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Direct Stereoselective Synthesis of Enantiomerically Pure *anti*-β-Amino Alcohols

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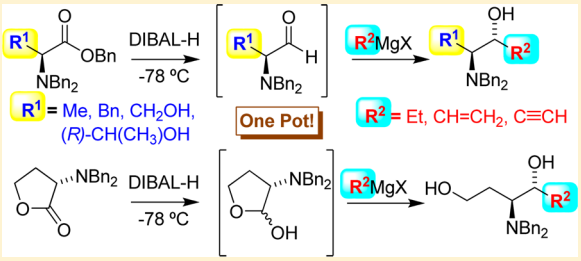
Supporting Information

ABSTRACT: Enantiomerically pure *anti*-β-amino alcohols were synthesized from optically pure α-(*N*,*N*-dibenzylamino)benzyl esters, derived from α-amino acids, by the sequential reduction to aldehyde with DIBAL-H at −78 °C and subsequent in situ addition of Grignard reagents. Besides *anti*-β-amino alcohols, *anti*-2-amino-1,3-diols and *anti*-3-amino-1,4-diols were obtained in good yields (60−95%) and excellent stereoselectivity (de > 95%). Our technique is compatible with free hydroxyl groups present in the substrate. To demonstrate the versatility of the method, spisulosine and sphinganine were synthesized in two steps from the appropriate *N*,*N*-dibenzyl-L-aminobenzyl ester in 42% and 45% yield, respectively.



INTRODUCTION

β-Amino alcohols have received much attention in the scientific community due to their versatility. They can be used as chiral ligands in asymmetric synthesis,[1,2] as chiral synthons in the synthesis of natural products,[3,4] as well as in the synthesis of products with diverse biological activities.[5−7] In addition, long-chain amino alcohols exhibit promising activity as antitumor agents.[8] An important class of amino alcohols is the sphingolipids (SLs)[9] represented by dihydrosphingosine (**1a**) and sphinganine (**1b**), which show a 2-amino-1,3-diol fragment with an *anti*-2*S*,3*R* configuration (Figure 1).[5] Another relevant

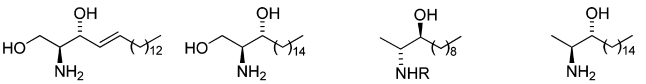


Figure 1. Dihydrosphingosine, sphinganine, and related 1-deoxy-sphingolipids.

group of long-chain amino alcohols are the 1-deoxysphingolipids from marine origin, such as the clavaminols A (**2a**), C (**2b**), and H.[10,11] These compounds have an *anti*-2*R*,3*S* amino alcohol motif, opposite to that of SLs, and have shown cytotoxic and pro-apoptotic properties.[6] Furthermore, spisulosine[12] (**2c**) having the same *anti*-2*S*,3*R* configuration as SLs was initially a promising antiproliferative agent against diverse human tumor cell lines.[13] However, clinical studies were discontinued in phase I.[14] In the literature, there are many SLs reported with antiproliferative activity,[15−17] and the number is still growing.

There is a close structural relationship between long-chain amino alcohols, including SLs, and cytotoxic properties, which make this type of compounds an attractive scaffold for anticancer drug discovery programs.

To shed light on the above compounds and their associated bioactive properties, and as part of our interest in synthesis of nitrogen-containing bioactive molecules,[18−23] we were engaged in the development of a more versatile and efficient methodology to synthesize *anti*-β-amino alcohols in order to obtain new SL analogues and test their antiproliferative activity.

We pondered a general *one-pot* methodology for the synthesis of functionalized *anti*-β-amino alcohols based on the in situ DIBAL-H reduction of α-(*N*,*N*-dibenzylamino)benzyl esters (**4**, **6**, **10**, and **11**, Tables 1−4) to their corresponding aldehyde, followed by the sequential addition of commercially available Grignard reagents. This methodology is an extension of the well-known Reetz protocol, but avoiding the three-step sequence, namely reduction of the ester to alcohol and later oxidation to aldehyde and addition of the organometallic reagent.[24−26] A related one-pot process has been explored in the literature, using *N*-Boc-protected amino esters but obtaining *syn*-β-amino alcohols.[27−29] We found also a precedent in the synthesis of *anti*-β-amino alcohols using benzostabase (BSB) as the *N*-protecting group.[30] However, this methodology has never been further used, maybe due to the difficulty in preparing *N*-BSB-protected amino esters. In this paper, we describe how our one-pot approach is a very attractive form to generate *anti*-β-amino alcohols (**1**), *anti*-2-

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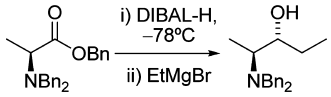
Table 1. Reaction Parameters for the Synthesis of 5a



entry	reduction time[a] (h)	EtMgBr (equiv)	solvent	DIBAL-H (equiv)	*anti*/*syn*[b]	yield (%)
1	1	3	Et_2O	2.5	>95/1	35
2	1	3	Et_2O	3.6		
3	2	3	Et_2O	2.5	>95/1	55
4	2	3	Et_2O	1.4	>95/1	70
5	2	1	Et_2O	1.4	>95/1	26
6	2	2	Et_2O	1.4	>95/1	33
7	2	4	Et_2O	1.4	>95/1	68
8	2	3	Et_2O	1.1	>95/1	48
9	1	3	DCM	3.6		
10	2	3	DCM	2.5	>95/1	28
11	2	3	DCM	1.4	>95/1	13
12	2	3	THF	1.4	>95/1	38
13	2	3	toluene	1.4	>95/1	63

[a]Delay time between the addition of DIBAL-H and the Grignard reagent. [b]Diastereoisomeric ratio as determined by ^{1}H NMR analysis of the crude product **5a**.

amino-1,3-diols (**2**), and *anti*-3-amino-1,4-diols (**3**) (Figure 2), reducing the number of chemical steps when compared to the methods reported in the literature for the synthesis of similar compounds[31−38] (Figure 2).

We also demonstrate that our method can be applied to serine and threonine derivatives without the need to use protecting groups for the hydroxyl moiety. This reaction proceeds in good yields and high enantioselectivity (de > 95%). Therefore, we report the first one-pot diastereoselective addition of Grignard reagents using serine and threonine derivatives without *O*-protecting groups.

In addition, to test the applicability of this new methodology, we describe the synthesis of the naturally occurring compounds spisulosine and sphinganine.

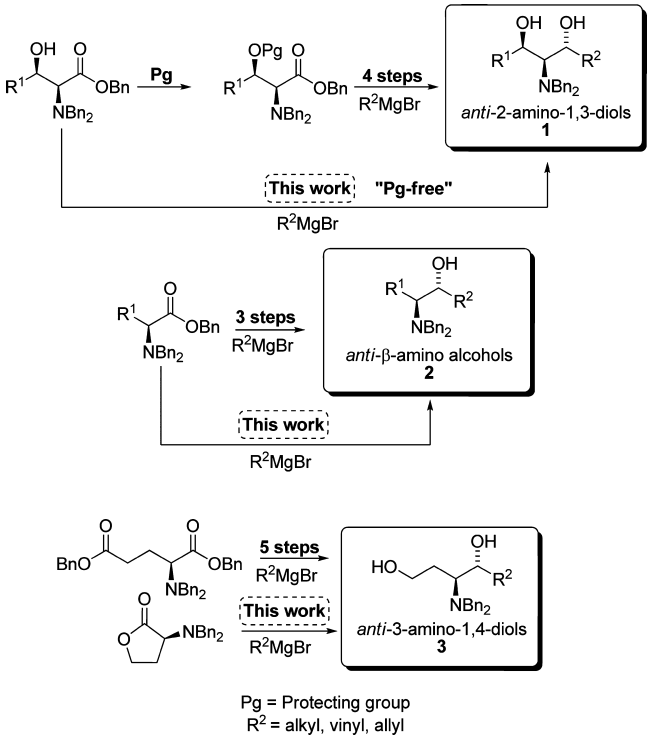


Figure 2. One-pot synthesis of *anti*-β-amino alcohols.

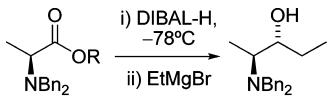
RESULTS AND DISCUSSION

Synthesis of *anti*-β-Amino Alcohols. The key step of this one-pot reaction is the DIBAL-H reduction of a *N,N*-dibenzyl-α-amino ester (synthesized by perbenzylation of the corresponding α-amino acid)[39,40] to its corresponding aldehyde, at −78 °C, followed by the in situ sequential addition of the suitable Grignard reagent. First, we studied the influence of the reaction conditions taking into account the effect of solvents on the nucleophilicity, basicity of organomagnesium, and reducing ability of DIBAL-H.[28−30] We also evaluated the amount of DIBAL-H equivalents, as well as reduction time, using 3 equiv of EtMgBr. The ratio of Grignard reagent used was chosen based on literature precedents,[41] and it is consistent with our observations. The results obtained using the benzyl ester of *N,N*-dibenzyl-L-alanine (**4a**) as starting material are summarized in Table 1.

We observed that Et_2O was the best solvent, and we also determined that DIBAL-H amount and reduction time were a contributing factor in the yield of the reaction. When 3.6 equiv of DIBAL-H during 1 h was used, a complete over-reduction to the alcohol was observed (entries 2 and 9, Table 1). After the amount of DIBAL-H was decreased to 1.4 equiv and the reduction time was increased to 2 h, a better yield (70%) was obtained (entry 4). The *anti*/*syn* ratio was determined by ^{1}H NMR (400 MHz) of the crude reaction. The *anti*-diastereoisomer was always formed as the major stereoisomer, and the ratio was not affected either by the reaction solvent, the amount of DIBAL-H, or the reduction times.

The stereochemical course of the process is consistent with the generation of a free aldehyde, while the nucleophilic attack of the Grignard reagent on the carbonyl follows a nonchelating Felkin−Anh model.[42] An S_N2-like mechanism involving elimination of a metalalkoxy group could explain the intermediate aldehyde.[41] In agreement with this proposal, the identity of the alkoxy group of the aluminoxy acetal should not affect the stereoselectivity of the alkylation reaction. To test this hypothesis, a series of alanine esters (synthesized using different procedures)[43,44] were analyzed by ^{1}H NMR to determine the effect of increasing the steric bulk of the alkoxy group of the ester on the stereoselectivity of the DIBAL-H reduction in Et_2O and subsequent EtMgBr addition (Table 2). From the results,

Table 2. Influence of the Alkoxy Group Bulkiness in Esters of *N,N*-Dibenzyl-L-alanine



entry	compd	R	*anti*/*syn*[a]	yield (%)
1	**4a**	Bn	>95/1	70
2	**4b**	*t*-Bu	92/8	68
3	**4c**	Et	94/6	65
4	**4d**	Me	>95/1	66

[a]Diastereoisomeric ratio determined by ^{1}H NMR analysis of the crude products.

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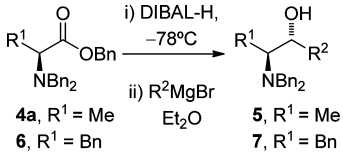
we inferred that there is no correlation between the bulkiness of the ester group and the stereoselectivity of the reaction. We also concluded that the ester did not affect the yield of the reaction. The benzyl ester was the best choice because it is synthesized in one step by the direct perbenzylation of the free α-amino acid.

Once we had adjusted the conditions, we studied the scope. Thus, **4** and **6** (synthesized by perbenzylation of the α-amino acids L-alanine and L-phenylalanine, respectively) were submitted, at −78 °C, to our one-pot sequence using commercially available ethyl-, vinyl-, and ethynylmagnesium bromide solutions affording the corresponding amino alcohols **5a−c** and **7a−c** (Table 3).

Table 3. Synthesis of *anti*-β-Amino Alcohols 5 and 7



4a, R^1 = Me
6, R^1 = Bn
5, R^1 = Me
7, R^1 = Bn

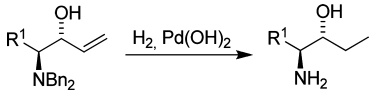
entry	compd	R^1	R^2	*anti*/*syn*[a]	yield (%)
1	**5a**	Me	Et	>95/1	70
2	**5b**	Me	vinyl	>95/1	60
3	**5c**	Me	ethynyl	87/13	65
4	**7a**	Bn	Et	>95/1	72
5	**7b**	Bn	vinyl	>95/1	63
6	**7c**	Bn	ethynyl	90/10	70

[a]Diastereoisomeric ratio determined by ^{1}H NMR analysis of the crude products.

The *anti* diastereoselectivity (>95/1) of the reaction was determined by ^{1}H NMR spectroscopy (400 MHz). We observed that the diastereoselectivity was not affected by the size of the substituent R^1 (Table 3), while the Grignard reagent produced a small influence. In this particular context, we observed a lower diastereomeric ratio using ethynylmagnesium bromide (entries 3 and 6). Fortunately, pure diastereoisomers of compounds **5** and **7** were obtained in good yields by flash column chromatography. The pure compounds showed good physical and spectroscopic data compliance, within the limits of experimental error, with those reported previously for **5a**,[31−33] **5c**,[35] **7a**,[31,32] and **7c**[35] (see the Supporting Information). To the best of our knowledge, products **5b** and **7b** are described for the first time in this work. To corroborate their structures, we synthesized the amino alcohols **8** and **9** by *N*-deprotection and double-bond reduction of **5b** and **7b** respectively, with Pearlman's catalyst under hydrogen pressure (Scheme 1). The physical and spectral data of these compounds agree with those reported for **8** and **9** (Scheme 2)[31] (see the Supporting Information).

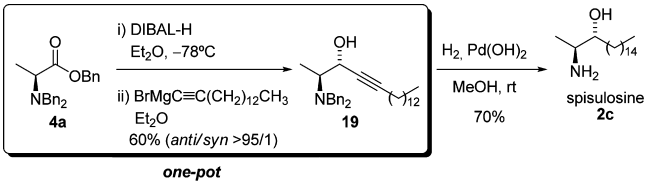
It has been described in the literature that during the DIBAL-H treatment it is possible that some racemization of the enantiomerically pure aldehydes occurs. Therefore, we

Scheme 1. Synthesis of Amino Alcohols 8 and 9



5b, R^1 = Me
7b, R^1 = Bn
8, R^1 = Me
9, R^1 = Bn

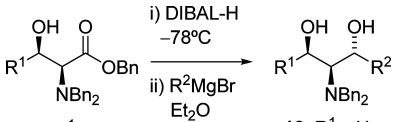
Scheme 2. Synthesis of Spisulosine (2c)



submitted both commercially available DL-phenylalanine and L-phenylalanine to our one-pot procedure using as Grignard reagent ethylmagnesium bromide. The resulting compounds *rac*-**7a** and **7a** were analyzed by chiral HPLC to check their enantiomeric purity. The results showed that no loss of enantiomeric purity was observed (see the Supporting Information).

Preparation of *anti*-2-Amino-1,3-diols. We wondered if our technique could be extended to the synthesis of more substituted β-amino alcohols and, more importantly, if it is compatible with free hydroxyl groups present in the substrate. To test this idea, we selected *N,N*-dibenzylamino esters **10** and **11**, which were prepared by conventional methods using L-serine and L-threonine, respectively.[45] Gratifyingly, the synthesis of amino alcohols **12a−c** and **13a−c** were carried out using the same one-pot approach described above with good yields and excellent stereoselectivity (Table 4).

Table 4. Synthesis of *anti*-2-Amino-1,3-diols 12 and 13



10, R^1 = H
11, R^1 = Me
12, R^1 = H
13, R^1 = Me

entry	compd	R^1	R^2	*anti*/*syn*[a]	yield (%)
1	**12a**	H	Et	>95/1	60
2	**12b**	H	vinyl	>95/1	70
3	**12c**	H	ethynyl	>95/1	63
4	**13a**	Me	Et	>95/1	60
5	**13b**	Me	vinyl	>95/1	63
6	**13c**	Me	ethynyl	>95/1	58

[a]Diastereoisomeric ratio determined by ^{1}H NMR analysis of the crude products.

In this particular case, we needed to fine-tune the reaction conditions to improve the yield of **12** and **13**. We found that by using the general conditions described above, namely 1.4 equiv of DIBAL-H in ether (−78 °C, 2 h) and 3 equiv of Grignard reagent, we could obtain **12** and **13** although in low yields (~40%). The contaminating products were the carbinols resulting of the undesired addition of Grignard reagents to the ester groups. We suspected that because of the presence of the free hydroxy group, an additional amount of DIBAL-H should be used. Fortunately, when we added, after 1 h, an extra amount of 0.7 equiv of DIBAL-H allowing the reduction time to reach 2 h, the Grignard reagent addition produced the *anti*-diols **12** and **13** in good yields as shown in Table 4. It should be pointed out that necessarily the DIBAL-H addition must be done in two portions. When 2.1 equiv of the reducing agent was added in one portion and maintained during 2 h, a substantial amount of the primary alcohol was produced. In all cases, the reaction took place with a good yield and excellent

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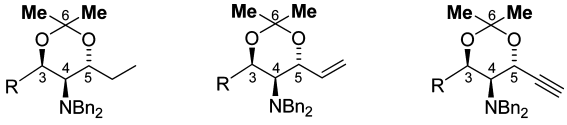
stereoselectivity (*anti*/*syn* > 95/1). Once again, the stereochemical course of the reaction could be explained by a Felkin–Anh model where the presence of a free hydroxy group did not affect the stereoselectivity. Finally, it is important to mention that our approach avoids the use of *O*-protecting groups, the latter being used in all previously reported procedures for the synthesis of related compounds.[46−48]

In order to determine the relative configuration of the obtained 1,3-diols, the six-membered acetonides **14a−c** and **15a−c** were synthesized (Figure 3) by treatment of diols **12a−c** and **13a−c**, respectively, with 2,2-dimethoxypropane (DMP) in the presence of pyridinium *p*-toluensulfonate (PPTS) in DCM.



14a, R = H
15a, R = Me

14b, R = H
15b, R = Me

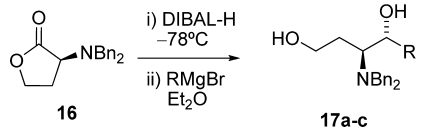
14c, R = H
15c, R = Me

Figure 3. Acetonides prepared to assign the relative configuration.

The acetonides **14a−c** showed a $J_{4,5}$ value of approximately 9.8 Hz which is in agreement with the *anti*-configuration reported.[49−51] Moreover, in acetonides **15a** and **15b** the 1,3-*anti* relation was established by ^{13}C NMR analysis of methyl (marked in bold face, Figure 3) signals (24.5 and 24.8 ppm for **15a** and 24.6 and 24.9 ppm for **15b**), and C-6 (100.3 and 100.4 ppm for **15a** and **15b**, respectively). In addition, the *anti*-relation of H-4 and H-5 was determined by the value of the coupling constant ($J_{4,5}$ = 7.4 Hz for both) which is in agreement with previous data reported.[52] The relative configuration of compound **15c** was determined by the $J_{5,6}$ = 4.8 Hz value, which is in agreement with the *anti*-configuration data reported.[53]

Synthesis of *anti*-3-Amino-1,4-diols. In a third application of the methodology, we examined the addition of EtMgBr to lactone **16** previously treated with DIBAL-H (Table 5).

Table 5. Synthesis of *anti*-3-Amino-1,4-diols 17a−c



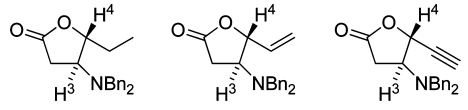
16 **17a-c**

entry	compd	R	*anti*/*syn*[a]	yield (%)
1	**17a**	Et	>95/1	95
2	**17b**	vinyl	>95/1	96
3	**17c**	ethynyl	>95/1	80

[a]Diastereoisomeric ratio determined by ^{1}H NMR analysis of the crude products.

Lactone **16** was synthesized using methionine as starting material.[54] For the synthesis of **17a**, we decided to test the same one-pot methodology as for the compounds **3a−c** and **4a−c** (1.4 equiv of DIBAL-H, at −78 °C for 2 h and subsequently addition of EtMgBr). Under the reaction conditions, the desired product **17a** was obtained in high yield and stereoselectivity (95% yield and *anti*/*syn* > 95/1, Table 5). Furthermore, we tested this reaction with diverse Grignard reagents, allowing the synthesis of **17b** and **17c**.

The relative configuration of **17a−c** was determined by converting them to the lactones **18a−c** with tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO) (Figure 4). The ^{1}H NMR vicinal coupling constant between the protons H-3 and H-4 in the lactones **18a−c** showed a $J_{3,4}$ = 4.3 Hz, indicating an *anti*-configuration.[31,55,56]



18a **18b** **18c**

Figure 4. Lactones prepared to assign the relative configuration.

Synthetic Applications. In order to assess the wider application of our methodology, we turned our attention to spisulosine (**2c**). Using the same experimental procedure described above for the synthesis of *anti*-*β*-amino alcohols, **2c** could be prepared in just two steps from **4a** using pentadecynylmagnesium bromide as the Grignard reagent (Scheme 2). We observed that our one-pot methodology provided **19** as only one diastereomer (within limits of ^{1}H NMR detection in the crude reaction mixture) in good yield. The *N*-deprotection and reduction of the triple bond using hydrogenation with Pearlman's catalyst provided spisulosine (**2c**), in 42% overall yield.[6,57,58]

Similarly, the synthesis of sphinganine (**1b**) was carried out using the same experimental procedure described for the synthesis of compounds **12a−c**, and it is shown in Scheme 3. First, we obtained product **20** by the addition of pentadecynylmagnesium bromide to the aldehyde previously formed from **10**, in 75% yield and with high diastereoselectivity (*anti*/*syn* > 95/1), without using protecting groups.[36] Further hydrogenation of **20** with Pearlman's catalyst provided sphinganine (**1b**) in 45% overall yield.[59]

■ CONCLUSION

In summary, a new general one-pot methodology has been developed for the synthesis of enantiopure *anti*-*β*-amino alcohols from *α*-dibenzylamino esters having their origin in *α*-amino acids, in good yields and excellent diastereoselectivity. Our results showed that optically active *α*-dibenzylamino esters can be reduced and converted into *β*-amino alcohols by subsequent addition of diverse Grignard reagents avoiding the problem of instability of the aldehydes. Presumably, these additions proceed under nonchelation control involving the aldehyde formed in situ using DIBAL-H at −78 °C. Similarly, *anti*-2-amino-1,3-diols and *anti*-3-amino-1,4-diols were obtained. Our technique is compatible with free hydroxyl groups present in the substrate. Considering the simplicity of preparing these products, we tested this methodology synthesizing spisulosine and sphinganine. Further studies on the synthesis of other derivatives and related natural products are in progress. The in vitro antiproliferative activity against human solid tumor cells is being evaluated with promising results and will be reported in due course.

■ EXPERIMENTAL SECTION

General Remarks. Reactions were performed using oven-dried glassware under an atmosphere of argon. Reagent-grade chemicals were obtained from diverse commercial suppliers and were used as received. Optical rotations were measured with a polarimeter at the sodium line at different temperatures in $CHCl_3$. ^{1}H/^{13}C NMR spectra

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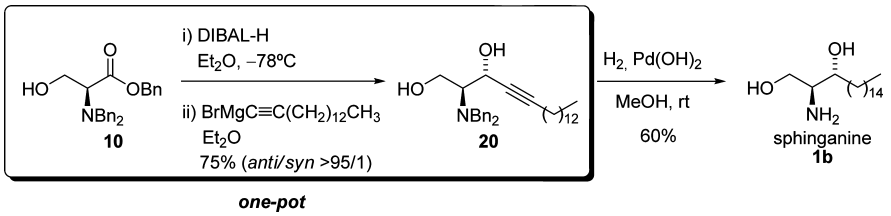
Scheme 3. Synthesis of Sphinganine (1b)



of the samples as $CDCl_3$ solutions were recorded at 400/100 MHz or at 500/125 MHz or 600/150 MHz, respectively, at 298 K. Chemical shifts (δ) are quoted in ppm and referenced to internal TMS (δ = 0 ppm) for ^{1}H NMR and $CDCl_3$ (δ = 77.0 ppm) for ^{13}C NMR; coupling constants (J) are quoted in hertz. Data are reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet, sex, sextet, sep, septet, m, multiplet; br, broad. 2D NMR techniques were used to assist in structure elucidation. IR spectra were recorded neat on a FT-ATR IR system and the data are reported in reciprocal centimeters (cm^{-1}). Accurate mass (HRMS) were determined by electrospray ionization (ESI-TOF) and electronic impact (EI-TOF). Reactions were monitored using thin-layer chromatography (TLC) on aluminum packed percolated Silica Gel 60 F_{254} plates. Flash column chromatography was carried out with silica gel 60 (particle size less than 0.020 mm) by using appropriate mixtures of ethyl acetate and hexanes as eluent. Compounds were visualized by use of UV light and 2.5% phosphomolybdic acid in ethanol. All reactions involving air- or moisture-sensitive materials were carried out under argon atmosphere. Anhydrous magnesium sulfate was used for drying solutions. Melting points were measured with a micro melting point apparatus. Chemical nomenclature was generated using Chem Bio Draw Ultra 13.0.

(2*S*,3*R*)-2-(Dibenzylamino)pentan-3-ol (5a).[28−30] To a cooled (−78 °C) solution of **4a** (100 mg, 0.28 mmol) in dry Et_2O (3 mL) under argon was added DIBAL-H (0.4 mL, 0.4 mmol, 1 M in hexane). After the solution was stirred for 2 h, ethylmagnesium bromide solution (0.3 mL, 0.84 mmol, 3 M in Et_2O) was carefully added at −78 °C, and the mixture was allowed to warm to −10 °C and stirred for 18 h. Then, the mixture was warmed to 0 °C and quenched with saturated NH_4Cl (8 mL). The mixture was extracted with Et_2O (10 mL × 3). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (eluent AcOEt/PE, 98:2) to give **5a** (56.6 mg, 0.20 mmol, 70% yield) as a colorless oil: $[\alpha]^{25}_D$ +48.1 (*c*, 1.0, $CHCl_3$).

(3*R*,4*S*)-4-(Dibenzylamino)pent-1-en-3-ol (5b). The procedure described above was applied to **4a** on a 0.28 mmol (100 mg) scale with vinylmagnesium bromide solution (0.84 mL, 0.84 mmol, 1 M in THF) to give **5b** (47 mg, 0.17 mmol, 60% yield) as a colorless oil: $[\alpha]^{25}_D$ = +5.99 (*c*, 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (d, 3H, J = 6.9 Hz), 2.76 (br, 1H), 2.87 (q, 1H, J = 6.6 Hz), 3.33 (d, 2H, J = 13.7 Hz), 3.73 (d, 2H, J = 13.7 Hz), 3.94 (br, 1H), 5.07 (d, 1H, J = 10.4 Hz), 5.26 (dd, 1H, J_1 = 17.3, J_2 = 1.3 Hz), 5.90 (ddd, 1H, J_1 = 16.2, J_2 = 10.5, J_3 = 5.5 Hz); ^{13}C{^{1}H} (100 MHz, $CDCl_3$) δ 139.8, 139.2, 128.9, 128.4, 127.1, 115.2, 73.8, 57.1, 54.9, 9.0; IR (ATR-neat) ν_{max} = 3409, 3031, 1644, 1605, 1455, 924; HRMS (ESI-TOF) (m/z) [M + H$^+$] = calcd for $C_{19}H_{24}NO$ 282.1858, found 282.1861.

(3*R*,4*S*)-4-(Dibenzylamino)pent-1-yn-3-ol (5c).[32] The procedure described above was applied to **4a** on a 0.28 mmol (100 mg) scale with ethynylmagnesium bromide solution (1.68 mL, 0.84 mmol, 0.5 M in THF) to give **5c** (50.8 mg, 0.18 mmol, 65% yield) as a solid: mp = 54−55 °C; $[\alpha]^{25}_D$ = +31.0 (*c*, 0.6, $CHCl_3$).

(2*S*,3*R*)-2-(Dibenzylamino)-1-phenylpentan-3-ol (7a).[28,29] The procedure described for the synthesis of compound **5a** was applied to **6** (100 mg, 0.23 mmol) using DIBAL-H (0.32 mL, 0.32 mmol, 1 M in hexane) and ethylmagnesium bromide solution (0.23 mL, 0.69 mmol, 3 M in Et_2O), to give **7a** (59.4 mg, 0.17 mmol, 72% yield) as a colorless oil: $[\alpha]^{25}_D$ = +21.0 (*c*, 1.0, $CHCl_3$).

(3*R*,4*S*)-4-(Dibenzylamino)-5-phenylpent-1-en-3-ol (7b). The procedure described for the synthesis of compound **7a** was applied to **6** (100 mg, 0.23 mmol) using vinylmagnesium bromide solution (0.69 mL, 0.69 mmol, 1 M in THF) to give **7b** (51.8 mg, 0.15 mmol, 63% yield) as a colorless oil: $[\alpha]^{25}_D$ = +3.6 (*c*, 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.76 (dd, 1H, J_1 = 13.7, J_2 = 8.1 Hz), 2.92 (d, 1H, J = 7.3 Hz), 3.10 (dd, 1H, J_1 = 13.7, J_2 = 6.5 Hz), 3.17−3.21 (m, 1H), 3.52 (d, 2H, J 13.6 Hz), 3.86 (d, J = 13.6 Hz), 4.04−4.05 (m, 1H), 5.17 (d, J = 10.5 Hz), 5.38 (d, J = 17.3 Hz), 6.06 (ddd, 1H, J_1 = 15.9, J_2 = 10.5, J_3 = 5.0 Hz), 7.17−7.31 (m, 15H); ^{13}C{^{1}H} (100 MHz, $CDCl_3$) δ 139.8, 139.5, 138.5, 129.3, 128.9, 128.5, 128.4, 127.2, 126.2, 115.5, 71.0, 63.2, 55.3, 31.7; IR (ATR-neat) ν_{max} = 3435, 3026, 1641, 1602, 1453, 922, 920; HRMS (ESI-TOF) (m/z) [M + H$^+$] = calcd for $C_{25}H_{28}NO$ 358.2171, found 358.2160.

(3*R*,4*S*)-4-(Dibenzylamino)-5-phenylpent-1-yn-3-ol (7c).[32] The procedure described for the synthesis of compound **7a** was applied to **6** (100 mg, 0.23 mmol), with ethynylmagnesium bromide solution (1.38 mL, 0.69 mmol, 0.5 M in THF), to give **7c** (57.2 mg, 0.161 mmol, 70% yield) as a colorless solid: mp = 131−132 °C; $[\alpha]^{25}_D$ = +63.1.0 (*c*, 1.0, $CHCl_3$).

(2*S*,3*R*)-2-Aminopentan-3-ol (8).[28] To a solution of **5b** (100 mg, 0.36 mmol) in 5 mL of dry MeOH was added 10 mg of 20% Pd $(OH)_2$−C in one portion. The mixture was stirred under 1 atm of H_2 at room temperature for 18 h. After completion of the reaction, the catalyst was removed by filtration through Celite and washed with 20 mL of MeOH. The solvent was evaporated under reduced pressure to afford **8** (36.2 mg, 0.32 mmol, 90% yield) as a colorless oil: $[\alpha]^{25}_D$ = +14.6 (*c*, 1.0, $CHCl_3$).

(2*S*,3*R*)-2-Amino-1-phenylpentan-3-ol (9).[28] The procedure described above was applied to **7b** on a 0.28 mmol (100 mg) scale, to give **9** (42.5 mg, 0.26 mmol, 92% yield) as a colorless solid: mp = 104−106 °C; $[\alpha]^{25}_D$ = +39.0 (*c*, 1.0, $CHCl_3$).

(2*S*,3*R*)-2-(Dibenzylamino)pentane-1,3-diol (12a). To a cooled (−78 °C) and stirred solution of *N*,*N*-aminobenzyl ester **10** (100 mg, 0.27 mmol) in dry Et_2O (3 mL) under argon was added DIBAL-H in two portions (0.38 mL, 0.38 mmol, 1 M in hexane; and 1 h later 0.19 mL, 0.19 mmol). One hour after the addition of the second portion of DIBAL-H, ethylmagnesium bromide solution (0.27 mL, 0.81 mmol, 3 M in Et_2O) was carefully added and the mixture was allowed to warm to −10 °C and stirred for 18 h. Then, the mixture was warmed to 0 °C and quenched with saturated NH_4Cl (8 mL). The mixture was extracted with Et_2O (10 mL × 3), and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuum. The residue was purified by flash chromatography on silica gel flash (eluent gradient AcOEt/PE, 8:2 to 7:3) to give **12a** (48.5 mg, 0.16 mmol, 60% yield) as a colorless oil: $[\alpha]^{25}_D$ = −7.5 (*c*, 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (t, 3H, J = 7.4 Hz), 1.34 (sep, 1H, J = 7.5 Hz), 1.67 (m, 1H), 2.63 (q, 1H, J = 5.8 Hz), 3.64 (d, 2H, J = 13.7 Hz), 3.72−3.75 (m, 3H), 3.82 (m, 1H), 7.18−7.27 (m, 10H); ^{13}C{^{1}H} (100 MHz, $CDCl_3$) δ 139.6, 129.0, 128.4, 127.1, 72.7, 61.9, 59.0, 54.6, 28.6, 9.9; IR (ATR-neat) ν_{max} = 3371, 3062, 3028, 2962, 1493, 1453, 1365; HRMS (ESI-TOF) (m/z) [M + H$^+$] = calcd for $C_{19}H_{25}NO_2$ 300.1964, found 300.1968.

(2*S*,3*R*)-2-(Dibenzylamino)pent-4-ene-1,3-diol (12b). The procedure described above for the synthesis of compound **12a** was applied to **10** on a 0.27 mmol (100 mg) scale using vinylmagnesium bromide solution (0.81 mL, 0.81 mmol, 1 M in THF) to give **12b** (56 mg, 0.19 mmol, 70% yield) as a colorless oil: $[\alpha]^{25}_D$ = −23.0 (*c*, 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.80 (q, 1H, J = 5.8 Hz), 3.67−3.79 (m, 5H), 3.84−3.87 (m, 1H), 4.41 (t, 1H, J = 5.8 Hz), 5.14 (d, 1H, J = 10.4 Hz), 5.25 (d, 1H, J = 17.3 Hz), 5.88 (ddd, J_1 = 16.8, J_2

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= 10.4; J_3 = 6.1 Hz), 7.18−7.27 (m, 10H); $^{13}C\{^1H\}$ (100 MHz, $CDCl_3$) δ 139.9, 139.5, 129.0, 128.6, 128.4, 127.2, 115.7, 72.0, 62.4, 59.0, 54.6; IR (ATR-neat) ν_{max} = 3361, 3063, 3027, 1602, 1493, 1452, 1365; HRMS (ESI-TOF) (m/z) [M + H^+] = calcd for $C_{19}H_{23}NO_2$ 298.1807, found 298.1816.

(2*S*,3*R*)-2-(Dibenzylamino)pent-4-yne-1,3-diol (12c). The procedure described above for the synthesis of compound **12a** was applied to **10** on a 0.27 mmol (100 mg) scale using ethynylmagnesium bromide solution (1.62 mL, 0.81 mmol, 0.5 M in THF) to give **12c** (50.2 mg, 0.17 mmol, 63% yield) as a colorless oil: $[\alpha]^{25}_D$ = −18.8 (*c*, 0.83, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.46 (d, 1H, *J* = 1.9 Hz), 3.04 (t, 1H, *J* = 6.1 Hz), 3.17 (br, 1H), 3.72 (d, 2H, *J* = 13.3 Hz), 3.81−3.84 (m, 1H), 3.92−3.98 (m, 3H), 4.46 (br, 1H), 7.19−7.27 (m, 10H); $^{13}C\{^1H\}$ (100 MHz, $CDCl_3$) δ 139.1, 129.2, 128.5, 127.4, 83.8, 74.8, 61.8, 60.3, 59.6, 54.8; IR (ATR-neat) ν_{max} = 3371, 3292, 3062, 3028, 1602, 1494, 1452, 1366; HRMS (ESI-TOF) (m/z) [M + Na^+] = calcd for $C_{19}H_{21}NO_2$ 318.1470, found 318.1474.

(2*R*,3*S*,4*R*)-3-(Dibenzylamino)hexane-2,4-diol (13a). The procedure described above for the synthesis of compound **12a** was applied to **11** on a 0.26 mmol (100 mg) scale using ethylmagnesium bromide solution (0.26 mL, 0.78 mmol, 3 M in Et_2O) to give **13a** (50.1 mg, 0.16 mmol, 60% yield) as a colorless oil: $[\alpha]^{25}_D$ = −43.0 (*c*, 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, 3H, *J* = 7.6 Hz), 1.18 (d, 3H, *J* = 6.1 Hz), 1.67−1.58 (m, 2H), 2.10 (br, 1H), 2.36 (dd, 1H, J_1 = 7.1, J_2 = 1.9 Hz), 3.48 (d, 2H, *J* = 13.5 Hz), 3.93−3.96 (m, 1H), 4.01 (d, 2H, *J* = 13.5 Hz), 4.13 (quin, 1H, *J* = 6.2 Hz), 7.16−7.29 (m, 10H); $^{13}C\{^1H\}$ (100 MHz, $CDCl_3$) δ 139.4, 129.1, 128.4, 127.2, 70.9, 65.8, 64.9, 55.1, 30.2, 20.9, 18.8; IR (ATR-neat) ν_{max} = 3415, 3062, 3026, 2968, 2922, 1496, 1455, 1374; HRMS (ESI-TOF) (m/z) [M + H^+] = calcd for $C_{20}H_{27}NO_2$ 314.2120, found 314.2118.

(2*R*,3*S*,4*R*)-3-(Dibenzylamino)hex-5-ene-2,4-diol (13b). The procedure described above for the synthesis of compound **12a** was applied to **11** on a 0.26 mmol (100 mg) scale using vinylmagnesium bromide solution (0.78 mL, 0.78 mmol, 1 M in THF) to give **13b** (50.9 mg, 0.16 mmol, 63% yield) as a colorless oil: $[\alpha]^{25}_D$ = −42.7 (*c*, 0.93, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.14 (d, 3H, *J* = 6.1 Hz), 2.52 (dd, 1H, J_1 = 7.6, J_2 = 2.2 Hz), 3.60 (d, 2H, *J* = 13.5 Hz), 4.03 (d, 2H, *J* = 13.5 Hz), 4.12 (quin, 1H, *J* = 6.3 Hz), 4.56 (br, 1H), 5.11 (d, 1H, *J* = 10.5), 5.27 (d, 1H, *J* = 17.2 Hz) 5.86 (ddd, 1H, J_1 =16.7, J_2 = 10.5, J_3 = 5.2 Hz), 7.17−7.31 (m 10H); $^{13}C\{^1H\}$ (100 MHz, $CDCl_3$) δ 140.4, 139.2, 129.1, 128.9, 128.5, 127.3, 114.8, 69.9, 66.4, 65.2, 55.3, 21.0; IR (ATR-neat) ν_{max} = 3391, 3063, 3026, 1603, 1494, 1454; HRMS (ESI-TOF) (m/z) [M + H^+] = calcd for $C_{20}H_{25}NO_2$ 312.1964, found 312.1972.

(2*R*,3*S*,4*R*)-3-(Dibenzylamino)hex-5-yne-2,4-diol (13c). The procedure described above for the synthesis of compound **12a** was applied to **11** on a 0.26 mmol (100 mg) scale using ethynylmagnesium bromide solution (1.56 mL, 0.78 mmol, 1 M in THF) to give **13c** (46 mg, 0.15 mmol, 58% yield) as a colorless oil: $[\alpha]^{25}_D$ = −33.8 (*c*, 1.02, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (d, 3H, *J* = 6.0 Hz), 2.49 (d, 1H, *J* = 1.7 Hz), 2.77 (dd, 1H, J_1 =8.9, J_2 =4.9 Hz), 4.01 and 4.06 (2 × 2H, AB system, *J* = 13.1 Hz), 4.34−4.44 (m, 2H), 7.23−7.34 (m, 10H); $^{13}C\{^1H\}$ (100 MHz, $CDCl_3$) δ 139.2, 129.5, 128.5, 127.3, 83.7, 74.7, 66.8, 65.6, 59.5, 55.5, 21.2; IR (ATR-neat) ν_{max} = 3379, 3224, 3063, 3025, 1495, 1454, 1364; HRMS (ESI-TOF) (m/z) [M + H^+] = calcd for $C_{20}H_{23}NO_2$ 310.1807, found 310.1805.

(4*R*,5*S*)-*N*,*N*-Dibenzyl-4-ethyl-2,2-dimethyl-1,3-dioxan-5-amine (14a). To a solution of **12a** (20.0 mg, 0.07 mmol) were added DMS (0.8 mL, 0.85 mmol) and PPTS (5 mg, 0.02 mmol) in 2 mL of dry DCM. The solution was stirred for 18 h at room temperature. The solvent was then evaporated, and the residue was chromatographed on silica gel flash (eluent AcOEt/PE, 95:5) to give **14a** (19.0 mg, 0.06 mmol, 80% yield) as a colorless oil: $[\alpha]^{25}_D$ = +68.1 (*c*, 0.93, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.75 (t, 3H, *J* = 7.4 Hz), 1.22 (s + m 4H), 1.29 (s, 3H), 1.83 (dsext, 1H, J_1 = 7.4, J_2 = 2.6 Hz), 2.64 (td, 1H, J_1 = 9.6, J_2 = 5.6 Hz), 3.45 (d, 2H, *J* = 14.3 Hz) 3.62 (dt, 1H, J_1 = 9.6, J_2 = 2.6 Hz), 3.76 (dd, 1H, J_1 = 11.9, J_2 = 5.6 Hz), 3.83 (d + dd, 3H, J_1 = 14.3, J_2 = 11.9, J_3 = 5.6 Hz) 7.13−7.26 (m, 10H); $^{13}C\{^1H\}$ (100 MHz, $CDCl_3$) δ 139.7, 128.7, 128.0, 127.0, 99.0, 71.3, 58.2, 57.8, 54.8, 26.6, 25.6, 21.7, 9.7; IR (ATR-neat) ν_{max} = 3068, 2938, 2880, 1457, 1379, 1227, 1204, 1116; HRMS (ESI-TOF) (m/z) [M + H^+] = calcd for $C_{22}H_{30}NO_2$ 340.2277, found 340.2271.

(4*R*,5*S*)-*N*,*N*-Dibenzyl-2,2-dimethyl-4-vinyl-1,3-dioxan-5-amine (14b). The procedure described above for the synthesis of compound **14a** was applied to **12b** (20 mg, 0.067 mmol) to give **14b** (18.5 mg, 0.05 mmol, 82% yield) as a colorless oil: $[\alpha]^{25}_D$ = +19.7 (*c*, 1.01, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.37 (s, 3H), 1.47 (s, 3H), 2.88 (ddd, 1H, J_1 =9.5, J_2 = 7.8, J_3 = 5.6 Hz), 3.66 (d, 2H, *J* = 13.8 Hz), 3.88 (dd, 1H, J_1 = 11.7, J_2 = 5.6 Hz), 3.93 (d, 2H, *J* = 13.8 Hz), 3.97 (dd, 1H, J_1 = 11.7, J_2 = 7.8 Hz), 4.40 (dd, 1H, J_1 = 9.8, J_2 = 6.5 Hz), 5.32 (d, 1H, *J* = 10.5 Hz), 5.42 (d, 1H, *J* = 17.1 Hz), 5.93 (ddd, 1H, J_1 = 17.1, J_2 = 10.5, J_3 = 6.5 Hz), 7.24−7.37 (m, 10H); $^{13}C\{^1H\}$ (100 MHz, $CDCl_3$) δ 139.5, 137.7, 128.7, 127.1, 117.5, 98.8, 71.4, 59.1, 57.4, 54.7, 27.6; IR (ATR-neat) ν_{max} = 3503, 3063, 3027, 2989, 2936, 2887, 1602, 1493, 1453, 1200; HRMS (ESI-TOF) (m/z) [M + H^+] = calcd for $C_{22}H_{27}NO_2$ 338.2120, found 338.2117.

(4*R*,5*S*)-*N*,*N*-Dibenzyl-4-ethynyl-2,2-dimethyl-1,3-dioxan-5-amine (14c). The procedure described above for the synthesis of compound **14a** was applied to **12c** (20 mg, 0.068 mmol) to give **14c** (18.2 mg, 0.05 mmol, 80% yield) as a colorless oil: $[\alpha]^{25}_D$ = +29.2 (*c*, 0.96, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.39 (s, 3H), 2.59 (d, 1H, *J* = 2.1 Hz), 3.18 (ddd, 1H, J_1 = 9.8, J_2 = 7.5, J_3 = 5.6 Hz), 3.74 (d, 2H, *J* = 13.9 Hz), 3.79 (dd, 1H, J_1 = 10.4, J_2 = 5.6 Hz), 3.84 (dd, 1H, J_1 = 10.4, J_2 = 7.5 Hz), 3.97 (d, 1H, *J* = 13.9 Hz), 4.66 (dd, 1H, J_1 = 9.8, J_2 = 2.1 Hz), 7.22−7.40 (m, 10H); $^{13}C\{^1H\}$ (100 MHz, $CDCl_3$) δ 139.4, 128.7, 128.3, 127.1, 99.4, 82.6, 74.3, 61.3, 60.2, 57.6, 54.7, 27.1, 20.8; IR (ATR-neat) ν_{max} = 3288, 3062, 3028, 2991, 2124, 1703; HRMS (ESI-TOF) (m/z) [M + H^+] = calcd for $C_{22}H_{25}NO_2$ 336.1964, found 336.1969.

(4*R*,5*S*,6*R*)-*N*,*N*-Dibenzyl-4-ethyl-2,2,6-trimethyl-1,3-dioxan-5-amine (15a). The procedure described above for the synthesis of compound **14a** was applied to **13a** (20 mg, 0.064 mmol) to give **15a** (18.1 mg, 0.05 mmol, 80% yield) as a colorless oil: $[\alpha]^{25}_D$ = +27.2 (*c*, 0.3, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 0.83 (s, 3H), 1.26 (s, 3H), 1.33 (s, 3H), 1.27 (m, 1H), 1.40 (d, 1H, *J* = 7.0 Hz), 1.69 (dsext, 1H, J_1 = 7.4, J_2 = 2.8 Hz), 2.60 (dd, 1H, J_1 = 7.4, J_2 = 5.0 Hz), 3.68 (td, 1H, J_1 = 7.4, J_2 = 2.8 Hz), 4.01−4.03 (br + m, 3H), 7.19−7.27 (m, 10H); $^{13}C\{^1H\}$ (100 MHz, $CDCl_3$) δ 140.5, 128.6, 128.2, 126.8, 100.3, 70.9, 68.6, 61.0, 55.8, 24.8, 24.5, 17.8, 10.3; IR (ATR-neat) ν_{max} = 3067, 2987, 2936, 2855, 1458, 1380, 1228; HRMS (ESI-TOF) (m/z) [M + H^+] = calcd for $C_{23}H_{31}NO_2$ 354.2433, found 354.2437.

(4*R*,5*S*,6*R*)-*N*,*N*-Dibenzyl-2,2,4-trimethyl-6-vinyl-1,3-dioxan-5-amine (15b). The procedure described above for the synthesis of compound **14a** was applied to **13b** (20 mg, 0.057 mmol) to give **15b** (15.8 mg, 0.05 mmol, 79% yield) as a colorless oil: $[\alpha]^{25}_D$ = −7.5 (*c*, 0.30, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 1.29 (s, 3H), 1.39 (s, 3H), 1.37 (d, 3H, *J* = 6.9 Hz), 2.79 (dd, 1H, J_1 = 7.4, J_2 = 5.3 Hz), 3.89 (br, 2H), 4.07−4.11 (br + m, 3H), 4.46 (t, 1H, *J* = 7.4 Hz), 5.21 (d, 1H, *J* = 10.4 Hz), 5.32 (d, 1H, *J* = 17.2 Hz), 5.88 (ddd, 1H, J_1 = 17.2, J_2 = 10.4, J_3 = 6.6 Hz), 7.19−7.37 (m, 10H); $^{13}C\{^1H\}$ (100 MHz, $CDCl_3$) δ 140.1, 139.1, 128.6, 128.2, 126.8, 116.7, 100.4, 69.7, 67.9, 60.7, 55.4, 29.7, 25.0, 24.6, 17.4; IR (ATR-neat) ν_{max} = 3330, 3063, 3027, 2925, 2852, 1603, 1494, 1454, 1224; HRMS (ESI-TOF) (m/z) [M + H^+] = calcd for $C_{23}H_{29}NO_2$ 352.2277, found 352.2268.

(4*R*,5*S*,6*R*)-*N*,*N*-Dibenzyl-4-ethynyl-2,2,6-trimethyl-1,3-dioxan-5-amine (15c). The procedure described above for the synthesis of compound **14a** was applied to **13c** (20 mg, 0.065 mmol), to give **15c** (18.8 mg, 0.05 mmol, 83% yield) as a colorless oil: $[\alpha]^{25}_D$ = +3.5 (*c*, 0.34, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 1.34 (d, 3H, *J* = 6.5 Hz), 1.37 (s, 3H), 1.48 (s, 3H), 2.54 (d, 1H, *J* = 2.4 Hz), 2.87 (1H, t, *J* = 4.8 Hz), 3.70 (d, 2H, *J* = 13.4 Hz), 4.16 (br, 2H), 4.29 (dq, 1H, J_1 = 6.6, J_2 = 4.8 Hz), 4.94 (dd, 1H, J_1 = 4.8, J_2 = 2.4 Hz), 7.20−7.36 (m, 10H); $^{13}C\{^1H\}$ (100 MHz, $CDCl_3$) δ 139.8, 128.7, 128.3, 126.9, 100.7, 84.4, 74.6, 66.5, 59.6, 58.8, 55.3, 27.2, 23.4, 17.4; IR (ATR-neat) ν_{max} = 3400, 3063, 3028, 2925, 2336, 2963, 1734; HRMS (ESI-TOF) (m/z) [M + H^+] = calcd for $C_{23}H_{27}NO_2$ 350.2120, found 350.2129.

(3*S*,4*R*)-3-(Dibenzylamino)hexane-1,4-diol (17a). The procedure described for the synthesis of compound **5a** was applied to **16** on a 0.7 mmol (200 mg) scale using ethylmagnesium bromide solution (0.7 mL, 2.1 mmol, 3 M in Et_2O). The residue was purified by flash

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chromatography on silica gel (eluent gradient AcOEt/PE, 8:2 to 7:3) to give **17a** (203.9 mg, 0.65 mmol, 95% yield) as a colorless oil: $[\alpha]^{25}_{D}$ = −34.0 (*c*, 1.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (t, 3H, *J* = 7.4 Hz), 1.30 (sep, 1H, *J* = 7.4 Hz), 1.43−1.56 (m, 1H), 1.96−2.05 (m, 1H), 2.60−2.64 (m, 1H), 3.46 (d, 2H, *J* = 13.6 Hz), 3.58 (br, 2H), 3.72−3.74 (d + m, 3H, *J* = 13.6 Hz), 7.50−7.24 (m, 10H); ^{13}C{^{1}H} (100 MHz, $CDCl_3$) δ 139.4, 129.1, 128.4, 127.2, 71.4, 62.4, 61.1, 54.5, 28.7, 27.2, 10.4; IR (ATR-neat) ν_{max} = 3314, 3063, 3028, 2930, 2960, 1494, 1453, 1365; HRMS (ESI-TOF) (*m*/*z*) [M + H$^+$] = calcd for $C_{20}H_{27}NO_2$ 314.2120, found 314.2119.

(3*S*,4*R*)-3-(Dibenzylamino)hex-5-ene-1,4-diol (17b). The procedure described for the synthesis of compound **5a** was applied to **16** on a 0.7 mmol (200 mg) scale using vinylmagnesium bromide solution (2.1 mL, 2.1 mmol, 1 M in THF) to give **17b** (209.1 mg, 0.67 mmol, 96% yield) as a colorless oil: $[\alpha]^{25}_{D}$ = −31.4 (*c*, 1.26, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59−1.68 (m, 1H), 2.10−2.19 (m, 1H), 2.88−2.92 (m, 1H), 3.68−3.72 (d + m, 4H, *J* = 13.5 Hz), 3.83 (d, 2H, *J* = 13.5 Hz), 4.45 (br, 1H), 5.2 (d, 1H, *J* = 10.4 Hz), 5.33 (d, 1H, *J* = 17.2 Hz), 5.93 (ddd, 1H, J_1 = 16.4, J_2 = 10.4, J_3 = 5.4 Hz), 7.28−7.37 (m, 10H); ^{13}C{^{1}H} (100 MHz, $CDCl_3$) δ 140.1, 139.3, 129.1, 128.5, 127.3, 115.1, 70.9, 62.0, 60.8, 54.7, 27.2; IR (ATR-neat) ν_{max} = 3337, 3063, 3027, 1602, 1494, 1452; HRMS (ESI-TOF) (*m*/*z*) [M + H$^+$] = calcd for $C_{20}H_{25}NO_2$ 312.1964, found 312.1964.

(3*S*,4*R*)-3-(Dibenzylamino)hex-5-yne-1,4-diol (17c). The procedure described for the synthesis of compound **5a** was applied to **16** on a 0.7 mmol (200 mg) scale using ethynylmagnesium bromide solution (4.2 mL, 2.1 mmol, 0.5 M in THF) to give **17c** (173.1 mg, 0.56 mmol, 80% yield) as a colorless oil: $[\alpha]^{25}_{D}$ = −13.7. (*c*, 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.78−1.86 (m, 1H), 2.01−2.09 (m, 1H), 2.40 (d, 1H, *J* = 6.2 Hz), 3.55−3.57 (d + m, 3H, *J* = 13.3 Hz), 3.62−3.69 (m, 1H), 3.92 (d, 2H, *J* = 13.3 Hz), 4.38 (d, 1H, *J* = 4.4 Hz), 7.18−7.25 (m, 10H); ^{13}C{^{1}H} (100 MHz, $CDCl_3$) δ 139.0, 129.3, 128.6, 127.4, 84.1, 74.6, 60.9, 60.7, 58.8, 54.8, 28.2; IR (ATR-neat) ν_{max} = 3379, 3296, 3066, 3032, 1498, 1456, 1370; HRMS (ESI-TOF) (*m*/*z*) [M + H$^+$] = calcd for $C_{20}H_{23}NO_2$ 310.1807, found 310.1813.

(4*S*,5*R*)-4-(Dibenzylamino)-5-ethyldihydrofuran-2(3*H*)-one (18a).[31] TPAP (32.0 mg, 0.09 mmol) was added to a stirred mixture of **17a** (278.7 mg, 0.89 mmol), NMO (320.0 mg, 2.67 mmol), and activated powdered molecular sieves (60 mg) in dry DCM (1 mL) at room temperature under argon. After being stirred for 2 h, the reaction mixture was purified by column chromatography flash (eluent AcOEt/PE, 8:2) to give **18a** (137.6 mg, 0.45 mmol, 50% yield) as a colorless oil: $[\alpha]^{25}_{D}$ = +84.3 (*c*, 0.4, $CHCl_3$).

(4*S*,5*R*)-4-(Dibenzylamino)-5-vinyldihydrofuran-2(3*H*)-one (18b). The procedure described for the synthesis of compound **18a** was applied to **17b** (50 mg, 0.16 mmol) to give **18b** (26.0 mg, 0.08 mmol, 51% yield) as a colorless oil: $[\alpha]^{25}_{D}$ = +27.8 (*c*, 0.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.60.(d, 2H, *J* = 7.1 Hz), 3.53 (ddd, 1H, J_1 = 7.3, J_2 = 6.7, J_3 = 4.6 Hz), 3.57 (d, 2H, *J* = 13.8 Hz), 3.71 (d, 2H, *J* = 13.8 Hz), 4.98 (ddd, 1H, J_1 = 5.4, J_2 = 4.6, J_3 = 1.4 Hz), 5.24 (dd, 1H, J_1 = 10.5, J_2 = 1.0), 5.34 (dt, 1H, J_1 = 17.2, J_2 = 1.0 Hz), 5.76 (ddd, 1H, J_1 = 5.4, J_2 = 4.6, J_3 = 1.4 Hz), 7.25−7.34 (m, 10H); ^{13}C{^{1}H} (100 MHz, $CDCl_3$) δ 175.6, 138.2, 134.8, 128.5, 127.5, 117.3, 81.7, 60.6, 54.3, 29.7; IR (ATR-neat) ν_{max} = 3029, 2921, 1778, 1646, 1184, 1163, 987, 738, 700; HRMS (ESI-TOF) (*m*/*z*) [M + H$^+$] = calcd for $C_{20}H_{21}NO_2$ 308.1651, found 308.1651.

(4*S*,5*R*)-4-(Dibenzylamino)-5-ethynyldihydrofuran-2(3*H*)-one (18c). The procedure described for the synthesis of compound **18a** was applied to **17c** (50 mg, 0.16 mmol) to give **18c** (24.4 mg, 0.08 mmol, 49% yield) as a colorless oil: $[\alpha]^{25}_{D}$ = +25.0 (*c*, 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.57 (dd, 1H, J_1 = 18.4, J_2 = 4.4 Hz), 2.65 (d, 1, H, *J* = 2.2 Hz), 2.79 (dd, J_1 = 18.4, J_2 = 8.8 Hz), 3.63 (2 × 2AB system, 4H, *J* = 13.8 Hz), 3.89 (qd, 1H, J_1 = 4.3, J_2 = 4.3 Hz), 5.13 (dd, J_1 = 4.3, J_2 = 2.2 Hz), 7.26−7.34 (m, 10H); ^{13}C{^{1}H} (100 MHz, $CDCl_3$) δ 174.7, 137.7, 128.7, 128.6, 127.6, 79.4, 70.3, 62.6, 54.1, 29.7; IR (ATR-neat) ν_{max} = 3283, 2925, 2123, 1787, 1453, 1194, 970, 911, 736, 631 ; HRMS (ESI-TOF) (*m*/*z*) [M + Na$^+$] = calcd for $C_{20}H_{19}NO_2$ 328.1313, found 328.1316.

(2*S*,3*R*)-2-(Dibenzylamino)octadec-4-yn-3-ol (19). To a solution of 1-nonyne (0.14 mL, 0.84 mmol) in dry Et_2O (10 mL) was added ethylmagnesium bromide solution (0.28 mL, 0.84 mmol, 3 M in THF). The mixture was refluxed for 2.5 h, and then it was allowed to cool to room temperature. In parallel, to a cooled (−78 °C) solution of **4a** (100 mg, 0.28 mmol) in dry Et_2O (3 mL) was added DIBAL-H (0.4 mL, 0.4 mmol, 1 M in hexane) under argon atmosphere. After being stirred for 2 h, a solution of alkynylmagnesium bromide previously formed was carefully added at −78 °C. The mixture was allowed to warm to −10 °C and stirred for 18 h. Then, the mixture was warmed to 0 °C and quenched with saturated NH_4Cl (8 mL). The mixture was extracted with Et_2O (10 mL × 3), and the organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (eluent AcOEt/PE, 9:1) to give **19** (77.5 mg, 0.17 mmol, 60% yield) as a colorless oil: $[\alpha]^{25}_{D}$ = −10.2 (*c*, 0.89, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, 3H, *J* = 7.0 Hz), 1.14−1.25 (m, 23H), 1.39 (quin, 2H, *J* = 7.0 Hz), 2.13 (td, 2H, J_1 = 7.0, J_2 = 2.0 Hz), 2.95 (quin, 1H, *J* =6.6 Hz), 3.32 (d, 2H, *J* = 13.3 Hz), 3.89 (br, 1H), 4.14 (d + m, 3H, *J* = 13.3 Hz), 7.17−7.27 (m, 10H); ^{13}C{^{1}H} (100 MHz, $CDCl_3$) δ 139.4, 129.1, 128.4, 127.2, 86.8, 80.0, 63.2, 56.0, 54.7, 31.9, 29.7, 29.5, 29.4, 29.1, 28.9, 28.6, 22.7, 18.8, 14.1, 9.5; IR (ATR-neat) ν_{max} = 3425, 2925, 2853, 1332, 747, 699; HRMS (EI-TOF) (*m*/*z*) [M − H_2O^+] = calcd for $C_{32}H_{47}NO$ 443.3552, found 443.3541.

(2*S*,3*R*)-2-(Dibenzylamino)octadec-4-yne-1,3-diol (20).[36] To a solution of 1-nonyne (0.13 mL, 0.81 mmol) in dry Et_2O (10 mL) was added ethylmagnesium bromide solution (0.27 mL, 0.81 mmol, 3 M in THF). The mixture was refluxed for 2.5 h, and then it was allowed to cool to room temperature. In parallel, to a cooled (−78 °C) solution of **10** (100 mg, 0.27 mmol) in dry Et_2O (3 mL) under argon was added DIBAL-H in two portions (0.38 mL, 0.38 mmol, 1 M in hexane; and 45 min later 0.19 mL, 0.19 mmol). After additional stirring for 40 min at −78 °C, a solution of the alkynylmagnesium bromide previously formed was carefully added at −78 °C and the mixture was allowed to warm to −10 °C and stirred for 18 h. Then, the mixture was cooled to 0 °C and quenched with saturated NH_4Cl (8 mL). The mixture was extracted with Et_2O (10 mL × 3), and the organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel flash (eluent AcOEt/PE, 8:2) to give **20** (90.2 mg, 0.19 mmol, 70% yield) as a colorless oil: $[\alpha]^{25}_{D}$ = −37.6 (*c*, 0.94, $CHCl_3$).

(2*S*,3*R*)-2-Aminooctadecan-3-ol (Spisulosine, 2c).[6,53,54] The procedure described for the synthesis of compound **8** was applied to **19** (50 mg, 0.11 mmol) to give **2c** (25,1 mg, 0.09 mmol, 70% yield) as a white solid: mp = 65−67 °C; $[\alpha]^{25}_{D}$ = +25.3 (*c*, 0.94, $CHCl_3$).

(2*S*,3*R*)-2-Aminooctadecane-1,3-diol (Sphinganine, 1b).[55] The procedure described for the synthesis of compound **8** was applied to **20** (50 mg, 0.10 mmol) to give **1b** (19.0 mg, 0.06 mmol, 60% yield) as a white solid: mp = 70−72 °C; $[\alpha]^{25}_{D}$ = +0.62 (*c*, 0.57, EtOH).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full characterization of all new compounds. 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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