3,4,3′,4′-Tetramethoxyazoxybenzene. To a refluxing solution of triphenylphosphine[12] (333 mg, 1.27 mmol) in 2.5 mL of pyrrolidine was added a solution of 26.5 mg of 3,4-dimethoxynitrosobenzene (0.16 mmol) in 2.5 mL of pure ether. After $^1/_2$ h, the solution was evaporated and the residue extracted with ethanol. Evaporation of this solution and separation by TLC on silica gel/dichloromethane gave 2 mg of a yellow compound (mp 172–182 °C) considered from a comparison of its spectra with those of the azo compound to be the corresponding azoxy compound: IR (KBr) 1235, 1255 cm^{-1}; UV nm 210, 236 (sh), 251, 371, 382; MS, *m/e* (%) 318 (8), 302 (39), 137 100).

Another product, orange crystals (mp 100–115 °C; MS, *m/e* (M^+, 238)) is thought to be *N*-(3,4-dimethoxyphenyl)-*N*-hydroxy-*N*′-aminopyrrolidine.

5-Carboxy-4-methoxy-2,3-dihydro-1*H*-azepin-2-one (5, R = H). The ester **5** (R = Me) (16 mg 0.08 mmol) in 10 mL of dry dichloromethane at −80 °C was treated with excess (1 mL) boron trichloride. After 1 h the mixture was left to warm up overnight, and volatiles were evaporated off. Methanol (10 mL) was added and volatiles were removed. This was repeated twice with 5 Ml of methanol each time, finally leaving 16 mg of free acid: mp 154–155 °C dec; IR (KBr) 1245, 1280, 1375, 1445, 1600, 1650, 1675, 2950, 3085, 3195 cm^{-1}; UV (MeOH) nm (log ε) 218 (4.27), 263 (3.83), plus OH^- 210 (4.26) 295 (4.16); ^{1}H NMR δ 3.13 (s, 2 H), 3.8 (s, 3 H), 6.02 (m, 2 H), 8.3 (br, 1 H), 12.28 (s, 1 H); MS, *m/e* (%) 183 (29), 67 (100).

Anal. Calcd for $C_8H_9NO_4$: C, 52.45; H, 4.96; N, 7.65. Found: C, 52.3; H, 4.85; N, 7.65.

Acknowledgment. We thank the National Sciences and Engineering Research Council and Trent University (R. A. Mustill, M.Sc. Thesis 1982) for financial support.

Registry No. **3**, 87587-56-2; **4**, 87587-57-3; **5** (R = Me), 87587-58-4; **5** (R = H), 87587-59-5; methyl 4-amino-2-methoxybenzoate, 27492-84-8; 3-methoxy-4-(methoxycarbonyl)benzenediazonium sulfate, 87587-61-9; 3,4-dimethoxyphenyl azide, 87587-62-0; 3,4-dimethoxyaniline, 6315-89-5; 3,4-dimethoxybenzenediazonium sulfate, 87587-63-1; 3,4,3′,4′-tetramethoxyazobenzene, 31237-07-7; 3,4-dimethoxynitrosobenzene, 87587-64-2; 3,4,3′,4′-tetramethoxyazoxybenzene, 87587-65-3.

(12) (a) Bunyan, P. J.; Cadogan, J. I. G. *J. Chem. Soc.*, **1963**, 42. (b) Cadogan, J. I. G. *Q. Rev. Chem. Soc.* **1968**, *22*, 222. (c) Cadogan, J. I. G.; Cameron-Wood, M.; Mackie, R. K.; Searle, R. J. G. *J. Chem. Soc.* **1965**, 4831.

Chemistry of Naturally Occurring Polyamines. 7.[1] Selective Functionalization of Hydroxyputrescine

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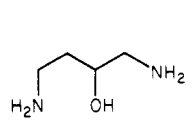
As part of a program to synthesize biologically interesting polyamines and their conjugates, we report studies on the structure and reactivity of hydroxyputrescine–aldehyde adducts which permit regioselective functionalization of this rather rare naturally occurring diamine. When reacted with *p*-nitrobenzaldehyde (2 equiv) in $CHCl_3$, **1** forms predominantly **6b** (as well as **5b** and **7b**) in an equilibrium which is highly solvent dependent. The results of various regioselective acylations of the **5b/6b/7b** mixture are reported. With carbobenzoxy chloride–pyridine in CH_2Cl_2, amine **8b** forms in high yield and serves as a useful synthon for N^1-functionalized hydroxyputrescines. Total syntheses of amide **2**, an abnormal metabolite of rust-infected wheat, and of the unusual amino acid hypusine (**4**) are described by using this methodology.

Hydroxyputrescine (**1**) is an unusual, chiral polyamine that has been isolated from several strains of *Pseudomonas*.[2] Besides the parent dextrorotatory polyamine, higher conjugates of both (*R*)- and (*S*)-**1** have been found in nature. Amides **2** and **3** of hydroxyputrescine are abnormal



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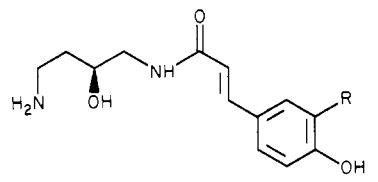
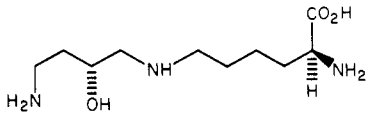


2, R = H
3, R = OCH_3



4

Table I. Solvent Dependence of the Ratio of Bis(imine) 5 and Tetrahydro-1,3-oxazine 6

solvent	5a:6a	5b:6b
pyridine-d_5	4:1	2:1
acetonitrile-d_3		1.5:1
benzene-d_6		1:2
chloroform-*d*	3:1	1:3

metabolites isolated from rust-infected wheat,[3] and the unusual amino acid hypusine (**4**), formally a conjugate between **1** and lysine,[4] has been identified in the hydrolysate of a protein which serves as a translation initiation factor in growing eucaryotic cells.[4e]

As part of a program to synthesize biologically interesting polyamines and their conjugates, we wish to report

(1) For part 6, in this series, see ref 6.
(2) Tobari, J.; Tchen, T. T. *J. Biol. Chem.* **1971**, *246*, 1262.

(3) Stoessl, A.; Rohringer, R.; Samborski, D. J. *Tetrahedron Lett.* **1969**, 2807.
(4) (a) Shiba, T.; Mizote, H.; Kaneho, T.; Nakajima, T.; Kakimoto, Y.; Sano, I. *Biochim. Biophys. Acta* **1971**, *244*, 523. (b) Shiba, T.; Akiyama, H.; Umeda, I.; Okada, S.; Wakamiya, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 899. (c) Park, M. H.; Cooper, H. L.; Fok, J. E. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 2869. (d) Park, M. H.; Cooper, H. L.; Folk, J. E. *J. Biol. Chem.* **1982**, *257*, 7217. (e) Cooper, H. L.; Park, M. H.; Folk, J. E.; Safer, B.; Braverman, R. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 1854.

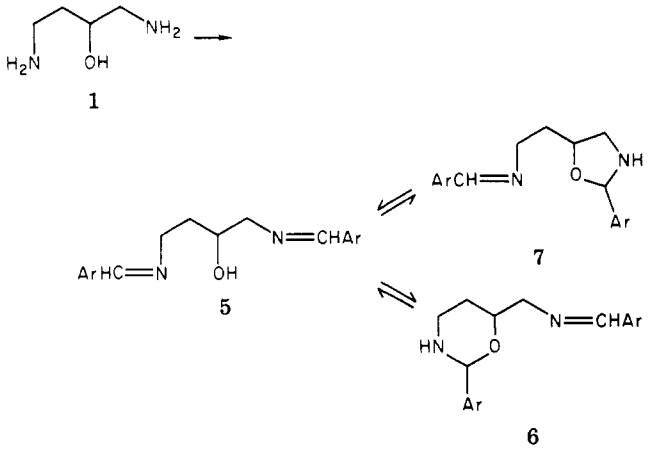
0022-3263/83/1948-5043$01.50/0

Table II. Acylation Reactions of Aldehyde-Protected Hydroxyputrescine

acylating agent	solvent	ratio 8:9 (yield)
PhCOCl	pyridine	1:1 (64%)
PhCOCl/2 equiv pyridine	CH_2Cl_2	5:1 (39%)
$PhCH_2OCOCl$	pyridine	2.5:1 (85%)
$PhCH_2OCOCl$/2 equiv pyridine	CH_2Cl_2	4:1 (86%)
$PhCO_2H$/DCC	CH_2Cl_2	1:6 (40%)

studies on the structure and reactivity of hydroxyputrescine–aldehyde adducts which permit regioselective functionalization of 1.[5,6]

Diamine 1[7] reacted with benzaldehyde (2 equiv) to furnish a mixture of two compounds, which, judging from several ^1H NMR spectral features at 300 MHz, were bis(imine) **5a** and the six-membered ring structure **6a**. These

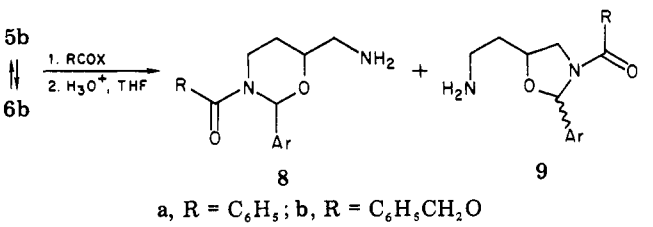


a, Ar = C_6H_5; b, Ar = p-$NO_2C_6H_4$

assignments were also in accord with literature precedent.[8] The ratio of **5a:6a** proved to be slightly solvent dependent, as shown in Table I. Small amounts of the five-membered isomer **7a** were probably present (<10%) although the quantity could not be determined accurately by NMR spectroscopy.

When p-nitrobenzaldehyde (2 equiv) was used in place of benzaldehyde and the ^1H NMR spectrum examined in a given solvent, the equilibrium was shifted more towards the cyclic form **6b**, a result best understood in terms of electronic factors. Data presented in Table I also indicate that the ratio of **5b:6b** varied from 2:1 in pyridine to 1:3 in $CHCl_3$.

The results of various acylations of the **5b/6b/7b** mixture are presented in Table II. To simplify product analysis, the remaining imine group was hydrolyzed in each instance with dilute aqueous HCl. No stable products of O-acylation were detected, however both five- and six-membered structures **8** and **9** were produced, and could be separated by column chromatography. Again, a significant solvent effect was observed which generally tended to favor **8**, especially in CH_2Cl_2. This outcome was unexpectedly and dramatically reversed when benzoylation was performed with dicyclohexylcarbodiimide–benzoic acid. Under these conditions, 1,3-oxazolidine **9a** was re-

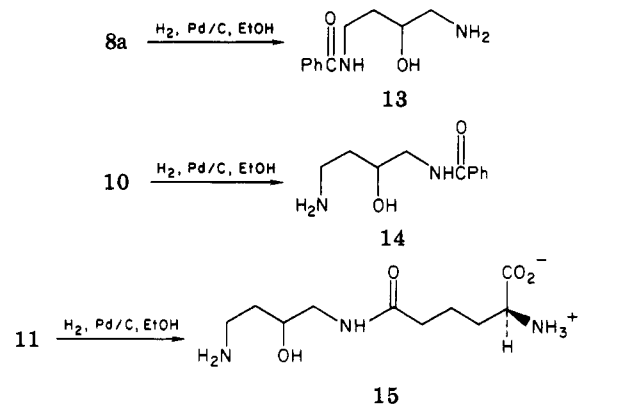


a, R = C_6H_5; b, R = $C_6H_5CH_2O$

producibly formed as the predominant product.

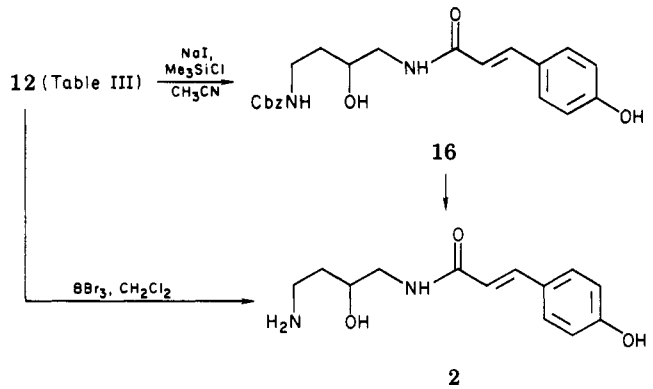
Amine **8b** is a useful synthon for N^1-functionalized hydroxyputrescines. We have now prepared both (*R*)- and (*S*)-**8b** in over 60% yield from the enantiomeric hydroxyputrescines (*R*)- or (*S*)-**1**, which themselves are readily available from the corresponding antipodes of malic acid.[9] Table III presents the results of several acylations of **8b**.

The products shown in Table III were converted to amino alcohols by one of several different methods. Exhaustive hydrogenation of **8a** and **10** led to the isomeric



N-benzoylated hydroxyputrescines **13** and **14**. Under these conditions, **11** was converted to **15**, the 6-oxo analogue of hypusine (**4**).

Treatment of **12** with a mixture of NaI–Me_3SiCl in acetonitrile rapidly removed the p-nitrobenzyl group to give **16**. Cleavage of the Cbz group to afford **2** was slow.[10]



Smooth conversion of **12** to **2** was more easily accomplished using BBr_3 in dichloromethane at low temperature.[11]

For the synthesis of hypusine from **8b**, aldehyde **21** was prepared as outlined below. Borane reduction of acid **17**[12] gave alcohol **18** in high yield. Oxidation of **18** with PCC[13]

(5) Ganem, B. *Acc. Chem. Res.* **1982**, *15*, 290.
(6) Tice, C. M.; Ganem, B. *J. Org. Chem.* **1983**, *48*, 2106.
(7) Racemic **1** was prepared according to the procedure of Macholan, L. *Collect. Czech. Chem. Commun.* **1965**, *30*, 2074.
(8) (a) Srivastav, R.; Weiseman, K.; Clapp, L. B. *J. Heterocyclic Chem.* **1967**, *4*, 114. (b) Paukstelis, J. V.; Hammaker, R. M. *Tetrahedron Lett.* **1968**, 3557. (c) McDonagh, A. F.; Smith, H. E. *J. Org. Chem.* **1968**, *33*, 1. (d) For related studies in a 1,2,4-triol series, see Meyers, A. I.; Lawson, J. P. *Tetrahedron Lett.* **1982**, *23*, 4883.
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(10) (a) Lott, R. R.; Chauhan, V. S.; Stammer, C. H. *J. Chem. Soc., Chem. Commun.* **1979**, 495. (b) Olah, G. A.; Narang, S. C.; Balaram Grupta, B. G.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247.
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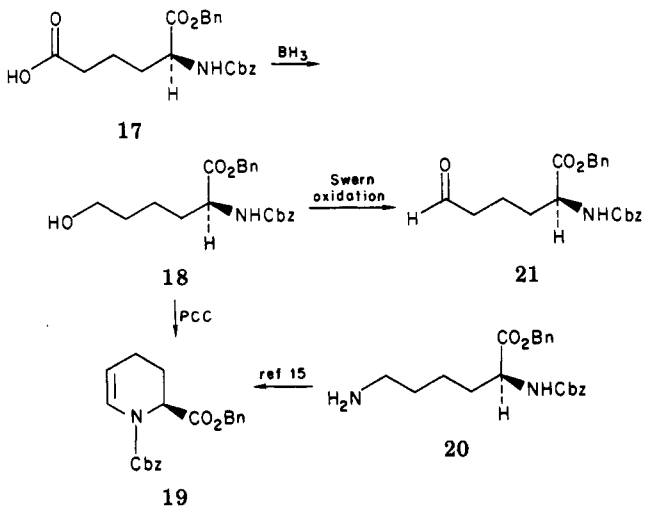
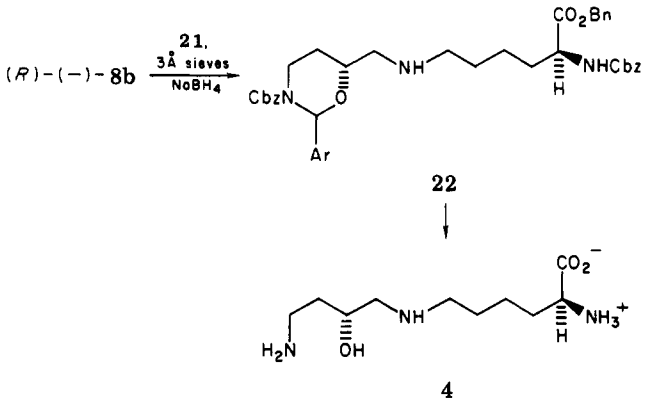


17 18 21 19 20

afforded no aldehyde; instead, cyclic carbamate **19** was obtained in 46% yield. Likewise, application of Rapoport's oxidative deamination procedure to lysine derivative **20**[14] gave no aldehyde and only a poor yield of **19**.[15] Ultimately, the mild conditions of the Swern oxidation afforded **21**.[16]

Reductive amination of **21** with **8b** proceeded poorly. When Borch's conditions were used, **22** was produced in 15% yield.[17] Reduction of a preformed imine with $NaBH_4$



22 4

furnished **22** in 35–45% yield accompanied by ca. 20% of alcohol **18**. Exhaustive hydrogenation of **22** afforded synthetic hypusine (**4**) whose ^1H NMR, IR, and mass spectral data were in good agreement with those published for the natural material[4] and a previously synthesized sample.[4b]

In conclusion, we have described methodology for the selective functionalization of both amine groups in hydroxyputrescine, culminating in the synthesis of two natural products.

Experimental Section

General Section. Dichloromethane, benzene, triethylamine, pyridine, oxalyl chloride, benzoyl chloride, and dimethyl sulfoxide (Me_2SO) were distilled from CaH_2 prior to use. Tetrahydrofuran (THF) was distilled from sodium–benzophenone. All reactions were conducted under a nitrogen or argon atmosphere. IR spectra were determined on a Perkin-Elmer 681 infrared spectrophotometer. ^1H NMR spectra were recorded on a Varian CFT-20 spectrometer at 80 MHz or on a Bruker WM300 spectrometer at 300 MHz and at room temperature unless otherwise stated. Chemical shifts are expressed relative to internal tetramethylsilane ($CDCl_3$), to HOD at 4.60 ppm (D_2O), or to Me_2SO at 2.49 ppm (Me_2SO-d_6). ^{13}C NMR spectra were recorded on a JEOL FX90Q spectrometer at 22.49 MHz relative to $CDCl_3$ at 77.0 ppm or to internal dioxane at 67.4 ppm (D_2O). Mass spectra were obtained on a computerized AEI MS902 instrument. Thin-layer chromatography (TLC) was carried out on Merck precoated silica gel 60F-254 plates. Flash chromatography refers to the technique described by Still et al.[18] Analytical high-pressure liquid chromatography (HPLC) was carried out on Waters 6000A system. Preparative HPLC was performed on a Waters Prep LC/500. Optical rotations were determined on a Perkin-Elmer Model 141 polarimeter.

Synthesis of (*S*)-5b ⇄ (*S*)-6b ⇄ (*S*)-7b. To a solution of (*S*)-(+)-hydroxyputrescine dihydrochloride (**1**) (.793 g, 4.48 mmol) in 18 mL of 0.5 M aqueous sodium hydroxide (9.0 mmol) was added a solution of *p*-nitrobenzaldehyde (1.39 g, 8.9 mmol) in 40 mL of THF. The mixture was stirred overnight, diluted with 50 mL of water, and extracted with two 80-mL portions of dichloromethane. The combined organic layers were washed with 50 mL of brine and dried over $MgSO_4$. Removal of the solvent left 1.64 g (99%) of a pale yellow solid, mp 136–138 °C.

5b: ^1H NMR ($CDCl_3$) 1.8–2.1 (2 H, m), 3.6–4.0 (4 H, m), 4.22 (1 H, m), 7.92 (4 H, d, J = 8.6 Hz), 8.25 (4 H, J = 8.6), 8.43 (2 H, s).

6b: ^1H NMR ($CDCl_3$) 1.62 (1 H, m), 1.74 (1 H, m), 3.18 (1 H, dt, J = 12.3, 3.2 Hz), 3.38 (1 H, dd, J = 13, 4.6 Hz), 3.85 (2 H, d, J = 6.8 Hz), 4.22 (1 H, m), 5.27 (1 H, s), 7.67 (2 H, d, J = 8.8 Hz), 7.92 (2 H, d, J = 8.7 Hz), 8.16 (2 H, d, J = 8.8 Hz), 8.25 (2 H, d, J = 8.7 Hz), 8.43 (1 H, s).

IR ($CHCl_3$) 1650, 1610, 1530, 1350 cm^{-1}; CIMS (isobutane) 371 (100, M + 1), 238 (16.11), 221 (45.78).

The *R* enantiomer and the racemate of **5b**/**6b**/**7b** were prepared in similar yield from the appropriate starting material using the same procedure.

Synthesis of 8a. A stirred solution of **5b**/**6b** (0.298 g, 0.81 mmol) and pyridine (160 μL, 1.20 mmol) in CH_2Cl_2 (20 mL) was cooled to −20 °C, and benzoyl chloride (140 μL, 1.20 mmol) was added. The cooling bath was allowed to expire and the mixture was stirred for 40 h. Removal of the solvent left a viscous orange oil which was dissolved in 30 mL of 2:1 THF:0.2 M aqueous HCl and stirred for 3 h. The mixture was diluted with 80 mL of 0.1 M aqueous HCl, washed with two 30-mL portions of ether, made basic with sodium carbonate, and extracted with two 40-mL portions of CH_2Cl_2. After drying ($MgSO_4$), the solution was concentrated to give 0.142 g of an orange oil consisting of a 5:1 mixture of **8a** and **9a**. Flash chromatography on 10 g of silica gel eluting with 47:2:1 CH_2Cl_2:MeOH:NH_4OH (lower layer used) furnished 0.084 g (31%) of **8a** and 0.024 g (9%) of a mixture of **8a** and **9a**. Amine **8a** exhibited the following spectral characteristics: ^1H NMR (Me_2SO-d_6, 380 K) δ 1.68 (1 H, m), 1.96 (1 H, m), 2.72 (2 H, d, J = 5.2 Hz), 3.46 (1 H, m), 3.71 (1 H, m), 3.83 (1 H, m), 6.39 (1 H, s), 7.44 (5 H, s), 7.76 (2 H, d, J = 8.7 Hz), 8.20 (2 H, d, J = 8.7 Hz); IR (film) 1635, 1540, 1350 cm^{-1}; CIMS (isobutane) 342 (100, M + 1); R_f (17:2:1, CH_2Cl_2:MeOH:NH_4OH) 0.64.

Synthesis of 8b. A solution of **5b**/**6b** (2.04 g, 5.5 mmol) and pyridine (1.4 mL, 17.4 mmol) in CH_2Cl_2 (60 mL) was cooled to 5 °C and benzyl chloroformate (1.5 mL, 10.5 mmol) was added dropwise over 5 min. The cooling bath was allowed to expire and stirring was continued overnight. The bulk of the solvent was removed in vacuo leaving a yellow gum. This material was dissolved in 200 mL of 2:1 THF:0.2 M aqueous HCl and stirred for 20 h. The mixture was diluted with 500 mL of 0.1 M aqueous HCl and washed with two 200-mL portions of ether. The aqueous phase was made basic with solid sodium carbonate and extracted with two 200-mL portions of CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated to give 2.226 g of a 4:1 mixture of **8b** and **9b** as a yellow oil.

Flash chromatography on 100 g of silica gel eluting with 47:2:1 CH_2Cl_2:MeOH:NH_4OH (lower layer used) gave 1.244 g (61%) of pure **8b** and 0.508 g (25%) of mixed fractions containing **8b** and **9b**.

Amine **8b** displayed the following spectral characteristics: ^1H

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(14) Bezas, B.; Zervas, L. *J. Am. Chem. Soc.* **1961**, *83*, 719.
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(16) Mancuso, A. J.; Huang, S-L; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
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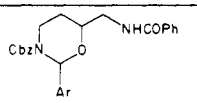
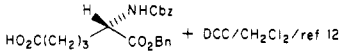
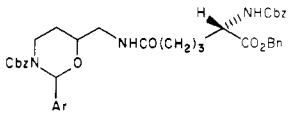
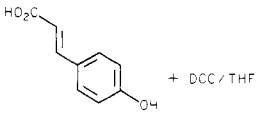
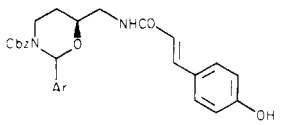
(18) Still, W. C.; Kahn, M. *J. Org. Chem.* **1978**, *43*, 2923.

Table III. Representative Acylations of 8b

8b chirality	acylating agent/solvent	product (yield)
R,S	PhCOCl/pyridine	 10 (70%)
R,S		 11 (82%)
S		 12 (82%)

NMR ($CDCl_3$) δ 1.67 (1 H, m), 2.01 (1 H, m), 2.85 (2 H, d, *J* = 5.9 Hz), 4.44 (1 H, m), 4.76 (1 H, m), 4.94 (1 H, m), 5.09 (2 H, AB quartet, *J* = 12.2 Hz), 6.15 (1 H, s), 7.21 (2 H), 7.32 (3 H), 7.59 (2 H, d, *J* = 9.8 Hz), 8.15 (2 H, d, *J* = 9.8 Hz); ^1H NMR (Me_2SO-d_6, 380 K) δ 1.65 (1 H, m), 1.9 (1 H, m), 2.70 (2 H, d, *J* = 5.5 Hz), 3.48 (1 H, m), 3.74 (1 H, m), 3.82 (1 H, m), 5.04 (2 H, s), 6.1 (1 H, s), 7.22 (2 H), 7.29 (3 H), 7.65 (2 H, d, *J* = 8.7 Hz), 8.13 (2 H, d, *J* = 8.7 Hz); IR (film) 3390, 1705, 1620, 1520, 1350 cm^{-1}; CIMS (isobutane) 372 (100, M + 1); R_f (17:2:1, CH_2Cl_2:MeOH:NH_4OH) 0.47. The *R* isomer of **8b** gave $[\alpha]_D^{23}$ −54° (*c* 1.92, $CHCl_3$). (*S*)-**8b** gave $[\alpha]_D^{23}$ + 65° (*c* 2.6, $CHCl_3$).

Careful chromatography of the mixed fractions allowed separation of **9b** as a 1:1 mixture of diastereomers. The mixture displayed the following spectral characteristics: ^1H NMR (Me_2SO-d_6, 380 K) δ 1.77 (2 H, m), 2.68 (2 H, m), 3.24 ($^1/_2$ H, t, *J* = 9.8 Hz), 3.5 ($^1/_2$ H, dd, *J* = 6.9, 9.7 Hz), 3.76 ($^1/_2$ H, dd, *J* = 6.2, 9.9 Hz), 4.03 ($^1/_2$ H, dd, *J* = 5.3, 10.1 Hz), 4.28 ($^1/_2$ H, m), 4.37 ($^1/_2$ H, m), 5.04 (2 H, m), 6.03 ($^1/_2$ H, s), 6.24 ($^1/_2$ H, s), 7.27 (5 H), 7.65 (2 H, d, *J* = 7.6 Hz), 8.13 (1 H, d, *J* = 7.6 Hz), 8.17 (1 H, d, *J* = 7.6 Hz); IR ($CHCl_3$) 1705, 1535, 1350 cm^{-1}; CIMS (isobutane) 372 (100, M + 1); R_f (17:2:1, CH_2Cl_2:MeOH:NH_4OH) 0.34.

Synthesis of 9a. A solution of benzoic acid (0.184 g, 1.53 mmol) in CH_2Cl_2 (20 mL) was cooled to 5 °C and solid DCC (0.337 g, 1.63 mmol) was added. The mixture was stirred for 3 h at 5–10 °C and for 0.5 h at room temperature. Solid **5b**/**6b** (0.485 g, 1.29 mmol) was added and the mixture was stirred for 40 h. The solvent was removed and the residue taken up in 30 mL of 2:1 THF:0.2 M aqueous HCl. After stirring for 3 h, the mixture was diluted with 0.1 M aqueous HCl (50 mL), washed with two 30-mL portions of ether, made basic with solid Na_2CO_3, and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to afford 0.231 g of an oily solid consisting of a 6:1 mixture of **9a**:**8a**. Flash chromatography on 10 g of silica gel eluting with 47:2:1 CH_2Cl_2:CH_3OH:NH_4OH (lower layer) furnished 0.023 g (6%) of a **9a**:**8a** mixture and 0.151 g (34%) of pure **9a** as a 3:1 mixture of diastereomers.

9a (major diastereomer): ^1H NMR (Me_2SO-d_6, 380 K) υ 1.8 (2 H, m), 2.7 (2 H, m), 3.58 (1 H, t, *J* = 9.9 Hz), 3.89 (1 H, dd, *J* = 5.4, 10 Hz), 4.27 (1 H, m), 6.34 (1 H, s), 7.44 (3 H), 7.55 (2 H), 7.75 (2 H, d, *J* = 7.7 Hz), 8.18 (2 H, d, *J* = 8.7 Hz).

9a (minor diastereomer): ^1H NMR (Me_2SO-d_6, 380 K) 3.46 (1 H, dd, *J* = 6, 10.3 Hz), 3.99 (1 H, dd, *J* = 6.4, 10.1 Hz), 4.42 (1 H, m), 6.53 (1 H, s).

The mixture of isomers gave IR (film) 3370, 1640, 1520, 1410, 1345 cm^{-1}; CIMS (isobutane) 342 (69.9, M + 1), 122 (10.2).

Synthesis of 10. A solution of amine **8b** (0.137 g, 0.37 mmol) in pyridine (2 mL) was cooled to 5 °C and benzoyl chloride (50 μL, 0.43 mmol) was added. After 1 h the cooling bath was removed and stirring was continued overnight. The solvent was removed in vacuo and the residue was taken up in CH_2Cl_2 (30 mL), washed with two 20-mL portions of 3% aqueous HCl and 20 mL of saturated aqueous $NaHCO_3$, and then dried over $MgSO_4$. Removal of the solvent left 0.155 g of a dark oil. Flash chromatography on 3 g of silica gel eluting with 1:1 ethyl acetate:hexanes provided 0.122 g (70%) of **10** as a pale yellow oil: ^1H NMR (Me_2SO-d_6, 380 K) δ 1.73 (1 H, m), 1.97 (1 H, m), 3.48 (2 H, t, *J* = 5.7 Hz), 3.56 (1 H, m), 3.86 (1 H, m), 4.07 (1 H, m), 5.05 (1 H, s), 6.17 (1 H, s), 7.2–8.2 (14 H); IR (film) 3340, 1700, 1650, 1525, 1350 cm^{-1}; CIMS (isobutane) 476 (31.58, M + 1), 325 (100.00), 222 (22.34), 91 (20.24); R_f (ethyl acetate) 0.48.

Synthesis of 11. To a stirred solution of diprotected α-aminoadipic acid (**17**) (0.140 g, 0.36 mmol) in CH_2Cl_2 (5 mL) at 5 °C was added 1-hydroxybenzotriazole (0.041 g, 0.30 mmol) and dicyclohexylcarbodiimide (0.084 g, 0.41 mmol). The mixture was stirred for 1 h at 5 °C and at room temperature for 1 h. A solution of racemic amine **8b** (0.114 g, 0.31 mmol) in CH_2Cl_2 (2 mL) was added. After stirring for 20 h, the mixture was diluted with 10 mL of CH_2Cl_2, washed with 10 mL of 5% aqueous HCl and 10 mL of saturated aqueous $NaHCO_3$, and dried over $MgSO_4$. Removal of the solvent left 0.299 g of an orange oil which was purified by flash chromatography on 15 g of silica gel eluting with 10:10:3 ethyl acetate:hexanes:*N*-methylpyrrolidine to furnish 0.189 g (82%) of **11** as an oil: ^1H NMR (Me_2SO-d_6, 395 K) δ 1.5–2.0 (4 H), 2.15 (2 H, t, *J* = 7.2 Hz), 3.28 (2 H, m), 3.49 (1 H, m), 3.82 (1 H, m), 3.87 (1 H, m), 4.16 (1 H, m), 5.07 (4 H, s), 5.12 (2 H, s), 6.13 (1 H, s), 7.34 (15 H), 7.67 (2 H, d, = 7.6 Hz), 8.13 (2 H, d, *J* = 7.6 Hz); IR ($CHCl_3$) 3440, 1720, 1680, 1525, 1350 cm^{-1}; CIMS (isobutane) no M + 1; HPLC retention time μ-Porasil, ethyl acetate, 0.5 mL min^{-1}) 10.8 min.

Synthesis of 12. To a solution of amine (*S*)-(+)-**8b** (4.11 g, 1.11 mmol) and *p*-coumaric acid (0.192 g, 1.17 mmol) in THF (10 mL) was added solid dicyclohexylcarbodiimide (0.249 g, 1.21 mmol). The mixture was stirred for 22 h at room temperature. The turbid mixture was filtered, concentrated in vacuo, diluted with 80 mL of CH_2Cl_2, washed with 30 mL of 10% aqueous HCl and 30 mL of saturated aqueous $NaHCO_3$, and then dried over $MgSO_4$. Removal of the solvent left 0.606 g of an oily solid. Flash chromatography on 30 g of silica gel eluting with 80% ethyl acetate in hexanes furnished 0.468 g (82%) of amide **12** as a golden foam: ^1H NMR (Me_2SO-d_6, 385 K) δ 1.68 (1 H, m), 1.99 (1 H, m), 3.37 (2 H, m), 3.52 (1 H, m), 3.83 (1 H, m), 3.96 (1 H, m), 5.06 (2 H, s), 6.16 (1 H, s), 6.44 (1 H, d, *J* = 15.8), 6.79 (2 H, d, *J* = 8.4 Hz), 7.1–7.5 (8 H), 7.68 (2 H, d, *J* = 8.6 Hz), 8.12 (2 H, d, *J* = 8.6 Hz); IR ($CHCl_3$) 3600, 3450, 1700, 1665, 1610, 1520, 1350 cm^{-1}; CIMS (isobutane) 518 (75.07, M + 1), 367 (58.14), 91 (100.00); R_f (ethyl acetate) 0.30; $[\alpha]_D^{23}$ + 11° (*c* 1.0, $CHCl_3$).

Synthesis of N^4-Benzoylhydroxyputrescine (13). A solution of **8a** (0.015 g, 0.044 mmol) in 3 mL of ethanol and 0.4 mL of 0.1 M aqueous HCl (40 μmol) was stirred with 10% palladium-on-carbon (0.011 g) under 2 atm of hydrogen for 11 h. The mixture was filtered through Celite and concentrated to leave 0.016 g of an oily solid. Flash chromatography on 3 g of silica gel eluting with 7:2:1 CH_2Cl_2:MeOH:NH_4OH (lower layer used) provided **13** which was immediately converted to its hydrochloride salt as an oil (0.012 g): ^1H NMR (D_2O) δ 1.47 (2 H, m), 2.70 (1 H), 2.95 (1 H, 3.28 (2 H, m), 3.72 (1 H, m), 7.1–7.6 (5 H); ^{13}C NMR (D_2O) δ 34.4, 37.1, 45.4, 66.6, 127.7, 129.6, 132.8; IR (KBr) 1640 cm^{-1}; CIMS (methane) 209 (28.20, M + 1), 191 (19.98), 105 (99.68); R_f (6:3:1, CH_2Cl_2:MeOH:NH_4OH) 0.65.

Synthesis of N^1-Benzoylhydroxyputrescine (14). A solution of **10** (0.060 g, 0.127 mmol) in 3.5 mL of ethanol and 0.25 mL of 1.0 M aqueous HCl was stirred with 10% palladium-on-carbon (0.058 g) under 2 atm of hydrogen for 12 h. The mixture was filtered through Celite and concentrated to leave a yellow oil, which was chromatographed on 3 g of silica gel eluting with 7:2:1 CH_2Cl_2:MeOH:NH_4OH (lower layer used) to furnish **14**. This amine was immediately coverted to its hydrochloride as a white solid (0.026 g): mp 220–5 °C dec; ^1H NMR (D_2O) δ 1.63 (2 H, m), 2.93 (2 H, m), 3.24 (2 H, m), 3.72 (1 H, m), 7.2–7.6 (5 H); ^{13}C NMR (D_2O) δ 32.0, 38.1, 46.2, 69.2, 127.8, 129.6, 132.9; IR (KBr) 3400, 1640 cm^{-1}; CIMS (methane) 209 (85.62, M + 1), 191 (90.19), 162 (87.28), 105 (81.42); R_f (6:3:1, CH_2Cl_2:MeOH:NH_4OH) 0.52.

Synthesis of 15. A solution of **11** (0.060 g, 0.081 mmol) in 1.5 mL of ethanol and 0.5 mL of 1.0 M aqueous HCl was stirred with 10% palladium-on-carbon (0.003 g) under 1.7 atm of hydrogen for 24 h. The mixture was filtered through Celite and concentrated to leave 0.029 g of **15** as a foam: ^1H NMR (D_2O) 1.25–1.75 (6 H), 2.12 (2 H, t, J = 6 Hz), 2.93 (2 H, m), 3.07 (2 H, m), 3.48 (1 H, m), 3.65 (1 H, m); IR (KBr) 3380, 1735, 1640 cm^{-1}; CIMS (methane) 230 (0.6, M + 1 – H_2O), 184 (4.3), 172 (8.5), 144 (100), 88 (49.0).

Synthesis of N^1-*p*-Coumarylhydroxyputrescine (2). Method I. To a stirred solution of amide **12** (0.066 g, 0.128 mmol) and sodium iodide (0.194 g, 1.29 mmol) in acetonitrile (4 mL) at room temperature was added dropwise chlorotrimethylsilane (160 μL, 1.27 mmol) over 1 min. Thin-layer chromatography (ethyl acetate) indicated rapid conversion to a less polar product **16** which was slowly converted to a very polar product.

Intermediate **16** could be isolated from an aqueous workup after 2 h and exhibited the following spectral characteristics: ^1H NMR ($CDCl_3$) δ 1.43 (1 H, m), 1.60 (1 H, m), 2.85 (1 H, m), 3.28 (1 H, m), 3.58 (1 H, m), 3.76 (1 H, m), 4.17 (1 H, m), 5.25 (2 H, s), 6.32 (1 H, d, J = 15.3 Hz), 6.81 (2 H, d, J = 8.5 Hz), 7.30 (7 H), 7.58 (2 H, J = 15.3 Hz); IR ($CHCl_3$) 3600, 3450, 1705, 1670, 1600 cm^{-1}; CIMS (isobutane) 367 (30.09, M + 1 – H_2O), 91 (100); R_f (ethyl acetate) 0.52.

The reaction mixture containing **16** was stirred for 46 h and partitioned between 30 mL of 3% aqueous HCl and two 25-mL portions of ether. The aqueous layer was concentrated to leave 0.189 g of a brown solid which was chromatographed on 10 g of silica gel eluting with 6:3:1 CH_2Cl_2:MeOH:NH_4OH to give 0.134 g of a yellow oil. This material was applied to a $4^1/_2$-in. × $^1/_2$-in. column of Dowex-50(H^+) and the column was eluted with 100 mL of 3:1 ethanol:water to remove neutral material. The column was then eluted with 3:1 ethanol:concentrated NH_4OH to furnish 0.020 g of **2** which was converted to the corresponding hydrochloride (24.1 mg, 66%).

Method II. A solution of amide **12** (0.309 g, 0.60 mmol) in 8 mL of CH_2Cl_2 was cooled to –70 °C and BBr_3 (1.2 mL of 1.0 M solution) in CH_2Cl_2 was added dropwise. The mixture was stirred at –70 °C for 1 h, quenched by addition of 4 mL of methanolic HCl, allowed to warm to room temperature, and concentrated to leave a yellow oil. This material was loaded onto a 7-in. × $^1/_2$-in. column of Dowex-50 (H^+ form). The column was eluted with 125 mL of 3:1 ethanol:water to remove neutral material and then with 3:1 ethanol:concentrated NH_4OH to furnish **2**, which was immediately converted to its hydrochloride salt (0.139 g, 80%): ^1H NMR (D_2O) 1.61 (1 H, m), 1.72 (1 H, m), 2.98 (2 H, m), 3.16 (1 H, dd, J = 6.8, 13.9 Hz), 3.28 (1 H, dd, J = 4.2, 13.9 Hz), 3.73 (1 H, m), 6.33 (1 H, d, J = 15.8 Hz), 6.75 (2 H, d, J = 8.5 Hz), 7.29 (1 H, d, J = 15.8 Hz), 7.37 (2 H, d, J = 8.5 Hz); IR (KBr) 3400, 1650 cm^{-1}; CIMS (methane) 251 (M + 1, 78.12), 233 (56.68), 147 (81.47), 70 (100); R_f (6:3:1, CH_2Cl_2:MeOH:NH_4OH) 0.29; $[\alpha]_D^{23}$ 15.4° (*c* 1.04, 6 M HCl).

Synthesis of 18. To a solution of acid **17** (0.565 g, 1.47 mmol) in THF (4 mL) at 0 °C was added 2.4 mL of a 1.0 M solution of borane in THF (2.40 mmol) dropwise over 3 min. The mixture was stirred at 0–10 °C for 2 h and partitioned between 20 mL of saturated aqueous $NaHCO_3$ and three 30-mL portions of CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated to leave 0.497 g of an oil. Flash chromatography on 30 g of silica gel eluting with 3:2 ethyl acetate:hexanes furnished 0.399 g (74%) of **18** as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.3–2.0 (6 H), 3.56 (2 H, t, J = 6.5 Hz), 4.42 (1 H, m), 5.10 (2 H, s), 5.17 (2 H, q, J = 6.2 Hz), 5.40 (1 H, br d, J = 8.1 Hz), 7.34 (5 H); IR (film) 3340, 1720 cm^{-1}; CIMS (isobutane) 372 (M + 1, 100), 328 (26.3); R_f ethyl acetate) 0.50.

Synthesis of 19. To a well-stirred suspension of PCC (0.013 g, 0.062 mmol) in 150 μL of CH_2Cl_2 was added a solution of alcohol **18** (0.015 g, 0.041 mmol) in 350 μL of CH_2Cl_2. The mixture was stirred for 2.5 h and filtered through a short column of Florisil eluting with ether. The eluant was concentrated to leave 0.015 g of an oil which was purified by flash chromatography with 1:3 ether:hexanes. This afforded 6.6 mg (46%) of **19** as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.9 (3 H, m), 2.35 (1 H, m), 4.8–5.3 (6 H), 6.8 ($^1/_2$ H, d, J = 8.5 Hz), 6.46 ($^1/_2$ H, d, J = 8.5 Hz); 7.33 (10 H); IR ($CHCl_3$) 1745, 1710, 1660 cm^{-1}; CIMS (isobutane) 352 (10.64, M + 1), 308 (100); R_f (1:1, ether:hexane) 0.51.

Synthesis of 21. A solution of oxalyl chloride (70 μL, 0.80 mmol) in 2 mL of CH_2Cl_2 was cooled to –70 °C and a solution of Me_2SO (100 μL, 1.55 mmol) in 1 mL of CH_2Cl_2 was added. The mixture was stirred for 5 min and a solution of alcohol **18** (0.145 g, 0.39 mmol) in 1.5 mL of CH_2Cl_2 was added. The mixture was stirred for 25 min at –70 °C and triethylamine (1.0 mL, 7.0 mmol) was added. After stirring for 20 min, the cooling bath was removed and stirring was continued for 15 min. The mixture was poured into 50 mL of water and extracted with two 40 mL portions of ether. The combined ethereal extracts were dried ($MgSO_4$) and concentrated to afford 0.131 g (91%) of aldehyde **21**. This sensitive compound could not be chromatographed on silica gel and was used immediately: ^1H NMR ($CDCl_3$) δ 1.5–2.1 (4 H), 2.44 (2 H, m), 4.41 (1 H, m), 5.09 (2 H, s), 5.17 (2 H, q, J = 6.2 Hz), 7.34 (10 H), 9.68 (1 H, s).

Synthesis of 22. A solution of aldehyde **21** (0.087 g, 0.24 mmol) and amine (*R*)-(–)-**8b** (0.347 g, 0.94 mmol) in THF (3.5 mL) was stirred for 15 min with powdered 3-Å molecular sieves. The mixture was cooled to 5 °C and solid $NaBH_4$ (0.051 g, 1.34 mmol) was added followed by CH_3OH (4 mL), which had been precooled to 5 °C. After stirring 1 h at 5 °C, the mixture was filtered and the bulk of the solvent removed with the rotary evaporator. The residue was partitioned between saturated aqueous Na_2CO_3 (50 mL) and CH_2Cl_2 (2 × 40 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to afford 0.391 g of an oil. Flash column chromatography on 15 g of silica gel eluting with 47:2:1 CH_2Cl_2:CH_3OH:NH_4OH (lower layer) gave 0.100 g of recovered **8b** and 0.209 g of crude amine **22**. A second flash chromatography on 10 g of silica gel eluting with 19:1 ethyl acetate:triethylamine gave 0.079 g (46%) of the desired product **22**. An additional 0.100 g of **8b** was also recovered. Amine **22** exhibited the following spectral data: ^1H NMR (Me_2SO-d_6, 380 K) δ 1.37 (4 H), 1.69 (3 H), 1.93 (1 H, m), 2.63 (4 H, m), 3.47 (1H, m), 3.84 (2 H, m), 4.11 (1 H, m), 5.03 (4 H, s), 5.11 (2 H, s), 6.09 (1 H, s), 7.31 (15 H), 7.63 (2 H, d, J = 8.6 Hz), 8.11 (2 H, d, J = 8.6 Hz); IR ($CHCl_3$) 3440, 1710, 1520, 1345 cm^{-1}; CIMS (isobutane) 725 (11.25, M + 1), 707 (50.86), 462 (100); R_f (19:1, ethylacetate:triethylamine) 0.24; HPLC retention time (μ-Bondapak NH_2, acetonitrile, 1.0 mL min^{-1}) 9.8 min; $[\alpha]_D^{23}$ + 32.6° (*c* 2.74, $CHCl_3$).

Synthesis of Hypusine (4) Dihydrochloride. To a solution of amine **22** (0.045 g, 0.062 mmol) in 3:3:1 EtOH:THF:H_2O (3.5 mL) was added 1.0 M aqueous HCl (0.12 mL, 0.12 mmol) and 10% palladium-on-carbon (0.035 g). The mixture was stirred under 2.3 atm of hydrogen for 5 h, filtered through Celite, and concentrated to furnish 0.027 g of white solid. When this material was dissolved in 9:1 CH_3OH:H_2O (2 mL) and ether added, a white precipitate appeared which was filtered and dried to afford **4** (8.5 mg): mp 235–238 °C dec; (lit.[4b] mp 234–236 °C; ^1H NMR (D_2O) δ 1.27 (2 H, m), 1.65 (6 H, m), 2.95 (6 H, m), 3.56 (1 H, t, J = 6.1 Hz), 3.86 (1 H, m); IR (KBr) 3400, 3040, 1610 cm^{-1}; R_f (2:2:1, CH_2Cl_2:CH_3OH:NH_4OH) 0.14; $[\alpha]_D^{23}$ +7.2° (*c* 0.25, 6 M HCl) [lit.[4b] $[\alpha]_D^{23}$ +6.8°, +9.9° (*c* 0.12, 6 M HCl)].

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Registry No. (*S*)-**1**·2HCl, 26097-54-1; (*S*)-**2**, 24177-22-8; (*S*)-**2**·HCl, 87829-56-9; (L-(*R*))-**4**·2HCl, 82310-93-8; (*S*)-**5b**,

87829-57-0; **6b**, 87829-58-1; **8a**, 87829-59-2; **8b**, 87829-60-5; *cis*-**9a**, 87829-61-6; *trans*-**9a**, 87829-62-7; *cis*-**9b**, 87829-63-8; *trans*-**9b**, 87829-64-9; **10**, 87829-65-0; **11**, 87829-66-1; **12**, 87829-67-2; **13**, 87829-68-3; **13**·HCl, 87829-69-4; **14**, 87829-70-7; **14**·HCl, 87841-51-8; (L)-**15**, 87829-71-8; **16**, 87829-72-9; (*S*)-**17**, 24325-17-5; (L)-**18**, 84246-49-1; (*S*)-**19**, 87829-73-0; (L)-**21**, 87829-74-1; **22**, 87829-75-2; *p*-nitrobenzaldehyde, 555-16-8; benzoyl chloride, 98-88-4; benzyl chloroformate, 501-53-1; *p*-coumaric acid, 7400-08-0.

Chemistry of Naturally Occurring Polyamines. 8.[1] Total Synthesis of (+)-Hypusine

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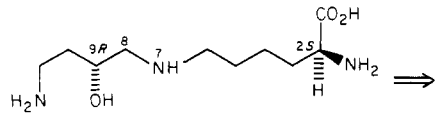
As part of a program to synthesize biologically interesting polyamines and their conjugates, we report a new approach to the synthesis of hypusine (1), an unusual amino acid constituent of the eucaryotic translation initiation factor elF-4D. Hypusine is formally a conjugate between (2*R*)-2-hydroxyputrescine and (2*S*)-lysine, and retrosynthetic analysis suggested that protected lysine **3** might be joined with isoxazolidine (**2**) to form the N7–C8 bond in 1. Chiral isoxazolidines described in this article were prepared by the cycloaddition of chiral nitrones such as **5** with alkenes. Allyl alcohol formed diastereomeric adducts **6** and **7**, which were easily separated by preparative HPLC. Levorotatory **6** could be oxidized to aldehyde **11** and then reductively condensed with lysine derivative **3** to furnish **13**. Exhaustive hydrogenation of the protecting groups in **13** led to (+)-hypusine (1).

The amino acid hypusine (1) ((2*S*,9*R*)-2,11-diamino-9-hydroxy-7-azaundecanoic acid) is a rare and unusual naturally occurring polyamine, first isolated in 1971 by Nakajima et al. from extracts of bovine brain.[2] Ten years later, Folk et al. discovered radiolabeled hypusine in the protein fraction of human peripheral lymphocytes grown in the presence of ^{3}H-labeled putrescine or spermidine.[3] Structure 1 is formally a conjugate between 2-hydroxyputrescine and lysine, and recent evidence suggests that protein-bound hypusine in these lymphocytes indeed arises by the posttranslational modification of lysine residues. Moreover, deoxyhypusine lacking the C9-hydroxyl has been implicated as a key transitory intermediate.[4]

Hypusine in these lymphocytes occurs predominantly in a single low molecular weight protein. Earlier this year, it was suggested that this peptide serves as an important translation initiation factor, designated elF-4D, in all growing eucaryotic cells.[5] The unusual structure of 1, its atypical biosynthesis, and potential biochemical importance all stimulated our interest in the synthesis of this substance. One synthesis of 1 has been published.[6] Another, based on methods we developed for the selective functionalization of hydroxyputrescine, is described in an accompanying article.[1] Here we report yet a third approach using nitrone dipolar cycloadditions, which has culminated in the efficient, chiral synthesis of dextrorotatory hypusine.

Retrosynthetic analysis of 1 suggested that the N7–C8 bond might be formed by reductive amination of an aldehyde having general structure **2** with a suitably protected form of lysine **3**. Isoxazolidines such as **2** could arise by



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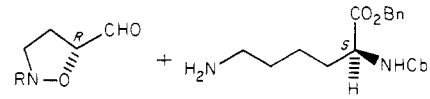
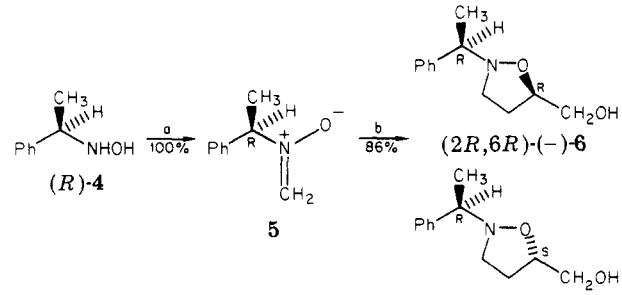


2 3

nitrone cycloadditions with alkenes.[7] We envisioned that a chiral R group on the nitrone might induce asymmetry at C9 (hypusine numbering).[8]

Both enantiomers of *N*-(α-methylbenzyl)hydroxylamine (**4**) were readily prepared.[9] Formaldehyde treatment of



(*R*)-4 5 (2*R*,6*R*)-(−)-6

(2*S*,6*R*)-(+)-7

(*R*)-**4** cleanly produced the optically active nitrone **5**,[10] which with allyl alcohol in refluxing benzene gave a 1:1 mixture of cycloadducts.

Diastereomeric alcohols **6** and **7** were the anticipated regioisomers on the basis of literature precedent.[7] Their

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