A Novel Approach To the Synthesis of Chiral Terminal 1,2-Diamines

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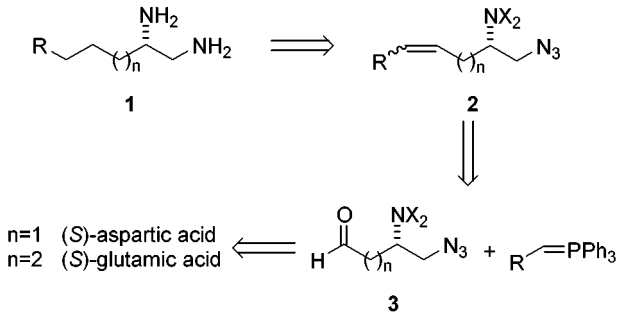
Introduction

Compounds incorporating the 1,2-diamine functionality are of current interest, because they find wide applications in several fields. Many natural products that exhibit interesting biological properties, for example, biotin,[1] emeriamines,[2] and antibacterial peptides,[3] contain the 1,2-diamino moiety. In recent years several synthetic diamines have been employed as medicinal agents, particularly in chemotherapy. Cisplatin[4] and some other 1,2-diaminoplatinum complexes[5] are currently used clinically or are at an advanced stage of testing. Alkyl-substituted amino acid amides and di- and triamines, including 1,2-diamines, have been reported to be potent direct non-peptide activators of heterotrimeric G proteins.[6] We have recently shown that racemic long-chain 1,2-diamines, such as 1,2-hexadecanediamine, exhibit interesting antiinflammatory[7] and cytotoxic activity.[8,9] The importance of 1,2-diamines and of compounds that are easily prepared from 1,2-diamines, such as 1,2-bisimines and 1,2-diamides, in organic synthesis is high; 1,2-diamino compounds are valuable synthetic intermediates for the preparation of heterocycles[10] and for the construction of nitrogen-containing macrocycles finding applications in the field of supramolecular and host−guest chemistry.[11] In addition, enantiomerically pure 1,2-diamines and their derivatives are particularly useful as chiral auxiliaries or ligands, and they have found tremendous applications in stereoselective synthesis.[12] The chemistry of vicinal diamines has been recently reviewed.[13]

Scheme 1. Retrosynthetic Pathway to Key Intermediate Aldehydes 3



There are several methods for the preparation of 1,2-diamines that consist of the introduction of a second amino group into compounds already containing a nitrogen functionality. 2-Amino alcohols easily obtained from natural amino acids[14,15] or ephedrine and pseudoephedrine have been used as starting materials for the synthesis of chiral vicinal diamines.[16−18] Natural α-amino acids with one functional group in the side chain may be modified in several ways, and thus functionalized vicinal diamines and triamines such as 2,3-diaminopropanol,[19,20] 4,5-diaminopentanoic acid,[21] and 1,2,6-triaminohexane[21] have been prepared from serine, glutamic acid, and lysine, respectively. The biological importance of long-chain 1,2-diamines and the synthetic importance of 1,2-diamines bearing a third functional group prompted us to develop a general method for the synthesis of enantiomerically pure 1,2-diamines starting from natural α-amino acids (Glu or Asp). The novel method we present here is based on a Wittig type reaction utilizing chiral aldehydes already containing two nitrogen atoms.

Results and Discussion

The retrosynthetic pathway to 1,2-diamines **1** is outlined in Scheme 1. Our strategy to synthesize 2-amino-protected azides **2** was based on the possibility of building the chain using Wittig type reactions from aldehydes such as **3**, which could be obtained from glutamic or aspartic acid. These amino acids are inexpensive and available in both enantiomeric forms. In addition, this approach permits both convergence in the synthetic

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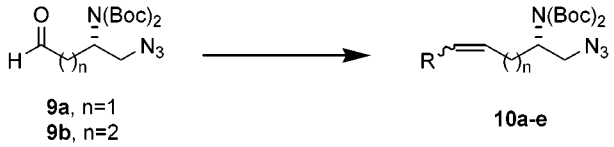
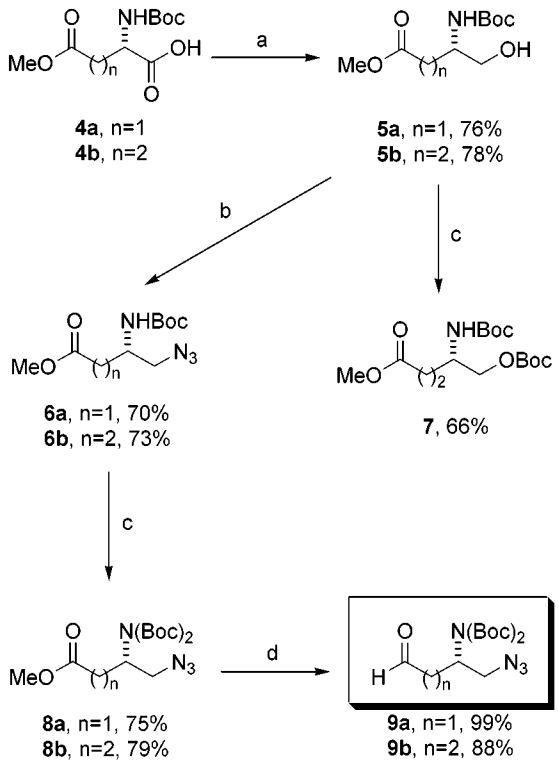
Table 1. Wittig Reaction of Aldehydes 9a,b with Various Ylides



			reaction conditions			product				
entry	**9**	ylide used	solvent	*T* (°C)	time (h)	**10**	*n*	R	*Z*:*E*	yield (%)
1	**b**	$Br^-Ph_3P^+(CH_2)_{10}CH_3$, KHMDS	toluene	−78 to rt	20	**a**	2	$C_{10}H_{21}$	only *Z*	83
2	**b**	$Br^-Ph_3P^+(CH_2)_{14}CH_3$, KHMDS	toluene	−78 to rt	20	**b**	2	$C_{14}H_{29}$	only *Z*	86
3	**b**	$Br^-Ph_3P^+CH_2Ph$, KHMDS	THF	55	6	**c**	2	Ph	1:3	63
4	**a**	$Ph_3P{=}CHCOOEt$	THF	50	1	**d**	1	COOEt	only *E*	74
5	**b**	$Ph_3P{=}CHCOOEt$	THF	50	2	**e**	2	COOEt	only *E*	81

Scheme 2. Synthesis of the Key Intermediate Aldehydes 9a,b[a]



[a] Reagents and conditions: (a) (i) $ClCO_2Et$, *N*-methylmorpholine, THF, −10 °C, (ii) $NaBH_4$, MeOH, 0 °C to rt; (b) (i) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, (ii) NaN_3, DMF, 55 °C; (c) $(Boc)_2O$, DMAP, MeCN, 55 °C; (d) (i) DIBALH, Et_2O, −78 °C, (ii) H_2O.

procedure and stereoselectivity in the formation of the double bond.

Methyl esters of *N*-Boc-protected Glu and Asp (**4a**,**b**) were converted into alcohols **5a**,**b** (Scheme 2) by reduction of their corresponding mixed anhydrides with $NaBH_4$.[14] The hydroxy group of **5a**,**b** was activated by conversion to mesylate and replaced by the azido group. A second Boc group was introduced[22] by treatment of **6a**,**b** with $(Boc)_2O$ in the presence of DMAP. The presence of the second *N*-Boc group in compounds **8a**,**b** minimizes the nucleophilic power of the nitrogen and is critical, since reduction of *N*-monoprotected derivative leads to a mixture of products. Treatment of amino alcohol **5b** with $(Boc)_2O$ in the presence of DMAP produced *N*,*O*-di-Boc-protected amino alcohol **7**, indicating that the second *N*-Boc group must be introduced after conversion of the hydroxy group to the azide group. Reduction of the methyl ester group of compounds **8a**,**b** using DIBALH under controlled conditions produced aldehydes **9a**,**b** in excellent isolated yield.

These chiral aldehydes **9a**,**b** may find wide synthetic applications as key intermediates. In the present work we studied the Wittig olefination of **9a**,**b** using a number of stabilized and nonstabilized ylides (Table 1). The generation of the nonstabilized ylides was performed by treatment of the corresponding triphenylphosphonium bromides with KHMDS in toluene at 0 °C (entries 1 and 2). The Wittig reaction was carried out at −78 °C and produced δ,ϵ-unsaturated azides **10a**,**b** in high yield. Both compounds were identified as *Z*-olefins after ^1H NMR analysis. It is known that the use of KHMDS under such experimental conditions for the generation of nonstabilized ylides leads to high *Z*-selectivity.[23,24] The ylide prepared from benzyl-triphenylphosphonium bromide and KHMDS in THF at room temperature was submitted to Wittig reaction with aldehyde **9b** at 55 °C, affording compound **10c** in 63% yield as a 3:1 *E*:*Z* mixture (entry 3). Treatment of aldehydes **9a**,**b** with ethyl (triphenylphosphoranylidene)acetate in THF at 50 °C gave the *E* derivatives **10d**,**e** in high yield (entries 4 and 5).

The Boc protecting groups of **10** can be removed quantitatively by treatment with HCl in THF. Selective reduction of the azide group of **10a**,**b** was carried out by $NaBH_4$ in the presence of 10% Pd/C. Under these conditions the double bond remained unaffected, while a partial removal of one Boc group was observed. Thus, free unsaturated amines **11a**,**b** can be preferably obtained by treatment with $NaBH_4$−Pd/C and subsequently HCl/THF (Scheme 3). Catalytic hydrogenation of compounds **10c**,**e** in the presence of $(Boc)_2O$ led to the saturated protected 1,2-diamines **12a**,**b**.

To confirm if any racemization had occurred to the (2*S*) chiral center, amino azide **13**, obtained from **10b** by treatment with HCl in THF, was converted into the corresponding MTP amides.[25] Coupling of **13** with (*S*)-(−) -and (*R*)-(+)-α-methoxy-α-trifluoromethyl phenylacetic acid (MTPA) using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) as a condensing agent afforded the amides **14a**,**b** (Scheme 4). The ^1H NMR spectra of the two amides were compared. An enantiomeric excess > 95% was indicated for **13** by the

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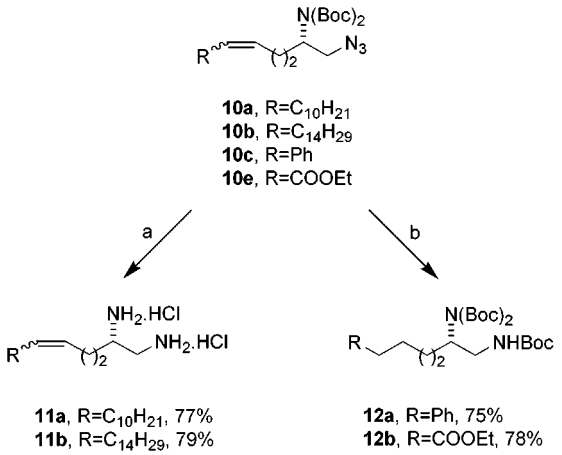
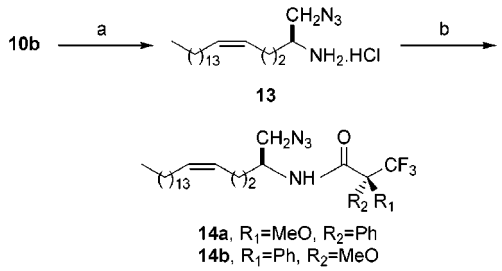
Scheme 3. Synthesis of Chiral 1,2-Diamines[a]



[a] Reagents and conditions: (a) (i) $NaBH_4$, 10% Pd/C, MeOH, THF, rt, (ii) 4 N HCl/THF, rt; (b) H_2, 10% Pd/C, $(Boc)_2O$, MeOH, rt.

Scheme 4. Mosher Amides Prepared for Determination of Enantiopurity[a]



[a] Reagents and conditions: (a) 4 N HCl/THF, rt; (b) (*S*)-(−)- or (*R*)-(+)-MTPA, EDC, Et_3N, CH_2Cl_2, rt.

absence of any diastereomeric proton signal in the spectrum of each MTP amide, since the NH proton and the methoxy protons are well resolved. Furthermore, the ^{19}F NMR spectrum of **14b** showed only one signal, indicating that **13** was a single isomer. Thus, the configuration of the (2*S*) chiral center was not affected throughout the synthesis.

Conclusions

In conclusion, we have developed a novel general method for the synthesis of enantiomerically pure 1,2-diamines using the aldehydes **9a**,**b** as key intermediates. The strengths of the method are in its (1) simplicity and efficiency, (2) flexibility with respect to the substituent groups that can be introduced through the olefination reaction and the chirality of the product, which depends on the chirality of Glu or Asp, and (3) applicability to the development of new 1,2-diamines with desired target structures for biological studies.

Experimental Section

Melting points were determined on a melting point apparatus and are uncorrected. Specific rotations were measured on a polarimeter using a 10 cm cell. NMR spectra were recorded on a 200 or a 300 MHz spectrometer. Where applicable, structural assignments were based on DEPT and COSY experiments. Analytical TLC plates (silica gel 60 F_{254}) and silica gel 60 (70−230 or 230−400 mesh) for column chromatography were purchased from Merck. Visualization of spots was effected with UV light and/or phosphomolybdic acid and/or ninhydrin, both in ethanol stain. THF, toluene, and Et_2O were dried by standard procedures and stored over molecular sieves or Na. *N*-Methylmorpholine was distilled from ninhydrin. All other solvents and chemicals were of reagent grade and used without further purification. The phosphonium salts were prepared[26] by refluxing PPh_3 and the corresponding alkyl halide in MeCN and were used in the Wittig reactions without purification. $EtO_2CCH{=}P(C_6H_5)_3$ was prepared[27] by treatment of the corresponding triphenylphosphonium bromide with NaOH in water at 0 °C for 15 min and was used in the Wittig reactions without purification. The starting compounds **4a**[28] and **4b**[29] were prepared as described in the literature.[30,31]

General Procedure for the Preparation of *N*-Protected Amino Alcohols 5a,b. To a stirred solution of *N*-protected amino acid **4a**,**b** (50.0 mmol) in THF (250 mL) at −10 °C was added *N*-methylmorpholine (5.50 mL, 50.0 mmol) followed by ethyl chloroformate (4.80 mL, 50.0 mmol). After 10 min, $NaBH_4$ (5.67 g, 150 mmol) was added in one portion. MeOH (500 mL) was then added dropwise to the mixture over a period of 20 min at 0 °C. The solution was stirred for an additional 20 min and then neutralized with 1 M $KHSO_4$. The organic solvents were removed, and the product was extracted with EtOAc (3 × 200 mL). The combined organic phases were washed consecutively with 1 M $KHSO_4$, H_2O, 5% aqueous $NaHCO_3$, and H_2O and dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by column chromatography using $CHCl_3$ as eluent.

Methyl (3*S*)-3-[(*tert*-butoxycarbonyl)amino]-4-hydroxybutanoate (5a): yield 76%; colorless oil; $[\alpha]^{23}_D$ +6.3 (*c* 0.5, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.49 (br s, 9H), 2.62 (d, 2H, J = 6.3 Hz), 3.65−3.70 (m, 5H), 3.92−4.07 (m, 1H), 5.29 (d, 1H, J = 7.8 Hz); FAB MS *m*/*z* (%) 256 (M^+ + Na, 13), 234 (M^+ + 1, 29), 178 (100), 160 (11), 134 (94), 116 (8). Anal. Calcd for $C_{10}H_{19}NO_5$ (233.26): C, 51.49; H, 8.21; N, 6.00. Found: C, 51.23; H, 8.32; N, 5.89.

Methyl (4*S*)-4-[(*tert*-butoxycarbonyl)amino]-5-hydroxypentanoate (5b): yield 78%; colorless oil; $[\alpha]^{23}_D$ −12.8 (*c* 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.49 (br s, 9H), 1.72−1.98 (m, 2H), 2.45 (t, 2H, J = 7.5 Hz), 3.53−3.76 (m, 6H), 4.80 (d, 1H, J = 7.8 Hz); FAB MS *m*/*z* (%) 270 (M^+ + Na, 100), 238 (3), 214 (23), 173 (10), 148 (3). Anal. Calcd for $C_{11}H_{21}NO_5$ (247.29): C, 53.43; H, 8.56; N, 5.66. Found: C, 53.51; H, 8.63; N, 5.41.

General Procedure for the Preparation of Azides 6a,b. To a stirred solution of *N*-protected amino alcohol **5a**,**b** (37.0 mmol) in CH_2Cl_2 (60 mL) were added triethylamine (7.77 mL, 55.5 mmol) and methanesulfonyl chloride (4.44 mL, 55.5 mmol) portionwise at 0 °C. The mixture was stirred at 0 °C for 30 min and at room temperature for 30 min. The organic phase was washed consecutively with brine, 1 M $KHSO_4$, brine, 5% aqueous $NaHCO_3$, and brine and dried (Na_2SO_4), and the solvent was removed.

The mesylate was dissolved in DMF (102 mL). Sodium azide (7.22 g, 111 mmol) was added, and the mixture was heated at 60 °C for 6 h. The solvent was removed, and the residue was taken up in EtOAc (3 × 350 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography using a mixture of EtOAc:petroleum ether 1:1 as eluent.

Methyl (3*S*)-4-azido-3-[(*tert*-butoxycarbonyl)amino]butanoate (6a): yield 70%; colorless oil; $[\alpha]^{23}_D$ −19.6 (*c* 0.5, $CHCl_3$);^1H NMR (300 MHz, $CDCl_3$) δ 1.49 (br s, 9H), 2.63 (d, 2H, J = 6.3 Hz), 3.48 (dd, 1H, J = 12.4, 9.0 Hz), 3.58 (dd, 1H, J = 12.4, 5.8 Hz), 3.72 (s, 3H), 4.05−4.20 (m, 1H), 5.12 (br s, 1H); FAB MS *m*/*z* (%) 259 (M^+ + 1, 22), 233 (8), 203 (100), 159 (61).

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Anal. Calcd for $C_{10}H_{18}N_4O_4$ (258.28): C, 46.50; H, 7.02; N, 21.69. Found: C, 46.80; H, 7.11; N, 21.75.

Methyl (4*S*)-5-azido-4-[(*tert*-butoxycarbonyl)amino]pentanoate (6b): yield 73%; light yellow solid; mp 44−46 °C; $[\alpha]^{23}_D$ −25.2 (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.49 (br s, 9H), 1.73−1.95 (m, 2H), 2.38 (t, 2H, *J* = 7.5 Hz), 3.33−3.58 (m, 2H), 3.64−3.85 (m, 4H), 4.66 (d, 1H, *J* = 7.8 Hz); FAB MS *m*/*z* (%) 295 (M^+ + Na, 100), 267 (4), 239 (23), 217 (11), 173 (12). Anal. Calcd for $C_{11}H_{20}N_4O_4$ (272.30): C, 48.52; H, 7.40; N, 20.58. Found: C, 48.75; H, 7.45; N, 20.75.

General Procedure for the Introduction of the Second Boc Group (Compounds 7 and 8a,b). To a solution of compound **5b** or **6a**,**b** (25.0 mmol) in MeCN (42 mL) were added DMAP (610 mg, 5.00 mmol) and Boc_2O (6.00 g, 27.5 mmol), and the mixture was stirred at room temperature for 3 h. Then, DMAP (305 mg, 2.50 mmol) and Boc_2O (3.01 g, 13.8 mmol) were added and the mixture was heated at 55 °C for 7 h and stirred at room temperature overnight. The solvent was removed, and the residue was purified by column chromatography using a mixture of EtOAc:petroleum ether 1:4 as eluent.

Methyl (4*S*)-4-[(*tert*-butoxycarbonyl)amino]-5-[(*tert*-butoxycarbonyl)oxy]pentanoate (7): yield 66%; colorless oil; $[\alpha]^{23}_D$ −20.9 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49 [br s, 9H, $C(CH_3)_3$], 1.52 [br s, 9H, $C(CH_3)_3$], 1.73−1.98 (m, 2H, C*H*$_2$-CH), 2.43 (t, 2H, *J* = 7.5 Hz, CH_2CO), 3.70 (s, 3H, OMe), 3.82−3.95 (m, 1H, CH), 4.02−4.16 (m, 2H, CH_2O), 4.72 (d, 1H, *J* = 7.8 Hz, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.8, 27.6, 28.2, 30.5, 49.1, 51.6, 68.3, 79.4, 82.3, 153.3, 155.3, 173.5.

Methyl (3*S*)-4-azido-3-[bis(*tert*-butoxycarbonyl)amino]-butanoate (8a): yield 75%; light yellow oil; $[\alpha]^{23}_D$ −12.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.49 [br s, 18H, 2 × $C(CH_3)_3$], 2.67 (dd, 1H, *J* = 16.2, 6.6 Hz, CH*H*CH), 2.86 (dd, 1H, *J* = 16.2, 7.8 Hz, C*H*HCH), 3.41 (dd, 1H, *J* = 12.4, 5.8 Hz, CH*H*N_3), 3.66 (s, 3H, OMe), 3.74 (dd, 1H, *J* = 12.4, 9.0 Hz, C*H*HN_3), 4.66−4.84 (m, 1H, CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.9 (CH_3), 35.6 (CH_2), 51.8 (CH_3), 52.4 (CH_2), 53.1 (CH), 82.9 (C), 152.6 (C), 170.9 (C); FAB MS *m*/*z* (%) 381 (M^+ + Na, 10), 359 (M^+ + 1, 5), 303 (37), 247 (87), 203 (40), 159 (100). Anal. Calcd for $C_{15}H_{26}N_4O_6$ (358.40): C, 50.27; H, 7.31; N, 15.63. Found: C, 50.43; H, 7.40; N, 15.80.

Methyl (4*S*)-5-azido-4-[bis(*tert*-butoxycarbonyl)amino]-pentanoate (8b): yield 79%; light yellow oil; $[\alpha]^{23}_D$ −7.1 (*c* 1.1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.49 [br s, 18H, 2 × $C(CH_3)_3$], 1.78−1.98 (m, 1H, CH*H*CH), 2.02−2.22 (m, 1H, C*H*HCH), 2.38 (t, 2H, *J* = 7.5 Hz, CH_2CO), 3.33 (dd, 1H, *J* = 12.4, 5.8 Hz, CH*H*N_3), 3.68 (s, 3H, OMe), 3.79 (dd, 1H, *J* = 12.4, 9.0 Hz, C*H*HN_3), 4.24−4.40 (m, 1H, CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.2 (CH_2), 27.9 (CH_3), 30.6 (CH_2), 51.7 (CH_3), 53.3 (CH_2), 56.2 (CH), 82.8 (C), 153.0 (C), 173.1 (C); FAB MS *m*/*z* (%) 395 (M^+ + Na, 22), 373 (M^+ + 1, 4), 347 (5), 317 (22), 217 (19), 173 (100). Anal. Calcd for $C_{16}H_{28}N_4O_6$ (372.42): C, 51.60; H, 7.58; N, 15.04. Found: C, 51.41; H, 7.66; N, 15.17.

General Procedure for the Preparation of Aldehydes 9a,b. A stirred solution of **8a**,**b** (18.0 mmol) in dry Et_2O (180 mL) was purged with N_2 and cooled to −78 °C, and a 1 M solution of DIBALH (19.8 mL, 19.8 mmol) in hexane was slowly added. The mixture was stirred at −78 °C for 5 min, and then the excess of DIBALH was destroyed with H_2O (3 mL). The temperature was raised to room temperature, and the mixture was stirred for 30 min, dried (Na_2SO_4), and filtered through Celite. The solvent was evaporated, and the residue was purified by column chromatography using a mixture of EtOAc:petroleum ether 3:7 as eluent.

(2*S*)-1-Azido-2-[bis(*tert*-butoxycarbonyl)amino]-4-oxobutane (9a): yield 99%; colorless oil; $[\alpha]^{23}_D$ +7.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.49 (br s, 18H), 2.79 (ddd, 1H, *J* = 17.8, 6.2, 1.0 Hz), 3.01 (ddd, 1H, *J* = 17.8, 7.8, 2.0 Hz), 3.40 (dd, 1H, *J* = 12.4, 5.8 Hz), 3.73 (dd, 1H, *J* = 12.4, 9.0 Hz), 4.77−4.92 (m, 1H), 9.72 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.9 (CH_3), 44.9 (CH_2), 51.0 (CH), 52.4 (CH_2), 83.1 (C), 152.8 (C), 198.8 (CH); FAB MS *m*/*z* (%) 351 (M^+ + Na, 51), 329 (M^+ + 1, 7), 273 (39), 251 (68), 233 (14), 228 (9), 217 (100), 211 (27), 173 (34). Anal. Calcd for $C_{14}H_{24}N_4O_5$ (328.37): C, 51.21; H, 7.37; N, 17.06. Found: C, 51.42; H, 7.33; N, 17.39.

(2*S*)-1-Azido-2-[bis(*tert*-butoxycarbonyl)amino]-5-oxopentane (9b): yield 88%; colorless oil; $[\alpha]^{23}_D$ −3.8 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49 (br s, 18H), 1.87−1.98 (m, 1H), 2.05−2.20 (m, 1H), 2.51−2.60 (m, 2H), 3.38 (dd, 1H, *J* = 12.4, 5.8 Hz), 3.82 (dd, 1H, *J* = 12.4, 9.0 Hz), 4.25−4.37 (m, 1H), 9.80 (s, 1H); FAB MS *m*/*z* (%) 365 (M^+ + Na, 10), 247 (70), 225 (51). Anal. Calcd for $C_{15}H_{26}N_4O_5$ (342.39): C, 52.62; H, 7.65; N, 16.36. Found: C, 52.83; H, 7.68; N, 16.41.

General Procedure for the Wittig Reaction with Nonstabilized Ylides (Compounds 10a,b). To a stirred suspension of the phosphonium salt (3.60 mmol) in dry toluene (20 mL) was added a 0.5 M solution of KHMDS (6.60 mL, 3.30 mmol) in toluene dropwise over a period of 5 min at 0 °C under N_2. The bright red solution was stirred for another 15 min and cooled to −78 °C, and a solution of the aldehyde **9b** (1.03 g, 3.00 mmol) in dry toluene (3 mL) was instantly added. The light yellow mixture was stirred at room temperature for 20 h. Then, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (26 mL) and extracted with Et_2O (3 × 6 mL). The combined organic phases were washed with brine and dried (Na_2SO_4). The solvent was removed, and the residue was purified by column chromatography using a mixture of EtOAc:petroleum ether 1:9 as eluent.

(2*S*,5*Z*)-1-Azido-2-[bis(*tert*-butoxycarbonyl)amino]hexadec-5-ene (10a): yield 83%; colorless oil; $[\alpha]^{23}_D$ −2.4 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3H, *J* = 6.7 Hz), 1.26 (br s, 16H), 1.51 (br s, 18H), 1.52−1.62 (m, 1H), 1.79−1.91 (m, 1H), 1.98−2.15 (m, 4H), 3.29 (dd, 1H, *J* = 12.4, 5.8 Hz), 3.75 (dd, 1H, *J* = 12.4, 9.0 Hz), 4.28−4.37 (m, 1H), 5.28−5.43 (m, 2H); FAB MS *m*/*z* (%) 503 (M^+ + Na, 29), 425 (5), 403 (9), 347 (31), 325 (9), 281 (100). Anal. Calcd for $C_{26}H_{48}N_4O_4 \cdot 0.5H_2O$ (489.70): C, 63.77; H, 10.08; N, 11.44. Found: C, 63.61; H, 10.01; N, 11.44.

(2*S*,5*Z*)-1-Azido-2-[bis(*tert*-butoxycarbonyl)amino]eicos-5-ene (10b): yield 86%; colorless oil; $[\alpha]^{23}_D$ −2.3 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3H, *J* = 6.7 Hz), 1.26 (br s, 24H), 1.51 (br s, 18H), 1.52−1.67 (m, 1H), 1.79−1.93 (m, 1H), 1.99−2.12 (m, 4H), 3.29 (dd, 1H, *J* = 12.4, 5.8 Hz), 3.75 (dd, 1H, *J* = 12.4, 9.0 Hz), 4.27−4.38 (m, 1H), 5.28−5.45 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (CH_3), 22.6 (CH_2), 23.9 (CH_2), 27.2 (CH_2), 28.0 (CH_3), 29.3 (CH_2), 29.5 (CH_2), 30.2 (CH_2), 31.9 (CH_2), 53.5 (CH_2), 56.6 (CH), 82.4 (C), 127.9 (CH), 131.1 (CH), 153.1 (C); FAB MS *m*/*z* (%) 559 (M^+ + Na, 23), 511 (8), 403 (24), 381 (10), 337 (87). Anal. Calcd for $C_{30}H_{56}N_4O_4$ (536.80): C, 67.13; H, 10.51; N, 10.44. Found: C, 67.32; H, 10.60; N, 10.37.

1-{(5*S*)-6-Azido-5-[bis(*tert*-butoxycarbonyl)amino]hex-1-enyl}benzene (10c). The general conditions used to prepare **10a**,**b** were applied to aldehyde **9b**, but the ylide was prepared at room temperature, the solution of the aldehyde was added at 55 °C, and the Wittig reaction was carried out at 55 °C for 6 h. The product was purified by column chromatography using a mixture of EtOAc:petroleum ether 1:4 as eluent, yielding **10c** (63%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.49 [br s, 18H, 2 × $C(CH_3)_3$], 1.57−1.81 (m, 1H, C*H*HCH), 1.91−2.13 (m, 1H, CH*H*CH), 2.18−2.43 (m, 2H, C*H*$_2$CH=CH), 3.24−3.39 (m, 1H, C*H*HN_3), 3.70−3.88 (m, 1H, CH*H*N_3), 4.28−4.46 (m, 1H, CH), 5.64 (dt, 0.25H, *J* = 11.6, 7.0 Hz, CH_2CH=CH, *Z* isomer), 6.20 (dt, 0.75H, *J* = 15.8, 7.0 Hz, CH_2CH=CH, *E* isomer), 6.36−6.51 (m, 1H, C*H*Ph), 7.17−7.40 (m, 5H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.2, 27.8, 27.9, 29.7, 29.8, 30.3, 53.3, 53.5, 56.4, 56.5, 82.5, 82.6, 126.0, 126.6, 127.0, 128.1, 128.4, 128.7, 129.1, 129.7, 130.7, 131.0, 137.5, 153.2; FAB MS *m*/*z* (%) 439 (M^+ + Na, 28), 417 (M^+ + 1, 14), 388 (9), 361 (9), 339 (14), 317 (8), 283 (21), 261 (25), 233 (100), 215 (20). Anal. Calcd for $C_{22}H_{32}N_4O_4$ (416.52): C, 63.44; H, 7.74; N, 13.45. Found: C, 63.72; H, 7.79; N, 13.31.

General Procedure for the Wittig Reaction with Stabilized Ylide (Compounds 10d,e). To a solution of aldehyde **9a**,**b** (3.00 mmol) in THF (30 mL) was added EtO_2CCH=$P(C_6H_5)_3$ (1.57 g, 4.50 mmol), and the solution was heated at 50 °C for 1 or 2 h. Then, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (26 mL) and extracted with Et_2O (3 × 6 mL). The combined organic phases were washed with brine and dried (Na_2SO_4). The solvent was removed, and the residue was purified by column chromatography using a mixture of EtOAc:petroleum ether 3:7 as eluent.

Ethyl (*E*,5*S*)-6-azido-5-[bis(*tert*-butoxycarbonyl)amino]-hex-2-enoate (10d): yield 74%; colorless oil; $[\alpha]^{23}_D$ −35.7 (*c* 2.4, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.28 (t, 3H, *J* = 7.0 Hz, CH_3), 1.49 [br s, 18H, 2 × $C(CH_3)_3$], 2.40−2.55 (m, 1H, C*H*HCH),

2.65−2.83 (m, 1H, CH*H*CH), 3.36 (dd, 1H, J = 12.4, 5.8 Hz, C*H*HN$_3$), 3.77 (dd, 1H, J = 12.4, 9.0 Hz, CH*H*N$_3$), 4.16 (q, 2H, J = 7.0 Hz, CH_2CH$_3$), 4.36−4.53 (m, 1H, CH), 5.85 (dt, 1H, J = 15.8, 1.0 Hz, CH=C*H*CO), 6.75−6.92 (m, 1H, C*H*=CHCO); ^{13}C NMR (50 MHz, CDCl$_3$) δ 14.2 (CH$_3$), 27.9 (CH$_3$), 33.2 (CH$_2$), 52.8 (CH$_2$), 55.5 (CH), 60.2 (CH$_2$), 82.9 (C), 124.3 (CH), 143.6 (CH), 152.8 (C), 165.9 (C); FAB MS m/z (%) 421 (M$^+$ + Na, 8), 399 (M$^+$ + 1, 91), 299 (7), 281 (5), 255 (5), 243 (64), 197 (20). Anal. Calcd for $C_{18}H_{30}N_4O_6$ (398.46): C, 54.26; H, 7.59; N, 14.06. Found: C, 54.58; H, 7.65; N, 13.83.

Ethyl (*E*,6*S*)-7-azido-6-[bis(*tert*-butoxycarbonyl)amino]-hept-2-enoate (10e): yield 81%; colorless oil; $[\alpha]^{23}_D$ +21.2 (*c* 1, CHCl$_3$); ^{1}H NMR (200 MHz, CDCl$_3$) δ 1.28 (t, 3H, J = 7.0 Hz, CH$_3$), 1.49 [br s, 18H, 2 × C(CH$_3$)$_3$], 1.53−1.73 (m, 1H, C*H*HCH), 1.88−2.10 (m, 1H, CH*H*CH), 2.17−2.32 (m, 2H, CH_2CH=CH), 3.30 (dd, 1H, J = 12.4, 5.8 Hz, C*H*HN$_3$), 3.77 (dd, 1H, J = 12.4, 9.0 Hz, CH*H*N$_3$), 4.21 (q, 2H, J = 7.0 Hz, CH_2CH$_3$), 4.23−4.38 (m, 1H, CH), 5.82 (dt, 1H, J = 15.6, 1.6 Hz, CH=C*H*CO), 6.92 (dt, 1H, J = 15.6, 6.8 Hz, C*H*=CHCO); ^{13}C NMR (50 MHz, CDCl$_3$) δ 14.2 (CH$_3$), 27.9 (CH$_3$), 28.4 (CH$_2$), 28.9 (CH$_2$), 53.4 (CH$_2$), 56.4 (CH), 60.2 (CH$_2$), 82.8 (C), 122.0 (CH), 147.4 (CH), 153.0 (C), 166.4 (C); FAB MS m/z (%) 435 (M$^+$ + Na, 12), 413 (M$^+$ + 1, 100), 385 (8), 355 (7), 313 (33), 257 (23), 239 (12), 211 (80), 197 (16). Anal. Calcd for $C_{19}H_{32}N_4O_6$ (412.48): C, 55.33; H, 7.82; N, 13.58. Found: C, 55.22; H, 7.86; N, 13.50.

General Procedure for the Preparation of the Free Diamines 11a,b. To a stirred mixture of the azide **10a**,**b** (2.00 mmol) and 10% Pd/C (80 mg) in THF (10 mL), through which N_2 had been passed for 5 min, were added $NaBH_4$ (227 mg, 6.00 mmol) and MeOH (20 mL) dropwise. After stirring for 20 min, the catalyst was filtered, the solution was neutralized with 1 M $KHSO_4$, and the organic solvents were removed. The aqueous phase was extracted with EtOAc (2 × 30 mL), the combined organic phases were dried (Na_2SO_4), and the solvent was removed.

The *tert*-butoxycarbonyl group was removed by treatment with 4 N HCl in THF (24.0 mL) for 30 min at room temperature. After evaporation, Et_2O was added and the product was filtered and recrystallized from MeOH/Et_2O.

(2*S*,5*Z*)-Hexadec-5-ene-1,2-diamine dihydrochloride (11a): yield 77%; light yellow solid; $[\alpha]^{23}_D$ −13.1 (*c* 0.4, MeOH);^{1}H NMR (200 MHz, CD$_3$OD) δ 0.86 (t, 3H, J = 6.7 Hz), 1.24 (br s, 16H), 1.59−1.72 (m, 2H), 1.96−2.20 (m, 4H), 2.98−3.15 (m, 2H), 3.32−3.45 (m, 1H), 5.22−5.45 (m, 2H); FAB MS m/z (%) 255 (M$^+$ + 1 − 2HCl, 100), 238 (31), 224 (30). Anal. Calcd for $C_{16}Cl_2H_{36}N_2 \cdot H_2O$ (345.39): C, 55.64; H, 11.09; N, 8.11. Found: C, 55.88; H, 11.07; N, 8.23.

(2*S*,5*Z*)-Eicos-5-ene-1,2-diamine dihydrochloride (11b): yield 79%; light yellow solid; $[\alpha]^{23}_D$ −12.0 (*c* 0.5, MeOH); ^{1}H NMR (300 MHz, d_6-DMSO) δ 0.86 (t, 3H, J = 6.7 Hz, CH$_3$), 1.24 [br s, 24H, (CH$_2$)$_{12}$], 1.59−1.72 (m, 2H, CH_2CH), 1.96−2.20 (m, 4H, CH_2CH=CHCH_2), 3.07 (br s, 2H, CH$_2$N), 5.28−5.46 (m, 2H, CH=CH), 8.46 (br s, 6H, 2 × NH$_3$);^{1}H NMR (200 MHz, d_6-DMSO, irradiation at 2.06 ppm) δ 0.86 (t, 3H, J = 6.7 Hz, CH$_3$), 1.24 [br s, 24H, (CH$_2$)$_{12}$], 1.60−1.69 (m, 2H, CH_2CH), 3.08 (d, 2H, J = 6.0 Hz, CH$_2$N), 3.38−3.44 (m, 1H, CH), 5.32 (d, 1H, J = 10.6 Hz, C*H*=CH), 5.41 (d, 1H, J = 10.6 Hz, CH=C*H*); ^{13}C NMR (50 MHz, d_6-DMSO) δ 15.1, 23.2, 23.5, 27.8, 29.8, 30.1, 31.1, 32.4, 50.0, 128.8, 132.2; FAB MS m/z (%) 311 (M$^+$ + 1 − 2HCl, 24), 294 (8), 280 (16). Anal. Calcd for $C_{20}Cl_2H_{44}N_2$ (383.49): C, 62.64; H, 11.56; N, 7.30. Found: C, 62.61; H, 11.60; N, 7.18.

General Procedure for the Preparation of the Protected Diamines 12a,b. To a solution of **10c**,**e** (1.00 mmol) in MeOH (10 mL) were added 10% Pd/C (40 mg) and Boc_2O (284 mg, 1.30 mmol). The reaction mixture was stirred under H_2 for 16 h at room temperature. After filtration through a pad of Celite, the solvent was removed and the product was purified by column chromatography using a mixture of EtOAc:petroleum ether 1:4 as eluent.

1-{(5*S*)-5-[Bis(*tert*-butoxycarbonyl)amino]-6-[(*tert*-butoxycarbonyl)amino]hexyl}benzene (12a): yield 75%; colorless oil; $[\alpha]^{23}_D$ +22.0 (*c* 0.8, CHCl$_3$); ^{1}H NMR (200 MHz, CDCl$_3$) δ 1.31−1.82 [m, 33H, (CH_2)$_3$CH, 3 × C(CH$_3$)$_3$], 2.60 (t, 2H, J = 7.2 Hz, CH_2Ph), 3.25−3.45 (m, 2H, CH$_2$N), 4.17−4.37 (m, 1H, CH), 4.87 (m, 1H, NH), 7.10−7.38 (m, 5H, Ph). Anal. Calcd for $C_{27}H_{44}N_2O_6$ (492.65): C, 65.83; H, 9.00; N, 5.69. Found: C, 65.75; H, 9.06; N, 5.61.

Ethyl (6*S*)-6-[bis(*tert*-butoxycarbonyl)amino]-7-[(*tert*-butoxycarbonyl)amino]heptanoate (12b): yield 78%; colorless oil; $[\alpha]^{23}_D$ +37.6 (*c* 0.5, CHCl$_3$); ^{1}H NMR (200 MHz, CDCl$_3$) δ 1.28 (t, 3H, J = 7.0 Hz, CH$_3$), 1.31−1.82 [m, 33H, (CH_2)$_3$CH, 3 × C(CH$_3$)$_3$], 2.27 (t, 2H, J = 7.5 Hz, CH$_2$CO), 3.28−3.46 (m, 2H, CH$_2$N), 4.14 (q, 2H, J = 7.0 Hz, CH_2CH$_3$), 4.17−4.31 (m, 1H, CH), 4.87 (m, 1H, NH); ^{13}C NMR (50 MHz, CDCl$_3$) δ 14.2 (CH$_3$), 24.7 (CH$_2$), 25.8 (CH$_2$), 27.9 (CH$_3$), 28.3 (CH$_3$), 29.7 (CH$_2$), 34.2 (CH$_2$), 43.3 (CH$_2$), 56.9 (CH), 60.2 (CH$_2$), 82.3 (C), 153.4 (C), 155.7 (C), 173.5 (C). Anal. Calcd for $C_{24}H_{44}N_2O_8$ (488.62): C, 59.00; H, 9.08; N, 5.73. Found: C, 58.79; H, 9.15; N, 5.65.

General Procedure for the Preparation of Mosher Amides of Amino Azide 13 (Compounds 14a,b). To a stirred solution of amino azide **13** (93 mg, 0.25 mmol) in CH_2Cl_2 (2.5 mL) were added Et_3N (0.042 mL, 0.30 mmol), (*R*)-(+)- or (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (70 mg, 0.30 mmol), and EDC (58 mg, 0.30 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and at room temperature overnight. After removal of the solvent and column chromatography using a mixture of EtOAc:petroleum ether 1:9 as eluent, the product isolated (yield 85% for **14a**, 88% for **14b**) was used for NMR analysis.

Characteristic NMR Chemical Shifts (in ppm). (2*S*,5*Z*)-1-Azidoeicos-5-en-2-amine (*S*)-Mosher amide (14a): ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.48 (q, 3H, J = 1.5 Hz), 5.24−5.47 (m, 2H), 6.80 (d, 1H, J = 8.4 Hz).

(2*S*,5*Z*)-1-Azidoeicos-5-en-2-amine (*R*)-Mosher amide (14b): ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.44 (q, 3H, J = 1.5 Hz), 5.30−5.52 (m, 2H), 6.89 (d, 1H, J = 8.4 Hz); ^{19}F NMR (188 MHz, CDCl$_3$, reference with external TFA) δ 8.94 (s).

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