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Stereoselective Synthesis of (2*S*,3*R*)-α-Hydroxy-β-Amino Acids (AHBAs): Valinoctin A, (2*S*,3*R*)-3-Amino-2-Hydroxydecanoic Acid, and a Fluorescent-Labeled (2*S*,3*R*)-AHBA

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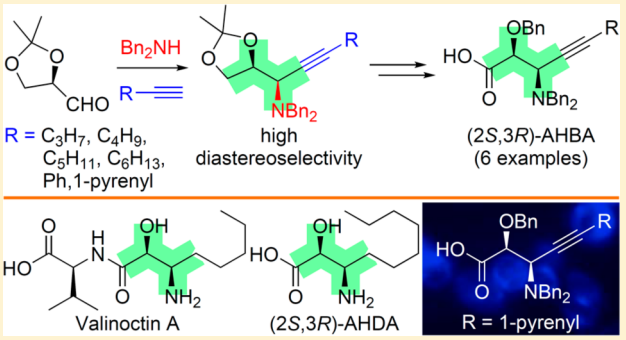
Supporting Information

ABSTRACT: We report the stereoselective synthesis of an alkynyl side-chain containing (2*S*,3*R*)-α-hydroxy-β-amino acid ((2*S*,3*R*)-AHBA) analogues. The Cu(I)-catalyzed reactions of (*R*)-glyceraldehyde acetonide and dibenzylamine with terminal alkynes provided the corresponding (2*S*,3*R*)-α-amino alcohols with good-to-excellent diastereoselectivity. Subsequent chemical transformations provided easy access to the alkynyl side-chain containing (2*S*,3*R*)-AHBAs. The utility of the methodology was demonstrated by the stereoselective synthesis of valinoctin A and (2*S*,3*R*)-3-amino-2-hydroxydecanoic acid ((2*S*,3*R*)-AHDA). Photophysical properties and cell permeability of a pyrene-labeled (2*S*,3*R*)-AHBA were also determined.



The nonproteinogenic amino acids are pivotal structural subunits of many natural products[1] and molecules of pharmaceutical interest.[2] α-Hydroxy-β-amino acids (AHBAs), especially the (2*S*,3*R*)-AHBAs, are present in several naturally occurring and biologically active peptides.[3] For example, bestatin (**1**),[4] phebestin,[5] and probestin[6] are a class of potent aminopeptidase N (APN) inhibitors[7] consisting of (2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanoic acid ((2*S*,3*R*)-AHPA) as the common AHBA subunit (Figure 1). Amastatin (**2**)[8] is a reversible metalloprotease inhibitor and also a competitive inhibitor of leucine aminopeptidase (LAP) and aminopeptidase A (APA). This natural tripeptide consists of (2*S*,3*R*)-3-amino-2-hydroxy-5-methylhexanoic acid as the key *N*-terminal residue. Valinoctin A (**3**) is a farnesyl protein transferase inhibitor, isolated from the fermentation broth of *Streptomyces* strain MJ858-NF.[9] In this dipeptide natural product, (2*S*,3*R*)-3-amino-2-hydroxyoctanoic acid is found as the key AHBA subunit.[9] Similarly, (2*S*,3*R*)-3-amino-2-hydroxydecanoic acid ((2*S*,3*R*)-AHDA) is present in the naturally occurring linear pentapeptide, microginin (**4**), which exhibits inhibitory activities against the angiotensin-converting enzyme (ACE).[10] Scytonemin A (**5**), a natural cyclic peptide with (2*S*,3*R*,5*S*)-3-amino-2,5,9-trihydroxy-10-phenyldecanoic acid as the AHBA component, possesses potent calcium antagonistic properties.[11]

Structural activity relationship (SAR) studies on bestatin (**1**), phebestin, probestin, and other related molecules suggested that the (2*S*,3*R*)-stereochemistry around the α-amino alcohol moiety is essential to their activity. Intrinsic stereospecificity at the indicated domain is also responsible for the binding of structurally different AHBA-containing peptides to the same protein and, therefore, similar inhibitory activity. For example, the crystal structures of bovine lens leucine aminopeptidase (blLAP) protein with bestatin (**1**),[12] and amastatin (**2**)[13] confirm that the (2*S*)-hydroxyl group of an ABHAs involved in the Zn^{2+} ion binding. As a result, synthesis of enantioenriched AHBAs has received considerable attention.[14] For example, carbohydrate based precursors with two defined chiral centers were occasionally used to delineate the stereochemistry around the α-amino alcohol component.[15] Although, these chiron approaches are efficient to access AHBAs in enantiopure form, they are synthetically less demanding due to the presence of predefined stereocenters. Various diastereoselective methodologies, on the other hand, were applied extensively as the more flexible and challenging chiron route to chiral AHBAs. In each of these strategies, a tailored chiral precursor was used for diastereospecific construction of the second chirality. The reported examples following such approaches are (1) diastereospecific reaction on either carbohydrate or α-amino acid based precursors,[16] (2) nucleophilic opening of chiral epoxides,[17] (3) electrophilic hydroxylation of chiral enolates,[18] (4) nucleophilic addition to chiral α-amino aldehydes and imines,[19] (5) stereoselective reduction of ketones,[20] and (6) multicomponent reactions.[21] Asymmetric synthetic strategies for AHBAs were also reported based on (1) chemoenzymolytic,[22] (2) dynamic kinetic resolution,[23] and (3) chiral catalysis.[24] However, most of these approaches have limitations due to the formation of either diastereomer or enantiomer as an undesired product.

A simple and suitable solution to the aforementioned critical limitations was proposed based on our recent report on diastereoselective construction of (2*S*,3*R*)-α-amino alcohols.

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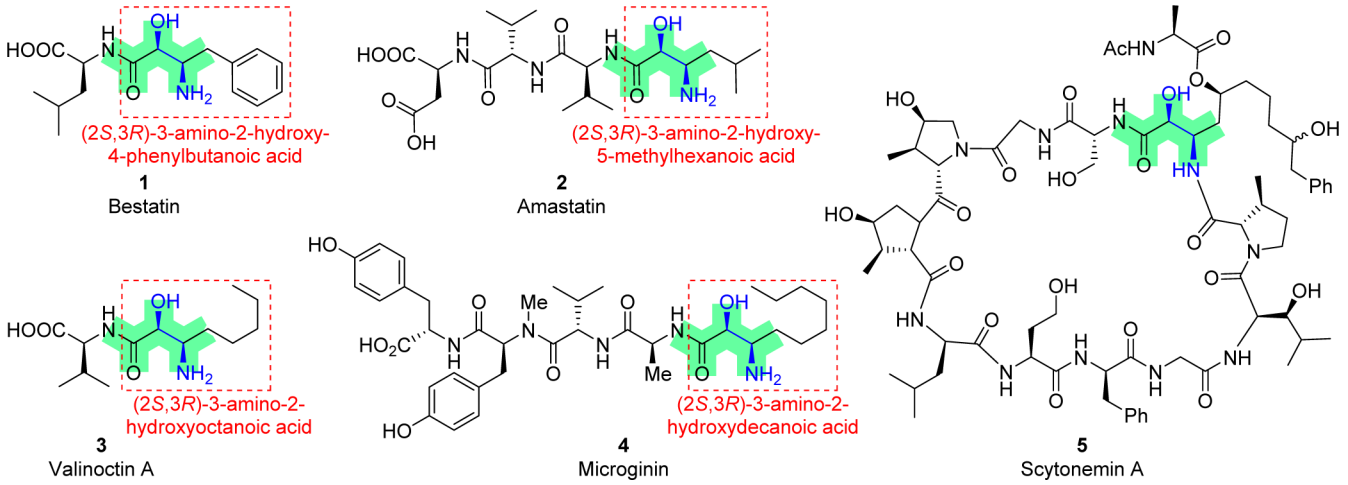
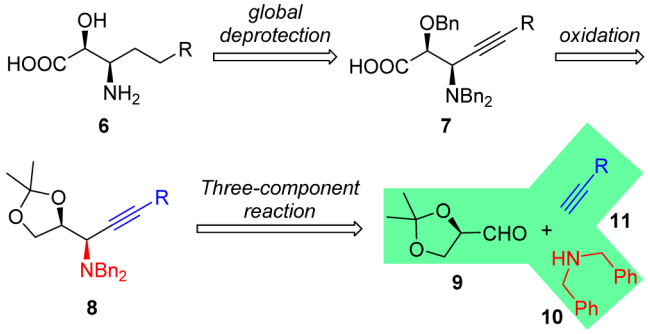


Figure 1. Structures of natural products bestatin (**1**), amastatin (**2**), valinoctin A (**3**), microginin (**4**), and scytonemin A (**5**) having a (2*S*,3*R*)-α-hydroxy-β-amino acid ((2*S*,3*R*)-AHBA) subunit.

The Cu(I)-catalyzed reaction of (*R*)-glyceraldehyde acetonide, dibenzylamine, and terminal alkyne was reported for the formation of a (2*S*,3*R*)-α-amino alcohol.[25] A plausible mechanism for the reaction was proposed via the formation of an iminium cationic intermediate, followed by the addition of the alkynide anion, generated in the reaction. In this three-component methodology, the (2*S*,3*R*)-α-amino alcohol derivative was formed as a single diastereomer whenever a terminal alkyne with an aliphatic side-chain was introduced. To explain these observations, geometry optimization of the iminium cation was carried out, and the result indicates large steric hindrance on its *si* face. Therefore, addition of the alkynide anion from the more accessible *re* face led to the formation of the (2*S*,3*R*)-diastereomer. The (2*S*,3*R*)-stereochemistry around the α-amino alcohol moiety was confirmed by single-crystal X-ray diffraction studies. The three-component coupling reaction was also amenable for incorporating either an alkenyl or an aryl group on the terminal alkyne, although, with slight loss of diastereoselectivity. Formation of the minor (2*S*,3*S*)-diastereomer was rationalized based on the π-stacking interaction between a phenyl group of the iminium cation and an alkenyl/aryl group of the approaching anion. This noncovalent interaction led to the addition of the alkynide anion from the sterically crowded *si* face. The presence of (1) the (2*S*,3*R*)-stereochemistry around the α-amino alcohol moiety, and (2) an aliphatic side-chain, in various naturally occurring AHBAs (**1**−**5**), encouraged us to apply the three-component reaction as a diastereoselective route to this class of amino acids. Such a strategy was planned also to access alkynyl side-chain containing (2*S*,3*R*)-AHBA analogues. Synthesis of this new class of molecules can be indispensable for building SAR and understanding their binding to the target proteins. Fluorescent-labeled (2*S*,3*R*)-AHBAs are already known for the determination of their absolute configuration.[26] Peptides and proteins derived from these types of compounds are also the powerful tools for investigating receptor−ligand binding,[27] protein structures,[28] and enzyme activity in vitro as well as in vivo. Therefore, synthesis of a fluorescent-labeled (2*S*,3*R*)-AHBA was also envisaged.

To address all these aims, a general retrosynthetic analysis was planned (Scheme 1). Synthesis of the representative (2*S*,3*R*)-AHBA **6** was proposed from the corresponding alkynyl side-chain containing (2*S*,3*R*)-AHBA **7**. Benzyl (Bn) protective

Scheme 1. Retrosynthetic Analysis for the Generation of (2*S*,3*R*)-AHBA Analogues



groups on **7** were selected to ensure a single-step protocol for the reduction of the C≡C bond and removal of all benzyl protective groups. Synthesis of AHBA **7** was planned from ketal **8**. Diastereoselective synthesis of the ketal **8** was proposed based on our reported reaction involving (*R*)-glyceraldehyde acetonide **9**, dibenzylamine **10**, and terminal alkyne **11**. A manipulation of the R-group, comprising aliphatic (R = $-C_3H_7$, $-C_4H_9$, $-C_5H_{11}$, and $-C_6H_{13}$), and aromatic (R = −Ph, −1-pyrenyl) functionalities, was proposed to synthesize various alkynyl side-chain containing (2*S*,3*R*)-AHBA analogues. The pyrene moiety was selected as the tethered group, due to its intrinsic fluorescence. To demonstrate the usefulness of the proposed methodology, synthesis of valinoctin A (**3**) was planned from 1-pentynyl side-chain containing (2*S*,3*R*)-AHBA. Similarly, synthesis of (2*S*,3*R*)-AHDA was also considered from 1-heptynyl side-chain containing (2*S*,3*R*)-AHBA.

To accomplish the forenamed aims, three-component reactions were carried out using (*R*)-glyceraldehyde acetonide **9**,[29] dibenzylamine **10**, and a series of terminal alkynes (**11a**−**11f**) as the coupling partner (Table 1). Thus, applying the previously optimized conditions, 1 equiv of **9** and 1 equiv of **10** in the presence of 0.05 equiv of CuBr and molecular sieves (4 Å) in toluene at room temperature, **11a** (R = $-C_3H_7$) provided ketal **8a** in 76% yield (Table 1, series a, step I). Interestingly, the reaction using **11a** gave exclusively the (2*S*,3*R*)-ketal **8a**; no trace of the corresponding (2*S*,3*S*)-diastereomer product was observed when analyzed using ^{1}H NMR and reversed phased HPLC. Introduction of other terminal alkynes (**11b**−**11d**),

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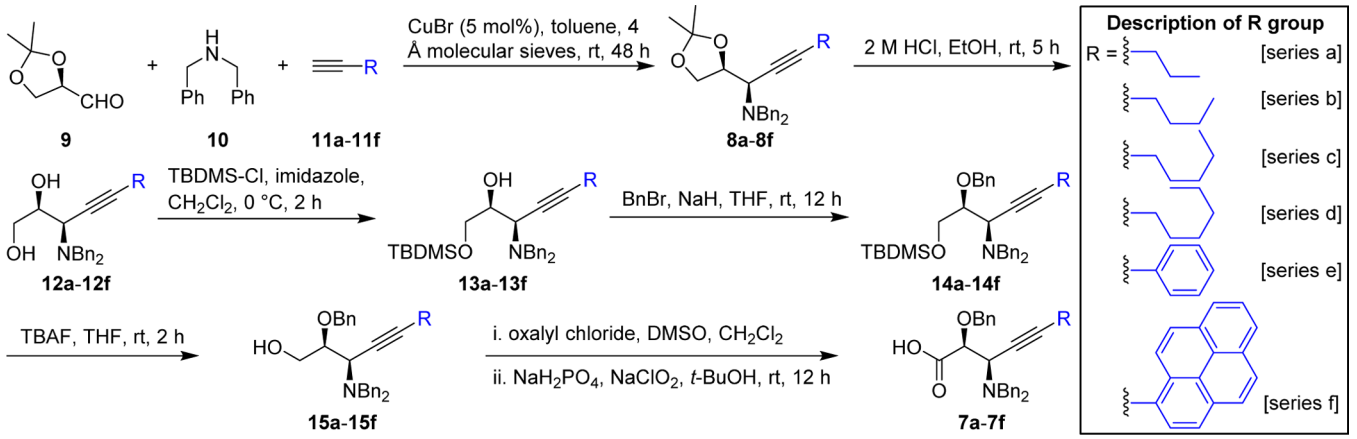
Table 1. Synthesis of Alkynyl Side-Chain Containing Protected (2*S*,3*R*)-AHBAs 7a−7f



	step											
	I			II		III		IV		V		VI	
series	product	*dr*[a]	yield (%)	product	yield (%)	product	yield (%)	product	yield (%)	product	yield (%)	product	yield (%)
a	**8a**	>99/1[b]	76	**12a**	87	**13a**	86	**14a**	79	**15a**	93	**7a**	84
b	**8b**	>99/1[b]	73	**12b**	88	**13b**	88	**14b**	83	**15b**	94	**7b**	82
c	**8c**	>99/1[b]	80	**12c**	90	**13c**	92	**14c**	88	**15c**	94	**7c**	85
d	**8d**	>99/1[b]	78	**12d**	87	**13d**	92	**14d**	85	**15d**	90	**7d**	84
e	**8e**[25]	78:22	68	**12e**	85	**13e**	78	**14e**	84	**15e**	88	**7e**	72
f	**8f**	90:10	72	**12f**	80	**13f**	81	**14f**	74	**15f**	82	**7f**	79

[a]*dr* = diastereomeric ratio = the ratio of (2*S*,3*R*)-ketal and (2*S*,3*S*)-ketal determined based on ^{1}H NMR and reversed phase HPLC analyses. [b]Formation of the (2*S*,3*S*)-diastereomer was not observed under the conditions of ^{1}H NMR and reversed phase HPLC analyses; however, 99:1 is reported taking into account the instrumental limitation.

each bearing an aliphatic chain (R = $-C_4H_9$, $-C_5H_{11}$, and $-C_6H_{13}$), also provided (2*S*,3*R*)-ketals (**8b−8d**) as exclusive products in 73−80% yields (Table 1, series b−d, step I). Subsequently, the methodology was applied for the synthesis of (2*S*,3*R*)-AHBAs with arylalkynyl side-chains. For this purpose, previously reported reaction of **9** and **10** with phenylacetylene **11e** was repeated.[25] The reaction provided ketal **8e** in 68% with *dr* = 78:22 (Table 1, series e, step I), and this outcome was consistent with our reported results. To introduce the pyrene fluorophore on the (2*S*,3*R*)-AHBA moiety, 1-pyrenylacetylene **11f**[30] was used as a substrate. The reaction of the alkyne **11f** with **9** and **10** provided the (2*S*,3*R*)-ketal **8f** with *dr* = 90:10 and 72% isolated yield (Table 1, series f, step I). The improved diastereoselectivity observed for **11f** (R = 1-pyrenyl) was correlated to the larger steric effect between the pyrene ring, and the *si* face of the iminium cation.

Subsequently, the ketal groups of three-component coupling products **8a−8f** was deprotected by methanolic HCl to form the corresponding diols **12a−12f** in 80−90% yields (Table 1, series a−f, step II). A TEMPO-mediated selective oxidation of the primary hydroxyl group of diol **12b** provided a low yield of the corresponding carboxylic acid.[31] Therefore, a protection−deprotection strategy was explored in the synthesis of (2*S*,3*R*)-AHBAs. At first, the primary hydroxyl groups of **12a−12f** were protected selectively to obtain the corresponding silyl ethers **13a−13f** in 78−92% yields (Table 1, series a−f, step III). Subsequent secondary hydroxyl groups of **13a−13f** were protected using benzyl bromide to form the corresponding benzyl ethers **14a−14f** in 74−88% yields (Table 1, series a−f, step IV). Compounds **14a−14f**, upon subsequent desilylation using tetrabutylammonium fluoride (TBAF), provided conditions corresponding primary alcohols **15a−15f** in 82−94% yields (Table 1, series a−f, step V). In the next step, Swern oxidation conditions were applied during the conversion of **15a−15f** to the corresponding aldehydes. The extremely mild oxidation protocol is well-known in the literature for the oxidation of the primary hydroxyl group, avoiding epimerization on the chiral α-carbon.[32] Crude aldehydes were then used directly in the next step, without column chromatographic purification. The crude aldehydes were oxidized further using Pinnick reaction conditions to furnish alkynyl side-chain containing (2*S*,3*R*)-AHBA derivatives **7a−7f** in 72−85% yields (Table 1, series a−f, step VI). In the two-step oxidation protocol, alcohols bearing R = alkyl groups (**15a−15d**) provided slightly better yields compared to those with R = aryl groups (**15e−15f**). Apart from NMR spectroscopic characterization of all synthesized compounds, pyrene-containing (2*S*,3*R*)-AHBA **7f** was also analyzed by high-performance liquid chromatography (HPLC) for purity (Figure S1, Supporting Information).

On the basis of the fruitful outcome of alkynyl side-chain containing (2*S*,3*R*)-AHBA analogues, synthesis of the natural product valinoctin A (**3**) was planned. Therefore, the 1-pentynyl side-chain containing (2*S*,3*R*)-AHBA **7a** was selected as the suitable substrate. The reaction of carboxylic acid **7a** and *L*-valine benzyl ester 4-toluenesulfonate **16** under *N*-(3-(dimethylamino)propyl)-*N*′-ethylcarbodiimide hydrochloride (EDC·HCl), 1-hydroxybenzotriazole monohydrate (HOBt) coupling conditions afforded the dipeptide **17** in 85% yield (Scheme 2A). The dipeptide **17** under the $Pd(OH)_2$-catalyzed hydrogenation conditions provided valinoctin A (**3**) in 90% yield. Starting from (*R*)-glyceraldehyde acetonide **9**, the natural product valinoctin A (**3**) was synthesized in 9 steps with an overall yield of 27%. ^{1}H NMR, ^{13}C{H} NMR, melting point,

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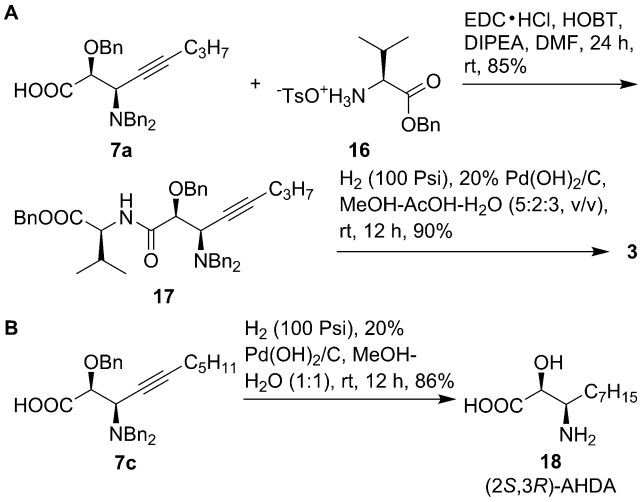
Scheme 2. Synthesis of Valinoctin A (3) (A) and (2*S*,3*R*)-3-Amino-2-hydroxydecanoic Acid ((2*S*,3*R*)-AHDA) 18 (B)



and specific rotation analyses of **3** were adequate to match with previously reported data.[33] We further demonstrated another application of the three-component coupling reaction in the synthesis of (2*S*,3*R*)-3-amino-2-hydroxydecanoic acid ((2*S*,3*R*)-AHDA) **18**, a key component of the natural product microginin (**4**). For this purpose, the 1-heptynyl side-chain containing (2*S*,3*R*)-AHBA **7c** (R = C_5H_{11}) was selected as the ideal substrate. Compound **7c**, upon $Pd(OH)_2$-catalyzed hydrogenation, provided crude (2*S*,3*R*)-AHDA **18** (Scheme 2B). Purification of **18** was carried out by ion-exchange chromatography (Dowex 50w × 8, 200−400 mesh) to achieve 86% yield (overall 40% yield in 8 steps). The structure of the (2*S*,3*R*)-AHDA **18** was adequately confirmed by comparing the recorded ^{1}H NMR, melting point, and specific rotation data with those available in the literature.[34]

After achieving all synthetic goals, the UV−visible and fluorescence properties of the fluorescent-labeled (2*S*,3*R*)-AHBA **7f** were also investigated in chloroform (Figure 2). Compound **7f** (2.0 μM) displayed absorption bands at λ = 331 (ε = 22,000 M^{-1} cm^{-1}), 347 (ε = 48 000 M^{-1} cm^{-1}), and 366 nm (ε = 68 400 M^{-1} cm^{-1}). Upon excitation at λ = 366 nm, **7f** displayed fluorescence bands at λ = 385, 406, and 428 nm. The fluorescence quantum yield, Φ_f = 0.23, was determined for **7f** in chloroform using the reference quinine sulfate (Φ_f = 0.55, in 0.1 M H_2SO_4). When placed under the hand-held UV lamp (λ_{ex} = 365 nm), **7f** (50 μM in chloroform) displayed the characteristic blue fluorescence (Figure 2, inset).

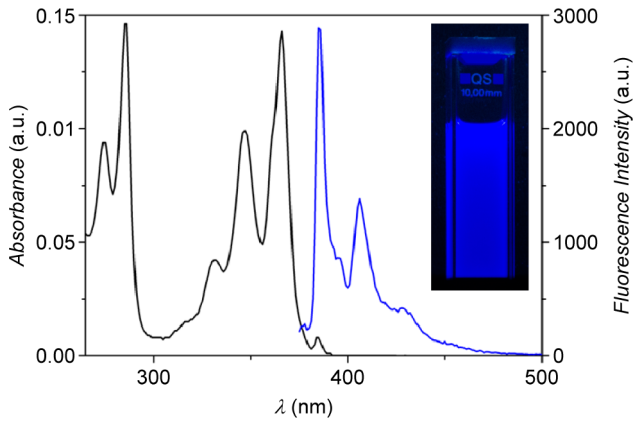


Figure 2. UV−visible (black) and fluorescence (blue) spectra of pyrene substituted (2*S*,3*R*)-AHBA **7f** (2.0 μM) in chloroform. Cuvette image of **7f** (50 μM) in chloroform taken under hand-held UV lamp (inset).

We further evaluated the permeability of the fluorescent-labeled (2*S*,3*R*)-AHBA **7f** in DLD1 cancer cells by fluorescence microscopy techniques. When these cells were incubated with compound **7f** (20 μM) in 1:1000 (DMSO:OptiMEM) media at 37 °C for 30 min, strong fluorescence was observed within incubated cells (Figure 3).

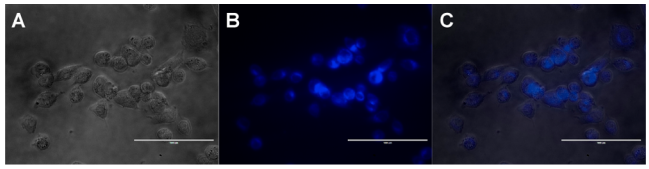


Figure 3. Transmission (A), fluorescence (B), and overlay (C) images of DLD1 cancer cells upon incubation of fluorescent-labeled (2*S*,3*R*)-AHBA **7f**.

In summary, a new stereoselective methodology was developed for the synthesis of (2*S*,3*R*)-α-hydroxy-β-amino acid ((2*S*,3*R*)-AHBA) analogues via the Cu(I)-catalyzed (*R*)-glyceraldehyde acetonide-dibenzylamine-terminal alkyne coupling reaction. Tuneability of the terminal alkyne with either an aliphatic (propyl, butyl, pentyl, and hexyl) or an aromatic (phenyl and 1-pyrenyl) side-chain, and good-to-excellent diastereoselectivity rendered the three-component reactions as an efficient strategy for the synthesis of alkynyl side-chain containing (2*S*,3*R*)-AHBA derivatives. The generality of the approach was demonstrated by the stereoselective synthesis of valinoctin A, a naturally occurring farnesyl protein transferase inhibitor. Synthesis of (2*S*,3*R*)-3-amino-2-hydroxydecanoic acid (AHDA), the *N*-terminal residue of the natural linear pentapeptide microginin, was also achieved based on the methodology. Considering the broad applications of fluorescent-labeled amino acids, the UV−visible and fluorescence spectra of the pyrene-containing compound AHBA were determined. Cell permeability of the compound was also demonstrated by live-cell imaging studies.

EXPERIMENTAL SECTION

General Considerations. All reactions were carried out under a nitrogen atmosphere. All the chemicals were purchased from commercial sources and used as received unless stated otherwise. Solvents such as petroleum ether, ethyl acetate (EtOAc), dichloromethane (CH_2Cl_2), and methanol (MeOH) were distilled prior to thin-layer and column chromatography. Column chromatographies were performed on silica gel (100−200 mesh). TLCs were carried out on silica gel 60-F-254 precoated plates.

^{1}H NMR spectra were recorded at 400 or 500 MHz using tetramethylsilane as an internal standard (δ: 0.0 ppm) and ^{13}C{H} NMR spectra at 100 or 125 MHz using $CDCl_3$ as an internal standard (δ: 77.16 ppm). The ^{1}H NMR spectra were reported as follows: δ (position of the proton, multiplicity, coupling constant J in Hz, number of protons), and the ^{13}C{H} NMR spectra were reported as follows: δ (position of carbon). The following abbreviations were used to describe peak patterns wherever appropriate: b, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants were reported in hertz (Hz). High-resolution mass spectra (HRMS) were recorded either on an electron spray ionization time-of-flight (ESI-TOF) or on a Matrix-assisted laser desorption/ionization (MALDI-

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TOF-TOF) mass spectrometer. Melting points were determined with a micro melting point apparatus. HPLC analyses were performed on an apparatus equipped with either an analytical reversed-phase column or an analytical reversed-phase chiral column. Photophysical properties were determined on a UV−visible spectrophotometer and a steady-state spectrophotometer. Live cell imaging studies were carried out using a fluorescence microscope.

General Copper(I)-Catalyzed Aldehyde-Amine-Alkyne Reaction Procedure (*Method A*). To a solution of (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde **9** (2.50 g, 19.20 mmol) in dry toluene (40 mL) were added dibenzylamine **10** (3.80 g, 19.20 mmol), alkyne **11a** (1.30 g, 19.20 mmol), CuBr (138 mg, 0.96 mmol), and 4 Å molecular sieves (10.00 g), and the reaction mixture was stirred at room temperature for 48 h. During this time, the reaction was monitored periodically by TLC. Subsequently, the reaction mixture was filtered through a Celite bed and washed with Et_2O (2 × 30 mL). The combined filtrate was concentrated under reduced pressure, and the resulting crude mixture was purified by column chromatography on silica gel (eluent: 2% EtOAc in petroleum ether) to furnish **8a** (5.50 g, 76%) as a colorless oil.

*Characterization Data of (R)-N,N-Dibenzyl-1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)hex-2-yn-1-amine **8a**.* IR (KBr) ν (cm^{-1}): 2966, 2876, 1497, 1453, 1372, 1214, 1148, 1069; $[\alpha]_D^{25}$ = −118.8 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.44 (d, *J* = 5.7 Hz, 4H), 7.30 (t, *J* = 7.2 Hz, 4H), 7.22 (t, *J* = 6.6 Hz, 2H), 4.26 (q, *J* = 6.6 Hz, 1H), 4.00 (dd, *J* = 8.2, 6.4 Hz, 1H), 3.87−3.83 (m, 3H), 3.56 (d, *J* = 5.6 Hz, 1H), 3.46 (d, *J* = 13.4 Hz, 2H), 2.25 (t, *J* = 6.1 Hz, 2H), 1.56−1.16 (m, 2H), 1.33 (s, 3H), 1.27 (s, 3H), 1.05 (t, *J* = 7.4 Hz, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 139.8 (2C), 129.0 (4C), 128.2 (4C), 127.0 (2C), 109.6, 86.9, 76.6, 74.7, 67.6, 55.7, 55.5 (2C), 26.6, 25.7, 22.6, 20.8,13.7; HRMS (ESI) Calcd 378.2433 for $C_{25}H_{32}NO_2$ $[M + H]^+$, found 378.2434.

*Synthesis of (R)-N,N-Dibenzyl-1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)hept-2-yn-1-amine **8b**.* Following the *Method A*, reaction of **9** (2.00 g, 15.40 mmol), **10** (3.05 g, 15.40 mmol), and **11b** (1.27 g, 15.40 mmol) was carried out in dry toluene (30 mL) in the presence of CuBr (110 mg, 0.77 mmol) and 4 Å molecular sieves (7.50 g). The crude product was subjected to column chromatography on silica gel (Eluent: 2% EtOAc in petroleum ether) to furnish **8b** (4.40 g, 73%) as a colorless oil. IR (KBr) ν (cm^{-1}): 2932, 2871, 1496, 1454, 1373, 1250, 1214, 1148, 1069; $[\alpha]_D^{25}$ = −63.4 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.44 (d, *J* = 7.4 Hz, 4H), 7.29 (t, *J* = 7.2 Hz, 4H), 7.21 (t, *J* = 7.3 Hz, 2H), 4.25 (q, *J* = 6.4 Hz, 1H), 3.99 (dd, *J* = 8.3, 6.4 Hz, 1H), 3.87−3.82 (m, 3H), 3.55 (dt, *J* = 7.2, 2.1 Hz, 1H), 3.45 (d, *J* = 13.9 Hz, 2H), 2.27 (td, *J* = 6.8, 2.0 Hz, 2H), 1.57−1.50 (m, 4H), 1.33 (s, 3H), 1.26 (s, 3H), 0.96 (t, *J* = 7.2 Hz, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 139.8 (2C), 128.9 (4C), 128.2 (4C), 126.9 (2C), 109.6, 87.0, 76.5, 74.5, 67.5, 55.7, 55.4 (2C), 31.2, 26.6, 25.7, 22.0, 18.5, 13.7; HRMS (ESI) Calcd 392.2589 for $C_{26}H_{34}NO_2$ $[M + H]^+$, found 392.2589.

*Synthesis of (R)-N,N-Dibenzyl-1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)oct-2-yn-1-amine **8c**.* Following the *Method A*, reaction of **9** (2.00 g, 15.40 mmol), **10** (3.05 g, 15.40 mmol), and **11c** (1.48 g, 15.40 mmol) was carried out in dry toluene (30 mL) in the presence of CuBr (110 mg, 0.77 mmol) and 4 Å molecular sieves (7.50 g). The crude product was subjected to column chromatography on silica gel (Eluent: 2% EtOAc in petroleum ether) to furnish **8c** (4.98 g, 80%) as a colorless oil. IR (KBr) ν (cm^{-1}): 2929, 2858, 1499, 1455, 1367, 1214, 1100, 1031; $[\alpha]_D^{25}$ = −88.8 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.45 (d, *J* = 7.3 Hz, 4H), 7.31 (t, *J* = 7.4 Hz, 4H), 7.22 (t, *J* = 7.3 Hz, 2H), 4.25 (q, *J* = 6.4 Hz, 1H), 4.01 (dd, *J* = 8.2, 6.4 Hz, 1H), 3.89−3.82 (m, 3H), 3.56 (dt, *J* = 7.6, 2.2 Hz, 1H), 3.46 (d, *J* = 13.9 Hz, 2H), 2.27 (td, *J* = 7.0, 2.1 Hz, 2H), 1.61−1.51 (m, 2H) 1.48−1.36 (m, 4H), 1.34 (s, 3H), 1.27 (s, 3H), 0.95 (t, *J* = 7.2 Hz, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 139.8 (2C), 129.0 (4C), 128.3 (4C), 127.0 (2C), 109.7, 88.7, 76.6, 74.6, 67.6, 55.7, 55.5 (2C), 31.2, 28.8, 26.7, 25.7, 22.4, 18.8, 14.2; HRMS (ESI) Calcd 406.2746 for $C_{27}H_{36}NO_2$ $[M + H]^+$, found 406.2746.

*Synthesis of (R)-N,N-Dibenzyl-1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)non-2-yn-1-amine **8d**.* Following the *Method A*, reaction of **9** (2.00 g, 15.40 mmol), **10** (3.05 g, 15.40 mmol), and **11d** (1.70 g, 15.40 mmol) was carried out in dry toluene (30 mL) in the presence of CuBr (110 mg, 0.77 mmol) and 4 Å molecular sieves (7.50 g). The crude product was subjected to column chromatography on silica gel (Eluent: 2% EtOAc in petroleum ether) to furnish **8d** (5.04 g, 78%) as a colorless oil. IR (KBr) ν (cm^{-1}): 2933, 1517, 1457, 1374, 1215, 1215, 1150, 1073; $[\alpha]_D^{25}$ = −74.4 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.44 (d, *J* = 7.3 Hz, 4H), 7.29 (dd, *J* = 10.2, 4.6 Hz, 4H), 7.21 (t, *J* = 7.3 Hz, 2H), 4.25 (q, *J* = 6.4 Hz, 1H), 4.00 (dd, *J* = 8.3, 6.4 Hz, 1H), 3.87−3.82 (m, 3H), 3.55 (dt, *J* = 7.5, 2.1 Hz, 1H), 3.45 (d, *J* = 13.9 Hz, 2H), 2.26 (td, *J* = 6.9, 2.1 Hz, 2H), 1.61−1.50 (m, 4H), 1.49−1.41 (m, 2H), 1.37−1.33 (m, 2H), 1.32 (s, 3H), 1.26 (s, 3H), 0.92 (t, *J* = 6.9 Hz, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 139.8 (2C), 129.0 (4C), 128.3 (4C), 127.0 (2C), 109.7, 87.1, 76.6, 74.5, 67.5, 55.6, 55.4 (2C), 31.4, 29.1, 28.6, 26.6, 25.7, 22.7, 18.8, 14.2; HRMS (ESI) Calcd 420.2903 for $C_{28}H_{38}NO_2$ $[M + H]^+$, found 420.2911.

*Synthesis of (R)-N,N-Dibenzyl-1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-phenylprop-2-yn-1-amine **8e**.* Following the *Method A*, reaction of **9** (3.00 g, 23.0 mmol), **10** (4.56 g, 23.10 mmol), and **11e** (2.50 g, 24.40 mmol) was carried out in dry toluene (50 mL) in the presence of CuBr (180 mg, 1.3 mmol) and 4 Å molecular sieves (15.0 g). The crude product was subjected to column chromatography on silica gel (Eluent: 1% EtOAc in petroleum ether) to furnish **8e** (6.44 g, 68%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.48−7.46 (m, 6H), 7.35−7.32 (m, 3H), 7.31 (t, *J* = 7.3 Hz, 4H), 7.23 (t, *J* = 7.3 Hz, 2H), 4.38 (q, *J* = 6.5 Hz, 1H), 4.08 (dd, *J* = 8.1, 6.6 Hz, 1H), 3.99−3.92 (m, 3H), 3.82 (d, *J* = 7.4 Hz, 1H), 3.56 (d, *J* = 13.9 Hz, 2H), 1.36 (s, 3H), 1.30 (s, 3H). ^1H NMR data of **8e** was matched with the reported data.[25]

*Synthesis of (R)-N,N-Dibenzyl-1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(pyren-1-yl)prop-2-yn-1-amine **8f**.* Following the *Method A*, reaction of **9** (2.00 g, 15.4 mmol), **10** (3.05 g, 15.4 mmol), and **11f** (3.51 g, 15.4 mmol) was carried out in dry toluene (30 mL) in the presence of CuBr (110 mg, 0.77 mmol) and 4 Å molecular sieves (7.50 g). The crude product was subjected to column chromatography on silica gel (Eluent: 5% EtOAc in petroleum ether) to furnish **8f** (5.92 g, 72%) as a pale yellow oil. IR (KBr) ν (cm^{-1}): 3021, 2364, 1647, 1427, 1368, 1214; $[\alpha]_D^{25}$ = −149.4 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.60 (d, *J* = 9.1 Hz, 1H), 8.27−8.19 (m, 3H), 8.17 (t, *J* = 7.3 Hz, 2H), 8.12 (d, *J* = 8.8 Hz, 1H), 8.09−8.03 (m, 2H), 7.56 (d, *J* = 7.3 Hz, 4H), 7.36 (t, *J* = 7.4 Hz, 4H), 7.29−7.25 (m, 2H), 4.56 (q, *J* = 6.3 Hz, 1H), 4.22 (dd, *J* = 8.4, 6.3 Hz, 1H), 4.17 (dd, *J* = 8.3, 6.2 Hz, 1H), 4.11−4.06 (m, 3H), 3.76 (d, *J* = 13.9 Hz, 2H), 1.42 (s, 3H), 1.38 (s, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 139.5 (2C), 132.1, 131.4 (2C), 131.1, 130.2 (2C), 129.1 (4C), 128.6 (2C), 128.3 (4C), 127.4, 127.2 (2C), 126.4, 125.8 (2C), 125.5, 124.6, 124.4, 117.5, 109.9, 90.2, 85.9, 76.6, 67.7, 56.7, 55.9 (2C), 26.7, 25.7; HRMS (ESI) Calcd for 536.2590 $C_{38}H_{34}NO_2$ $[M + H]^+$, found 536.2586.

General Procedure for Deprotection of Acetonides (*Method B*). To a solution of **8a** (5.00 g, 13.3 mmol) in methanol (30 mL) was added 2 M HCl (6.5 mL), and the mixture was stirred at room temperature for 5 h. During this time, the reaction was monitored periodically by TLC. After the completion of the reaction, the solution was neutralized with solid K_2CO_3 and the reaction mixture was concentrated. The reaction mixture was diluted by adding H_2O (50 mL), followed by the extraction of the product in ethyl acetate (2 × 50 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel (Eluent: 10% EtOAc in petroleum ether) to furnish **12a** (3.90 g, 87%) as a colorless oil.

*Characterization Data of (2S,3R)-3-(Dibenzylamino)oct-4-yne-1,2-diol **12a**.* IR (KBr) ν (cm^{-1}): 3445, 3062, 2962, 2930, 1495, 1454, 1375, 1335, 1287, 1249, 1100, 1071, 1036; $[\alpha]_D^{25}$ = −113.8 (*c* = 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.37−7.25 (m, 9H), 7.24−7.23 (m, 1H), 3.86 (d, *J* = 13.4 Hz, 2H), 3.84−3.79 (m, 1H), 3.67−3.63 (m, 1H), 3.55 (dd, *J* = 11.7, 3.5 Hz, 1H), 3.51 (dt, *J* = 9.9, 2.1 Hz, 1H), 3.44 (d, *J* = 13.4 Hz, 2H), 2.28 (td, *J* = 7.0, 2.1 Hz, 2H), 1.64−1.58 (m, 2H), 1.05 (t, *J* = 7.4 Hz, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 138.5 (2C), 129.3 (4C), 128.7 (4C), 127.6

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(2C), 88.5, 73.6, 70.5, 63.4, 55.3 (2C), 54.0, 22.5, 20.9, 13.7; HRMS (ESI) Calcd 338.2120 for $C_{22}H_{28}NO_2$ $[M + H]^+$, found 338.2117.

Synthesis of (2S,3R)-3-(Dibenzylamino)non-4-yne-1,2-diol ***12b***. Following the *Method B*, the reaction of **8b** (4.00 g, 10.2 mmol) with 2 M HCl (5.0 mL) was carried out in methanol (20 mL). The crude mixtrure was subjected to column chromatography on silica gel (Eluent: 10% EtOAc in petroleum ether) to furnish **12b** (3.16 g, 88%) as a colorless oil. IR (KBr) ν (cm^{-1}): 3438, 3061, 2956, 2930, 1496, 1454, 1371, 1335, 1290, 1248, 1100, 1070; $[\alpha]_D^{25}$ = −99.8 (c = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.35−7.23 (m, 10H), 3.85 (d, J = 13.4 Hz, 2H), 3.83−3.77 (m, 1H), 3.67−3.62 (m, 1H), 3.55 (d, J = 11.6 Hz, 1H), 3.50 (dt, J = 9.9, 2.1 Hz, 1H), 3.43 (d, J = 13.3 Hz, 2H), 2.30 (td, J = 7.0, 2.1 Hz, 2H), 1.59−1.43 (m, 4H), 0.97 (t, J = 7.3 Hz, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 138.5 (2C), 129.3 (4C), 128.7 (4C), 126.7 (2C), 88.7, 73.4, 70.5, 63.4, 55.2, 53.9 (2C), 31.1, 22.1, 18.6, 13.8; HRMS (ESI) Calcd 352.2277 for $C_{23}H_{30}NO_2$ $[M + H]^+$, found 352.2277.

Synthesis of (2S,3R)-3-(Dibenzylamino)dec-4-yne-1,2-diol ***12c***. Following the *Method B*, the reaction of **8c** (4.50 g, 11.1 mmol) with 2 M HCl (6.0 mL) was carried out in methanol (25 mL). The crude mixture was subjected to column chromatography on silica gel (Eluent: 12% EtOAc in petroleum ether) to furnish **12c** (3.65 g, 90%) as a colorless oil. IR (KBr) ν (cm^{-1}): 3438, 3025, 2928, 1498, 1455, 1367, 1214, 1101, 1068; $[\alpha]_D^{25}$ = −59.2 (c = 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.35−7.23 (m, 10H), 3.89−3.79 (m, 3H), 3.67−3.62 (m, 1H), 3.55 (dd, J = 11.7, 3.7 Hz, 1H), 3.51 (dt, J = 9.9, 2.1 Hz, 1H), 3.44 (d, J = 13.3 Hz, 2H), 2.29 (td, J = 7.1, 2.2 Hz, 2H), 1.62−1.54 (m, 2H), 1.46−1.34 (m, 4H), 0.95 (t, J = 7.2 Hz, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 138.4 (2C), 129.2 (4C), 128.6 (4C), 127.5 (2C), 88.7, 73.3, 70.4, 63.3, 55.2, 53.9 (2C), 31.2, 28.7, 22.3, 18.8, 14.2; HRMS (ESI) Calcd 366.2433 for $C_{24}H_{32}NO_2$ $[M + H]^+$, found 366.2429.

Synthesis of (2S,3R)-3-(Dibenzylamino)undec-4-yne-1,2-diol ***12d***. Following the *Method B*, the reaction of **8d** (4.50 g, 9.54 mmol) with 2 M HCl (5.0 mL) was carried out in methanol (20 mL). The crude mixture was subjected to column chromatography on silica gel (Eluent: 10% EtOAc in petroleum ether) to furnish **12d** (3.15 g, 87%) as a colorless oil. IR (KBr) ν (cm^{-1}): 3436, 3023, 2929, 2856, 1496, 1454, 1371, 1289, 1215, 1098, 1069; $[\alpha]_D^{25}$ = −115.8 (c = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.36−7.26 (m, 9H), 7.25−7.23 (m, 1H), 3.98−3.76 (m, 3H), 3.65 (dt, J = 9.9, 3.4 Hz, 1H), 3.59−3.53 (m, 1H), 3.51 (dt, J = 9.8, 2.0 Hz, 1H), 3.44 (d, J = 13.3 Hz, 2H), 2.29 (td, J = 6.9, 2.1 Hz, 2H), 1.68−1.53 (m, 2H), 1.51−1.42 (m, 2H), 1.39−1.29 (m, 4H), 0.93 (t, J = 6.9 Hz, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 138.5 (2C), 129.2 (4C), 128.7 (4C), 127.5 (2C), 88.7, 73.4, 70.5, 63.3, 55.2, 53.9 (2C), 31.4, 29.0, 28.7, 22.7, 18.8, 14.2; HRMS (ESI) Calcd 380.2589 for $C_{25}H_{34}NO_2$ $[M + H]^+$, found 380.2584.

Synthesis of (2S,3R)-3-(Dibenzylamino)-5-phenylpent-4-yne-1,2-diol ***12e***. Following the *Method B*, the reaction of **8e** (3.50 g, 8.51 mmol) with 2 M HCl (4.25 mL) was carried out in methanol (18 mL). The crude mixture was subjected to column chromatography on silica gel (Eluent: 14% EtOAc in petroleum ether) to furnish **12e** (2.70 g, 85%) as a pale yellow oil. IR (KBr) ν (cm^{-1}): 2987, 2808, 1592, 1495, 1370, 1256, 1210, 1149, 1067; $[\alpha]_D^{25}$ = −70.30 (c = 0.5, MeOH); ^1H NMR (400 MHz, CD_3OD) δ (ppm): 7.53−7.48 (m, 2H), 7.41−7.36 (m, 6H), 7.33−7.31 (m, 5H), 7.26 (t, J = 7.2 Hz, 2H), 3.98 (d, J = 13.4 Hz, 2H), 3.84−3.74 (m, 3H), 3.62−3.54 (m, 3H); $^{13}C\{H\}$ NMR (100 MHz, CD_3OD) δ (ppm): 139.9, 132.8 (2C), 130.3 (4C), 129.5 (8C), 128.4(2C), 124.1, 88.9, 84.5, 72.7, 64.4, 56.5 (2C), 55.8; HRMS (ESI) Calcd 372.1964 for $C_{25}H_{26}NO_2$ $[M + H]^+$, found 372.1967.

Synthesis of (2S,3R)-3-(Dibenzylamino)-5-(pyren-1-yl)pent-4-yne-1,2-diol ***12f***. Following the *Method B*, the reaction of **8f** (3.00 g, 5.60 mmol) with 2 M HCl (3.00 mL) was carried out in methanol (12 mL). The crude mixture was subjected to column chromatography on silica gel (Eluent: 18% EtOAc in petroleum ether) to furnish **12f** (2.22 g, 80%) as a yellow oil. IR (KBr) ν (cm^{-1}): 3743, 3023, 2967, 2364, 1647, 1547, 1532, 1516, 1453, 1427, 1368, 1222; $[\alpha]_D^{25}$ = −96.6 (c = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.55 (d, J = 9.1 Hz, 1H), 8.25−8.19 (m, 3H), 8.18−8.09 (m, 3H), 8.06−8.02 (m, 2H), 7.42−7.35 (m, 8H), 7.33−7.27 (m, 2H), 4.11 (d, J = 13.3 Hz, 2H), 4.07−4.01 (m, 2H), 3.96 (dt, J = 9.9, 3.1 Hz, 1H), 3.81 (dd, J = 11.8, 3.4 Hz, 1H), 3.74 (d, J = 13.3 Hz, 2H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 138.2 (2C), 132.1, 131.5 (2C), 131.1, 130.2 (2C), 129.3 (4C), 128.8 (2C), 128.7, 127.7 (4C), 127.3, 126.4, 125.8 (2C), 125.3, 124.6 (2C), 124.4, 117.1, 88.3, 87.2, 70.5, 63.3, 55.6, 54.7 (2C); HRMS (ESI) Calcd 496.2276 for $C_{35}H_{30}NO_2$ $[M + H]^+$, found 496.2279.

General Procedure of Selective Protection of Primary Hydroxyl Groups (*Method C*). To a cold (0 °C) solution of the diol **12a** (3.00 g, 8.90 mmol) and imidazole (727 mg, 10.68 mmol) in dry CH_2Cl_2 (35 mL) was added dropwise a solution of TBDMS-Cl (1.14 g, 9.79 mmol) in CH_2Cl_2 (35 mL). The reaction mixture was stirred at 0 °C for 2 h and monitored periodically by TLC. Subsequently, a saturated aqueous solution of $NaHCO_3$ (20 mL) was added, and then the reaction was stirred vigorously for 5 min. The resulting mixture was poured into a 250 mL separatory funnel, and the compound was extracted in the organic layer. The resulting aqueous layer was washed further with CH_2Cl_2 (2 × 25 mL). The combined organic layer was washed with a saturated solution of NaCl (30 mL) and dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (Eluent: 3% EtOAc in petroleum ether) to furnish **13a** (3.45 g, 86%) as a colorless oil.

Characterization Data of (2S,3R)-1-((tert-Butyldimethylsilyl)oxy)-3-(dibenzylamino)oct-4-yn-2-ol ***13a***. IR (KBr) ν (cm^{-1}): 3449, 3062, 3029, 2957, 2930, 2857, 1495, 1458, 1404, 1367, 1291, 1211, 1252, 1125, 1030; $[\alpha]_D^{25}$ = −105.2 (c = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): δ 7.31−7.27 (m, 8H), 7.24−7.21 (m, 2H), 3.88−3.83 (m, 3H), 3.67−3.62 (m, 2H), 3.57−3.52 (m, 1H), 3.41 (d, J = 13.3 Hz, 2H), 2.28 (td, J = 6.9, 1.9 Hz, 2H), 1.63−1.54 (m, 2H), 1.06 (t, J = 7.4 Hz, 3H), 0.76 (s, 9H), −0.04 (s, 3H), −0.07 (s, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 138.7 (2C), 129.3 (4C), 128.6 (4C), 127.4 (2C), 87.8, 74.3, 71.3, 64.2, 55.1 (2C), 53.4, 26.0 (3C), 22.6, 20.9, 18.4, 13.7, −5.3, −5.4; HRMS (ESI) Calcd 452.2985 for $C_{28}H_{42}NO_2Si$ $[M + H]^+$, found 452.2985.

Synthesis of (2S,3R)-1-((tert-Butyldimethylsilyl)oxy)-3-(dibenzylamino)non-4-yn-2-ol ***13b***. Following the *Method C*, the reaction of **12b** (2.50 g, 7.12 mmol) and TBDMS-Cl (911 mg, 7.83 mmol) was carried out in dry CH_2Cl_2 (25 mL) in the presence of imidazole (581 mg, 8.54 mmol). The crude mixture was subjected to column chromatography on silica gel (Eluent: 3% EtOAc in petroleum ether) to furnish **13b** (2.92 g, 88%) as a colorless oil. IR (KBr) ν (cm^{-1}): 3023, 2930, 2858, 1498, 1459, 1366, 1293, 1251, 1215, 1125; $[\alpha]_D^{25}$ = −74.2 (c = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.29−7.25 (m, 8H), 7.23−7.20 (m, 2H), 3.88−3.78 (m, 4H), 3.66−3.58 (m, 2H), 3.53 (dt, J = 9.5, 1.7 Hz, 1H), 3.39 (d, J = 13.3 Hz, 2H), 2.29 (td, J = 6.8, 2.0 Hz, 2H), 1.58−1.45 (m, 4H), 0.96 (t, J = 7.2 Hz, 2H), 0.75 (s, 9H), −0.05 (s, 3H), −0.08 (s, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 138.7 (2C), 129.3 (4C), 128.6 (4C), 127.4 (2C), 88.9, 74.0, 71.2, 64.2, 55.0 (2C), 53.4, 31.2, 26.0 (3C), 22.1, 18.6, 18.4, 13.7, −5.3, −5.4; HRMS (ESI) Calcd 466.3141 for $C_{29}H_{44}NO_2Si$ $[M + H]^+$, found 466.3146.

Synthesis of (2S,3R)-1-((tert-Butyldimethylsilyl)oxy)-3-(dibenzylamino)dec-4-yn-2-ol ***13c***. Following the *Method C*, the reaction of **12c** (3.00 g, 8.21 mmol) andTBDMS-Cl (1.05 g, 9.03 mmol) was carried out in dry CH_2Cl_2 (30 mL) in the presence of imidazole (671 mg, 9.86 mmol). The crude mixture was subjected to column chromatography on silica gel (Eluent: 3% EtOAc in petroleum ether) to furnish **13c** (3.62 g, 92%) as a colorless oil. IR (KBr) ν (cm^{-1}): 3029, 2929, 2857, 1532, 1497, 1459, 1367, 1292, 1251, 1125, 1070; $[\alpha]_D^{25}$ = −75.0 (c = 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.31−7.27 (m, 8H), 7.26−7.21 (m, 2H), 3.89−3.77 (m, 4H), 3.67−3.61 (m, 2H), 3.55 (dt, J = 9.6, 2.0 Hz, 1H), 3.40 (d, J = 13.3 Hz, 2H), 2.29 (td, J = 7.0, 2.0 Hz, 2H), 1.60−1.54 (m, 2H), 1.49−1.33 (m, 4H), 0.95 (t, J = 7.2 Hz, 3H), 0.76 (s, 9H), −0.04 (s, 3H), −0.07 (s, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 138.7(2C), 129.3 (4C), 128.6 (4C), 127.4 (2C), 87.9, 74.1, 71.4, 64.2, 55.1 (2C), 53.4, 31.2, 28.8, 26.0 (3C), 22.3, 19.0, 18.4, 14.2, −5.3, −5.4; HRMS (ESI) Calcd 480.3298 for $C_{30}H_{46}NO_2Si$ $[M + H]^+$, found 480.3293.

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Synthesis of (2S,3R)-1-((tert-Butyldimethylsilyl)oxy)-3-(dibenzylamino)undec-4-yn-2-ol ***13d***. Following the *Method C*, the reaction of **12d** (3.10 g, 8.18 mmol) and TBDMS-Cl (1.05 g, 9.00 mmol) was carried out in dry CH_2Cl_2 (30 mL) in the presence of imidazole (668 mg, 9.82 mmol). The crude miture was subjected to column chromatography on silica gel (Eluent: 3% EtOAc in petroleum ether) to furnish **13d** (3.71 g, 92%) as a colorless oil. IR (KBr) ν (cm^{-1}): 3021, 2931, 2858, 1516, 1490,1461, 1368, 1290, 1215, 1120; $[\alpha]_D^{25}$ = −94.25 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.27 (m, 8H), 7.26−7.22 (m, 2H), 3.88−3.79 (m, 4H), 3.67−3.61 (m, 2H), 3.54 (dt, J = 9.6, 1.9 Hz, 1H), 3.40 (d, J = 13.3 Hz, 2H), 2.29 (td, J = 6.9, 2.0 Hz, 2H), 1.62−1.43 (m, 4H), 1.39−1.29 (m, 4H), 0.93 (t, J = 7.3 Hz, 3H), 0.76 (s, 9H), −0.04 (s, 3H), −0.07 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ (ppm): 138.6 (2C), 129.2 (4C), 128.6 (4C), 127.4 (2C), 87.9, 74.0, 71.2, 64.1, 55.03 (2C), 53.3, 31.4, 29.0, 28.7, 26.0 (3C), 22.7, 18.8, 18.3, 14.2, −5.3, −5.5; HRMS (ESI) Calcd 494.3454 for $C_{31}H_{48}NO_2Si$ [M + H]$^+$, found 494.3454.

Synthesis of (2S,3R)-1-((tert-Butyldimethylsilyl)oxy)-3-(dibenzylamino)-5-phenylpent-4-yn-2-ol ***13e***. Following the *Method C*, the reaction of **12e** (2.10 g, 5.66 mmol) and TBDMS-Cl (724 mg, 6.23 mmol) was carried out in dry CH_2Cl_2 (20 mL) in the presence of imidazole (462 mg, 6.79 mmol). The crude mixture was subjected to column chromatography on silica gel (Eluent: 3% EtOAc in petroleum ether) to furnish **13e** (2.17 g, 78%) as a white solid. m.p.: 79−81 °C. IR (KBr) ν (cm^{-1}): 2987, 2808, 1592, 1495, 1370, 1256, 1210, 1149, 1067; $[\alpha]_D^{25}$ = −70.30 (c = 0.5, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 7.50−7.47 (m, 2H), 7.41−7.35 (m, 7H), 7.35−7.29 (m, 4H), 7.27−7.20 (m, 2H), 3.96 (d, J = 13.3 Hz, 2H), 3.88 (dd, J = 15.1, 5.9 Hz, 2H), 3.81 (dd, J = 11.2, 3.0 Hz, 1H), 3.78−3.73 (m, 1H), 3.53 (d, J = 13.3 Hz, 2H), 0.77 (s, 9H), −0.02 (s, 3H), −0.05 (s, 3H); ^{13}C{H} NMR (100 MHz, CD_3OD) δ (ppm): 139.9 (2C), 132.8 (2C), 130.3 (5C), 129.6 (4C), 129.5 (2C), 128.4 (2C), 124.1, 88.7, 84.8, 72.5, 65.0, 56.4 (2C), 54.9, 26.4 (3C), 19.1, −5.2, −5.3; HRMS (ESI) Calcd 486.2828 for $C_{31}H_{40}NO_2Si$ [M + H]$^+$, found 486.2824.

Synthesis of (2S,3R)-3-(Dibenzylamino)-5-(pyren-1-yl)pent-4-yne-1,2-diol ***13f***. Following the *Method C*, the reaction of **12f** (1.60 g, 3.23 mmol) and TBDMS-Cl (413 mg, 3.55 mmol) was carried out in dry CH_2Cl_2 (15 mL) in the presence of imidazole (264 mg, 3.88 mmol). The crude mixture was subjected to column chromatography on silica gel (Eluent: 5% EtOAc in petroleum ether) to furnish **13f** (1.59 g, 81%) as a yellow thick oil. IR (KBr) ν (cm^{-1}): 3026, 2967, 2942, 1647, 1547, 1532, 1516, 1453, 1368, 1220, 1099; $[\alpha]_D^{25}$ = −101.20 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.58 (d, J = 9.1 Hz, 1H), 8.24 (d, J = 7.6 Hz, 1H), 8.23−8.12 (m, 4H), 8.12−8.06 (m, 2H), 8.04 (t, J = 6.0 Hz, 1H), 7.42 (d, J = 7.2 Hz, 4H), 7.35 (t, J = 7.5 Hz, 4H), 7.28 (t, J = 7.2 Hz, 2H), 4.13−4.07 (m, 3H), 4.04 (dd, J = 12.3, 3.0 Hz, 1H), 3.97−3.89 (m, 2H), 3.86 (s, 1H), 3.71 (d, J = 13.3 Hz, 2H), 0.79 (s, 9H), 0.01 (s, 3H), −0.03 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ (ppm): 138.4 (2C), 132.1, 131.4, 131.3, 131.1, 130.1 (2C), 129.4 (4C), 128.8 (4C), 128.6, 128.3, 127.6 (2C), 127.3, 126.4, 125.8 (2C), 125.4, 124.6, 124.4, 117.5, 89.7, 86.7, 71.2, 64.1, 55.5 (2C), 54.3, 26.1 (3C), 18.4, −5.2, −5.4; HRMS (ESI) Calcd 610.3141 for $C_{41}H_{44}NO_2Si$ [M + H]$^+$, found 610.3142.

General Procedure of Protection of Secondary Hydroxyl Groups (*Method D*). To the suspension of NaH (60% in mineral oil, 334 mg, 8.31 mmol) in dry THF (30 mL) placed at 0 °C under an inert atmosphere was added alcohol **13a** (2.50 g, 5.54 mmol). After stirring the reaction for 10 min at 0 °C, benzyl bromide (1.42 g, 8.31 mmol) was added and the reaction mixture was stirred at room temperature for 12 h. During this time, the reaction was monitored periodically by TLC. The reaction mixture was quenched with methanol (10 mL) and extracted with ethyl acetate (2 × 30 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel (Eluent: 1% EtOAc in petroleum ether) to furnish **14a** (2.37 g, 79%) as a colorless oil.

Characterization Data of (2S,3R)-N,N-Dibenzyl-2-(benzyloxy)-1-((tert-butyldimethylsilyl)oxy)oct-4-yn-3-amine ***14a***. IR (KBr) ν (cm^{-1}): 3062, 3028, 2957, 2930, 2859, 1647, 1546, 1532, 1498, 1458, 1366, 1252, 1211, 1137, 1101, 1031; $[\alpha]_D^{25}$ = −59.75 (c = 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): δ 7.36 (t, J = 6.3 Hz, 6H), 7.30 (t, J = 6.3 Hz, 2H), 7.26−7.24 (m, 5H), 7.18 (t, J = 7.2 Hz, 2H), 4.71 (d, J = 2.2 Hz, 2H), 3.96 (d, J = 13.8 Hz, 2H), 3.82−3.80 (m, 2H), 3.67−3.58 (m, 2H), 3.40 (d, J = 13.8 Hz, 2H), 2.26 (td, J = 6.9, 1.6 Hz, 2H), 1.59−1.56 (m, 2H), 1.05 (t, J = 7.4 Hz, 3H), 0.81 (s, 9H), −0.03 (s, 6H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ (ppm): 140.0 (2C), 139.5, 129.1 (4C), 128.3 (4C), 128.2 (2C), 127.6 (2C), 127.2, 126.9 (2C), 86.8, 82.0, 75.4, 73.2, 65.6, 55.9 (2C), 53.6, 26.0 (3C), 22.7, 21.0, 18.4, 13.8, −5.3 (2C); HRMS (ESI) Calcd 542.3454 for $C_{35}H_{48}NO_2Si$ [M + H]$^+$, found 542.3467.

Synthesis of (2S,3R)-N,N-Dibenzyl-2-(benzyloxy)-1-((tert-butyldimethylsilyl)oxy)non-4-yn-3-amine ***14b***. Following the *Method D*, the reaction of **13b** (2.20 g, 4.73 mmol) and benzyl bromide (1.21 g, 7.09 mmol) was carried out in dry THF (25 mL) in the presence of NaH (60% in mineral oil, 284 mg, 7.09 mmol). The crude mixture was subjected to column chromatography on silica gel (Eluent: 1% EtOAc in petroleum ether) to furnish **14b** (2.18 g, 83%) as a colorless oil. IR (KBr) ν (cm^{-1}): 3023, 2930, 2858, 1498, 1459, 1366, 1293, 1251, 1215, 1125, 1057; $[\alpha]_D^{25}$ = −40.40 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.39−7.35 (m, 6H), 7.34−7.29 (m, 2H), 7.28−7.24 (m, 5H), 7.22−7.17 (m, 2H), 4.73 (d, J = 2.8 Hz, 2H), 3.98 (d, J = 13.8 Hz, 2H), 3.84 (d, J = 4.3 Hz, 2H), 3.68−3.59 (m, 2H), 3.41 (d, J = 13.8 Hz, 2H), 2.31 (td, J = 6.8, 1.7 Hz, 2H), 1.60−1.46 (m, 4H), 0.96 (t, J = 7.2 Hz, 3H), 0.83 (s, 9H), −0.01 (s, 6H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ (ppm): 140.0 (2C), 139.5, 129.1 (4C), 128.3 (4C), 128.2 (2C), 127.6 (2C), 127.2, 126.9 (2C), 86.9, 82.0, 75.2, 73.2, 65.6, 55.8 (2C), 53.6, 31.3, 26.0 (3C), 22.2, 18.6, 18.4, 13.8, −5.3 (2C); HRMS (ESI) Calcd 556.3611 for $C_{36}H_{50}NO_2Si$ [M + H]$^+$, found 556.3607.

Synthesis of (2S,3R)-N,N-Dibenzyl-2-(benzyloxy)-1-((tert-butyldimethylsilyl)oxy)dec-4-yn-3-amine ***14c***. Following the *Method D*, the reaction of **13c** (3.0 g, 6.26 mmol) and benzyl bromide (1.61 g, 9.39 mmol) was carried out in dry THF (35 mL) in the presence of NaH (60% in mineral oil, 376 mg, 9.39 mmol). The crude mixture was subjected to column chromatography on silica gel (Eluent: 1% EtOAc in petroleum ether) to furnish **14c** (3.14 g, 88%) as a colorless oil. IR (KBr) ν (cm^{-1}): 3020, 2932, 2857, 1517, 1460, 1366, 1251, 1215, 1101,1035; $[\alpha]_D^{25}$ = −41.25 (c = 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): δ 7.36 (t, J = 6.3 Hz, 6H), 7.32−7.27 (m, 2H), 7.26−7.22 (m, 5H), 7.20−7.16 (m, 2H), 4.71 (d, J = 2.0 Hz, 2H), 3.96 (d, J = 13.8 Hz, 2H), 3.82 (d, J = 4.4 Hz, 2H), 3.65−3.59 (m, 2H), 3.39 (d, J = 13.8 Hz, 2H), 2.28 (td, J = 6.9, 1.7 Hz, 2H), 1.60−1.55 (m, 2H), 1.48−1.42 (m, 2H), 1.40−1.31 (m, 2H), 0.92 (t, J = 7.2 Hz, 3H), 0.81 (s, 9H), −0.04 (s, 6H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ (ppm): 139.9 (2C), 139.4, 128.9 (4C), 128.1 (4C), 128.0 (2C), 127.5 (2C), 127.1, 126.7 (2C), 86.8, 81.9, 75.2, 73.1, 65.4, 55.7 (2C), 53.5, 31.2, 28.8 25.9 (3C), 22.3, 18.7, 18.2, 14.1, −5.4 (2C); HRMS (ESI) Calcd 570.3767 for $C_{37}H_{52}NO_2Si$ [M + H]$^+$, found 570.3767.

Synthesis of (2S,3R)-N,N-Dibenzyl-2-(benzyloxy)-1-((tert-butyldimethylsilyl)oxy)undec-4-yn-3-amine ***14d***. Following the *Method D*, the reaction of **13d** (3.2 g, 6.49 mmol) and benzyl bromide (1.67 g, 9.74 mmol) was carried out in dry THF (35 mL) in the presence of NaH (60% in mineral oil, 390 mg, 9.74 mmol). The crude mixture was subjected to column chromatography on silica gel (Eluent: 1% EtOAc in petroleum ether) to furnish **14d** (3.22 g, 85%) as a colorless oil. IR (KBr) ν (cm^{-1}): 3029, 2928, 2857, 1496, 1458, 1361, 1252, 1211, 1100, 1032; $[\alpha]_D^{25}$ = −54.80 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): δ 7.36 (t, J = 6.3 Hz, 6H), 7.32−7.27 (m, 2H), 7.26−7.22 (m, 5H), 7.18 (d, J = 7.1 Hz, 2H), 4.72 (d, J = 1.8 Hz, 2H), 3.97 (d, J = 13.8 Hz, 2H), 3.83−3.77 (m, 2H), 3.64−3.59 (m, 2H), 3.39 (d, J = 13.8 Hz, 2H), 2.28 (td, J = 6.8, 1.7 Hz, 2H), 1.60−1.56 (m, 2H), 1.50−1.42 (m, 2H), 1.28−1.34 (m, 4H), 0.90 (t, J = 7.0 Hz, 3H), 0.81 (s, 9H), −0.04 (s, 6H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ (ppm): 140.0 (2C), 139.5, 129.0 (4C), 128.3 (4C), 128.2 (2C), 127.6 (2C), 127.2, 126.9 (2C), 87.0, 82.0, 75.3, 73.2, 65.6, 55.9 (2C), 53.6, 31.5, 29.2, 28.8 26.0 (3C), 22.8, 19.0, 18.4, 14.3, −5.3 (2C); HRMS (ESI) Calcd 584.3924 for $C_{38}H_{54}NO_2Si$ [M + H]$^+$, found 584.3924.

Synthesis of (3R,4S)-N,N-Dibenzyl-4-(benzyloxy)-5-((tert-butyldimethylsilyl)oxy)-1-phenylpent-1-yn-3-amine ***14e***. Following the *Method D*, reaction of **13e** (1.75 g, 3.61 mmol) and benzyl bromide

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(925 mg, 5.41 mmol) was carried out in dry THF (20 mL) in the presence of NaH (60% in mineral oil, 216 mg, 5.41 mmol). The crude mixture was subjected to column chromatography on silica gel (Eluent: 1% EtOAc in petroleum ether) to furnish **14e** (1.74 g, 84%) as a colorless oil. IR (KBr) ν (cm^{-1}): 3028, 2854, 1600, 1492, 1455, 1358, 1254, 1144, 1099, 1068, 1028; $[\alpha]_D^{25} = -69.00$ (c = 0.5, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 7.50−7.46 (m, 2H), 7.42−7.33 (m, 9H), 7.33−7.23 (m, 7H), 7.23−7.19 (m, 2H), 4.72 (s, 2H), 4.04 (d, J = 13.7 Hz, 2H), 3.96 (dd, J = 10.5, 6.1 Hz, 2H), 3.88 (dd, J = 11.2, 2.9 Hz, 1H), 3.78−3.73 (m, 1H), 3.50 (d, J = 13.6 Hz, 2H), 0.82 (s, 9H), −0.02 (s, 6H); ^{13}C{H} NMR (100 MHz, CD_3OD) δ (ppm): 140.8 (2C), 140.3, 132.8 (3C), 130.1 (4C), 129.5 (2C), 129.3 (2C), 129.2 (2C), 128.7 (2C), 128.4, 128.1 (2C), 124.5, 88.0, 86.1, 82.5, 73.8, 65.5, 57.0 (2C), 54.8, 26.4 (3C), 19.1, −5.2 (2C); HRMS (ESI) Calcd 576.3298 for $C_{38}H_{46}NO_2Si$ $[M + H]^+$, found 576.3298.

Synthesis of (3R,4S)-N,N-Dibenzyl-4-(benzyloxy)-5-((tert-butyldimethylsilyl)oxy)-1-(pyren-1-yl)pent-1-yn-3-amine ***14f***. Following the *Method D*, the reaction of **13f** (1.75 g, 2.05 mmol) and benzyl bromide (526 mg, 3.08 mmol) was carried out in dry THF (10 mL) in the presence of NaH (60% in mineral oil, 123 mg, 3.08 mmol). The crude mixture was subjected to column chromatography on silica gel (Eluent: 2% EtOAc in petroleum ether) to furnish **14f** (1.06 g, 74%) as a yellow oil. IR (KBr) ν (cm^{-1}): 3417, 3221, 2931, 1685, 1457, 1363, 1270, 1133, 1072, 1057; $[\alpha]_D^{25} = -69.00$ (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.64 (d, J = 9.1 Hz, 1H), 8.25−8.02 (m, 8H), 7.49 (d, J = 7.2 Hz, 4H), 7.43 (d, J = 7.2 Hz, 2H), 7.31 (q, J = 7.0 Hz, 6H), 7.26−7.23 (m, 3H), 4.91−4.82 (m, 2H), 4.24 (d, J = 13.8 Hz, 2H), 4.16 (d, J = 6.3 Hz, 1H), 4.09 (dd, J = 11.0, 6.3 Hz, 1H), 4.02 (dd, J = 11.1, 3.0 Hz, 1H), 3.94 (td, J = 6.2, 3.0 Hz, 1H), 3.71 (d, J = 13.8 Hz, 2H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ (ppm): 139.8 (2C), 138.5, 132.2, 131.4, 131.2, 130.1 (2C), 129.2 (4C), 128.5 (4C), 128.4 (2C), 128.3, 127.9 (2C), 127.7 (2C), 127.4, 127.1, 126.8 (2C), 126.6 (2C), 125.7, 125.8, 124.6, 118.1, 91.4, 85.8, 82.2, 73.5, 65.5, 56.4 (2C), 54.7, 29.9, 26.1 (3C), 18.4, −5.2 (2C); HRMS (ESI) Calcd 700.3611 for $C_{48}H_{50}NO_2Si$ $[M + H]^+$, found 700.3597.

General Procedure for the Deprotection of TBDMS Groups (*Method E*). To a solution of **14a** (1.75 g, 3.23 mmol) in dry THF (30 mL) placed at 0 °C was added dropwise TBAF (3.23 mL, 3.23 mmol, 1 M in THF), and the mixture was stirred at room temperature for 12 h. During this time, the reaction was monitored periodically by TLC. Subsequently, H_2O (20 mL) was added to the mixture, and volatiles were removed under reduced pressure. The reaction mixture was poured into a 125 mL separatory funnel and extracted with Et_2O (2 × 25 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was subjected to column chromatography on silica gel (Eluent: 8% EtOAc in petroleum ether) to furnish **15a** (1.28 g, 93%) as a colorless oil.

Characterization Data of (2S,3R)-2-(Benzyloxy)-3-(dibenzylamino)oct-4-yn-1-ol ***13a***. IR (KBr) ν (cm^{-1}): 3450, 3062, 3029, 2931, 2873, 1547, 1497, 1454, 1365, 1209, 1098, 1074, 1033; $[\alpha]_D^{25} = -26.40$ (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.39 (d, J = 7.2 Hz, 4H), 7.36−7.27 (m, 9H), 7.26−7.21 (m, 2H), 4.82 (d, J = 11.6 Hz, 1H), 4.65 (d, J = 11.6 Hz, 1H), 4.07 (d, J = 13.6 Hz, 2H), 3.83−3.76 (m, 1H), 3.69 (dt, J = 4.4, 2.2 Hz, 1H), 3.68−3.57 (m, 2H), 3.42 (d, J = 13.6 Hz, 2H), 2.31 (td, J = 7.1, 2.2 Hz, 2H), 1.68−1.59 (m, 2H), 1.08 (t, J = 7.4 Hz, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ (ppm): 139.3 (2C), 138.6, 129.1 (4C), 128.5 (4C), 128.4 (2C), 127.8 (2C), 127.7, 127.2 (2C), 87.6, 80.6, 74.3, 73.1, 63.3, 56.2 (2C), 54.6, 22.6, 20.9, 13.7; HRMS (ESI) Calcd 428.2589 for $C_{29}H_{34}NO_2$ $[M + H]^+$, found 428.2588.

Synthesis of (2S,3R)-2-(Benzyloxy)-3-(dibenzylamino)non-4-yn-1-ol ***15b***. Following the *Method E*, the reaction of **14b** (1.60 g, 2.88 mmol) and TBAF (2.88 mL, 2.88 mmol, 1 M in THF) was carried out in dry THF (25 mL). The crude mixture was subjected to column chromatography on silica gel (Eluent: 8% EtOAc in petroleum ether) to furnish **15b** (1.19 g, 94%) as a colorless oil. IR (KBr) ν (cm^{-1}): 3465, 3062, 3029, 2929, 2866, 1495, 1453, 1359, 1247, 1208, 1096, 1072, 1032; $[\alpha]_D^{25} = -58.20$ (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.39 (d, J = 7.1 Hz, 4H), 7.36−7.26 (m, 9H), 7.25−7.21 (m, 2H), 4.82 (d, J = 11.6 Hz, 1H), 4.65 (d, J = 11.6 Hz, 1H), 4.07 (d, J = 13.6 Hz, 2H), 3.80 (d, J = 10.3 Hz, 1H), 3.69 (dt, J = 4.3, 2.1 Hz, 1H), 3.64−3.57 (m, 2H), 3.42 (d, J = 13.6 Hz, 2H), 2.33 (td, J = 6.9, 2.1 Hz, 2H), 1.63−1.57 (m, 2H), 1.56−1.47 (m, 2H), 0.97 (t, J = 7.2 Hz, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ (ppm): 139.3 (2C), 138.6, 129.1 (4C), 128.5 (4C), 128.4 (2C), 127.8 (2C), 127.7, 127.2 (2C), 87.7, 80.6, 74.2, 73.2, 63.3, 56.2 (2C), 54.7, 31.2, 22.2, 18.6, 13.8; HRMS (ESI) Calcd 442.2746 for $C_{30}H_{36}NO_2$ $[M + H]^+$, found 442.2747.

Synthesis of (2S,3R)-2-(Benzyloxy)-3-(dibenzylamino)dec-4-yn-1-ol ***15c***. Following the *Method E*, the reaction of **14c** (2.50 g, 4.39 mmol) and TBAF (4.39 mL, 4.39 mmol, 1 M in THF) was carried out in dry THF (40 mL). The crude mixture was subjected to column chromatography on silica gel (Eluent: 8% EtOAc in petroleum ether) to furnish **15c** (1.88 g, 94%) as a colorless oil. IR (KBr) ν (cm^{-1}): 3465, 3062, 3021, 2928, 2860, 1516, 1461, 1368, 1247, 1214, 1100, 1072, 1030; $[\alpha]_D^{25} = -12.80$ (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.39 (d, J = 7.7 Hz, 4H), 7.34−7.28 (m, 9H), 7.25−7.21 (m, 2H), 4.83 (d, J = 11.7 Hz, 1H), 4.66 (d, J = 11.6 Hz, 1H), 4.08 (d, J = 13.6 Hz, 2H), 3.80 (dd, J = 10.4, 3.0 Hz, 1H), 3.70−3.3.68 (dd, J = 5.2, 1.9 Hz, 1H), 3.64−3.57 (m, 2H), 3.42 (d, J = 13.6 Hz, 2H), 2.89 (s, 1H), 2.36−2.29 (m, 2H), 1.64−1.58 (m, 2H), 1.51−1.34 (m, 4H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ (ppm): 139.4 (2C), 138.6, 129.1 (4C), 128.5 (4C), 128.4 (2C), 127.8 (2C), 127.7, 127.3 (2C), 87.8, 80.6, 74.2, 73.2, 63.3, 56.2 (2C), 54.7, 31.3, 28.8, 22.4, 18.9, 14.2; HRMS (ESI) Calcd 456.2903 for $C_{31}H_{38}NO_2$ $[M + H]^+$, found 456.2903.

Synthesis of (2S,3R)-2-(Benzyloxy)-3-(dibenzylamino)undec-4-yn-1-ol ***15d***. Following the *Method E*, the reaction of **14d** (2.50 g, 4.29 mmol) and TBAF (4.29 mL, 4.29 mmol, 1 M in THF) was carried out in dry THF (40 mL). The crude mixture was subjected to column chromatography on silica gel (Eluent: 8% EtOAc in petroleum ether) to furnish **15d** (1.80 g, 90%) as a colorless oil. IR (KBr) ν (cm^{-1}): 3468, 3060, 3027, 2921, 2860, 1510, 1441, 1358, 1246, 1213, 1101, 1073, 1028 $[\alpha]_D^{25} = -78.20$ (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.38 (d, J = 7.2 Hz, 4H), 7.36−7.26 (m, 9H), 7.26−7.21 (m, 2H), 4.82 (d, J = 11.6 Hz, 1H), 4.65 (d, J = 11.6 Hz, 1H), 4.07 (d, J = 13.6 Hz, 2H), 3.79 (dd, J = 10.3, 2.9 Hz, 1H), 3.68 (dt, J = 4.3, 2.1 Hz, 1H), 3.64−3.55 (m, 2H), 3.41 (d, J = 13.7 Hz, 2H), 2.87 (s, 1H), 2.32 (td, J = 7.0, 2.1 Hz, 2H), 1.63−1.57 (m, 2H), 1.51−1.45 (m, 2H), 1.38−1.28 (m, 4H), 0.92 (t, J = 7.0 Hz, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ (ppm): 139.4, 138.6 (2C), 129.1 (4C), 128.5 (6C), 127.8 (2C), 127.7 (2C), 127.3, 87.8, 80.6, 74.2, 73.2, 63.3, 56.2 (2C), 54.7, 31.5, 29.1, 28.8, 22.8, 18.9, 14.3; HRMS (ESI) Calcd 470.3059 for $C_{32}H_{40}NO_2$ $[M + H]^+$, found 470.3054.

Synthesis of (2S,3R)-2-(Benzyloxy)-3-(dibenzylamino)-5-phenylpent-4-yn-1-ol ***15e*** *($C_{32}H_{31}NO_2$).* Following the *Method E*, the reaction of **14e** (1.40 g, 2.43 mmol) and TBAF (2.43 mL, 2.43 mmol, 1 M in THF) was carried out in dry THF (25 mL). The crude mixture was subjected to column chromatography on silica gel (Eluent: 10% EtOAc in petroleum ether) to furnish **15e** (1.19 g, 88%) as a colorless oil. IR (KBr) ν (cm^{-1}): 3431, 3035, 2935, 2820, 2465, 1813, 1589, 1512, 1469, 1367, 1230, 1117, 1038; $[\alpha]_D^{25} = -93.25$ (c = 0.8, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 7.51−7.48 (m, 2H), 7.42−7.39 (m, 6H), 7.35−7.31 (m, 3H), 7.30−7.22 (m, 7H), 7.21−7.16 (m, 2H), 4.73 (s, 2H), 4.04 (d, J = 13.7 Hz, 2H), 3.90 (d, J = 6.3 Hz, 1H), 3.86−3.78 (m, 2H), 3.77−3.72 (m, 1H), 3.50 (d, J = 13.8 Hz, 2H); ^{13}C{H} NMR (100 MHz, CD_3OD) δ (ppm): 140.6 (2C), 140.1, 132.8 (3C), 130.1 (4C), 129.5 (4C), 129.3 (2C), 129.2 (2C), 128.8, 128.2 (2C), 128.1 (2C), 124.3, 88.2, 85.6, 82.5, 74.2, 64.0, 57.1 (2C), 55.7; HRMS (ESI) Calcd 462.2433 for $C_{32}H_{32}NO_2$ $[M + H]^+$, found 462.2431.

Synthesis of (2S,3R)-2-(Benzyloxy)-3-(dibenzylamino)-5-(pyren-1-yl)pent-4-yn-1-ol ***15f***. Following the *Method E*, the reaction of **14f** (1.10 g, 1.57 mmol) and TBAF (1.57 mL, 1.57 mmol, 1 M in THF) was carried out in dry THF (15 mL). The crude mixture was subjected to column chromatography on silica gel (Eluent: 12% EtOAc in petroleum ether) to furnish **15f** (755 mg, 82%) as a yellow oil. IR (KBr) ν (cm^{-1}): 3451, 3025, 2967, 2938, 1648, 1547, 1516, 1453,

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1427, 1368, 1219, 1100, 1070, 1030; $[\alpha]_D^{25} = -93.25$ (c = 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.65 (d, J = 9.1 Hz, 1H), 8.25−8.21 (m, 2H), 8.19−8.11 (m, 4H), 8.09−8.03 (m, 2H), 7.50 (d, J = 7.3 Hz, 4H), 7.39 (dt, J = 14.8, 7.0 Hz, 6H), 7.30 (ddd, J = 7.1, 5.1, 2.6 Hz, 5H), 4.94 (d, J = 11.6 Hz, 1H), 4.81 (d, J = 11.6 Hz, 1H), 4.35 (d, J = 13.5 Hz, 2H), 4.20 (d, J = 5.1 Hz, 1H), 4.01 (dd, J = 11.7, 4.7 Hz, 1H), 3.91 (q, J = 4.8 Hz, 1H), 3.79 (dd, J = 11.6, 4.9 Hz, 1H), 3.72 (d, J = 13.6 Hz, 2H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 139.2 (2C), 138.5, 132.3, 131.4, 131.2, 130.1 (2C), 129.3 (4C), 128.8, 128.7 (4C), 128.6 (2C), 128.4, 127.8 (2C), 127.5 (2C), 127.4, 126.8 (2C), 126.6 (2C), 125.6 (2C), 124.6, 124.5, 117.6, 90.1, 86.5, 80.9, 73.4, 63.3, 56.8 (2C), 55.4; HRMS (ESI) Calcd 586.2746 for $C_{42}H_{36}NO_2$ $[M + H]^+$, found 586.2751.

General Procedure for the Oxidation of Primary Alcohol to Acid (*Method F*). A solution of oxalyl chloride (445 mg, 3.51 mmol) in dry CH_2Cl_2 (20 mL) was cooled at −78 °C, DMSO (586 μL, 8.19 mmol) was added dropwise, and the mixture was stirred for 15 min. To this mixture was added a solution of alcohol **15a** (1.0 g, 2.34 mmol) in CH_2Cl_2 (20 mL), and the mixture was stirred at −78 °C for 30 min. Subsequently, Et_3N (1.71 mL, 12.20 mmol) was added, and the reaction mixture was stirred at 0 °C for an additional 30 min. During this time, the reaction was monitored by TLC. Then, the reaction mixture was diluted by adding CH_2Cl_2 (20 mL) and H_2O (30 mL). The resulting mixture was poured into a 125 mL separatory funnel, and the product was extracted into the organic layer. The aqueous layer was washed further with CH_2Cl_2 (2 × 10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give the corresponding crude aldehyde (974 mg). The crude product was used for the next step without further purification.

To a solution of the crude aldehyde (974 mg, 2.30 mmol) and 2-methyl-2-butene (3.28 g, 46.8 mmol) in 25 mL of ^tBuOH-H_2O (3:1) placed at 0 °C were added NaH_2PO_4 (281 mg, 2.34 mmol) and $NaClO_2$ (212 mg, 2.34 mmol), and the reaction mixture was stirred at rt for 10 h. During this time, the reaction was monitored periodically by TLC. The mixture was concentrated under reduced pressure, diluted with H_2O (10 mL), acidified to pH = 2−3 by dropwise addition of 1 N HCl, and subsequently extracted with ethyl acetate (2 × 20 mL). The combined organic layer was washed with saturated NaCl solution (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel (Eluent: 20% EtOAc in petroleum ether) to furnish **7a** (867 mg, 84% over two steps) as a colorless oil.

*Characterization Data of (2S,3R)-2-(Benzyloxy)-3-(dibenzylamino)oct-4-ynoic Acid **7a**.* IR (KBr) ν (cm^{-1}): 3743, 3061, 3027, 2963, 1726, 1612, 1497, 1455, 1373, 1213, 1143, 1101, 1028; $[\alpha]_D^{25}$ = −132.00 (c = 0.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.39 (dd, J = 8.0, 1.4 Hz, 2H), 7.36−7.27 (m, 13H), 4.91 (d, J = 11.8 Hz, 1H), 4.69 (d, J = 11.8 Hz, 1H), 4.37 (d, J = 13.1 Hz, 2H), 3.95 (d, J = 3.6 Hz, 1H), 3.91−3.86 (m, 1H), 3.48 (d, J = 13.3 Hz, 2H), 2.33 (td, J = 7.0, 2.2 Hz, 2H), 1.68−1.60 (m, 2H), 1.07 (t, J = 7.4 Hz, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 171.2, 137.3, 135.8 (2C), 129.8 (4C), 128.9 (4C), 128.4 (2C), 128.3 (2C), 128.2 (2C), 128.0, 89.6, 79.2, 74.0, 71.3, 56.5 (2C), 53.1, 22.3, 21.0, 13.7; HRMS (ESI) Calcd 442.2382 for $C_{29}H_{32}NO_3$ $[M + H]^+$, found 442.2382.

*Synthesis of (2S,3R)-2-(Benzyloxy)-3-(dibenzylamino)non-4-ynoic Acid **7b**.* Following the *Method F*, the Swern oxidation of alcohol **15b** (1.0 g, 2.34 mmol) was carried out to obtain the corresponding crude aldehyde (925 mg), which was further oxidized using NaH_2PO_4 (252 mg, 2.10 mmol), 2-methyl-2-butene (2.94 g, 42.0 mmol), and $NaClO_2$ (190 mg, 2.10 mmol) in 12.5 mL of ^tBuOH-H_2O (3:1). The crude mixture was purified by column chromatography on silica gel (Eluent: 20% EtOAc in petroleum ether) to furnish **7b** (784 mg, 82%) as a colorless oil. IR (KBr) ν (cm^{-1}): 3743, 3027, 2930, 2866, 1734, 1647, 1547, 1498, 1455, 1370, 1213, 1143, 1101, 1028; $[\alpha]_D^{25}$ = −75.80 (c = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.39 (dd, J = 7.9, 1.2 Hz, 2H), 7.36−7.33 (m, 2H), 7.33−7.29 (m, 10H), 7.28−7.26 (m, 1H), 4.92 (d, J = 11.8 Hz, 1H), 4.68 (d, J = 11.8 Hz, 1H), 4.37 (d, J = 13.3 Hz, 2H), 3.96 (d, J = 3.6 Hz, 1H), 3.91−3.87 (m, 1H), 3.47 (d, J = 13.2 Hz, 2H), 2.35 (td, J = 7.0, 2.1 Hz, 2H), 1.64−1.56 (m, 2H), 1.55−1.45 (m, 2H), 0.97 (t, J = 7.2 Hz, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 171.5, 137.3, 135.5 (2C), 129.9 (4C), 128.9 (4C), 128.4 (2C), 128.3 (2C), 128.2 (2C), 128.0, 89.9, 79.3, 73.9, 71.1, 56.5 (2C), 53.4, 30.9, 22.2, 18.6, 13.7; HRMS (ESI) Calcd 456.2539 for $C_{30}H_{34}NO_3$ $[M + H]^+$, found 456.2540.

*Synthesis of (2S,3R)-2-(Benzyloxy)-3-(dibenzylamino)dec-4-ynoic Acid **7c**.* Following the *Method F*, the Swern oxidation of alcohol **15c** (600 mg, 1.32 mmol) was carried out to obtain the corresponding crude aldehyde (598 mg), which was further oxidized using NaH_2PO_4 (158 mg, 1.32 mmol), 2-methyl-2-butene (1.85 g, 26.4 mmol), and $NaClO_2$ (119 mg, 1.32 mmol) in 15 mL of ^tBuOH-H_2O (3:1). The crude mixture was purified by column chromatography on silica gel (Eluent: 20% EtOAc in petroleum ether) to furnish **7c** (526 mg, 85%) as a colorless oil. IR (KBr) ν (cm^{-1}): 3744, 3023, 2931, 2863, 1740, 1648, 1516, 1454, 1368, 1214, 1101, 1033; $[\alpha]_D^{25}$ = −74.00 (c = 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.39−7.35 (m, 2H), 7.34−7.31 (m, 2H), 7.31−7.27 (m, 10H), 7.26−7.24 (m, 1H), 4.90 (d, J = 11.8 Hz, 1H), 4.67 (d, J = 11.8 Hz, 1H), 4.36 (d, J = 13.1 Hz, 2H), 3.96 (d, J = 3.7 Hz, 1H), 3.92−3.88 (m, 1H), 3.46 (d, J = 13.3 Hz, 2H), 2.33 (td, J = 7.0, 2.1 Hz, 2H), 1.62−1.57 (m, 2H), 1.47−1.43 (m, 2H), 1.40−1.32 (m, 2H), 0.92 (t, J = 7.2 Hz, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 170.9, 137.3, 135.8 (2C), 129.8 (4C), 128.9 (4C), 128.4 (2C), 128.3 (2C), 128.2 (2C), 128.0, 89.8, 79.2, 74.0, 71.1, 56.5 (2C), 53.1, 31.3, 28.5, 22.3, 18.9, 14.2; HRMS (ESI) Calcd 470.2695 for $C_{31}H_{36}NO_3$ $[M + H]^+$, found 470.2695.

*Synthesis of (2S,3R)-2-(Benzyloxy)-3-(dibenzylamino)undec-4-ynoic Acid **7d**.* Following the *Method F*, the Swern oxidation of alcohol **15d** (1.20 g, 2.56 mmol) was carried out to obtain the corresponding crude aldehyde (1.18 g), which was further oxidized using (307 mg, 2.56 mmol), 2-methyl-2-butene (3.59 g, 51.2 mmol), and $NaClO_2$ (232 mg, 2.56 mmol) in 30 mL of ^tBuOH-H_2O (3:1). The crude mixture was purified by column chromatography on silica gel (Eluent: 20% EtOAc in petroleum ether) to furnish **7d** (1.04 g, 84%) as a colorless oil. IR (KBr) ν (cm^{-1}): 3744, 3061, 3021, 2931, 1740, 1612, 1516, 1455, 1369, 1214, 1143, 1100, 1028; $[\alpha]_D^{25}$ = −114.50 (c = 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.41−7.37 (m, 2H), 7.36−7.26 (m, 13H), 4.92 (d, J = 11.8 Hz, 1H), 4.68 (d, J = 11.8 Hz, 1H), 4.38 (d, J = 13.0 Hz, 2H), 3.96 (d, J = 3.6 Hz, 1H), 3.92−3.88 (m, 1H), 3.48 (d, J = 13.2 Hz, 2H), 2.34 (td, J = 7.0, 2.1 Hz, 2H), 1.65−1.56 (m, 2H), 1.52−1.44 (m, 2H), 1.37−1.30 (m, 4H), 0.91 (t, J = 7.0 Hz, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 170.8, 137.2, 135.6 (2C), 129.9 (4C), 129.0 (4C), 128.4 (2C), 128.3 (2C), 128.2 (2C), 128.0, 89.9, 79.2, 74.1, 71.0, 56.5 (2C), 53.1, 31.5, 28.8 (2C), 22.8, 20.0, 14.2; HRMS (ESI) Calcd 484.2852 for $C_{32}H_{38}NO_3$ $[M + H]^+$, found 484.2850.

*Synthesis of (2S,3R)-2-(Benzyloxy)-3-(dibenzylamino)-5-phenylpent-4-ynoic Acid **7e**.* Following the *Method F*, the Swern oxidation of alcohol **15e** (1.00 g, 2.00 mmol) was carried out to obtain the corresponding crude aldehyde (998 mg), which was further oxidized using NaH_2PO_4 (264 mg, 2.20 mmol), 2-methyl-2-butene (3.14 g, 44.0 mmol), and $NaClO_2$ (199 mg, 2.20 mmol) in 25 mL of ^tBuOH-H_2O (3:1). The crude mixture was purified by column chromatography on silica gel (Eluent: 25% EtOAc in petroleum ether) to furnish **7e** (753 mg, 72%) as a white solid. mp.: 130−132 °C; IR (KBr) ν (cm^{-1}): 3744, 3565, 3022, 2964, 1740, 1532, 1516, 1454, 1427, 1368, 1215, 1100; $[\alpha]_D^{25}$ = −143.20 (c = 0.5, MeOH); ^1H NMR (400 MHz, CD_3OD) δ (ppm): 7.51−7.48 (m, 2H), 7.39 (dd, J = 7.4, 1.9 Hz, 2H), 7.39−7.35 (m, 7H), 7.27−7.21 (m, 7H), 7.20−7.15 (m, 2H), 4.79 (d, J = 11.9 Hz, 1H), 4.44 (d, J = 11.9 Hz, 1H), 4.20 (d, J = 5.2 Hz, 1H), 4.14 (s, 1H), 4.10 (d, J = 5.1 Hz, 2H), 3.42 (d, J = 13.6 Hz, 2H); $^{13}C\{H\}$ NMR (100 MHz, CD_3OD) δ (ppm): 173.4, 140.3, 139.0 (2C), 132.9 (2C), 130.3 (4C), 129.5 (2C), 129.3 (4C), 129.2 (2C), 129.0 (2C), 128.7 (2C), 128.1 (2C), 124.3, 88.7, 84.2, 82.4, 74.2, 57.4 (2C), 55.7; HRMS (ESI) Calcd 476.2226 for $C_{32}H_{30}NO_3$ $[M + H]^+$, found 476.2230.

*Synthesis of (2S,3R)-2-(Benzyloxy)-3-(dibenzylamino)-5-(pyren-1-yl)pent-4-ynoic Acid **7f**.* Following the *Method F*, the Swern oxidation of alcohol **15f** (275 mg, 0.47 mmol) was carried out to obtain the corresponding crude aldehyde (273 mg), which was further oxidized using NaH_2PO_4 (57 mg, 0.47 mmol), 2-methyl-2-butene (660 mg, 9.4

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mmol), and $NaClO_2$ (42 mg, 0.47 mmol) in 6 mL of ^tBuOH-H_2O (3:1). The crude mixture was purified by column chromatography on silica gel (Eluent: 30% EtOAc in petroleum ether) to furnish **7f** (184 mg, 79%) as a yellow solid. mp.: 214−216 °C; IR (KBr) ν (cm^{-1}): 3744, 3565, 3022, 2964, 1740, 1532, 1516, 1454, 1427, 1368, 1215, 1100; $[\alpha]_D^{25}$ = −143.20 (c = 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.55 (d, J = 9.1 Hz, 1H), 8.23 (d, J = 7.6 Hz, 2H), 8.19−8.12 (m, 3H), 8.10−8.03 (m, 3H), 7.43 (dd, J = 12.1, 4.8 Hz, 6H), 7.37 (t, J = 7.2 Hz, 4H), 7.31 (dd, J = 8.3, 5.8 Hz, 2H), 7.21 (dd, J = 6.4, 3.6 Hz, 3H), 5.02 (d, J = 11.7 Hz, 1H), 4.78 (d, J = 11.7 Hz, 1H), 4.56 (d, J = 13.1 Hz, 2H), 4.39 (d, J = 3.8 Hz, 1H), 4.28 (d, J = 3.8 Hz, 1H), 3.73 (d, J = 13.3 Hz, 2H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 170.8, 137.0, 136.3 (2C), 132.5, 131.8, 131.3, 131.0, 131.1, 130.2 (2C), 129.9 (4C), 129.0 (4C), 128.9, (2C), 128.7 (2C), 128.6, 128.3(2C), 128.2, 128.0, 127.3, 126.5, 126.0 (2C), 125.4, 124.6, 124.4, 87.8, 86.6, 79.6, 74.2, 56.9 (2C), 54.0; HRMS (ESI) Calcd 600.2539 for $C_{42}H_{34}NO_3$ $[M + H]^+$, found 600.2538.

Synthesis of Benzyl ((2S,3R)-2-(Benzyloxy)-3-(dibenzylamino)oct-4-ynoyl)-L-valinate ***17***. To a solution of **7a** (100 mg, 0.23 mmol) and *L*-valine benzyl ester 4-toluenesulfonate **16** (56 mg, 0.27 mmol) in DMF (2 mL) were added EDCl·HCl (52 mg, 0.27 mmol), HOBt (36 mg, 0.27 mmol), and DIPEA (100 μL, 0.58 mmol). The mixture was stirred at room temperature for 24 h. During this time, the reaction was monitored periodically by TLC. Subsequently, the solvent was removed under reduced pressure, and the residue was redissolved in EtOAc (10 mL). The organic layer was washed successively with 5% aqueous citric acid (3 mL), 5% aqueous $NaHCO_3$ (5 mL), and saturated aqueous NaCl (5 mL). The resulting organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was subjected to column chromatography on silica gel (Eluent: 6% EtOAc in petroleum ether) to furnish **17** (123 mg, 85%) as a colorless oil. IR (KBr) ν (cm^{-1}): 3565, 3022, 2964, 1740, 1680, 1532, 1516, 1454, 1427, 1368, 1215, 1100; $[\alpha]_D^{25}$ = −86.0 (c = 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.38−7.31(m, 14H), 7.26 (d, J = 2.9 Hz, 1H), 7.24 (d, J = 7.5 Hz, 3H), 7.22−7.17 (m, 2H), 7.05 (d, J = 8.9 Hz, 1H), 5.16 (q, J = 12.2 Hz, 2H), 4.63 (d, J = 11.4 Hz, 1H), 4.59 (dd, J = 8.9, 4.6 Hz, 1H), 4.53 (d, J = 11.4 Hz, 1H), 4.03−3.94 (m, 4H), 3.44 (d, J = 14.0 Hz, 2H), 2.26−2.22 (m, 2H), 2.18 (dt, J = 12.0, 4.5 Hz, 1H), 1.56 (dd, J = 14.4, 7.2 Hz, 2H), 1.04 (t, J = 7.3 Hz, 3H), 0.95 (d, J = 6.9 Hz, 3H), 0.86 (d, J = 6.9 Hz, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 171.8, 170.3, 139.5 (2C), 137.2, 135.5, 129.0 (4C), 128.7 (2C), 128.5 (4C), 128.3 (2C), 128.2 (4C), 128.1 (2C), 127.0 (2C), 87.6, 83.9, 74.4, 74.0, 57.0, 56.3 (2C), 54.8, 31.3, 22.5, 21.0, 19.1, 17.9 (2C), 13.8; HRMS (ESI) Calcd 631.3536 for $C_{41}H_{47}N_2O_4$ $[M + H]^+$, found 631.3529.

*Synthesis of Valinoctin A (****3****).* To a solution of **17** (80 mg, 0.127 mmol) in 5 mL of MeOH-AcOH-H_2O (5:2:3) placed in a parr apparatus was added 20% $Pd(OH)_2/C$ (4 mg, 0.0127 mmol), and the mixture was stirred under 100 psi H_2 pressure at room temperature for 12 h. During this time, the reaction was monitored periodically by TLC. The reaction mixture was filtered through a Celite bed, and the bed was washed further with methanol (2 × 10 mL). The combined filtrate was concentrated under reduced pressure. The crude mixture was purified by Sephadex LH-20 column chromatography (Eluent: 5% AcOH in methanol) to furnish **3** (31 mg, 90%) as a white solid. mp.: 214−216 °C [Lit. mp.: 212−215 °C];[9] IR (KBr) ν (cm^{-1}): 3344, 3265, 2964, 1670, 1532, 1516, 1454, 142, 1215, 1100; $[\alpha]_D^{25}$ = −23.5 (c = 0.5, MeOH) [Lit. $[\alpha]_D^{26}$ = −22.9 (c = 0.44, MeOH)];[9] ^1H NMR (400 MHz, CD_3OD) δ (ppm): 4.25 (d, J = 3.3 Hz, 1H), 4.22 (d, J = 4.4 Hz, 1H), 3.45−3.39 (m, 1H), 2.31−2.14 (m, 1H), 1.87−1.78 (m, 1H), 1.65−1.43 (m, 3H), 1.39−1.35 (m, 4H), 1.01−0.96 (m, 6H), 0.94 (t, J = 6.8 Hz, 3H); $^{13}C\{H\}$ NMR (125 MHz, $CDCl_3$) δ (ppm): 177.9, 173.0, 70.8, 61.4, 55.4, 32.7, 32.0, 30.5, 26.1, 23.4, 20.2, 18.4, 14.3; HRMS (ESI) Calcd 275.1971 for $C_{13}H_{27}N_2O_4$ $[M + H]^+$, found 275.1972.

Synthesis of (2S,3R)-3-Amino-2-hydroxydecanoic Acid ***18***. To a solution of **7c** (40 mg, 0.085 mmol) in 1:1 methanol−water (10 mL) placed in a parr apparatus was added 20% $Pd(OH)_2/C$ (3 mg, 0.0085 mmol), and the mixture was stirred under 100 psi H_2 pressure at room temperature for 12 h. During this time, the reaction was monitored periodically by TLC. The reaction mixture was filtered through a Celite bed, and the bed was washed further with 1:1 methanol−water (2 × 10 mL). The combined filtrate was concentrated under reduced pressure, and the crude mixture was purified by ion-exchange chromatography (Dowex 50w × 8, 200−400 mesh) with 5% aqueous NH_4OH as eluent to furnish **18** (14.8 mg, 86%) as a white solid. mp.: 218−220 °C [Lit. mp.: 219−220 °C];[35] $[\alpha]_D^{25}$ = +5.7 (c = 0.6, 1 M HCl) [Lit. $[\alpha]_D^{25}$ = +5.4 (c = 0.59, 1 M HCl)];[35] ^1H NMR (400 MHz, D_2O) δ (ppm): 4.08 (d, J = 3.5 Hz, 1H), 3.51−3.39 (m, 1H), 1.80−1.56 (m, 2H), 1.48−1.25 (m, 10H), 0.84 (t, J = 6.7 Hz, 3H). HRMS (ESI) Calcd 204.1599 for $C_{10}H_{22}NO_3$ $[M + H]^+$, found 204.1604.

UV−Visible Measurements. UV−visible studies for **7f** (1.0−2.0 μM) were carried out in chloroform. The molar extinction coefficient, ε, of **7f** was determined according to the Beer−Lambert Law (eq 1)

$$\varepsilon = A/(c \times l) \quad (1)$$

where A = absorbance, c = concentration of solution, and l = path length of cuvette = 1 cm.

Fluorescence Measurements. Fluorescence studies for **7f** (1.0−2.0 μM) were carried out in chloroform.

Fluorescence Quantum Yield Measurement. The quantum yield of **7f** was determined according to eq 2

$$\Phi_{7f} = \Phi_S \times [(I_{7f} \times A_S \times \lambda_{ex(S)} \times (\eta_{7f})^2)/[(I_S \times A_{7f} \times \lambda_{ex(7f)} \times (\eta_S)^2)] \quad (2)$$

where Φ is the quantum yield, I is the integrated area under the corrected emission spectra, A is the absorbance at the excitation wavelength, λ_{ex} is the excitation wavelength, and η is the refractive index of the solution. The subscripts **7f** and **S** refer to the compound under investigation and the standard, respectively. Quinine sulfate was used as the standard in 0.1 M H_2SO_4 (Φ_F = 0.55).

Cell Culture and Fluorescence Imaging. The 0.4 million human colorectal cancer cells (DLD1) were seeded in a 6-well flat-bottom culture plate in RPMI-1640 medium supplemented with 10% fetal bovine serum. Cells were grown at 37 °C in a CO_2 incubator for 24 h. For compound treatment, RPMI was replaced with 1 mL of reduced serum medium OptiMEM (Gibco), and cells were incubated with compound **7f** (20 μM) in DMSO-OptiMEM (1:1000) medium at 37 °C for 30 min. Subsequently, cells were washed three times with DPBS (Dulbecco's Phosphate Buffered Saline) to remove the remaining compound. Fluorescence images were acquired with a fluorescent microscope with a 40X objective. For compound **7f**, excitation and emission were done in the 4′,6-diamidino-2-phenylindole (DAPI) region.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

HPLC analysis of **8a−8f** and **7f**, ^1H and $^{13}C\{H\}$ NMR spectra for all compounds, and UV−visible and fluorescence spectra of **7f** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Wagner, I.; Musso, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 816−828. (b) Hur, G. H.; Vickery, C. R.; Burkart, M. D. *Nat. Prod. Rep.* **2012**, *29*, 1074−1098. (c) Walsh, C. T.; O'Brien, R. V.; K hosla, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 7098−7124.

(2) (a) Hubbard, B. K.; Thomas, M. G.; Walsh, C. T. *Chem. Biol.* **2000**, *7*, 931−942. (b) Dougherty, D. A. *Curr. Opin. Chem. Biol.* **2000**, *4*, 645−652. (c) Ma, J. S. *Chim. Oggi* **2003**, *21*, 65−68.

(3) (a) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, *25*, 117−128. (b) Chen, J.; Kuznetsova, L. V.; Ungreanu, I. M.; Ojima, I. Recent Advances in the Synthesis of α-Hydroxy-β-amino Acids and Their Use in the SAR Studies of Taxane Anticancer Agents. In *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.; Juaristi, E., Soloshonok, V., Eds.; John Wiley & Sons, Inc.: Hoboken, NJ, 2005; pp 447−476.

(4) Nakamura, H.; Suda, H.; Takita, T.; Aoyagi, T.; Umezawa, H.; Iitaka, Y. *J. Antibiot.* **1976**, *29*, 102−103.

(5) Nagai, M.; Kojima, F.; Naganawa, H.; Hamada, M.; Aoyagi, T.; Takeuchi, T. *J. Antibiot.* **1997**, *50*, 82−84.

(6) Yoshida, S.; Nakamura, Y.; Naganawa, H.; Aoyagi, T.; Takeuchi, T. *J. Antibiot.* **1990**, *43*, 149−153.

(7) Harbeson, S. L.; Rich, D. H. *Biochemistry* **1988**, *27*, 7301−7310.

(8) (a) Aoyagi, T.; Tobe, H.; Kojima, F.; Hamada, M.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1978**, *31*, 636−638. (b) Tobe, H.; Morishima, H.; Naganawa, H.; Takita, T.; Aoyagi, T.; Umezawa, H. *Agric. Biol. Chem.* **1979**, *43*, 591−596.

(9) Sekizawa, R.; Iinuma, H.; Muraoka, Y.; Naganawa, H.; Kinoshita, N.; Nakamura, H.; Hamada, M.; Takeuchi, T.; Umezawa, K. *J. Nat. Prod.* **1996**, *59*, 232−236.

(10) Okino, T.; Matsuda, H.; Murakami, M.; Yamaguchi, K. *Tetrahedron Lett.* **1993**, *34*, 501−504.

(11) Helms, G. L.; Moore, R. E.; Niemczura, W. P.; Patterson, G. M. L.; Tomer, K. B.; Gross, M. L. *J. Org. Chem.* **1988**, *53*, 1298−1307.

(12) (a) Burley, S. K.; David, P. R.; Taylor, A.; Lipscomb, W. N. *Proc. Nat. Acad. Sci. U.S.A.* **1990**, *87*, 6878−6882. (b) Burley, S. K.; David, p. R.; Lipscomb, W. N. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 6916−6920. (c) Kim, H.; Lipscomb, W. N. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 5006−5010.

(13) Kim, H.; Lipscomb, W. N. *Biochemistry* **1993**, *32*, 8465−8478.

(14) (a) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517−9582. (b) Hart, D. J.; Ha, D. C. *Chem. Rev.* **1989**, *89*, 1447−1465. (c) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991−8035.

(15) (a) Rohokale, R. S.; Dhavale, D. D. *Beilstein J. Org. Chem.* **2014**, *10*, 667−671. (b) Wee, A. G. H.; McLeod, D. D. *J. Org. Chem.* **2003**, *68*, 6268−6273. (c) Tuch, A.; Saniere, M.; Le Merrer, Y.; Depezay, J.-C. *Tetrahedron: Asymmetry* **1996**, *7*, 2901−2909.

(16) (a) Hook, D. F.; Gessier, F.; Noti, C.; Kast, P.; Seebach, D. *ChemBioChem* **2004**, *5*, 691−706. (b) Velmourougane, G.; Harbut, M. B.; Dalal, S.; McGowan, S.; Oellig, C. A.; Meinhardt, N.; Whisstock, J. C.; Klemba, M.; Greenbaum, D. C. *J. Med. Chem.* **2011**, *54*, 1655−1666. (c) Sleebs, B. E.; Hughes, A. B. *J. Org. Chem.* **2007**, *72*, 3340−3352. (d) Aoyagi, Y.; Jain, R. P.; Williams, R. M. *J. Am. Chem. Soc.* **2001**, *123*, 3472−3477.

(17) (a) Righi, G.; Rumboldt, G.; Bonini, C. *J. Org. Chem.* **1996**, *61*, 3557−3560. (b) Fringuelli, F.; Pizzo, F.; Rucci, M.; Vaccaro, L. *J. Org. Chem.* **2003**, *68*, 7041−7045. (c) Righi, G.; Chionnne, A.; D'Achille, R.; Bonini, C. *Tetrahedron: Asymmetry* **1997**, *8*, 903−907.

(18) Rubin, A. E.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1997**, *36*, 2637−2640.

(19) (a) Denis, J. N.; Correa, A.; Greene, A. E. *J. Org. Chem.* **1991**, *56*, 6939−6942. (b) Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A. *Tetrahedron: Asymmetry* **1996**, *7*, 529−536.

(20) Fraser, D. S.; Park, S. B.; Chong, J. M. *Can. J. Chem.* **2004**, *82*, 87−101.

(21) (a) Gassa, F.; Contini, A.; Fontana, G.; Pellegrino, S.; Gelmi, M. L. *J. Org. Chem.* **2010**, *75*, 7099−7106. (b) Semple, J. E.; Owens, T. D.; Nguyen, K.; Levy, O. E. *Org. Lett.* **2000**, *2*, 2769−2772. (c) Jiang, J.-L.; Yao, M.; Lu, C.-D. *Org. Lett.* **2014**, *16*, 318−321. (d) Torssell, S.; Kienle, M.; Somfai, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 3096−3099. (e) Xu, X.; Zhou, J.; Yang, L.; Hu, W. *Chem. Commun.* **2008**, 6564−6566.

(22) Anand, N.; Kapoor, M.; Koul, S.; Taneja, S. C.; Sharma, R. L.; Qazi, G. N. *Tetrahedron: Asymmetry* **2004**, *15*, 3131−3138.

(23) Goodman, C. G.; Do, D. T.; Johnson, J. S. *Org. Lett.* **2013**, *15*, 2446−2449.

(24) (a) Trost, B. M.; Terrell, L. R. *J. Am. Chem. Soc.* **2003**, *125*, 338−339. (b) Juhl, K.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 2420−2421. (c) Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III *Org. Lett.* **2004**, *6*, 3541−3544.

(25) Deshmukh, S. C.; Roy, A.; Talukdar, P. *Org. Biomol. Chem.* **2012**, *10*, 7536−7544.

(26) Lo, L.-C.; Chen, J.-Y.; Yang, C.-T.; Gu, D.-S. *Chirality* **2001**, *13*, 266−271.

(27) (a) Kenworthy, A. K. *Methods* **2001**, *24*, 289−296. (b) Hoppe, A.; Christensen, K.; Swanson, J. A. *Biophys. J.* **2002**, *83*, 3652−3664. (c) Ozawa, T.; Umezawa, Y. *Supramol. Chem.* **2002**, *14*, 271−280.

(28) (a) Peled, H.; Shai, Y. *Biochemistry* **1994**, *33*, 7211−7219. (b) Ben-Efraim, I.; Strahilevitz, J.; Bach, D.; Shai, Y. *Biochemistry* **1994**, *33*, 6966−6973. (c) Marme, N.; Knemeyer, J.-P.; Sauer, M.; Wolfrum, J. *Bioconjugate Chem.* **2003**, *14*, 1133−1139.

(29) Schmid, C. R.; Bryant, J. D.; Dowlatzedah, M.; Phillips, J. L.; Prather, D. E.; Schantz, R. D.; Sear, N. L.; Vianco, C. S. *J. Org. Chem.* **1991**, *56*, 4056−4058.

(30) Maisonneuve, S.; Xie, J. *Synlett* **2009**, 2977−2981.

(31) (a) Lucio Anelli, P.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559−2562. (b) Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1999**, *64*, 2564−2566.

(32) (a) Schrey, A.; Osterkamp, F.; Straudi, A.; Rickert, C.; Wagner, H.; Koert, U.; Herrschaft, B.; Harms, K. *Eur. J. Org. Chem.* **1999**, 2977−2990. (b) Garcia-Fortanet, J.; Murga, J.; Falomir, E.; Carda, M.; Marco, J. A. *J. Org. Chem.* **2005**, *70*, 9822−9827. (c) Schroeder, S.; Schrey, A. K.; Knoll, A.; Reiss, P.; Ziemer, B.; Koert, U. *Eur. J. Org. Chem.* **2006**, 2766−2776.

(33) Tsuda, M.; Muraoka, Y.; Takeuchi, T. *J. Antibiot.* **1996**, *49*, 1031−1035.

(34) Bunnage, M. E.; Burke, A. J.; Davies, S. G.; Goodwin, C. J. *Tetrahedron: Asymmetry* **1994**, *5*, 203−206.

(35) Bunnage, M. E.; Burke, A. J.; Davies, S. G.; Goodwin, C. J. *Tetrahedron: Asymmetry* **1995**, *6*, 165−176.

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