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Asymmetric Synthesis of ES-285, an Anticancer Agent Isolated from Marine Sources

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The asymmetric synthesis of (2*S*,3*R*)-2-amino-3-octanedecanol hydrochloride (ES-285·HCl) was achieved in eight steps in ca. 38% overall yield from the *N*-benzylimine-derived from (*R*)-2,3-*O*-isopropylidene glyceraldehyde, which is easily available on gram scale from the inexpensive precursor D-mannitol. Highly diastereoselective addition of methylmagnesium bromide to the *N*-benzylimine was the key step to create the *vic*-amino alcohol moiety with the appropriate configuration. Regioselective ring opening of an intermediate aminoepoxide enabled the introduction of the long hydrocarbon chain at C4.

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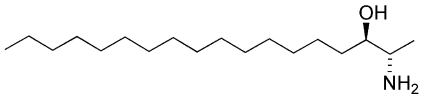
Introduction

Compounds of marine origin with structures from simple linear peptides to complex macrocyclic polyethers have shown potent activities such as antitumor, analgesic, anti-inflammatory, immunomodulation, allergy, and antiviral, amongst others.[1] As a result, in recent years a considerable number of drug candidates in preclinical or early clinical development, as well as drugs on the market or predicted to be approved soon, originated from the marine ecosystem.

(2*S*,3*R*)-2-Amin-3-octanedecanol (ES-285 or spisulosine; Figure 1) is a compound of marine origin and was first isolated from the North Arctic clam *Mactromeris polynyma*. The great antiproliferative activity[2] of its hydrochloride has led to inclusion of ES-285 in clinical trials as a potential antitumoral agent to treat advanced malignant solid tumors.[3]



ES-285

Figure 1. Structure of ES-285.

In previous asymmetric syntheses described in the literature, ES-285·HCl is obtained from L-alanine methyl ester hydrochloride in six steps and 28% overall yield,[3a] and an immediate precursor of this compound (i.e., **6**) was obtained from commercially available chiral 2-aziridine carboxylate in four steps and 70% overall yield.[4]

A synthetic protocol to obtain this valuable compound starting from a cheap and readily available precursor would be interesting and in this context we report here a new approach to the asymmetric synthesis of ES-285 by using the *N*-benzylimine derived from (*R*)-2,3-*O*-isopropylideneglyceraldehyde, which is easily available on a gram scale from the inexpensive precursor D-mannitol.[5]

Results and Discussion

In recent years, we have shown that imines derived from *O*-protected glyceraldehyde (**A**) diastereoselectively add organometallic reagents to afford aminodiol derivatives.[6] These compounds can be easily converted into 1-aminoalkil epoxides with retention or inversion of configuration by using the appropriate reaction sequence.[6d,7] Nucleophilic ring opening of *anti*-aminoepoxide derivative **C** with the *S*,*S* configuration with a C_{14} organometallic reagent would provide *vic*-amino alcohol derivative **D** with the right configuration for the synthesis of ES-285 in enantiomerically pure form. To obtain *anti*-aminoepoxide with the *S*,*S* configuration, *anti*-aminodiol derivative **B** with the 2*S*,3*S* configuration could be an appropriate precursor (Scheme 1).

According to our previous results, the addition of organomagnesium reagents to *N*-benzylimines derived from (*R*)-2,3-di-*O*-benzylglyceraldehyde usually provides aminodiols of *syn* configuration with almost total diastereoselectivity,[6c–6g,6i] whereas the stereochemical course of the addition of organomagnesium reagents to *N*-benzylimines derived from (*R*)-2,3-*O*-isopropylideneglyceraldehyde depends

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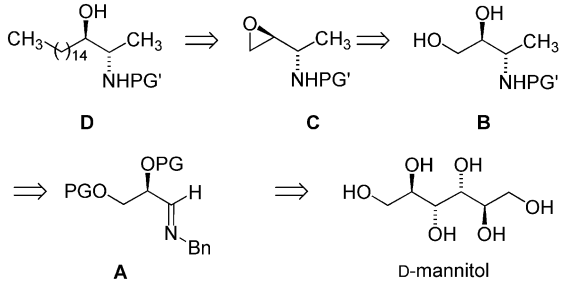


Scheme 1. Retrosynthetic analysis.

on the organometallic reagent and the reaction conditions. The addition of benzylmagnesium[6e] and allylmagnesium bromide to imine **1** diastereoselectively affords the corresponding aminodiols with *syn* configuration. The addition phenylmagnesium[6c,6d] and vinylmagnesium[6b,6g] bromide exclusively affords the corresponding aminodiols with *anti* configuration, but in the presence of ZnI_2, the addition of vinylmagnesium bromide preferentially leads to the aminodiol with *syn* configuration.[6g] The addition of methylmagnesium bromide to imine **1** is not diastereoselective.

The stereochemical course of the addition of alkynyllithium reagents to *N*-benzylimines derived from *O*-protected (*R*)-glyceraldehyde can be directed by using the appropriate Lewis acid.[8] In the absence of a Lewis acid or in the presence of $EtAlCl_2$, aminodiols of *syn* configuration are obtained preferentially, whereas in the presence of $BF_3{\cdot}OEt_2$ aminodiols of *anti* configuration are the major products.

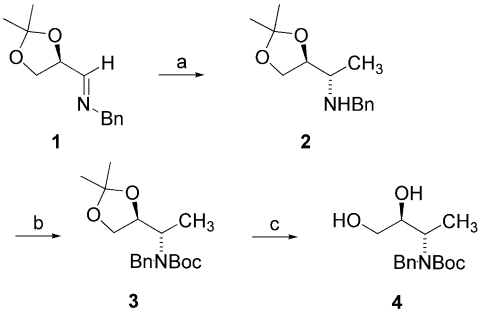
On the basis of these precedents we decided to test the addition of an excess amount of methyllithium or methylmagnesium bromide to imine **1** in the presence of $BF_3{\cdot}OEt_2$. In both cases, protected aminodiol **2** of *anti* configuration was obtained with a high diastereoselectivity and was easily isolated by column chromatography in high yield (Table 1).

Table 1. Study of the addition of CH_3M to imine **1** (1 mmol).

Entry	CH_3M (mmol)	$BF_3{\cdot}OEt_2$ [mmol]	*anti*/*syn*[a]	Yield [%]
1	CH_3MgBr (2.1)	–	45:55	36[b]
2	CH_3Li (2.5)	2	92:8	71[c]
3	CH_3Li (2.5)	1	90:10	70[c]
4	CH_3MgBr (2.5)	1	96:4	69[c]

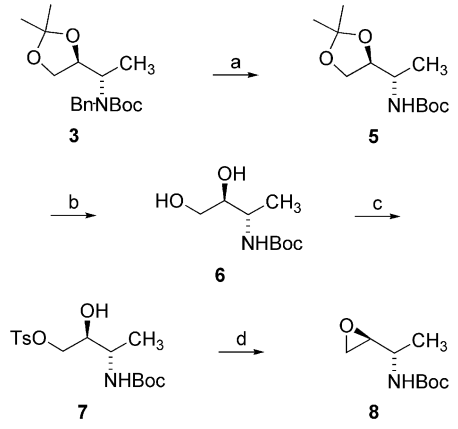
[a] Determined by ^1H NMR spectroscopic analysis of the crude reaction mixture. [b] Yield of the diastereomeric mixture. [c] Yield of the major compound isolated by column chromatography.

Next, compound **2** was converted into the corresponding *N*-Boc derivative **3** by treatment with di-*tert*-butyl dicarbonate in the presence of a tertiary amine. Yields obtained at 50 °C with the use of *i*$PrEt_2N$ in dioxane as the base (71%) were substantially improved (96%) when the reaction was performed at the same temperature with the use of Et_3N in methanol. From this compound, *N*-Boc aminodiol **4** was easily obtained in 89% yield by acidic hydrolysis with trifluoroacetic acid (TFA) (Scheme 2). Unfortunately, compound **4** could not be converted into the corresponding *anti*-aminoepoxide under any of the conditions assessed. Reaction under Mitsunobu conditions[9] promoted *N*-Boc deprotection as the main reaction, whereas compound **4** was inert to tosylation at room temperature and mainly led to the formation of a cyclic urethane upon heating.



Scheme 2. Synthesis of *N*-Boc aminodiol **4**. Reagents and conditions (a) CH_3MgBr, $BF_3{\cdot}OEt_2$, Et_2O, –20 °C (69%); (b) Boc_2O, CH_3OH/Et_3N, 50 °C (96%); (c) TFA (50 mol-%), CH_3OH/H_2O (3:1), r.t. (89%).

Conversion of enantiopure *N*-Boc derivative **3** into aminoepoxide **8** was performed as shown in Scheme 3. The *N*-benzyl group of **3** was removed at –50 °C by using lithium/liquid ammonia to afford compound **5** in 99% yield. Subsequent *p*-toluenesulfonic acid catalyzed acetonide hydrolysis in refluxing methanol afforded aminodiol **6** after 4 h in almost quantitative yield as described previously.[10] Chemoselective removal of the acetonide in compound **5** can be also performed at room temperature by treatment of compound **5** with TFA for 24 h or in only 30 min by using $BiCl_3$[11] (5 mol-%) in acetonitrile and trace amounts of water. These alternatives led to aminodiol **6** in 89 and 80%, respectively.



Scheme 3. Synthesis of aminoepoxide **8**. Reagents and conditions: (a) Li/NH_3, Et_2O, –50 °C (99%); (b) method A: TsCl, CH_3OH, reflux conditions (96%); method B: TFA (10 mol-%), CH_3OH/H_2O (3:1), r.t. (89%); method C: $BiCl_3$ (5 mol-%), CH_3CN/H_2O, r.t. (80%); (c) nBu_2SnO, Et_3N, TsCl, CH_2Cl_2, r.t. (96%); (d) K_2CO_3, CH_3OH, 0 °C (86%).

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The structure of compound **5** was unambiguously established by X-ray crystallography (Figure 2) and secures the *anti* relative configuration of compound **2** obtained by addition of methylmagnesium bromide to imine **1** in the presence of $BF_3{\cdot}OEt_2$.

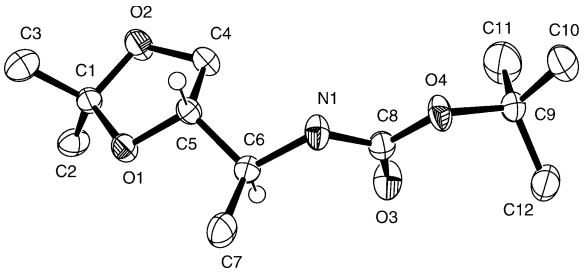


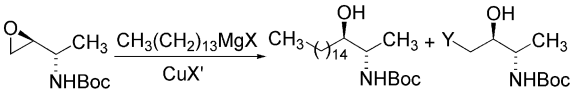
Figure 2. X-ray structure of compound **5**.

Conversion of diol **6** into epoxide **8** was previously performed by Pericas et al.[7c] by intramolecular Mitsunobu reaction with the use of PPh_3 and diethyl azodicarboxylate (DEAD) in refluxing $CHCl_3$ (68% yield) or by conversion of the diol into the corresponding tosylate by treatment with *p*-toluenesulfonyl chloride in pyridine at 4 °C for 64 h and subsequent NaH-promoted cyclization at room temperature[7b] (49% yield, two steps). In our hands, intramolecular Mitsunobu reaction using PPh_3 and the now more easily available diisopropyl or dibenzyl azodicarboxylate in refluxing $CHCl_3$ resulted in a crude product that was extremely difficult to purify. Better results were obtained when aminoepoxide **8** was obtained by the two-step procedure that involved tosylation of the primary alcohol and subsequent cyclization but with the use of different reaction conditions. Treatment of compound **6** with di-*n*-butyltin oxide, triethylamine, and *p*-toluenesulfonyl chloride at room temperature for 6 h provided a 96% yield of the corresponding tosylate **7**, which was immediately submitted to potassium carbonate promoted cyclization to smoothly lead to the desired aminoepoxide **8** in 86% yield. Aminoepoxide **8** obtained in this way showed physical and spectroscopic data and exhibited, within the limits of experimental error, values for specific rotation in full agreement with those previously described for the (2*S*,3*S*) diastereoisomer.[7c]

To complete the route, regioselective ring opening of aminoepoxide **8** with tetradecylmagnesium halide and a catalytic amount of a Cu^I salt was studied. Reaction conditions described by Hertweck et al.[12] (Table 2, Entry 1) were first investigated.

It was observed that nucleophilic ring opening of the epoxide by the halide from the Grignard reagent and/or from the copper(I) salt seriously competes even with the use of CuCN.[13] After considerable experimentation (Table 2) − varying the halide in the Grignard reagent, the copper salt and temperature and stoichiometry of the reaction − it was found that the most effective conditions involved the use of tetradecylmagnesium bromide (2 equiv.) and CuBr (15 mol-%) at 0 °C in THF as the solvent (Table 2, Entry 9). Under these conditions, *N*-Boc-amino alcohol **9**[14] was isolated in 80% yield.

Table 2. Screening of the nucleophilic ring opening of aminoepoxide **8**.



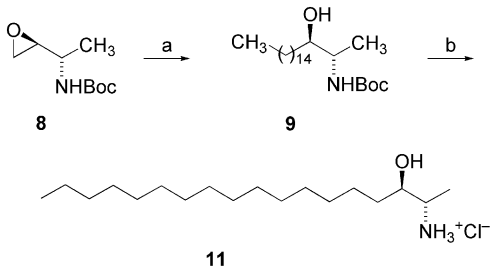
8 **9** **10a** Y = X **10b** Y = X'

Entry	X	CuX′ (%)	*T* [°C]	Yield [%]		
				9	**10a**	**10b**
1[a]	Cl	CuCN (15)	–78 → 0	36	19	–
2[a]	Cl	CuCN (15)	0	37	13	–
3	Cl	CuI (15)	0	52	3	12
4	Cl	CuBr (15)	0 → r.t.	65	4	15
5	Cl	CuI (15)	0	52	17	14
6[a]	Br	CuI (100)	0	49	1	23
7	Br	CuCN (15)	0	58	25	–
8	Br	CuI (15)	0	75	6	9
9	Br	CuBr (15)	0	80	16	
10	Br	CuBr (7)	0	73	17	
11	Br	CuBr (15)	–20	80	13	

[a] Conversion not complete.

Alexakis et al. previously reported[15] that in some cases the formation of halohydrins as side products in the nucleophilic ring opening of epoxides by using diethyl ether as the solvent could be minimized by working in the presence of $BF_3{\cdot}OEt_2$. In our case, this protocol was not applicable, as the amount of halide side product increased (38%) and the yield of the desired compound decreased (47%).

Finally, the HCl salt of ES-285 was prepared in 91% yield by acidic hydrolysis of compound **9** by treatment with a solution of ethyl acetate saturated with HCl (Scheme 4). Following this route, ES-285 hydrochloride (**11**) was obtained from imine **1** in eight steps and in 38% overall yield. To confirm the stereochemistry of the obtained compound, free amino alcohol was obtained in nearly quantitative yield from this salt by treatment with aqueous NaOH. This compound showed almost identical physical and spectroscopic data and exhibited, within the limits of experimental error, coincident values for specific rotation to those previously described for ES-285.[3a]



8 **9** **11**

Scheme 4. Synthesis of (2*S*,3*R*)-2-amino-3-octanedecanol hydrochloride from aminoepoxide **8**. Reagents and conditions: (a) *n*-$C_{14}H_{29}MgBr$ (2 equiv.), CuBr (15 mol-%), THF, 0 °C (80%); (b) EtOAc sat HCl, r.t. (91%).

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Conclusions

In conclusion, the asymmetric synthesis of ES-285 hydrochloride can be efficiently performed from the commercially available and inexpensive starting material D-mannitol. Key steps in the developed route are the $BF_3{\cdot}OEt_2$-mediated highly diastereoselective addition of methylmagnesium bromide to imine **1** and the regioselective ring opening of aminoepoxide **8**. The proposed route constitutes a valuable alternative to the established methodologies, as the raw material comes from renewable sources and most steps are operationally simple and high yielding. Moreover, this methodology should be readily amenable to the synthesis of other *vic*-amino alcohols − analogs of ES-285 with the same stereochemistry and different alkyl chains − that have shown[3b] antitumoral activities from the same starting material simply by varying the organometallic reagents used in the key steps.

Experimental Section

General: All reagents for reactions were of analytical grade and were used as obtained from commercial sources. Reactions were carried out with the use of anhydrous solvents. All manipulations with air-sensitive reagents were carried out under a dry argon atmosphere by using standard Schlenk techniques. Whenever possible, the reactions were monitored by thin-layer chromatography (TLC). TLC was performed on precoated silica gel polyester plates, and products were visualized with UV light (254 nm) or ninhydrine, or phosphomolybdic acid visualizing agents followed by heating. Column chromatography was performed by using silica gel (60 Å, 35–70 μm). *N*-{[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methylydene}-benzylamine (**1**) was prepared as described previously in the literature,[8] and tetradecylmagnesium bromide was prepared by extension of the described procedure[16] for tridecylmagnesium bromide synthesis. Melting points were determined in open capillaries by using a Gallenkamp capillary melting point apparatus and are not corrected. FTIR spectra of oils were recorded as thin films on NaCl plates and FTIR spectra of solids were recorded as KBr pellets, by using a Thermo Nicolet Avatar 360 FTIR spectrometer. Optical rotations were measured with a Jasco 1020 polarimeter at λ = 589 nm and 25 °C in a cell with a 10-cm path length. NMR spectra were acquired with Bruker AV-300, AV-400, or Bruker AV-500 instruments operating at 300, 400, or 500 MHz for ^{1}H NMR and 75, 100, or 125 MHz for ^{13}C NMR by using a 5-mm probe. The chemical shifts are referenced to the residual solvent peak. The following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet; br. s, broad singlet; dd, doublet of doublets; br. d, broad doublet; ddd, doublet of doublet of doublets. High-resolution mass spectra were recorded with a Bruker Daltonics MicroToF-Q electrospray instrument from methanolic solutions by using the positive electrospray ionization mode (ESI+). Microanalyses were performed with a Perkin–Elmer 2400 CHNS elemental analyzer.

(*S*)-*N*-Benzyl-1-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]ethanamine (2): To a solution of imine **1** (9.24 g, 42.2 mmol) in dry Et_2O (200 mL) at –20 °C under an argon atmosphere was added dropwise $BF_3{\cdot}OEt_2$ (5.34 mL, 42.2 mmol) and stirring was continued for 10 min at the same temperature. A solution of methylmagnesium bromide (3 M in ether, 35 mL, 105 mmol) was added, and the reaction mixture was stirred for 5 h at –20 °C. The reaction mixture was treated at 0 °C with saturated aqueous $NaHCO_3$ (25 mL) and water (25 mL). The mixture was filtered through a Celite pad, which was washed with Et_2O (2 × 30 mL). The organic phase was separated, and the aqueous layer was extracted with Et_2O (2 × 60 mL). The combined organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated to give **2** as a 96:4 *anti*/*syn* mixture of diastereoisomers. Purification of the crude product by silica gel column chromatography (Et_2O/hexanes, 1:1 → 3:1) afforded diastereomerically pure **2** (6.86 g, 69%) with the *anti* configuration as a colorless oil. $[\alpha]_D^{25}$ = +37.1 (*c* = 1.00, $CHCl_3$) {ref.[10] $[\alpha]_D$ = +24.3 (*c* = 0.50, $CHCl_3$)}. IR (neat): $\tilde{\nu}$ = 3321 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 (d, $^3J_{H,H}$ = 6.4 Hz, 3 H, CH_3CH), 1.29 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 1.47 (br. s, 1 H, NH), 2.74–2.80 (m, 1 H, CH_3CH), 3.68 [d, $^2J_{H,H}$ = 12.8 Hz, 1 H, CH(H_a)Ph], 3.80–3.87 [m, 1 H, OCH(H_a)CHO], 3.82 [d, $^2J_{H,H}$ = 12.8 Hz, 1 H, CH(H_b)Ph], 3.92–3.99 [m, 2 H, OCH(H_b)CHO, OCH_2CHO], 7.15–7.27 (m, 5 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.2, 25.1, 26.4, 51.2, 53.7, 66.2, 79.4, 108.8, 126.8, 127.9, 128.3, 140.5 ppm. HRMS (ESI+): calcd. for $C_{14}H_{22}NO_2$ [M + H]$^+$ 236.1645; found 236.1654.

(*S*)-*N*-Benzyl-*N*-*tert*-butoxycarbonyl-1-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]ethanamine (3): To a solution of compound **2** (5.92 g, 25.2 mmol) in a solution of 10% Et_3N in MeOH (70 mL) was added Boc_2O (11.0 g, 50.4 mmol), and the mixture was stirred for 90 min at 50 °C. After completion of the reaction, the solution was concentrated in vacuo. Purification of the crude product by silica gel column chromatography (Et_2O/hexanes, 1:5 → 1:2) afforded compound **3** (8.07 g, 96%) as a colorless oil. $[\alpha]_D^{25}$ = –2.5 (*c* = 1.00, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1691 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 328 K): δ = 1.19 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, CH_3CH), 1.25 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3), 1.41 [s, 9 H, C(CH_3)$_3$], 3.56–3.61 [m, 1 H, OCH(H_a)CHO], 3.77–3.82 [m, 1 H, OCH(H_b)CHO], 3.86–4.03 (m, 1 H, CH_3CH), 4.09–4.15 (m, 1 H, OCH_2CHO), 4.33 [d, $^2J_{H,H}$ = 15.9 Hz, 1 H, CH(H_a)Ph], 4.45 [d, $^2J_{H,H}$ = 15.9 Hz, 1 H, CH(H_b)-Ph], 7.17–7.29 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 328 K): δ = 14.7, 25.4, 26.7, 28.4, 48.6, 54.7, 67.4, 78.4, 80.1, 109.4, 126.9, 127.3, 128.3, 139.7, 155.7 ppm. HRMS (ESI+): calcd. for $C_{19}H_{29}NO_4Na$ [M + Na]$^+$ 358.1989; found 358.1993.

(2*S*,3*S*)-3-(*N*-Benzyl-*N*-*tert*-butoxycarbonylamino)-1,2-butanediol (4): A solution of compound **3** (837 mg, 2.5 mmol) in MeOH/water (3:1, 10 mL) was treated with TFA (96.3 μL, 1.25 mmol) and stirred for 17 h at room temperature. Saturated aqueous $NaHCO_3$ was added until the pH was basic, and the solution was concentrated in vacuo. The concentrate was diluted with water (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude product by silica gel column chromatography (Et_2O) afforded compound **4** (656 mg, 89%) as a colorless oil. $[\alpha]_D^{25}$ = –13.0 (*c* = 1.00, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3410, 1666 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 328 K): δ = 1.26 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, CH_3CH), 1.46 [s, 9 H, C(CH_3)$_3$], 2.54 (br. s, 2 H, OH, OH), 3.42–3.52 (m, 2 H, OCH_2-CHO), 3.58–3.64 (m, 1 H, OCH_2CHO), 3.70–3.79 (m, 1 H, CH_3CH), 4.36 [d, $^2J_{H,H}$ = 15.6 Hz, 1 H, CH(H_a)Ph], 4.45 [d, $^2J_{H,H}$ = 15.6 Hz, 1 H, CH(H_b)Ph], 7.20–7.32 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 328 K): δ = 13.9, 28.3, 49.7, 54.6, 63.6, 74.3, 80.7, 127.0, 127.1, 128.3, 139.0, 156.6 ppm. HRMS (ESI+): calcd. for $C_{16}H_{25}NO_4Na$ [M + Na]$^+$ 318.1676; found 318.1663.

(*S*)-*N*-*tert*-Butoxycarbonyl-1-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-ethanamine (5): To a solution of compound **3** (4.0 g, 11.9 mmol) in dry Et_2O (70 mL) and liquid ammonia (70 mL) at –50 °C was

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added lithium in small portions until the color of the solution remained blue. The reaction mixture was treated with saturated aqueous NH_4Cl (35 mL) and the ammonia was evaporated. The reaction mixture was diluted with water (35 mL). The aqueous phase was extracted with Et_2O (3 × 60 mL), and the combined organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude product by silica gel column chromatography (Et_2O/hexanes, 1:2) afforded compound **5** (2.90 g, 99%) as a white solid. M.p. 105.5–107 °C. $[\alpha]_D^{25}$ = –27.6 (*c* = 1.00, $CHCl_3$) {ref.[10] $[\alpha]_D$ = –10.9 (*c* = 0.34, $CHCl_3$)}. IR (KBr): $\tilde{\nu}$ = 3291, 1676 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 328 K): δ = 1.15 (d, $^3J_{H,H}$ = 6.4 Hz, 3 H, CH_3CH), 1.33 (s, 3 H, CH_3), 1.41 (s, 3 H, CH_3), 1.44 [s, 9 H, $C(CH_3)_3$], 3.67–3.78 [m, 2 H, CH_3CH, $OCH(H_a)CHO$], 3.98–4.04 [m, 2 H, $OCH(H_b)CHO$, OCH_2CHO], 4.96 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 328 K): δ = 16.2, 25.2, 26.3, 28.4, 48.7, 66.7, 78.9, 79.4, 109.5, 155.3 ppm. $C_{12}H_{23}NO_4$ (245.32): calcd. C 58.75, H 9.45, N 5.71; found C 58.21, H 9.54, N 5.76. HRMS (ESI+): calcd. for $C_{12}H_{23}NO_4Na$ $[M + Na]^+$ 268.1519; found 268.1508.

(2*S*,3*S*)-3-*tert*-Butoxycarbonylamino-1,2-butanediol (6)

Method A: A solution of compound **5** (1.2 g, 5 mmol) in dry methanol (125 mL) was treated with *p*-toluenesulfonic acid monohydrate (190 mg, 1 mmol) and stirred for 4 h under reflux conditions. After completion of the reaction, saturated aqueous $NaHCO_3$ (75 mL) was added, the solution was extracted with EtOAc (3 × 50 mL), and the combined organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude product by column chromatography (Et_2O/hexanes, 1:1; then, EtOAc) afforded compound **6** (985 mg, 96%) as a white solid.

Method B: A solution of compound **5** (1.7 g, 6.9 mmol) in MeOH/water (3:1, 28 mL) was treated with TFA (51 μL, 0.69 mmol) and stirred for 24 h at room temperature. Saturated aqueous $NaHCO_3$ was added until the pH was basic, and the solution was concentrated in vacuo. The concentrate was diluted with water (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude product by column chromatography (Et_2O/hexanes, 1:1; then, EtOAc) afforded compound **6** (1.26 g, 89%) as a white solid.

Method C: A solution of compound **5** (1.0 g, 4.1 mmol) in acetonitrile (20 mL) was treated with $BiCl_3$ (64.35 mg, 0.2 mmol) and four drops of water and stirred for 30 min at room temperature. After completion of the reaction, saturated aqueous $NaHCO_3$ (25 mL) was added, and the solution was concentrated in vacuo. The concentrate was diluted with water (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude product by silica gel column chromatography (Et_2O/hexanes, 1:1 → EtOAc) afforded compound **6** (668 mg, 80%) as a white solid. M.p. 77.5–79 °C (ref.[7c] m.p. 74–75 °C; ref.[10] m.p. 73–77 °C). $[\alpha]_D^{25}$ = –4.8 (*c* = 1.00, $CHCl_3$) {ref.[7c] $[\alpha]_D$ = –5.8 (*c* = 1.00, $CHCl_3$); ref.[10] $[\alpha]_D$ = –6.2 (*c* = 0.87, $CHCl_3$)}. IR (KBr): $\tilde{\nu}$ = 3299, 1673 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 328 K): δ = 1.24 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, CH_3CH), 1.44 [s, 9 H, $C(CH_3)_3$], 2.77 (br. s, 2 H, OH, OH), 3.34–3.40 (m, 1 H, OCH_2CHO), 3.59–3.74 (m, 3 H, CH_3CH, OCH_2CHO), 4.60 (br. s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 328 K): δ = 17.1, 28.3, 47.9, 63.0, 75.5, 80.1, 156.7 ppm. $C_9H_{19}NO_4$ (205.25): calcd. C 52.67, H 9.33, N 6.82; found C 52.71, H 9.37, N 6.76. HRMS (ESI+): calcd. for $C_9H_{19}NO_4Na$ $[M + Na]^+$ 228.1206; found 228.1201.

(2*S*,3*S*)-3-*tert*-Butoxycarbonylamino-1-tosyloxy-2-butanol (7): To a solution of compound **6** (644 mg, 3.14 mmol) in dry CH_2Cl_2 (8 mL) at room temperature was added successively nBu_2SnO (23.5 mg, 0.094 mmol), a solution of Et_3N (0.52 mL, 3.77 mmol) in dry CH_2Cl_2 (8 mL), and *p*-toluenesulfonyl chloride (719 mg, 3.77 mmol), and the reaction mixture was stirred for 6 h at room temperature. The reaction mixture was treated with saturated aqueous NaCl (8 mL). The organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude product by column chromatography (Et_2O/hexanes, 1:2 → 3:1) afforded compound **7** (1.08 g, 96%) as a colorless oil pure enough to be used in the following step. IR (neat): $\tilde{\nu}$ = 3392, 1683, 1366, 1177 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 328 K): δ = 1.13 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, CH_3CH), 1.41 [s, 9 H, $C(CH_3)_3$], 2.45 (s, 3 H, 4-$CH_3C_6H_4$), 2.83 (br. s, 1 H, OH), 3.71 (br. s, 1 H, CH_3CH), 3.83 (ddd, $^3J_{H,H}$ = 6.9, 4.2, 4.2 Hz, 1 H, OCH_2CHO), 3.96 [dd, $^2J_{H,H}$ = 10.2 Hz, $^3J_{H,H}$ = 4.2 Hz, 1 H, $OCH(H_a)CHO$], 4.04 [dd, $^2J_{H,H}$ = 10.2 Hz, $^3J_{H,H}$ = 6.9 Hz, 1 H, $OCH(H_b)CHO$], 4.71 (br. s, 1 H, NH), 7.32–7.38 (m, 2 H, Ar), 7.77–7.82 (m, 2 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 328 K): δ = 15.9, 21.7, 28.3, 48.8, 71.3, 72.5, 81.2, 128.1, 130.0, 132.4, 145.2 ppm. HRMS (ESI+): calcd. for $C_{16}H_{25}NO_6SNa$ $[M + Na]^+$ 382.1295; found 382.1300.

(2*S*,3*S*)-*N*-*tert*-Butoxycarbonyl-3,4-epoxy-2-butylamine (8): To a solution of compound **7** (1.07 g, 3.0 mmol) in dry MeOH (16 mL) at 0 °C was added anhydrous K_2CO_3 (494 mg, 3.58 mmol), and the mixture was stirred for 90 min at room temperature. The reaction mixture was treated with saturated aqueous NH_4Cl (5 mL) and water (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude product by column chromatography (Et_2O/hexanes, 1:2) afforded compound **8** (479 mg, 86%) as a brownish solid. M.p. 54.5–56 °C (ref.[17] m.p. 54–55 °C). $[\alpha]_D^{25}$ = –14.8 (*c* = 1.00, $CHCl_3$) {ref.[7c] $[\alpha]_D^{23}$ = –13.8 (*c* = 1.98, $CHCl_3$); ref.[17] $[\alpha]_D^{25}$ = –16.2 (*c* = 1.00, $CHCl_3$)}. IR (KBr): $\tilde{\nu}$ = 3348, 1683 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.11 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, CH_3CH), 1.41 [s, 9 H, $C(CH_3)_3$], 2.64–2.70 [m, 1 H, $CH(H_a)O$], 2.73 [dd, $^2J_{H,H}$ = 4.8 Hz, $^3J_{H,H}$ = 4.8 Hz, 1 H, $CH(H_b)O$], 2.84–2.92 (m, 1 H, CHO), 3.62 (br. s, 1 H, CH_3CH), 4.64 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.3, 28.3, 46.1, 47.2, 54.5, 79.4, 155.1 ppm. $C_9H_{17}NO_3$ (187.24): calcd. C 57.73, H 9.15, N 7.48; found C 58.31, H 9.09, N 7.37. HRMS (ESI+): calcd. for $C_9H_{17}NO_3Na$ $[M + Na]^+$ 210.1101; found 210.1096.

(2*S*,3*R*)-2-*tert*-Butoxycarbonylamino-3-octadecanol (9): To a suspension of CuBr (24.4 mg, 0.17 mmol) in dry THF (4 mL) at 0 °C under an argon atmosphere was added a solution of tetradecylmagnesium bromide, prepared from tetradecyl bromide (2.36 mmol),[15] in dry THF (2 mL). The mixture was stirred for 10 min at 0 °C and a solution of compound **8** (220 mg, 1.18 mmol) in dry THF (4 mL) was added dropwise at 0 °C under an argon atmosphere. The mixture was stirred for 5 h at the same temperature. The reaction mixture was treated with saturated aqueous NH_4Cl (4 mL) and water (4 mL) and extracted with Et_2O (3 × 15 mL). The combined organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude product by column chromatography (Et_2O/hexanes, 1:4 → 1:3 → 1:2 → 1:1) afforded compound **9** (365 mg, 80%) as a white solid. M.p. 84–85.5 °C (ref.[4] m.p. 82.9–84.4 °C). $[\alpha]_D^{25}$ = –4.4 (*c* = 1.00, $CHCl_3$) {ref.[4] $[\alpha]_D^{24}$ = +15.2 (*c* = 1.00, $CHCl_3$)}, IR (KBr): $\tilde{\nu}$ = 3352, 1684 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 328 K): δ = 0.88 [t, $^3J_{H,H}$ = 6.4 Hz, 3 H, $CH_3(CH_2)_{14}$], 1.07 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, CH_3CH), 1.27 [br.

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s, 26 H, $CH_3(CH_2)_{13}CH_2$], 1.35–1.45 [m, 2 H, $CH_3(CH_2)_{13}CH_2$], 1.44 [s, 9 H, $C(CH_3)_3$], 2.09 (br. s, 1 H, OH), 3.55–3.73 (m, 2 H, CH_3CH, CHO), 4.80 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 328 K): δ = 14.0, 14.4, 22.6, 26.0, 28.4, 29.3, 29.6, 29.6, 29.6, 29.7, 31.9, 33.6, 50.7, 74.5, 79.4, 155.8 ppm. $C_{23}H_{47}NO_3$ (385.62): calcd. C 71.64, H 12.28, N 3.63; found C 71.98, H 12.35, N 3.51. HRMS (ESI+): calcd. for $C_{23}H_{47}NO_3Na$ $[M + Na]^+$ 408.3448; found 408.3432.

(2*S*,3*R*)-2-Amino-3-octadecanol Hydrochloride (11): A solution of compound **9** (461 mg, 1.25 mmol) in HCl-saturated EtOAc (3 mL) was stirred for 1 h at room temperature. After completion of the reaction, the solvent was removed in vacuo. Filtration of an ethereal suspension of the residue afforded compound **11** (352 mg, 91%) as a white solid. M.p. 138–139.5 °C. $[\alpha]_D^{25}$ = +3.2 (c = 1.00, CH_3OH), IR (KBr): $\tilde{\nu}$ = 3395, 3300–2000 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ = 0.86 [t, $^3J_{H,H}$ = 6.4 Hz, 3 H, $CH_3(CH_2)_{14}$], 1.17 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, CH_3CH), 1.19–1.54 [br. s, 26 H, $CH_3(CH_2)_{13}CH_2$], 1.36–1.44 [m, 2 H, $CH_3(CH_2)_{13}CH_2$], 1.44–1.54 (br. s, 1 H, OH), 3.23 (qd, $^3J_{H,H}$ = 6.8, 2.8 Hz, 1 H, CH_3CH), 3.62–3.70 (m, 1 H, CHO), 4.60–4.73 (br. s, 3 H, NH_3^+) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 12.1, 14.5, 23.8, 27.0, 30.5, 30.7, 30.7, 30.8, 30.8, 30.8, 30.8, 33.1, 34.1, 52.7, 71.7 ppm. $C_{18}H_{40}ClNO$ (321.97): calcd. C 67.15, H 12.52, N 4.35; found C 67.30, H 12.59, N 4.41. HRMS (ESI+): calcd. for $C_{18}H_{40}NO$ $[M - Cl]^+$ 286.3104; found 286.3091.

(2*S*,3*R*)-2-Amino-3-octadecanol (ES-285): A solution of compound **11** (70 mg, 0.22 mmol) in CH_2Cl_2 (30 mL) was treated with 2 N aqueous NaOH (5 mL), and the organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford ES-285 in nearly quantitative yield as a white solid. M.p. 64.5–66 °C (ref.[3a] m.p. 66–67 °C). $[\alpha]_D^{25}$ = +24.0 (c = 1.00, $CHCl_3$) {ref.[3a] $[\alpha]_D^{26}$ = +24.9 (c = 1.00, $CHCl_3$)}. ^1H NMR (300 MHz, CD_3OD): δ = 0.89 [t, $^3J_{H,H}$ = 6.9 Hz, 3 H, $CH_3(CH_2)_{14}$], 1.03 (d, $^3J_{H,H}$ = 6.6 Hz, 3 H, CH_3CH), 1.20–1.58 [br. s, 31 H, $CH_3(CH_2)_{14}$, OH, NH_2], 2.77 (qd, $^3J_{H,H}$ = 6.6, 4.2 Hz, 1 H, CH_3CH), 3.40 (ddd, $^3J_{H,H}$ = 8.4, 4.2, 4.2 Hz, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 14.5, 17.3, 23.8, 27.4, 30.6, 30.8, 30.9, 30.9, 30.9, 30.9, 30.9, 33.2, 34.0, 52.2, 76.6 ppm. $C_{18}H_{39}NO$ (285.51): calcd. C 75.72, H 13.77, N 4.91; found C 75.77, H 13.69, N 5.02. HRMS (ESI+): calcd. for $C_{18}H_{40}NO$ $[M + H]^+$ 286.3104; found 286.3112.

Crystal Structure Determination of 5: Data for crystal structure analysis were collected at 150 K with a Xcalibur diffractometer by using graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å). The structure was solved by direct methods by using SHELXS 97[18] and refinement was performed by using SHELXL 97[19] by the full-matrix least-squares technique with anisotropic thermal factors for heavy atoms. Hydrogen atoms were calculated at idealized positions, and during refinement they were allowed to ride on their carrying atom with an isotropic thermal factor fixed to 1.2 times the U_{eq} value of the carrier atom (1.5 for the methyl protons). Colorless needles of **5** were obtained by slow evaporation from an ethanol solution. Crystallographic data: crystal size $0.29 \times 0.12 \times 0.06$ mm^3. M = 245.31, crystal system orthorhombic, space group $P2_12_12_1$, unit cell dimensions a = 9.4735(3) Å, b = 16.6944(4) Å, c = 18.0222(6) Å, V = 2850.29(15) $Å^3$, Z = 8, absorption coefficient μ (Mo-K_α) = 0.085 mm^{-1}, 18486 reflections collected 6428 unique [R(int) = 0.0526] which were used in all calculations. Final R indices [$I > 2\sigma(I)$] R_1 = 0.0417, wR_2 = 0.0476, R indices (all data) R_1 = 0.1062, wR_2 = 0.0536. CCDC-747000 (for **5**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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