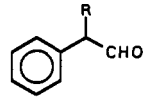
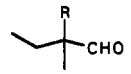


17 R = H

18 R = P(O)(OEt)$_2$



19 R = H

20 R = P(O)(OEt)$_2$

**Diethyl (1-Formyl-1-methyl-1-ethylphenyl)phosphonate (20).** A solution of 2-methyl butyraldehyde (19, 227 mg, 2.5 mmol) in THF (0.6 mL) was added dropwise to a suspension of potassium hydride (110 mg, 2.75 mmol) at rt. After 20 min, the resulting enolate solution was treated with diethyl phosphorochloridite (0.39 mL, 2.75 mmol) at 0 °C. Standard workup, air oxidation, and final purification by radial chromatography (1:1 EtOAc/hexane) gave the desired product 20 (227 mg, 41%): $^1$H NMR, $^{31}$P NMR, EIMS data are identical with previous data.[19]

**Triethyl α-Phosphonoacetate (21). General Procedure for the Prepration of α-Phosphono Esters.** A solution of ethyl acetate (0.49 mL, 5 mmol) in ether (1 mL) was added dropwise via syringe to a stirred solution of LDA (1.1 equiv) in ether (12 mL) at −78 °C. After 1 h, diethyl phosphorochloridite (0.77 mL, 5.25 mmol) was added dropwise to the resulting enolate, and the reaction mixture was allowed to warm to rt over 2 h. The reaction was quenched by slow addition of acetic acid in ether (1 N, 6 mL), and the mixture was filtered through a Florisil pad (60–120 mesh). After removal of solvent, the reaction vessel was opened to the air, and magnetically stirred for 2 h. Purification was effected by column chromatography (1:1 EtOAc/hexane, unless otherwise specified) to afford α-phosphono ester 21[20] (1.044 g, 93%): $^1$H NMR[21] and EIMS[22] data are identical with those previously reported; $^{31}$P NMR +19.8.

**Triethyl α-phosphonopropionate (22):** yield 938 mg (79%); $^1$H NMR,[21] $^{31}$P NMR,[6b] and EIMS[22] data identical with previous data.

**Triethyl α-phosphonobutyrate (23):** yield 851 mg (68%); $^1$H NMR, $^{31}$P NMR,[6b] and EIMS[22] data identical with previous data.

**Triethyl α-phosphono-3-methylbutyrate (24):** yield 833 mg (63%); $^1$H NMR identical with previous data[14]; $^{31}$P NMR 22.1.

**Triethyl α-phosphono-3,3-dimethylbutyrate (25):** yield 639 mg (46%); $^1$H NMR δ 4.23–4.05 (m, 6), 2.91 (d, 1, $J_{HP}$ = 21.7), 1.37–1.27 (m, 9), 1.19 (s, 9); $^{13}$C NMR δ 168.8 (d, $J_{CP}$ = 5.5 Hz), 62.5 (d, $J_{CP}$ = 6.8 Hz), 62.1 (d, $J_{CP}$ = 7.0 Hz), 56.3 (d, $J_{CP}$ = 133.6 Hz), 33.8 (d, $J_{CP}$ = 3.6 Hz), 29.3 (d, $J_{CP}$ = 7.5 Hz, 3), 16.4 (2), 16.3; $^{31}$P NMR δ 22.1; EIMS $m/z$ (rel intensity) 265 ($M^+$ − 15, 7), 224 (100), 197 (74), 179 (53), 152 (54), 123 (43); HRMS calcd for $C_{11}H_{22}O_5P$ 265.1205, found 265.1194.

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**Supplementary Material Available:** $^1$H and $^{13}$C NMR spectra for compounds 11, 15, and 25 (6 pages). Ordering information is given on any current masthead page.

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# The Total Synthesis of Alcaligin

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The first total synthesis of 1,8(*S*),11,18(*S*)-tetrahydroxy-1,6,11,16-tetraazaacycloeicosane-2,5,12,15-tetrone (alcaligin) is presented. The key step involves the coupling of *O*-benzyl-*N*-(*tert*-butoxycarbonyl)hydroxylamine to 2(*S*)-(benzyloxy)-1,4-bis(tosyloxy)butane (2). The resulting monotosylate 3 was then converted to the primary amine 5, which was subjected to a series of selective acylations and N-deprotections to produce the linear ω-amino acid 11. The ω-amino acid was next cyclized to the 20-membered ring, tetrabenzylalcaligin (12). Finally, deprotection of the hydroxamates and alcohols in the last step afforded the chiral natural product, alcaligin (1).

Microorganisms have adapted to the poor solubility of ferric ion in the biosphere by producing a group of low molecular weight iron chelators, siderophores.[1-5] The iron(III) complexes formed with these ligands provide a readily utilizable source of the metal. Although a substantial number of siderophores have been isolated and characterized, they fall largely into two structural classes: the catecholamides and the hydroxamates.[1] Of the latter group, desferrioxamine B,[5] a linear trihydroxamate ligand, has been the most widely studied. It exhibits a high specificity for iron(III), forming a stable hexacoordinate, octahedral iron(III) complex,[6] $K_f = 1 \times 10^{30}$ $M^{-1}$.

The same microorganism that produces desferrioxamine, *Streptomyces pilosus*, also synthesizes a number of other linear as well as macrocyclic hydroxamates, e.g., nocardamine.[4] More recently, two related macrocycles have been isolated: bisucaberin,[7] from *Alteromonas haloplanktis* and alcaligin (1), from *Alcaligenes denitrificans*[8] and *A. xylosoxidans*[9] (Figure 1). Both of these compounds are

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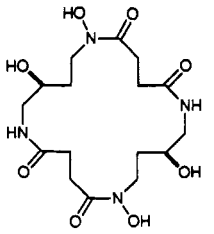


1 Alcaligin

**Figure 1.**

dihydroxamates; the first is a smaller version of nocardamine, while the second is a structurally somewhat more complicated ligand. Interestingly, bisucaberin slows the growth of both L-1210 and IMC carcinoma cells with $IC_{50}$'s of 9.7 and 12.7 $\mu$M, respectively,[7] and sensitizes tumor cells to macrophage-promoted cytolysis. By contrast, this activity is absent in nocardamine, the homologous 33-membered trihydroxamate cyclic siderophore. An investigation of the biological properties of alcaligin and its analogues is particularly attractive because of its structural relationship to both bisucaberin and nocardamine. A flexible synthetic approach to 1 would allow us to access naturally occurring cyclic hydroxamates and analogues.

X-ray crystallography revealed alcaligin to be a 20-membered ring containing two hydroxamate and two secondary amide functional groups, in addition to two alcoholic hydroxyls, both in the *S* configuration.[8] The presence of these rather unusual asymmetric hydroxyls makes this system an interesting synthetic target. The hydroxamate coordination sites in this tetracoordinate ligand are at opposite sides of the ring; the molecule falls into the $C_2$ point group. This chelator forms a 3:2 complex at pH of 6 with ferric ion of unspecified configuration with a stability constant[8] of $10^{37}$ $M^{-1}$.

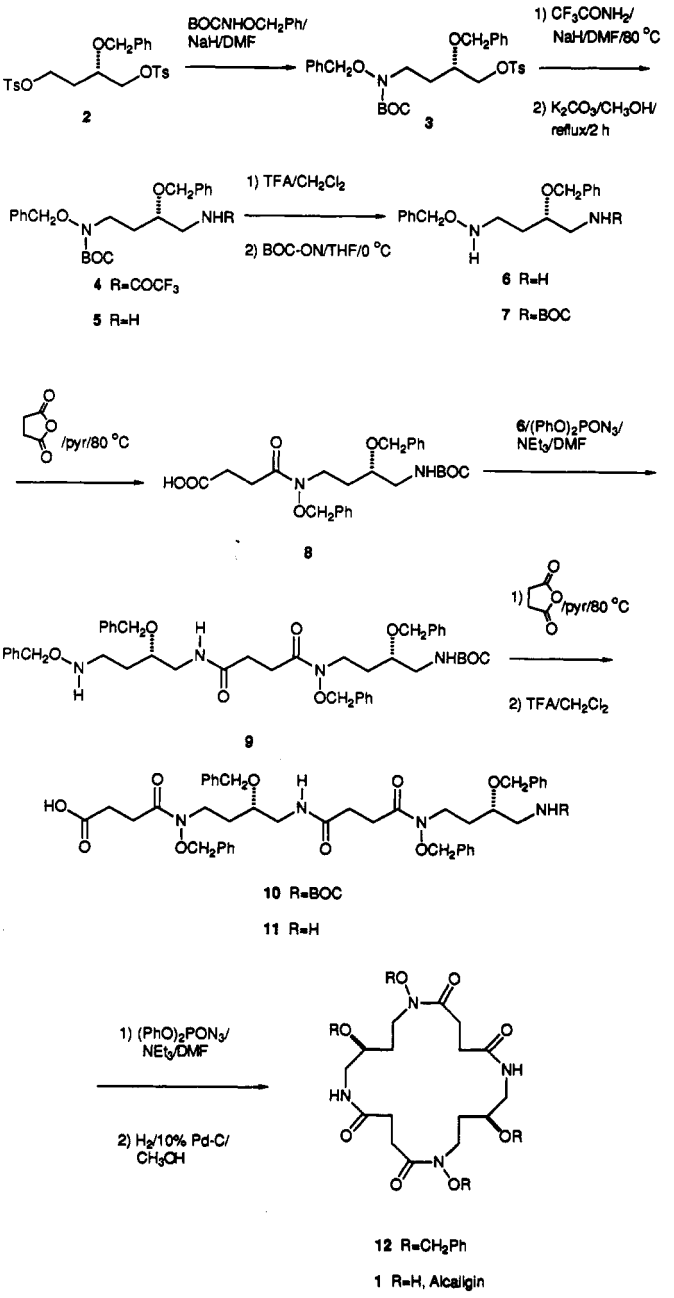
Retrosynthetic analysis of alcaligin (1) reveals that the molecule can be segmented into two repeating units, succinic acid and 1-amino-4-(*N*-hydroxyamino)-2(*S*)-butanol. Thus, it is based on the naturally occurring diamine 2(*S*)-hydroxyputrescine,[10] which has not previously been reported as a subunit in any siderophore.

## Results and Discussion

The methodology developed in this laboratory for the syntheses of bisucaberin, a 22-membered cyclic dihydroxamate,[11] and nocardamine, the corresponding 33-membered cyclic trihydroxamate,[12] has been adapted to the first total synthesis of alcaligin (1; Figure 1), a 20-membered macrocyclic dihydroxamate. An added challenge in the synthesis of this molecule is its 2(*S*)-hydroxyputrescine segment with different acyl groups at each nitrogen. The approach employs a number of highly regioselective reactions not required in our previous macrocycle syntheses (Scheme I).

The starting point in the alcaligin total synthesis was the regiospecific N-alkylation of *N*-(*tert*-butoxycarbonyl)-*O*-benzylhydroxylamine[13] with the known ditosylate 2[14] providing monotosylate 3. Although there are two primary tosylates in 2, the steric bulk of the 2-benzyloxy group guides the course of the reaction leading

**Scheme I**




2 3 4 R=COCF3 5 R=H 6 R=H 7 R=BOC 8 9 10 R=BOC 11 R=H 12 R=CH2Ph 1 R=H, Alcaligin

to selective alkylation at C-4 of the ditosylate. A second amino group was next fixed to C-1 by N-alkylation of trifluoroacetamide in NaH/DMF[15] with 3 producing the diamide 4. The primary amine 5 was generated by basic cleavage of the trifluoroacetamide 4.

In order to verify the stereochemical integrity of amine 5, its diasteromeric Mosher amides were prepared. Compound 5 was reacted separately with (*R*)- and (*S*)-$\alpha$-methoxy-$\alpha$-(trifluoromethyl)phenylacetyl chlorides, derived from the Mosher's acids,[16] and $^1$H NMR's of the resulting (*R*,*S*)-13 and (*S*,*S*)-14 amides were taken. There are unequivocal differences between these two spectra, verifying the existence of only one enantiomer of 5. The $^1$H NMR spectra of the two amides, although generally similar, are clearly unique in the C-2 benzyloxy ether region. Both spectra are characterized by two doublets with the same

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coupling constants but different chemical shifts. These data in conjunction with the fact that the rotation of the original ditosylate 2 was identical with the literature value[14] confirmed the stereochemistry of these reactants. Furthermore as there are not any reactions in the sequence that can compromise the stereochemical integrity of the 2-benzyloxy position, it is clear that these data suffice to ensure that the final product is of the correct configuration.

Brief exposure of this *N*-(*tert*-butoxycarbonyl)amine 5 to trifluoroacetic acid (TFA) in methylene chloride resulted in the bis(benzyloxy)putrescine (6), which was isolated as the free amine after a basic workup. Addition of 2-[[(*tert*-butoxycarbonyl)oxy]imino]-2-phenylacetonitrile (BOC-ON, 1 equiv) in THF to diamine 6 at 0 °C resulted in clean *tert*-butoxycarbonylation at the primary amine, providing 7. Both steric and electronic factors favor this regioselectivity. The benzyloxy amine 7 was then acylated with succinic anhydride (1.6 equiv) in hot pyridine to generate *tert*-butoxycarbonyl acid 8. A second dihydroxyputrescine unit 6 was next coupled to acid 8 using diphenyl phosphorazidate (the Yamada reagent)/triethylamine/DMF.[17] The condensation occurred regioselectively to produce the (benzyloxy)amine 9. This direct coupling avoids the tedious protection scheme of reacting 8 with *tert*-butoxycarbonyl primary amine 5, *tert*-butoxycarbonyl group removal, and selective attachment of a *tert*-butoxycarbonyl to give 9.

The second succinate unit was coupled to (benzyloxy)amine 9 as before to produce *tert*-butoxycarbonyl acid 10, which contains the open-chain framework of alcaligin. Carboxylic acid 10 was stirred with TFA in methylene chloride, liberating the ω-amino acid as its TFA salt 11. All that remained was formation of the 20-membered ring and unmasking of the hydroxamates.

We have previously shown the utility of diphenyl phosphorazidate in the formation of *O,O'*-dibenzylbisucaberine[11] and *O,O',O''*-tribenzylnocardamine,[12] 22- and 33-membered rings respectively, from the appropriate ω-amino acid. The same conditions were employed in this more highly substituted system with success. The azide (1.2 equiv) was added to a cold, 1.9 mM solution of amino acid salt 11 in DMF in the presence of triethylamine and stirred for 4–5 days at 5 °C. Thus, macrocyclic tetrabenzylalcaligin 12 was obtained without high-dilution or slow-addition techniques. Finally, the benzyl groups of 12 were removed under a hydrogen atmosphere (10% Pd–C, $CH_3OH$) to give (*S,S*)-alcaligin (1). The 300-MHz $^1H$ NMR of the product is essentially identical with that of the chiral natural product (spectrum obtained from the supplementary material section from the original paper).[8]

This total synthesis further illustrates the application of the methodology employed in the bisucaberine and nocardamine syntheses to a more complex, chiral molecule. Moreover, analogues of alcaligin can now be generated. For instance, if succinic anhydride were replaced with glutaric anhydride in Scheme I, a bis-homologue of alcaligin of the same ring size as bisucaberin would be available for comparison of their biological properties.

## Experimental Section

All reagents were purchased from Aldrich Chemical Co. and were used without further purification. Sodium sulfate was employed as a drying agent, and Fisher Optima grade solvents were routinely used. Silica gel 60 (70–230 mesh), obtained from EM Science, Darmstadt, West Germany, was used for column chromatography. Preparative layer chromatography was carried out on silica gel GF plates (2-mm thick) purchases from Analtech, Newark, DE. Optical rotations were run in $CHCl_3$ at 546 nm (Hg lamp) at 25 °C unless otherwise stated, with *c* as g of compound per 100 mL. $^1H$ NMR spectra were recorded at 90 or 300 MHz and are run in $CDCl_3$ unless otherwise indicated.

**2(*S*)-(Benzyloxy)-1,4-bis(tosyloxy)butane (2)** was prepared according to the literature[14]: $[\alpha]$ −34.9 (*c* 0.64) (lit.)[14] $[\alpha]$ −34.5 (20 °C) (*c* 3.14); mp 93 °C (lit.)[14] mp 93–93.5 °C.

***O*-Benzyl-*N*-(*tert*-butoxycarbonyl)-*N*-[4-(tosyloxy)-3-(*S*)-(benzyloxy)butyl]hydroxylamine (3).** NaH (80% oil dispersion, 0.605 g, 20.2 mmol) was added to *N*-(*tert*-butoxycarbonyl)-*O*-benzylhydroxylamine[13] (3.7 g, 16.6 mmol) in dry DMF (30 mL) at 0 °C. The suspension was stirred for 15 min at rT and was added by cannula to 2[14] (8.8 g, 17.4 mmol) in DMF (30 mL), which had been cooled to 0 °C. The mixture was stirred (0 °C to rT) for several h under $N_2$. Solvent was removed under vacuum, and the concentrate was quenched with ice–water then extracted with $CHCl_3$ (3×). The combined organic layers were washed with $H_2O$, and then solvent was evaporated in vacuo. Silica gel column chromatography (20% EtOAc/hexane) produced 7.7 g (83%) of 3: $[\alpha]_D$ −16.8 (22 °C) (*c* 1.98); NMR δ 1.48 (s, 9 H), 1.60–1.97 (m, 2 H), 2.37 (s, 3 H), 3.32–3.71 (m, 3 H), 3.97 (d, 2 H, *J* = 5 Hz), 4.38 (d, 1 H, *J* = 11 Hz), 4.51 (d, 1 H, *J* = 12 Hz), 4.73 (s, 2 H), 7.11–7.77 (m, 14 H). Anal. Calcd for $C_{30}H_{37}NO_7S$: C, 64.84; H, 6.71; N, 2.52. Found: C, 65.00; H, 6.75; N, 2.57.

***N*-(Trifluoroacetyl)-*N'*-(*tert*-butoxycarbonyl)-*N',*2(*S*)-bis(benzyloxy)-1,4-butanediamine (4).** NaH (80% oil dispersion, 0.20 g, 6.7 mmol) was added to trifluoroacetamide (0.85 g, 7.5 mmol) in dry DMF[15] (35 mL) at 0 °C, and stirring at rT was continued for 1 h under $N_2$. A solution of 3 (2.04 g, 3.67 mmol) in DMF (10 mL) was added by syringe, and heating at 70–80 °C was carried out for 18 h. After the mixture was cooled, solvent was removed under vacuum and the residue quenched with ice-water then extracted with ether (3×). The combined organic layers were washed with 5% $NaHCO_3$ and $H_2O$, and solvent was evaporated in vacuo. Silica gel chromatography (5% EtOAc/$CHCl_3$) gave 1.12 g (62%) of 4: $[\alpha]$ +14.9 (*c* 2.34); NMR δ 1.50 (s, 9 H), 1.64–1.93 (m, 2 H), 3.25–3.62 (m, 5 H), 4.39 (d, 1 H, *J* = 12 Hz), 4.55 (d, 1 H, *J* = 12 Hz), 4.77 (s, 2 H), 6.75 (br s, 1 H), 7.20–7.40 (m, 10 H). Anal. Calcd for $C_{25}H_{31}F_3N_2O_5$: C, 60.48; H, 6.29; N, 5.64. Found: C, 60.54; H, 6.34; N, 5.64.

***N'*-(*tert*-Butoxycarbonyl)-*N',*2(*S*)-bis(benzyloxy)-1,4-butanediamine (5).** $K_2CO_3$ (3.01 g, 21.8 mmol) was added to a solution of 4 (3.62 g, 7.28 mmol) in $CH_3OH$ (150 mL) and $H_2O$ (8 mL). The mixture was heated at reflux for 90 min, and after the mixture was cooled, solvent was removed by rotary evaporation. $H_2O$ was added to the residue, and the product was extracted with $CHCl_3$ (5×). The combined organic layers were washed with $H_2O$, and solvent was removed by rotary evaporation. Silica gel chromatography (50% $CH_3OH$/EtOAc) generated 2.49 g (85%) of 5: $[\alpha]$ +0.3 (*c* 2.11); NMR δ 1.35 (s, 2 H), 1.48 (s, 9 H), 1.67–1.97 (m, 2 H), 2.61–2.80 (m, 2 H), 3.22–3.60 (m, 3 H), 4.46 (s, 2 H), 4.75 (s, 2 H), 7.18–7.39 (m, 10 H). Anal. Calcd for $C_{23}H_{32}N_2O_4$: C, 68.97; H, 8.05; N, 6.99. Found: C, 68.93; H, 8.02; N, 6.89.

***N',*2(*S*)-Bis(benzyloxy)-1,4-butanediamine (6).** Trifluoroacetic acid (TFA, 40 mL) in $CH_2Cl_2$ (50 mL) was added over 2–3 min to 5 (4.5 g, 11.2 mmol) in $CH_2Cl_2$ (50 mL), which had been cooled to 0 °C. The solution was stirred at room temperature for 15 min (Drierite tube). Excess TFA was removed by rotary evaporation, the residue was basified with ice-cold 0.5 N NaOH, and the product was extracted into $CHCl_3$ (3×). After solvent removal, purification by silica gel chromatography (20% EtOAc/$CHCl_3$ then 20% $CH_3OH$/$CHCl_3$) gave 3.4 g (quantitative) of 6: $[\alpha]$ −7.11 (*c* 1.80); NMR δ 1.73 (q, 2 H, *J* = 7 Hz), 2.38 (br s, 3 H), 2.65–2.80 (m, 2 H), 3.00 (t, 2 H, *J* = 7 Hz), 3.46 (quintet, 1 H, *J* = 7 Hz), 4.48 (s, 2 H), 4.63 (s, 2 H), 7.30 (s, 10 H). Anal. Calcd for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.32. Found: C, 71.77; H, 7.96; N, 9.16.

***N*-(*tert*-Butoxycarbonyl)-*N',*2(*S*)-bis(benzyloxy)-1,4-butanediamine (7).** A solution of 6 (2.16 g, 7.19 mmol) in THF (190 mL) was cooled to 0 °C. BOC-ON (1.77 g, 7.19 mmol) in THF (105 mL) was dripped in over a period of 15 min, and the solution was stirred (0 °C to rT) for 17 h under nitrogen. THF was removed by rotary evaporation, cold 1 N NaOH (50 mL) was added, and the product was extracted into $CHCl_3$ (4×), which was

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washed with $H_2O$. The organic extracts were evaporated in vacuo to generate 3.06 g (quantitative) of **7**: NMR δ 1.45 (s, 9 H), 1.73 (q, 2 H, $J$ = 7 Hz), 2.90–3.32 (m, 4 H), 3.42–3.68 (m, 1 H), 4.47 (s, 2 H), 4.65 (s, 2 H), 4.77 (br s, 1 H), 5.56 (br s, 1 H), 7.30 (s, 10 H). Preparative layer chromatography of product (109 mg), eluting with 2% $CH_3OH/CHCl_3$, gave 104 mg of an analytical sample of **7**: [α] +1.7 (*c* 3.00). Anal. Calcd for $C_{23}H_{32}N_2O_4$: C, 68.97; H, 8.05; N, 6.99. Found: C, 68.87; H, 8.10; N, 6.96.

**10-(*tert*-Butoxycarbonyl)-5,8(*S*)-bis(benzyloxy)-4-oxo-5,10-diazadecanoic Acid (8).** A solution of **7** (2.95 g, 7.37 mmol) and succinic anhydride (1.2 g, 12 mmol) in pyridine (75 mL) was heated at 80 °C for 2 h under argon. After pyridine was removed in vacuo, the residue was combined with ether and then extracted with saturated $NaHCO_3$. The aqueous portion was extracted further with ether (3×), cooled to 0 °C, and cautiously acidified with cold 1 N HCl. Product was extracted into $CHCl_3$, which was washed with $H_2O$. Solvent removal in vacuo and silica gel chromatography eluting with 5% $CH_3OH/CHCl_3$ gave 2.41 g (65%) of **8**: [α] −6.5 (*c* 4.98); NMR δ 1.43 (s, 9 H), 1.70–2.05 (m, 2 H), 2.63 (s, 4 H), 3.11–3.85 (m, 5 H), 4.49 (s, 2 H), 4.80 (s, 2 H), 7.13 (br s, 2 H), 7.23–7.43 (m, 10 H). Anal. Calcd for $C_{27}H_{36}N_2O_7$: C, 64.78; H, 7.25; N, 5.60. Found: C, 64.63; H, 7.30; N, 5.55.

**1-(*tert*-Butoxycarbonyl)-3(*S*),6,13(*S*),16-tetrakis(benzyloxy)-1,6,11,16-tetraazahexadecane-7,10-dione (9).** Amine **6** (0.80 g, 2.66 mmol) and acid **8** (1.21 g, 2.42 mmol) were dissolved in distilled DMF (225 mL), and the solution was cooled to <0 °C (ice/salt) under $N_2$. Triethylamine (0.68 mL, 4.88 mmol) and diphenyl phosphorazidate (0.55 mL, 2.55 mmol) were added by syringe, and the solution was stirred at 0–15 °C for 10 h, then 1–2 days at rT. After removal of the solvent in vacuo, 5% $NaHCO_3$ (100 mL) was added, and the product was extracted with $CHCl_3$ (5×). The organic extracts were washed with $H_2O$ and 5% $NaHCO_3$ and evaporated in vacuo. Silica gel chromatography, eluting with 20% EtOAc/$CHCl_3$ then 5% $CH_3OH/CHCl_3$, gave 1.72 g (91%) of **9**: NMR δ 1.42 (s, 9 H), 1.62–1.96 (m, 4 H), 2.39 (t, 2 H, $J$ = 7 Hz), 2.73 (t, 2 H, $J$ = 7 Hz), 2.99 (t, 2 H, $J$ = 7 Hz), 3.15–3.80 (m, 8 H), 4.45 (s, 4 H), 4.60 (s, 2 H), 4.75 (br s, 1 H), 4.77 (s, 2 H), 6.05 (br s, 2 H), 7.20–7.38 (m, 20 H). Preparative layer chromatography of product (0.20 g), which is somewhat unstable, eluting with 5% $CH_3OH/CHCl_3$ gave 117 mg of an analytical sample of **9**: [α] −1.1 (*c* 5.16). Anal. Calcd for $C_{45}H_{58}N_4O_8$: C, 69.03; H, 7.47; N, 7.16. Found: C, 68.98; H, 7.47; N, 7.18.

**20-(*tert*-Butoxycarbonyl)-5,8(*S*),15,18(*S*)-tetrakis(benzyloxy)-4,11,14-trioxo-5,10,15,20-tetraazaeicosanoic Acid (10).** A solution of **9** (1.73 g, 2.21 mmol) and succinic anhydride (0.360 g, 3.60 mmol) in pyridine (80 mL) was heated at 80 °C for 2 h under nitrogen. After removing the pyridine in vacuo, the residue was acidified with ice-cold 1 N HCl followed by extraction with $CHCl_3$. The organic extracts were washed with $H_2O$ and evaporated in vacuo. Silica gel column chromatography, eluting with 5% $CH_3OH/CHCl_3$, furnished 1.65 g (85%) of **10**: [α] −30.3 (*c* 1.68); NMR δ 1.41 (s, 9 H), 1.64–2.02 (m, 4 H), 2.28–2.81 (m, 8 H), 3.07–3.80 (m, 10 H), 4.44 (s, 2 H), 4.48 (s, 2 H), 4.75 (s, 4 H), 6.45 (br s, 3 H), 7.15–7.38 (m, 20 H). Anal. Calcd for $C_{49}H_{62}N_4O_{11}$: C, 66.65; H, 7.08; N, 6.34. Found: C, 66.75; H, 7.10; N, 6.30.

**19-Amino-5,8(*S*),15,18(*S*)-tetrakis(benzyloxy)-4,11,14-trioxo-5,10,15-triazanonadecanoic Acid (11).** TFA (10 mL) in $CH_2Cl_2$ (20 mL) was added over 8 min to **10** (1.47 g, 1.66 mmol) in $CH_2Cl_2$ (30 mL) at 0 °C, and the solution was stirred at room temperature for 53 min ($N_2$). Solvents were removed by rotary evaporation, and then $CH_2Cl_2$ (2 × 50 mL) and $C_6H_6$ (2 × 50 mL) were added and removed under vacuum to furnish 1.59 g (quantitative) of **11**: NMR δ 1.60–2.03 (m, 4 H), 2.23–3.84 (m, 18 H), 4.45 (s, 4 H), 4.73 (s, 4 H), 6.57 (br s, 2 H), 7.15–7.50 (m, 20 H), 9.30 (br s, 3 H); liquid secondary ion mass spectrum (LSIMS, glycerol) calcd for $C_{44}H_{54}N_4O_9$ (zwitterion) 782, found 783 (M + 1). Anal. Calcd for $C_{46}H_{55}F_3N_4O_{11}$: C, 61.60; H, 6.18; N, 6.25. Found: C, 61.43; H, 6.13; N, 6.21.

**1,8(*S*),11,18(*S*)-Tetrakis(benzyloxy)-1,6,11,16-tetraazacycloeicosane-2,5,12,15-tetrone (12).** Amino acid salt **11** (0.72 g, 0.70 mmol) was dissolved in distilled DMF (375 mL), and triethylamine (0.13 mL, 0.93 mmol) was added by syringe. The pH of the solution was 7.2 by wet pHydrion Vivid 6–8 paper. The solution was cooled to 0 °C under $N_2$, and diphenyl phosphorazidate (0.18 mL, 0.84 mmol) was added by syringe. The solution was stirred at 0–7.5 °C for 4 days 14 h. After removal of solvent in vacuo, $H_2O$ was added, and extraction with $CHCl_3$ (5×) was carried out. The organic extracts were washed with cold 5% $NaHCO_3$, cold 1 N HCl, and $H_2O$ and evaporated. Column chromatography on silica gel eluting with 5% $CH_3OH/CHCl_3$ gave 0.30 g of **12**: 300-MHz NMR δ 1.73–2.13 (m, 4 H), 2.30–2.85 (m, 8 H), 3.23–3.85 (m, 10 H), 4.48 (d, 2 H, $J$ = 12 Hz), 4.57 (d, 2 H, $J$ = 10 Hz), 4.76 (s, 4 H), 6.74 (br s, 2 H), 7.15–7.45 (m, 20 H).

Preparative layer chromatography on impure fractions, eluting with the above solvent, produced an additional 53 mg (66%) of **12**: [α] −36.2 (*c* 2.06). Anal. Calcd for $C_{44}H_{52}N_4O_8$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.17; H, 6.85; N, 7.31.

**1,8(*S*),11,18(*S*)-Tetrahydroxy-1,6,11,16-tetraazacycloeicosane-2,5,12,15-tetrone (Alcaligin, 1).** Glassware was soaked in 3 N HCl, rinsed with distilled water and $CH_3OH$, and oven-dried. Compound **12** (0.14 g, 1.83 mmol) was dissolved in $CH_3OH$ (100 mL), 10% Pd–C (0.12 g) was added, and hydrogenation was carried out at 1 atm for 15 h. Catalyst was filtered, and solvent was removed in vacuo. Purification on Sephadex LH-20 (8.56 g), eluting with $CH_3OH$, provided 57.4 mg (78%) of **1** as an amorphous white solid. TLC was performed according to the literature:[9] 5:1 $CH_2Cl_2/CH_3OH$, $R_f$ = 0.48 (identical to literature[9]); 9:2:1 *i*-PrOH/concentrated $NH_4OH/H_2O$, $R_f$ = 0.35, $R_f$ = 0.30;[9] [α] +40.4 (27 °C) (*c* 0.54, $CH_3OH$). The high-resolution NMR spectrum of synthetic **1** in $CD_3OD$ is essentially identical with the published spectrum[8] of the natural product: LSIMS (glycerol) calcd for $C_{16}H_{28}N_4O_8$, 404, found 405 (M + 1), 389 (M + 1 −16). Anal. Calcd for $C_{16}H_{28}N_4O_8$: C, 47.52; H, 6.98; N, 13.85. Found: C, 47.30; H, 7.00; N, 13.58.

***N*-[(*R*)-α-Methoxy-α-(trifluoromethyl)phenylacetyl]-*N'*-(*tert*-butoxycarbonyl)-*N'*,2(*S*)-bis(benzyloxy)-1,4-butanediamine (13).** A solution of *R*-methoxy-α-(trifluoromethyl)phenylacetyl chloride, derived from (*R*)-Mosher's acid,[16] in $CCl_4$ (0.056 M, 9 mL, 0.50 mmol) was added to **5** (102 mg, 0.25 mmol) and triethylamine (0.2 mL, 1.4 mmol) in $CCl_4$ (6 mL), and stirring was continued for 1 day. After solvent was removed in vacuo, cold 0.5 N HCl (30 mL) was added to the residue, followed by extraction with either (3×). The organic extracts were washed with 5% $NaHCO_3$ and brine and evaporated. The 300-MHz NMR of this material showed a pair of doublets at δ 4.48 ($J$ = 11 Hz) and 4.54 ($J$ = 11 Hz) for the benzyl ether methylene. Preparative layer chromatography (5% EtOAc/$CHCl_3$) gave 108 mg (70%) of **13**: [α] −0.4 (*c* 1.63); 300 MHz NMR δ 1.49 (s, 9 H), 1.68–1.91 (m, 2 H), 3.33 (s, 3 H), 3.47–3.65 (m, 5 H), 4.48 (d, 1 H, $J$ = 11 Hz), 4.54 (d, 1 H, $J$ = 11 Hz), 4.80 (s, 2 H), 7.09 (br s, 1 H), 7.25–7.55 (m, 15 H). Anal. Calcd for $C_{33}H_{39}F_3N_2O_6$: C, 64.27; H, 6.37; N, 4.54. Found: C, 64.18; H, 6.37; N, 4.56.

***N*-[(*S*)-α-Methoxy-α-(trifluoromethyl)phenylacetyl]-*N'*-(*tert*-butoxycarbonyl)-*N'*,2(*S*)-bis(benzyloxy)-1,4-butanediamine (14).** A solution of (*S*)-methoxy-α-(trifluoromethyl)phenylacetyl chloride, derived from (*S*)-Mosher's acid,[16] in $CCl_4$ (0.071 M, 7 mL, 0.50 mmol) was added to **5** (96 mg, 0.24 mmol) and triethylamine (0.2 mL, 1.4 mmol) in $CCl_4$ (6 mL), and stirring was continued for 1 day. Workup by the method of **13** gave crude product. The 300-MHz NMR of this material showed a pair of doublets at δ 4.36 ($J$ = 11 Hz) and 4.48 ($J$ = 11 Hz) for the benzyl ether methylene. Preparative layer chromatography (5% EtOAc/$CHCl_3$) gave 121 mg (82%) of **14**: [α] +12.5 (*c* 1.65); 300-MHz NMR δ 1.49 (s, 9 H), 1.77–1.95 (m, 2 H), 3.36 (s, 3 H), 3.49–3.63 (m, 5 H), 4.36 (d, 1 H, $J$ = 11 Hz), 4.48 (d, 1 H, $J$ = 11), 4.81 (s, 2 H), 7.06 (t, 1 H, $J$ = 5 Hz), 7.18–7.53 (m, 15 H). Anal. Calcd for $C_{33}H_{39}F_3N_2O_6$: C, 64.27; H, 6.37; N, 4.54. Found: C, 64.30; H, 6.36; N, 4.50.

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