of weakly rotatory molecules, which strikes a cautionary note on the reliability of "reassignment" of natural product configurations based solely on specific rotation.



In 2016, two of us reported a new diyne-containing amino alcohol, distaminolyne A (**1a**), from a New Zealand ascidian, *Pseudodistoma opacum*, along with an unrelated *N*-hydroxy-*β*-carboline.[1] Compound **1a** is a member of a limited family of linear, long-chain aminoalkanol (LCAA)[2] natural products that are associated with marine invertebrates, mostly sponges within the genera *Haliclona*, *Leucetta*, *Rhizochalina*, and *Oceanapia* and several genera of ascidians, including *Didemnum*, *Pseudodistoma*,[3] and *Clavelina*[4] or, in rare exceptions, algae and bivalves.[5] LCAAs exhibit a range of biological properties, perhaps due to their structural resemblance to sphingosine (**2a**) and the versatile mammalian "second messenger", D-sphingosine 1-*O*-phosphate (**2b**). For example, most recently leucettamols A and B, originally discovered by the Faulkner group,[6] were identified by Fattorusso and co-workers as nonelectrophilic activators of TRPA1 and inhibitors of TRPM8 channels with micromolar potency.[7]

The configurations of LCAA natural products are highly heterogeneous. The simplest examples, 1-amino-2-alkanols, have been found in both *R* and *S* configurations, while more complex "two-headed" sphingolipids, such as rhizochalin[8] and oceanapiside,[9] bearing four stereogenic centers, occur in almost all of the 16 possible stereopermutations.[10] Notoriously, 1-amino-2-alkanols are weakly rotatory:[11] being either levorotatory or dextrorotatory with no simple correlation to the C-2 configuration (Table 1).[12] Consequently, the problem of assignment of configuration of LCAAs is not trivial and must be approached on a case-by-case basis. Because of the small specific rotations of aminoalkanols, creative solutions for their assignment have been developed and deployed. The configuration of **1a** was solved by a variant of the exciton coupling (EC) "dibenzoate method" in electronic circular dichroism (ECD) spectra pioneered by Nakanishi and

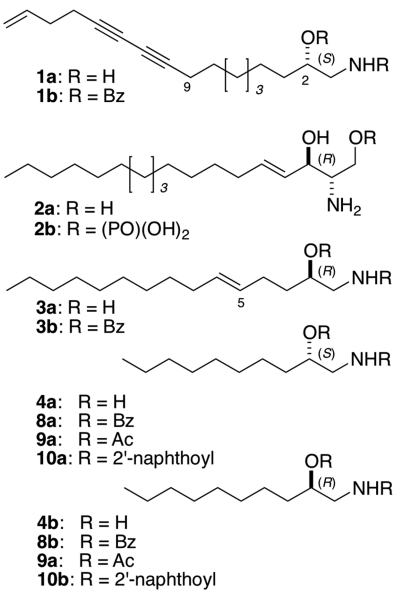


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Table 1. Specific Rotations of Natural and Synthetic Products

cmpd	$[\alpha]_D$[a]	c	solvent	ref
(*S*)-**1a**[c]	−1	0.44	MeOH	1
(*R*)-**3a**[d]	+1.9	0.36	MeOH	15
(*S*)-**1a**[b]	+0.8	1.0	MeOH	17
(*S*)-**1a**[c]	+1.2	0.1	MeOH	17
(*R*)-**1a**[b]	−2.0	0.1	MeOH	17
(*R*)-**1a**[c]	−0.9	0.1	MeOH	17
(*S*)-**1a**[d,e]	−5.0	0.1	MeOH	18
(*S*)-**4a**[b]	−1.4	1.76	MeOH	h
(*S*)-**4a**[d,f,g]	+5.3	1.78	MeOH	h
(*S*)-**4a**[c]	+5.2	2.46	MeOH	h
(*S*)-**8a**	+28.3	1.02	MeOH	h
(*S*)-**8a**	+17.8	0.45	$CHCl_3$	h
(*R*)-**8b**	−26.1	1.76	MeOH	h
(*R*)-**8b**	−19.3	1.72	$CHCl_3$	h
(*S*)-**9a**	+11.5	2.30	MeOH	h
(*S*)-**9a**	−7.6	2.02	$CHCl_3$	h
(*R*)-**9b**	−12.9	2.82	MeOH	h
(*R*)-**9b**	+8.6	2.82	$CHCl_3$	h
(*R*)-**10b**	−88.9	0.55	MeOH	h
(*R*)-**10b**	−104	0.43	$CHCl_3$	h

[a]CIP designation and values are taken, as reported, from original references. Concentration, c g/100 mL. Solvents were spectroscopic grade MeOH or $CHCl_3$ (stabilized with amylenes). [b]Free base. [c]TFA salt. [d]HCl salt. [e]A slightly different value, $[\alpha]_D$ −6.7 (c 0.1, MeOH), is reported for synthetic (*S*)-**1a**·HCl in the Supporting Information.[18] [f]Replicate measurements, n = 10 (standard deviation, $\sigma \pm 1.4$). [g]For $[\alpha]$ values of (*S*)-**4a**·HCl at different wavelengths, see Experimental Section. [h]This work.

Harada.[13,14] Briefly, the helicity, or "twist", of proximal dibenzoate charge transfer (CT) electronic transition dipole moments is correlated with a split-ECD spectrum due to Davydov coupling. Positive dipole helicity manifests a large maximum at a longer wavelength and a minimum at shorter wavelength; both are centered approximately at the λ_{max} of the benzoate chromophore.

A similar analysis can be applied to benzoate−benzamide chromophore pairs (Figure 1).[13,14] The dominant *gauche* rotamer—identified by conformational analysis of the vicinal benzoate−benzamide of (*R*)-**3b**, an *N*,*O*-dibenzoyl derivative of the marine-derived (*R*)-**3a**, reported from an Australian *Didemnum* sp. in 1993[15]—subtends negative helicity of the benzoyl electronic transition dipole moments (cf. Figure 1(b), **iii**) and manifests EC through a negative-split ECD spectrum.

For *N*,*O*-dibenzoyldistaminolyne A (**1b**), Copp and co-workers measured an antipodal positive-split ECD spectrum corresponding to a positive helicity (cf. Figure 1(a), **iii**), thereby assigning the 2*S* configuration for the natural product **1a**.[1] Since then, EC ECD of the vicinal benzoate−benzamide method has been applied successfully to other marine-derived 1-amino-2-alkanols.[16]

Recently, two independent reports of asymmetric synthesis of **1a** have appeared, one of which appears to contradict the forgoing configurational assignment. In 2017, Guo and co-workers reported the asymmetric syntheses of free bases of both (−)-(*R*)-**1a** and (+)-(*S*)-**1a** ($[\alpha]_D$ −2.0 and +0.9, respectively; see Table 1) along with their trifluoroacetic acid (TFA) salts.[17] Guo, interpreting the specific rotation reported for natural **1a** by Copp and co-workers ($[\alpha]_D$ −1 (c 0.44, MeOH)), concluded that the absolute configuration (AC) of

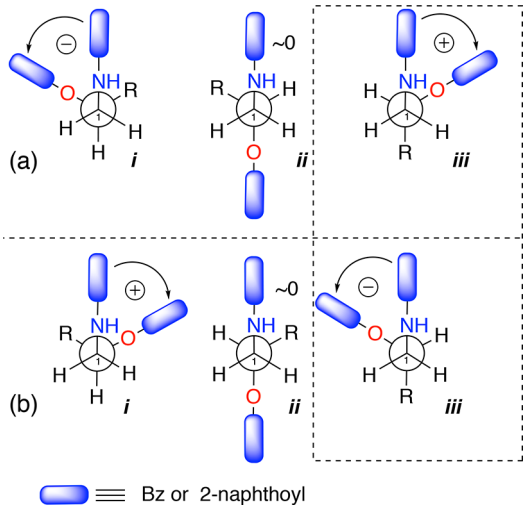

Figure 1. Newman diagrams of the three major conformers of *N*,*O*-acylated 1-amino-2-alkanols, (a) 2*S* enantiomer and (b) 2*R* enantiomer, showing helicities (+, −, or 0) and predicted signs of split Cotton effects in exciton-coupled ECD. Shaded box represents Bz or 2-naphthoyl, and the dominant conformer is **iii**.

distaminolyne A should be revised from 2*S* to 2*R*. A second asymmetric synthesis of (−)-**1a** ($[\alpha]_D$ −5.0 (c 0.1, MeOH)), published in the same year by Krishna and co-workers,[18] contradicted the Guo result, "since our values matched with reported one (sic)", referring to the original Copp assignment.[1] Introduction of asymmetry in both syntheses employed different, but reliable catalytic methodology, and the configurations of the *synthetic* samples of (−)- and (+)-**1a** are not in doubt. Yet, the conclusions of all three studies are inconsistent, and the true configuration of natural **1a** is brought into question.

Collectively, the $[\alpha]_D$ values measured and reported for **1a** span the range of −5 to +2, with little correlation with configuration; we concur with Krishna that, "inconsistencies might be due to the low optical rotational values".[18] Most importantly, neither of the two synthetic groups attempted to address how their results could be consistent with the EC ECD method used to assign (*S*)-**1a**[1] and, by corollary, (*R*)-**3a**.[15]

Being sufficiently stimulated by this paradox, and in confirming an unambiguous assignment of natural **1a**, we reexamined our EC ECD method by undertaking a chiroptical study of enantiomeric pairs of synthetic, configurationally well-defined LCAAs and their corresponding *N*,*O*-acylates and matched these against the claims of configurational "reassignment". We can now state, without doubt, that the configuration of **1a** is, indeed, 2*S* as originally reported. In addition, we conjecture that the origin of the paradox lies not in a need for reassignment of **1a**, but within instrumental limits of precision of modern polarimetry and the low values of $[\alpha]_D$ observed for weakly rotatory molecules. A timely cautionary note is offered for configurational assignment with sole reliance upon specific rotations and, in particular, the attendant risks in facile claims of "reassignment" based on the same.

RESULTS AND DISCUSSION

Distaminolyne A (**1a**) contains a conjugated 10,11-diyne (UV−vis, λ_{max} 215, 240, 253, 267, 283 nm). Based on prior observations,[19] this chromophore was deemed too remote from the vicinal amino alcohol moiety to interfere with EC

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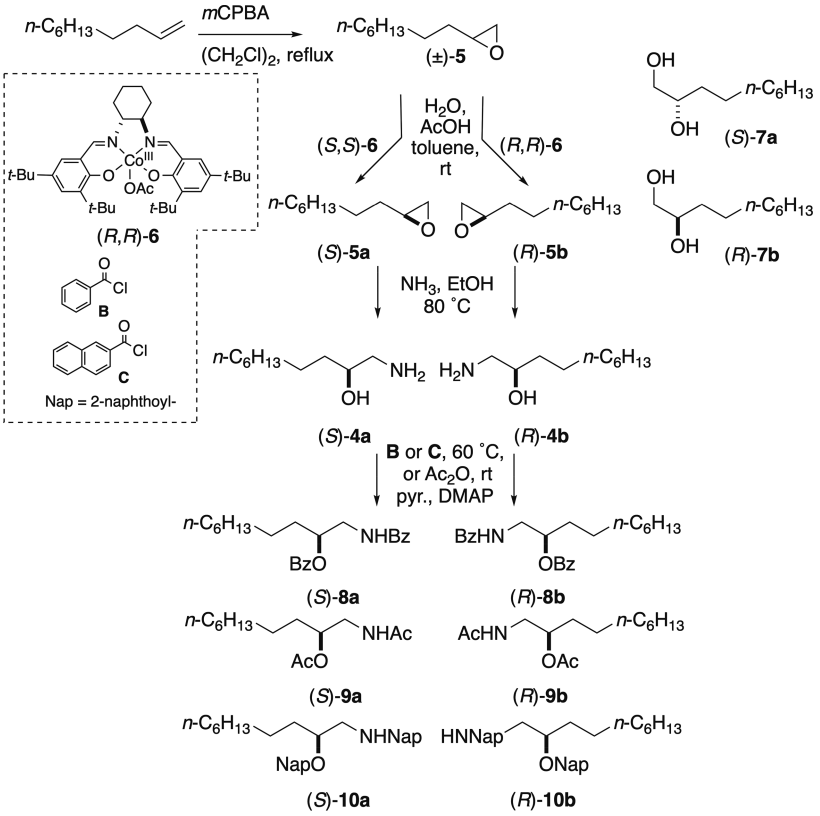
Scheme 1. Synthesis of (*S*)- and (*R*)-1-Amino-2-decanols (4a,b) and Selected Acylates (8−10)



ECD at the terminal benzoate−benzamide pair of **1b**. To simplify our analysis, we chose to synthesize *S* and *R* 1-amino-2-decanol (**4a** and **4b**, Scheme 1), by a well-defined asymmetric methodology, to remove the component of conformational analysis that was critical in proposing the AC of **3a,b**.[15] Compounds **4a,b** served as common platforms for the preparation of *N,O*-acylates for critical examination of the characteristics of both $[\alpha]_D$ and EC ECD. 1-Decene was epoxidized (*m*-CPBA, $(CH_2Cl)_2$, radical inhibitor,[20] reflux, 96%), affording (±)-**5**, which was subjected to kinetic hydrolytic resolution (H_2O, AcOH) in the presence of Jacobsen's catalyst ((*R,R*)-Co(salen) complex **6**[21] (0.48 mol %)) to give unreacted, optically pure 1,2-epoxydecane [(+)-(*R*)-**5b**, 41%, >97% ee, $[\alpha]_D$ +14.8 (*c* 1.12, Et_2O)]. The procedure was repeated with (±)-**5** and (*S,S*)-**6** to secure optically pure (*S*)-**5a** ($[\alpha]_D$ −12.3 (*c* 1.12, Et_2O); lit.[22] −12.9 (*c* 1.17, Et_2O), lit.[23] −13.9 (*c* 1.2, Et_2O)) and the corresponding diol (*R*)-**7b**. Each epoxide **5a** and **5b** was subjected to ammoniolysis (~20 w/v% NH_4OH(aq), 80% EtOH, 60 °C) to give (−)-(*S*)-**4a** and (+)-(*R*)-**4b**, respectively (>90%). The latter amino alcohols were used without further purification for the subsequent reactions to deliver the following pairs of enantiomeric acylates after purification by silica flash chromatography: (BzCl, dry pyridine, 60 °C)[24] *N,O*-dibenzoyl derivatives, (+)-(*S*)-**8a** and (−)-(*R*)-**8b**, and (Ac_2O, pyridine, 23 °C) *N,O*-acetyl derivatives (*S*)-**9a** and (*R*)-**9b**, respectively. Finally, (+)-(*R*)-**4b** was converted (2-naphthoyl chloride, DMAP, pyridine, 60 °C, 9%) to the bis-chromophoric derivative (−)-(*R*)-**10b** for comparison purposes.

The ECD spectra (Figure 2, Table S1) of (−)-(*R*)-**8b** [λ 221 nm ($\Delta\varepsilon$ +3.7); 238 (−7.7)] and (*R*)-**3b** [λ 221 nm ($\Delta\varepsilon$ +5.4); 237 (−10.2)][15] were the expected bisignate curves—opposite Cotton effects at long and short wavelengths—that were matched in sign and magnitude, proving that both the original conformational and chiroptical analysis of the EC ECD of (*R*)-**3b** were correct.[15] Moreover, comparison of the ECD spectra of (−)-(*R*)-**8b** and **1b**[1] again showed the two molecules were

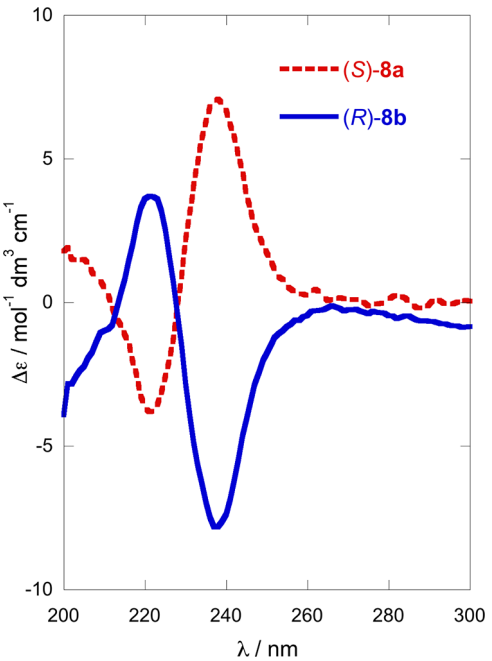


Figure 2. ECD spectra (MeOH, 23 °C) of (−)-(*R*)-**8b** (blue, solid line) and (+)-(*S*)-**8a** (red, dashed line).

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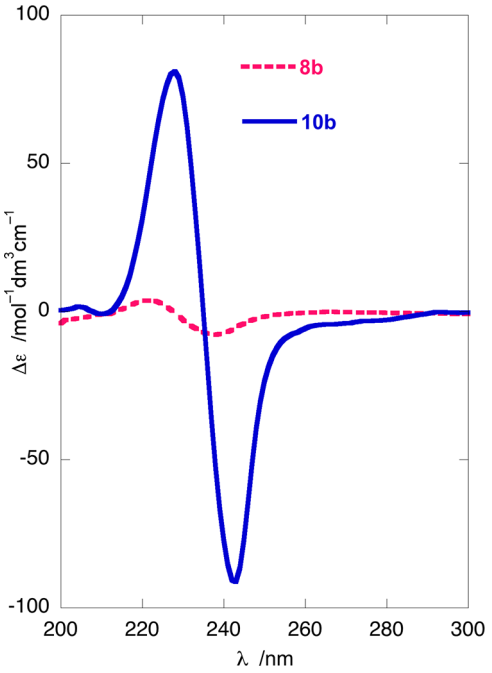

Figure 3. ECD spectra (MeOH, 23 °C) of (−)-(*R*)-**10b** (blue, solid line) and (−)-(*R*)-**8b** (red, dashed line).

antipodal and upheld the original 2*S* assignment for **1a**,**b**[1] and **3a**,**b**.[15]

Measurement of the ECD of compound (*R*)-**10b** revealed a split-Cotton effect of the same sign as (*R*)-**8b**, but of much larger magnitude [λ 229 nm ($\Delta\varepsilon$ −91.3); 242 (−91.3], as expected from the stronger CT band of the 2′-naphthoyl chromophore. The larger *A* value may also be a consequence of tighter conformational restraints on the favored *gauche* conformation imposed by the bulkier 2′-naphthoyl groups.

The optical rotations of 1-amino-2-decanols and their acylates (Table1) are informative. When measured in MeOH, the specific rotation of amino alcohol (*S*)-**4a**, like that of **1a**, is of low magnitude;[25] however, those of **8**−**10** (MeOH) are larger and reliably measured. The *R*-configured benzoyl or naphthoyl derivatives **8b** and **10b** are uniformly levorotatory and, conversely, their *S* enantiomers are dextrorotatory. In MeOH, acetyl derivative (*S*)-**9a** is dextrorotatory, but it is noteworthy that when measured in $CHCl_3$, the sign of $[\alpha]_D$ of **9a** inverts, but the signs of $[\alpha]_D$ for the pairs **8a**,**b** and **10a**,**b** remain the same in both solvents. Generally, characterization of LCAAs by specific rotations of their acylated derivatives is more reliable and reproducible than $[\alpha]_D$s of the free bases or salts.

A brief error analysis of measurements of $[\alpha]_D$ on optically pure samples **8**−**10** was conducted to identify the sources of random error that propagate in calculations of low $[\alpha]_D$ values (see Figure S24). In low-rotatory samples, such as natural **1a** and synthetic **4a** (free base, Table 1), the largest source of error was α of the solvent blank, the value of which approaches the sample α at close to the limit of detection of most modern polarimeters, and should be considered within the range of error. For example, back-calculation of α (Figure S24) from the low values of $[\alpha]_D$ of synthetic **1a** reported (Table 1) by Guo[17] and Krishna[18] leads to the same conclusion, only here, with lower values for *c*, the errors must be even greater. When samples of higher concentration are available, or with larger specific rotations (e.g., (*S*)-**4a**·HCl), these errors can be mitigated.

Both reported syntheses of **1a** utilized well-established asymmetric methodologies, and configurational assignments of the synthetic products are not in doubt.[17,18] Indeed, Guo prepared both enantiomers of **1a** and verified their configurations using Riguera's MPA double derivatization method[26] and the modified Mosher's method.[27] Both groups, however, recorded low-magnitude specific rotation values that either refute (Guo)[17] or confirm (Krishna)[18] the proposed configuration of the natural product **1a**.[1] Unfortunately neither group took the opportunity to prepare the corresponding *N*,*O*-dibenzoyl derivatives, which would have permitted comparison with **1b** by EC ECD as reported in the original isolation paper.[1]

Regardless of the errors and level of uncertainty associated with the use of specific rotation values to assign configuration to 1-amino-2-alkanols, what is unmistakable is that the EC ECD spectrum of **1b** clearly correlates with **8a** and the 2*S* configuration.[28] This current study also highlights that *N*,*O*-dinaphthoyl derivative **10b** demonstrates superior sensitivity when applied to the EC ECD of 1-amino-2-alkanols. We estimated the limits of detection (LOD) of the test cases **8b** and **10b** for unambiguous assignment by EC ECD to be ∼5.7 and ∼0.38 nmol, respectively (Figure S25).[29]

It should be mentioned that other chiroptical methods for assignment of AC have risen, of late, in popularity and reliability, namely, vibrational circular dichroism (VCD)[30] and Raman optical activity (ROA),[31] combined with quantum chemical calculations reliant upon time-dependent density functional theory (TDDFT). The advantages of both include assignments based on "fingerprint" vibrational transitions, independent of the presence of UV−vis chromophores, but at the disadvantage of much lower sensitivity than EC ECD.

Finally, the nonempirical EC ECD method is of superior reliability compared to single-point measurements, such as $[\alpha]$, for several reasons, but mostly because the method is exceptionally sensitive and absolute configurational assignments are supported by the well-developed quantum chemical theory of exciton coupling in the context of the dibenzoate method.[13]

In conclusion, the configuration of distaminolyne A (**1a**) is upheld as 2*S* by independent verification of the EC ECD method with standard compounds of defined configuration.[32] This suggests that "reassignment" of **1a** to 2*R* is unwarranted and in error, likely due to misinterpretation of the low rotatory strengths of unmodified 1-amino-2-alcohols and measurements of $[\alpha]_D$ that lie within random error. Caution should be applied to claims of reassignment of natural product configurations when specific rotations lie within the latter regime.

EXPERIMENTAL SECTION

General Experimental Procedures. Spectrometric measurements (UV, ECD) were measured in spectroscopic grade MeOH (Fisher), $CHCl_3$ (Acros, stabilized with amylene), or 2,2,2-trifluoroethanol (TFE, Acros). Specific rotations were measured on a Jasco P-2000 digital polarimeter at the D-line (Na^0 emission) or an Autopol IV at shorter wavelengths, with appropriate filters, in quartz cells of path length 0.100 or 0.500 dm at 23 °C. UV−vis spectra were measured on a Jasco V-630 spectrometer in a 1.00 or 0.20 cm quartz cuvette. FTIR spectra were collected on thin film samples using a Jasco FTIR-4100 spectrometer fitted with an ATR accessory (ZnSe plate). ECD spectra were measured on a Jasco J810 spectropolarim-

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eter on samples in 1.00 or 5.00 mm quartz cells. Inverse detected 2D NMR spectra were measured on a Jeol ECA (500 MHz) spectrometer, equipped with a 5 mm $^{1}H\{^{13}C\}$ probe, or a Bruker Avance III (600 MHz) NMR spectrometer with a 5 mm $^{1}H\{^{13}C,^{15}N\}$ cryoprobe or 1.7 mm $^{1}H\{^{13}C\}$ microcryoprobe. ^{13}C NMR spectra were collected on a Varian NMR spectrometer (125 MHz) equipped with a 5 mm Xsens $^{13}C\{^{1}H\}$ cryoprobe. NMR spectra were referenced to residual solvent signals, $CDCl_3$ (δ_H 7.26, δ_C 77.16). High-resolution ESITOF analyses were carried out on an Agilent 1200 HPLC coupled to an Agilent 6350 TOFMS. Low-resolution MS measurements were made on a Thermoelectron Surveyor UHPLC coupled to an MSD single-quadrupole detector. A semipreparative and chiral-phase HPLC system comprising dual Jasco pumps (PU-2086) and a UV−vis detector (UV-2075) or UV-CD detector (CD2095) in tandem with an ELSD detector (Softa-A model 300). Flash column chromatography was carried out with silica (Silicycle, particle size 40−63 μm) using HPLC grade solvents. Pyridine was distilled from CaH_2 under N_2. Commercial benzoyl chloride was washed with ice-cold 5% $NaHCO_3$, dried over anhydrous $CaCl_2$, and fractionally distilled under reduced pressure (32 mmHg). 2-Naphthoyl chloride was prepared by refluxing 2-naphthoic acid in $SOCl_2$ (cat. DMF, 1 h). After removal of volatiles, the residue was distilled (Kügelrohr) under reduced pressure (32 mmHg) before use.

***N,O*-Dibenzoylation of Distaminolyne A.** *Method A.* A solution of **1a** (17.5 mg, 46.6 μmol) and DMAP (1 crystal) was dissolved in dry pyridine (2.0 mL), treated with benzoyl chloride (17 μL, 26.2 mg, 187 μmol, 4.0 equiv), and heated at 60 °C under nitrogen for 21 h. The volatiles were removed under high vacuum, and the residue was dissolved in 1:4 EtOAc/hexanes and filtered through a plug of basic alumina. The fraction containing **1b** (6.5 mg, TLC) was concentrated and subjected to semipreparative HPLC (silica, 10 × 250 mm, 5 μ Dynamax, 1:4 EtOAc/hexane, 3.0 mL·min^{-1}, UV detection) to obtain pure **1b** (1.6 mg, 7%) with ^{1}H NMR and HRMS identical to the literature values.[1]

Method B. A solution of benzoic acid (8.0 mg, 0.07 mmol), EDC·HCl (16.0 mg, 0.08 mmol), and DMAP (15 mg, 0.125 mmol) was stirred at 0 °C in CH_2Cl_2 (0.5 mL) for 20 min under N_2, followed by addition of **1a** (3.7 mg, 0.014 mmol) in CH_2Cl_2 (0.5 mL). The solution was allowed to come to room temperature and was stirred for 24 h, after which CH_2Cl_2 (20 mL) was added and the mixture was washed successively with 10% HCl (20 mL), water (20 mL), saturated $NaHCO_3$ (20 mL), and finally water (20 mL) before removal of the volatiles under reduced pressure. Purification of the residue by reversed-phase column chromatography (C_{18}, gradient 100:0 to 0:100 H_2O (0.05% TFA)/MeOH) afforded **1b** (2.6 mg, 40%) with ^{1}H NMR and HRMS identical to the literature values.[1]

Epoxide (±)-5. To a solution of 1-decene (2.0 g, 14 mmol) in 1,2-dichloroethane (100 mL) were added *m*-CPBA (77% w/w, 3.81 g, 17 mmol) and the radical inhibitor TBM (300 mg).[20] The mixture was heated at reflux for 1.5 h, then cooled to room temperature and washed, sequentially, with Na_2SO_3 (10% w/v), $NaHCO_3$ (satd), and brine. The organic layer was dried over $MgSO_4$, and the volatiles were removed under reduced pressure to give a pale yellow residue, which was purified by flash chromatography (SiO_2, 1:4 Et_2O/pentane) to give racemic (±)-**5** as a clear oil (2.09 g, 96%): ^{1}H NMR (500 MHz) δ 2.90 (1H, m, H-2), 2.74 (1H, dd, J = 5.0, 4.0 Hz, H-1a), 2.45 (1H, dd, J = 5.0, 3.0 Hz, H-1b), 1.52 (2H, m, H_2-3), 1.43 (4H, m), 1.34−1.26 (12H, m), 0.87 (3H, t, J = 6.8 Hz, H_3-10); ^{13}C NMR (125 MHz) δ 52.6 (CH, C-2), 47.3 (C-1), 32.6 (CH_2), 29.653 (CH_2), 29.584 (CH_2), 29.358 (CH_2), 26.1 (CH_2), 22.8 (CH_2), 14.3 (CH_3, C-10).[22,23]

Epoxide (−)-(*S*)-5a and Diol (+)-(*R*)-7b. Racemic (±)-**5** (340 mg, 2.18 mmol) was kinetically resolved by hydrolysis, as described above, using (*S,S*)-**6** (2 °C, H_2O, 0.55 equiv) to obtain a mixture that was distilled (Kügelrohr, 90°/120 mmHg). The distillate was taken up in 1:9 Et_2O/hexane, and, upon standing, the solution deposited colorless plates of (+)-(*R*)-**7b**, which were filtered, washed with pentane, and dried (65 mg). Optically pure (−)-(*S*)-**5a** (45%) was obtained by flash chromatography of the mother liquors (1:9 Et_2O/pentane): $[\alpha]^{23}_D$ −14.4 (*c* 3.06, Et_2O); lit.[22] −12.9 (*c* 1.17, Et_2O), lit.[23] −13.9 (*c* 1.2, Et_2O).

Diol (+)-(*R*)-7b. Recrystallized from Et_2O/pentane, mp 58−59 °C; $[\alpha]^{23}_D$ +10.5 (*c* 2.92, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 3.56 (1H, m, H-2), 3.46 (1H, dd, J = 11.0, 4.5 Hz, H-1a), 3.42 (1H, dd, J = 11.0, 6.5 Hz, H-1b), 3.31 (1H, m, H-2), 1.48 (2H, m, H_2-3), 1.32 (12H, m), 0.90 (3H, t, J = 6.8 Hz, H_3-10); ^{13}C NMR (125 MHz, CD_3OD) δ 73.3 (CH, C-2), 67.4 (CH_2, C-1), 34.5 (CH_2), 33.1 (CH_2), 30.9 (CH_2), 30.8 (CH_2), 30.5 (CH_2), 26.7 (CH_2), 23.8 (CH_2), 14.5 (CH_3, C-10); HR-ESIMS *m/z* 173.1548 $[M - H]^-$ (calcd for $C_{10}H_{21}O_2^-$ 173.1547).

Epoxide (+)-(*R*)-5b. A sample of (±)-**5** was resolved with Jacobsen's catalyst, (*R,R*)-Co(salen) (**6**), according to the published procedure[21] (3 °C, 21 h) to give optically enriched (*R*)-**5b**, which was distilled under reduced pressure (90 °C, 120 mmHg). The distillate was subjected to flash chromatography, as described above for (±)-**5a**, to give pure (+)-(*R*)-**5b** (41%) as a clear oil ($[\alpha]_D$ +14.8 (*c* 1.12, Et_2O). ^{1}H and ^{13}C NMR matched those of (±)-**5**.

Amino Alcohol (*S*)-4a. A solution of epoxide (−)-(*S*)-**5a** (228 mg, 1.45 mmol) in EtOH (7.0 mL) and concentrated NH_4OH (7.0 mL) was heated at 60 °C for 17 h and worked up, as described below for (*R*)-**4b**, to obtain (*S*)-**4a** (218 mg, 86%), which was used in the subsequent acylation steps without further purification. A sample (30.8 mg) of (*S*)-**4a** was repurified by flash chromatography on a "pipet column" (5 × 80 mm, SiO_2, 1:9 MeOH/CH_2Cl_2/0.7 M NH_3) to give the free base as a pale yellow solid (6.9 mg): $[\alpha]_D$ −1.4 ± 1.4 (*c* 1.76, MeOH). A sample of (*S*)-**4a** (6.9 mg) was converted to the hydrochloride salt by dissolving in 1 M HCl in MeOH (1.8 mL) and removing the volatiles under reduced pressure, followed by re-evaporation from $CHCl_3$ (×2) to give (*S*)-**4a**·HCl (8.8 mg): $[\alpha]_D$ +5.3 ± 1.7 (*c* 1.78, MeOH), $[\alpha]^{24}_{365}$ +17.1 (*c* 0.387, MeOH), $[\alpha]^{24}_{405}$ +12.1, $[\alpha]^{24}_{436}$ +10.6, $[\alpha]^{24}_{546}$ + 5.7, $[\alpha]^{24}_{633}$ +3.9; see Table 1; ^{1}H NMR (400 MHz, CD_3OD) δ 3.50 (1H, m, H-2), 2.64 (1H, dd, J = 16.0, 3.5 Hz, H-1a), 2.50 (1H, ddd, J = 16.0, 8.0 Hz, H-1b), 1.48−1.25 (14H, m), 0.90 (3H, t, J = 6.8 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 73.3 (CH), 48.3 (CH_2), 36.0 (CH_2), 33.1 (CH_2), 30.8 (CH_2), 30.7 (CH_2), 30.5 (CH_2), 26.8 (CH_2), 23.8 (CH_2), 14.5 (CH_3); HR-ESIMS *m/z* 174.1851 $[M + H]^+$ (calcd for $C_{10}H_{24}NO$ 174.1852). Using a similar procedure, but with TFA in CH_2Cl_2, a separate sample of free base (*S*)-**4a** (8.8 mg) was converted to (*S*)-**4a**·TFA: $[\alpha]^{23}_D$ +5.2 ± 1.4 (*c* 2.46, MeOH). See Table 1.

Amino Alcohol (*R*)-4b. A solution of epoxide (+)-(*R*)-**5b** (200 mg, 1.28 mmol) in EtOH (7.0 mL) and concentrated NH_4OH (7.0 mL) was heated at 60 °C for 15 h.[17] The mixture was cooled, and the volatiles were removed under reduced pressure, giving 1-amino-2-decanol, (*R*)-**4b**, as a colorless solid (159 mg, 72%), which was used in the subsequent acylation steps without further purification. A sample of crude amino alcohol (~15 mg) was purified by flash chromatography (silica, elution with CH_2Cl_2, followed by 14:86 MeOH (10% saturated with NH_3)/CH_2Cl_2) to obtain pure free base (8.8 mg) (*R*)-**4b** as a colorless solid: HR-ESIMS *m/z* 174.1854 $[M + H]^+$ (calcd for $C_{10}H_{24}NO$ 174.1852).

(+)-(*S*)-*N,O*-Dibenzoyl-1-amino-2-decanol, 8a. A solution of amino alcohol (*S*)-**4a** (35 mg, 0.20 mmol) and DMAP (~2 mg) in dry pyridine (8 mL) was treated, dropwise, with freshly distilled benzoyl chloride (93 μL, 0.808 mmol), and the mixture heated to 60 °C for 5 h. After cooling, pyridine was removed by azeotropic co-distillation with *n*-heptane under reduced pressure, and the residue purified by flash chromatography (SiO_2, 1:9 EtOAc/hexanes) to provide pure (+)-(*S*)-**8a** (11.2 mg, 15%): $[\alpha]_D$ +28.3 (*c* 1.76, MeOH), $[\alpha]_D$ +17.8 (*c* 0.45, $CHCl_3$); UV−vis (CF_3CH_2OH) λ 196 nm ($\log_{10}$ ε 4.65), 227 (4.21); FTIR (ZnSe) ν 3349 bs, 1710s, 1645m, 1271s, 745s, 1711s cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (2H, d, J = 8.4 Hz, H-2′), 7.74 (2H, d, J = 7.6 Hz), 7.59 (2H, m), 7.5−7.39 (4H, m), 6.76 (1H, bt, NH), 5.30 (1H, m, H-2), 3.81 (1H, ddd, J = 14.4, 4.0, 4.0 Hz, H-1a), 3.73 (1H, ddd, J = 14.4, 8.0, 6.0 Hz, H-1b), 1.76−1.74 (2H, m, H_2-3), 1.45 (2H, m, H_2-4), 1.25 (10H, m), 0.86 (3H, t, J = 6.6 Hz); HR-ESIMS *m/z* 382.2376 $[M + H]^+$ (calcd for $C_{24}H_{31}NO_3$ 382.2377).

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(−)-(*R*)-*N*,*O*-Dibenzoyl-1-amino-2-decanol, (*R*)-8b. Amino alcohol (*R*)-**4b** (25 mg, 0.14 mmol) was benzoylated, using the above procedure (method A) to deliver (−)-(*R*)-**8b** (13.5 mg, 25%): $[\alpha]_D$ −26.1 (*c* 1.76, MeOH); $[\alpha]_D$ −19.3 (*c* 1.72, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) identical with **8a**; HR-ESIMS *m*/*z* 382.2373 $[M + H]^+$ (calcd for $C_{24}H_{31}NO_3$ 382.2377).

(*S*)-*N*,*O*-Diacetyl-1-amino-2-decanol, 9a. To a solution of amino alcohol (*S*)-**4a** (24 mg, 0.139 mmol) in dry pyridine (1.0 mL) was added acetic anhydride, and the mixture stirred at 23 °C under N_2 for 17 h. The volatiles were removed by bulb-to-bulb distillation under high vacuum, and the straw yellow residue was purified by flash chromatography (silica, 2:98 $MeOH/CH_2Cl_2$) to give pure *N*,*O*-diacetyl derivative (*S*)-**9a** as a colorless oil (9.2 mg, 26%): $[\alpha]_D$ +11.5 (*c* 2.3, MeOH); $[\alpha]_D$ −7.6 (*c* 2.02, $CHCl_3$); FTIR (ZnSe, neat) ν 3300bs, 1740s, 1665s, 1238s cm^{-1}; ^1H NMR (600 MHz) and ^{13}C NMR (125 MHz) identical with (*R*)-**9b**; HR-ESIMS *m*/*z* 280.1881 $[M + Na]^+$ (calcd for $C_{14}H_{27}NNaO_3$, 280.1883).

(*R*)-*N*,*O*-Diacetyl-1-amino-2-decanol, 9b. Compound (*R*)-**4b** (32.3 mg, 0.186 mmol) was acetylated, as described for (*S*)-**9a**, above, to give pure *N*,*O*-diacetyl derivative (*R*)-**9b** as a colorless oil (22.3 mg, 46%): $[\alpha]_D$ −6.8 (*c* 1.29, MeOH); $[\alpha]_D$ +7.1 (*c* 1.29, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 5.74 (1H, m, NH), 4.90 (1H, m, H-2), 3.46 (1H, ddd, *J* = 14.4, 5.4, 3.0 Hz, H-1a), 3.38 (1H, ddd, *J* = 14.4, 7.2, 6.0 Hz, H-1b), 2.08 (3H, s, OAc), 1.98 (3H, s, OAc), 1.51 (2H, m), 1.25 (12H), 0.87 (3H, t, *J* = 6.9 Hz, H_3-10); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5 (C, (O(*C*O)CH_3), 170.4 (O(*C*O)CH_3), 73.7 (CH, C-2), 43.3 (CH_2, C-1), 32.0 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 25.4 (CH_2), 22.4 (CH_3, O(CO)*C*H_3), 22.8 (CH_2), 21.3 (CH_3, O(CO)*C*H_3), 14.3 (CH_3, C-10); HR-ESIMS *m*/*z* 280.1885 $[M + Na]^+$ (calcd for $C_{14}H_{27}NNaO_3$, 280.1883).

(−)-(*R*)-*N*,*O*-Bis(2-naphthoyl)-1-amino-2-decanol, 10b. To a solution of amino alcohol (*R*)-**4b** (24 mg, 0.14 mmol) and DMAP (~2 mg) in dry pyridine (5.5 mL) was added freshly distilled 2-naphthoyl chloride (105 mg, 0.55 mmol), and the mixture heated at 60 °C for 17 h. After cooling, the residue was subjected to several rounds of coazeotropic distillation with *n*-heptane to provide a crude mixture of (*R*)-**10b** and 2-naphthoic acid, which were separated by "pencil column" chromatography (5 × 87 mm, basic Al_2O_3, elution with 1:9 *i*-PrOH/CH_2Cl_2) to deliver pure (−)-(*R*)-**10b** (6.6 mg, 9%): $[\alpha]_D$ −88.9 (*c* 0.55, MeOH); $[\alpha]_D$ −104 (*c* 0.43, $CHCl_3$); UV−vis (CF_3CH_2OH) λ 231 nm ($\log_{10}$ ε 4.93), 271 sh, 280 (4.05), 290 sh; ^1H NMR (600 MHz, $CDCl_3$) δ 8.64 (1H, s, H-1′), 8.27 (1H, s, H-1″), 8.08 (1H, dd, *J* = 8.4, 1.8 Hz, H-3′), 7.97 (1H, d, *J* = 8.4 Hz, H-3″), 7.91−7.84 (5H, m), 7.8 (1H, dd, *J* = 8.4, 1.8 Hz), 7.61 (1H, td, *J* = 7.5, 1.2 Hz), 7.56−7.26 (3H, m), 6.95 (1H, bt, NH), 5.42 (1H, m, H-2), 3.90 (1H, ddd, *J* = 14.4, 4.8, 3.0 Hz, H-1a), 3.83 (1H, ddd, *J* = 14.4, 9.0, 5.4 Hz, H-1b), 1.95 (1H, m, H-3a), 1.83 (1H, m, H-3b), 1.51(2H, m, H_2-4), 1.40−1.26 (13H, m), 0.86 (3H, t, *J* = 6.9 Hz, H_3-10); ^{13}C NMR (150 MHz, APT, $CDCl_3$) δ 167.8 (C, C = O), 167.7 (C, C = O), 141.6 (CH), 135.8 (C), 134.8 (C), 132.7 (C), 132.6 (C), 131.6 (C), 131.5 (CH), 129.5 (CH), 129.1 (CH), 128.6 (CH), 128.5 (CH), 127.9 CH), 127.8 (CH), 127.74 (CH), 127.67 (CH), 127.2 (C), 126.9 (CH), 126.8 (CH), 125.3 (CH), 123.6 (CH), 74.7 (CH), 44.6 (CH_2), 32.6 (CH_2), 32.0 (CH_2), 29.6 (2×CH_2), 29.4 (CH_2), 25.6 (CH_2), 22.8 (CH_2), 14.3 (CH_3); HR-ESIMS *m*/*z* 504.2508 $[M + Na]^+$ (calcd for $C_{32}H_{35}NNaO_3$ 504.2509).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.8b00937.

^1H NMR, ^{13}C NMR, ESI HRMS of **4a** and **5**−**10**, APT spectra of **9b** and **10b**, ECD data for **8a**,**b** and **10a**,**b**, error analysis of $[\alpha]_D$, and ECD of (−)-**10b** (sensitivity, limits of detection) (PDF)

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Notes

The authors declare no competing financial interest.

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(11) Similar notoriety is associated with other amino alkanols; for example, see clavaminols A−F from *Clavelina phlegraea* (a) ref 7 and (2*S*,3*R*)-2-aminododecan-3-ol from *C. oblonga* from Brazil (b) ref 4b.
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(28) See also Table S1. A slight difference is evident in the ratio of Cotton effects (negative vs positive peaks $R = |\Delta\varepsilon(\lambda\ 237)/\Delta\varepsilon(\lambda\ 221)|$ for (*R*)-**8b** (*R* = 0.48) compared to (*S*)-**1b** (*R* = 1.1),[1] which may reflect a weak interaction with the conjugated 1,3-diyne of the latter.
(29) The boundary conditions set for LOD (Figure S25) were the ability to discriminate a distinct bisignate Cotton effect with a signal of 3× the noise (S/N ≈ 3) at wavelengths where no ECD signal occurs (λ 360−400 nm), corresponding to the minimum detected mass in a 1 mm path length ECD cell of volume 330 μL and accumulated (averaged) number of scans *n* = 10 (20 min measurement). Obviously, larger values of *n* will improve LOD.
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