129679-98-7; **6d**, 129679-99-8; **6f**, 129680-00-8; **9a**, 129680-01-9; **9b**, 129783-78-4; **9c**, 129680-02-0; **9d**, 129680-03-1; **10a**, 129680-04-2; **10b**, 129783-79-5; (4*R*,5*R*)-2-phenyl-4-(hydroxymethyl)-5-methyl-4,5-dihydrooxazole, 104068-55-5; trifluorothreonine ethyl ester, 102608-32-2; (4*RS*,5*RS*)-2-phenyl-4-(ethoxycarbonyl)-5-(trifluoromethyl)-4,5-dihydrooxazole, 129680-05-3; 2-phenyl-4-(hydroxymethyl)-5-(trifluoromethyl)-4,5-dihydrooxazole, 129680-06-4; allylmagnesium chloride, 2622-05-1.

Lithium/Ammonia Cleavage of the N–N Bond in *N*-(Methoxycarbonyl)- and *N*-Acetylhydrazines

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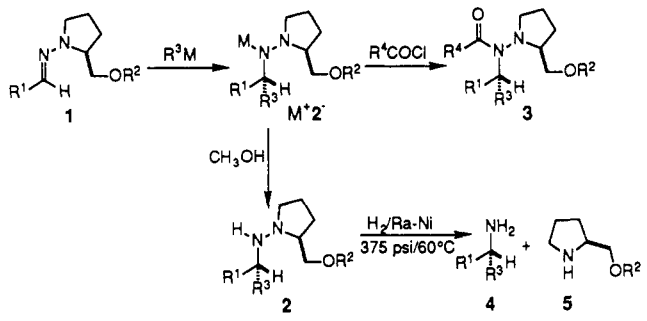
The diastereoselective addition of organocerium reagents to L-proline-derived hydrazones **1** has recently been reported from these laboratories[1] (Scheme I). The reaction is compatible with a wide range of substrates (R^1 = Ph, $PhCH_2$, $PhCH_2CH_2$, (*E*)-$CH_3CH{=}CH$) and accommodates a variety of unstabilized nucleophiles (R^3 = Me, *n*-Bu, *i*-Pr, *t*-Bu, Ph, *i*-$Pr_3SiCH{=}CH$) derived from either lithium or halomagnesium precursors. The additions proceed in good yield (67–81%) and with high diastereoselectivity (>93:7 ds).

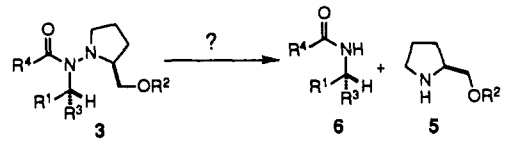
To facilitate isolation, characterization, and isomer analysis, the addition products M^+2^- were trapped as benzyl or methyl carbamates, **3**. However, to secure the scalemic amines **4**, ultimately desired as end products of this transformation, the crude, air-sensitive hydrazines were hydrogenated over W-2 Raney nickel[2] (Scheme I). Although usually successful, this N–N bond cleavage protocol[3] suffers from a number of disadvantages. Primarily, the conditions are rather harsh (375 psi/60 °C) and saturation of aromatic residues can become competitive.[4a] Further, we have found that certain chiral auxiliaries cannot be cleaved, and under still more forcing hydrogenolytic conditions, epimerization of the amine and the auxiliary occurred. Finally, the separation of the amine **4** from the auxiliary **5** requires selective Schiff-base formation and chromatography.[4a]

The development of an improved N–N bond cleavage protocol which addressed these problems focused on the protected hydrazines **3** (Scheme II). These stable derivatives offered several important advantages: (1) handling of sensitive hydrazines is avoided, (2) the products **3** can be further diastereomerically enriched by chromatography, (3) the amines **6** are produced in protected form, (4) the auxiliary **5** can be recovered by aqueous acidic extraction, and finally (5) the acyl group was expected to facilitate reductive cleavage of the hydrazine.[5]

Scheme I



Scheme II



Initial failures to cleave a methyl carbamate[4b] (**3**, R^4 = OCH_3) with H_2/Raney Ni, H_2/Pd–C, Na(Hg), Zn/AcOH, $TiCl_3$, and BH_3·THF are consistent with the resistance of doubly activated hydrazines to these reagents found by Mellor.[6] The preferred method for reductive cleavage of mono-,[7] *N,N'*-di-,[6,8] and tetraacylhydrazines[8a] is sodium in liquid ammonia.[9] In this paper, we report that lithium in ammonia is an equally effective reagent for the cleavage of scalemic, monoacylated hydrazines *with complete preservation of configuration on both sides of the hydrazine.*

Orienting experiments employed racemic *N,N*-dimethylhydrazine **7**. The results of these studies (Table I) may be summarized as follows: (1) 2 equiv (4 g-atom equiv) of the reducing agent was required to consume the substrate (entries 1, 2 and 4, 5), (2) with lithium, reaction times longer than 1 h did not improve the yield significantly (entries 5–7), (3) the isolated benzene ring was not reduced (no added proton source), (4) either THF or Et_2O are suitable cosolvents, and (5) lithium was marginally superior to sodium (entries 3, 6). Finally, an attempt to reduce the corresponding benzyl carbamate resulted only in deprotection without N–N bond cleavage.

With a workable method in hand, the optically active, acylated hydrazines **9** and **10** were next examined (Table II). In the SAMEMP[1b] series **9**, the reductions of both methyl carbamates (**9xa**) and an acetamide (**9cb**) proceeded smoothly to give the corresponding protected amines in good yield. The low recoveries of **12** and **13** in the table reflect the water solubility (**12**) and volatility (**13**) of the pyrrolidines. The auxiliary **12** was recovered by derivatization as a 1-naphthamide **15**. This derivative was directly analyzed by chiral HPLC[10a] and was enantio-

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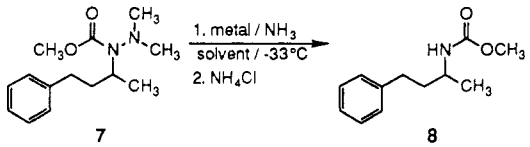
0022-3263/90/1955-6219$02.50/0

Table I. Metal/Ammonia Reduction of 7[a]

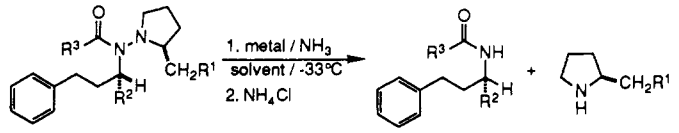


7 8

entry	metal	(equiv)[b]	cosolvent	time, h	yield (8), %	recovery (7), %
1	Na	(1.0)	Et_2O	1	47	25
2	Na	(2.0)	Et_2O	2	72	0.2
3	Na	(2.0)	THF	4	72	0
4	Li	(1.2)	THF	2	62	18
5	Li	(2.1)	THF	1	82	0
6	Li	(2.0)	THF	2	84	0
7	Li	(2.1)	THF	4	81	0

[a] All reactions carried out at −33 °C. [b] 1 equiv = 2 g-atom equiv.

Table II. Lithium/Ammonia Reduction of 9 and 10

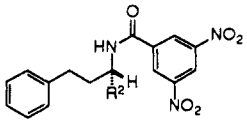


9/10 11 12/13

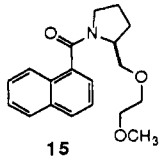
					11		12/13	
educt[a]	de, %	R^1	R^2	R^3	yield, %	ee, %[b]	yield, %	ee, %
9aa	92	$OCH_2CH_2OCH_3$	CH_3	CH_3O	84	92 *R*	52[c]	>99.9 *S*
9ba	90	$OCH_2CH_2OCH_3$	n-C_4H_9	CH_3O	81	88 *R*	28[c]	>99.9 *S*
9cb	>99	$OCH_2CH_2OCH_3$	t-C_4H_9	CH_3	71	>99 *S*[d]	50[c]	>99.9 *S*
9da	92	$OCH_2CH_2OCH_3$	C_6H_5	CH_3O	0[e]			
10bb	*f*	$CH(CH_3)_2$	n-C_4H_9	CH_3	83	76 *R*	31[g]	81 *S*

[a] Nxy, N = R^1; x = R^2; y = R^3. [b] Analysis of the 3,5-DNB after hydrolysis. [c] Isolated and analyzed as 1-naphthamide, **15**. [d] C-I-P priority change. [e] 1,3-Diphenylpropane isolated in 89% yield. [f] De unknown, ee of precursor hydrazone, 81%. [g] Isolated and analyzed as the 3,5-DNB, **16**.

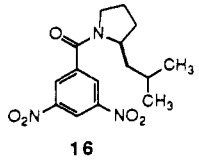
merically pure to the limits of detection. The enantiomeric composition of **11** was determined by deprotection to the parent amines by Me_3SiI[11] (yields: **11aa**, 82%; **11ba**, 76%) or $Me_3O^+BF_4^-$/6 N HCl[12] (yield: **11cb**, 61%) followed by chiral HPLC of the 3,5-dinitrobenzamide (3,5-DNB) derivatives **14a–c**.[10b,c] The enantiomeric purity of the amines (**11**) corresponded to the theoretical maximum of ee **12a** × de **9** with no more than 2% racemization. Although aromatic rings are not reduced, the benzylic hydrazine **9da** suffers hydrogenolysis of the C–N bond producing 1,3-diphenylpropane (89%) and the SAMEMP hydrazine.



14



15



16

The butylated acetylhydrazine **10bb** illustrates another important advantage of this method. Remarkably, the free NH hydrazine precursor resisted hydrogenolytic cleavage up to 2200 psi. Further, we were unable to determine the diastereomeric excess of derivatives by LC, GC, or NMR analysis. Thus, reduction of **10bb** (derived from hydrazone of 81% ee) with lithium in ammonia afforded **11bb** in 83% yield. Recovery and analysis of the volatile pyrrolidine **13** as its 3,5-DNB derivative **16** again assured that no epimerization of the auxiliary occurred at any stage in the sequence. Deprotection of **11bb** [(1) $Me_3O^+BF_4^-$, (2) 6 N HCl] afforded an amine with 76% ee as determined by chiral HPLC analysis of the 3,5-DNB derivative **14b**. Thus the construction of **10bb** according to Scheme I proceeded with >96:4 diastereoselectivity.

In summary, the reductive cleavage of enantiomerically enriched *N*-acetylhydrazines can be readily accomplished with lithium in ammonia. In all cases studied, both nitrogens of the hydrazine are bonded to sterogenic carbon centers. The configurational integrity of these centers is fully preserved in the amine products obtained from N–N bond scission.

Experimental Section

General Methods. Bulb-to-bulb distillations were done on a Büchi GKR-50 Kugelrohr apparatus; boiling points (bp) refer to air bath temperatures and are uncorrected. Melting points (mp) were determined on a Thomas-Hoover capillary melting point apparatus and are corrected. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 plates with QF-254 indicator. Visualization was accomplished with UV light, iodine, and/or vanillin solution. Solvents for extraction and chromatography were technical grade and distilled from the indicated drying agents: hexane, pentane, dichloromethane ($CaCl_2$); ether ($CaSO_4/FeSO_4$); ethyl acetate (K_2CO_3). Silica gel column (flash) chromatography was performed by the method of Still[13]

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(32–63 μm silica gel, Woelm). Analytical high-pressure liquid chromatography (HPLC) of compounds was performed on a Hewlett-Packard 1090 liquid chromatograph with a Perkin-Elmer LC-75 spectrophotometric detector. Columns: (A) Pirkle Covalent L-*N*-(2-naphthyl)alanine 5 μm,[10b] (B) a chiral stationary phase (CSP) derived from L-*N*-(1-naphthyl)leucine,[10c] (C) a CSP derived from (2*R*,3*R*)-11-triethoxysilylundecanyl *N*-(3,5-dinitrobenzoyl)-3-amino-3-phenyl-2-(1,1-dimethylethyl)propanoate.[10a] The detector wavelength = 254 nm. Retention times (t_R) and integrated ratios were obtained from a Hewlett-Packard 3390A recorder. Brine, NH_4Cl, and $NaHCO_3$ refer to saturated aqueous solutions unless otherwise indicated. All reactions were performed in oven (140 °C) or flame-dried glassware under an atmosphere of dry N_2.

^1H NMR and ^{13}C NMR spectra were recorded on either a Varian XL-200 (200 MHz ^1H) or General Electric QE-300 (300 MHz ^1H, 75.5 MHz ^{13}C) spectrometer in $CDCl_3$ with tetramethylsilane (TMS, δ = 0.00 for ^1H) or chloroform (δ = 7.26 for ^1H, 77.06 for ^{13}C) as an internal standard. Chemical shifts are given in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet), br (broadened), and exch (D_2O exchangeable). Coupling constants, *J*, are reported in hertz. Assignment of individual resonances are supported by APT and/or DEPT in most cases. Data are presented in the form: chemical shift (multiplicity, coupling constants, integration, assignment). Infrared spectra (IR) were obtained on an IBM IR/32 FT-IR spectrophotometer. Peaks are reported in cm^{-1} with the following relative intensities: s (strong, 67–100%), m (medium, 34–66%), w (weak, 0–33%). Electron impact (EI) mass spectra were obtained on a Varian MAT CH-5 spectrometer with ionization voltages of 10 and 70 eV. Data are reported in the form *m/z* (intensity relative to base = 100). Elemental combustion analyses were performed by the University of Illinois Microanalytical Service Laboratory.

Representative Procedure for the Li/NH_3 Cleavage. *N*-(Methoxycarbonyl)-2-amino-4-phenylbutane (8). To 15 mL of anhydrous liquid ammonia cooled to −78 °C was added a solution of **7** (148.9 mg, 0.595 mmol) in 2 mL of dry THF. Freshly cut lithium metal (17.2 mg, 2.478 mmol, 2.08 equiv) was added to the solution, and a permanent blue color developed. The cold bath removed, and the reaction mixture was stirred for 1 h at reflux (−33 °C). The reaction was quenched by addition of solid NH_4Cl (0.66 g, 12.34 mmol, 4.98 equiv), and the ammonia was allowed to evaporate. The residue was dissolved in water (5 mL) and extracted with Et_2O (3 × 30 mL). The extracts were combined, dried (Na_2SO_4), filtered through a pad of Celite, and concentrated in vacuo to afford a clear oil. This material was purified by column chromatography (hexane/EtOAc, 8/1) and Kugelrohr distillation to afford 101 mg (82%) of **8** as a colorless oil. Data for **8**: bp 120–125 °C (0.60 Torr (air bath)); ^1H NMR (300 MHz) 7.27–7.13 (m, 5 H, C_6H_5), 5.01 (br d, *J* = 8.8, 1 H, NH), 3.76–3.70 (m, 1 H, HC(2)), 3.63 (s, 3 H, OCH_3), 2.65–2.59 (m, 2 H, $H_2C(4)$), 1.75–1.66 (m, 2 H, $H_2C(3)$), 1.14 (d, *J* = 7.9, 3 H, $H_3C(1)$); ^{13}C NMR (75.5 MHz) 156.65 (C=O), 141.86, 128.41, 128.35, 125.88, 51.87 (OCH_3), 46.93 (C(2)), 38.91 (C(4)), 32.49 (C(3)), 21.34 (C(1)); IR (neat) 3320 (s), 3061 (m), 3027 (m), 2967 (s), 2861 (m), 1725 (s), 1603 (m), 1534 (s), 1453 (s), 1354 (m), 1248 (s), 1190 (s), 1107 (s), 1080 (s), 1057 (s), 1030 (w), 963 (w); MS (70 eV) 207 (M^+, 6), 133 (9), 132 (58), 131 (4), 118 (4), 117 (36), 103 (11), 102 (100), 92 (8), 91 (48), 88 (9), 77 (8), 65 (10), 59 (11), 58 (28); TLC R_f 0.59 (hexane/EtOAc, 1/1). Anal. Calcd for $C_{12}H_{17}NO_2$ (207.27): C, 69.54; H, 8.27; N, 6.76. Found: C, 69.53; H, 8.24; N, 6.71.

(*R*)-*N*-(Methoxycarbonyl)-2-amino-4-phenylbutane (11aa) and (*S*)-1-(1-Naphthoyl)-2-[(2-methoxyethoxy)methyl]-pyrrolidine (15). From 216 mg (0.593 mmol) of **9aa**, 19 mg (2.738 mmol, 2.31 equiv) of lithium metal, and 0.75 g (14.02 mmol, 5.12 equiv) of solid NH_4Cl, the crude material was purified by column chromatography (hexane/EtOAc, 2/1) to afford 103 mg (84%) of **11aa** as a colorless oil. The spectroscopic data and chromatographic behavior of **11aa** were identical with those reported above for **8**.

The acidic, aqueous layer from extraction of **11aa** with EtOAc was neutralized with 10% KOH and extracted with Et_2O (3 × 20 mL). The organic extracts were combined, dried (Na_2SO_4), filtered through a pad of Celite, and concentrated in vacuo to afford **12** as a pale yellow oil. The crude amine **12** was dissolved in CH_2Cl_2 (3 mL) and was treated with triethylamine (0.40 mL, 4.8 equiv) and a solution of 1-naphthoyl chloride (172.5 mg, 1.5 equiv) in CH_2Cl_2 (3 mL). The reaction mixture was refluxed overnight and then worked up by partitioning the mixture between CH_2Cl_2 (25 mL) and 10% KOH (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL), and the organic extracts were washed with brine (25 mL), dried (K_2CO_3), filtered through a pad of Celite, and concentrated in vacuo to afford a brown oil. Purification by column chromatography (hexane/EtOAc, 2/1) afforded 96 mg (52% from **9aa**) of **15** as a pale yellow oil. Data for (*S*)-**15** bp 150–155 °C (5 × 10^{-5} Torr); ^1H NMR (300 MHz) 7.95–7.92 (m, 1 H, ArH), 7.87–7.84 (m, 2 H, ArH), 7.54–7.46 (m, 4 H, ArH), 4.60–4.56 (m, 1 H, HC(2)), 3.94–3.84 (m, 2 H, $CHCH_2O$), 3.78–3.75 (t, *J* = 5.3, 2 H, $CH_2OCH_2CH_2$), 3.63–3.60 (t, *J* = 5.3, 2 H, CH_3OCH_2), 3.42 (s, 3 H, OCH_3), 3.19–3.04 (m, 2 H, $H_2C(5)$), 2.14–1.80 (m, 3 H, $H_2C(3)$, HC(4)), 1.75–1.68 (m, 1 H, HC(4)); ^{13}C NMR (75.5 MHz) 169.33 (C=O), 129.08, 128.35, 126.90, 126.22, 125.18, 124.96, 123.80, 71.99 ($CHCH_2$), 70.73 ($CH_2OCH_2CH_2$), 70.61 (CH_3OCH_2), 59.12 (OCH_3), 56.50 (C(2)), 49.39 (C(5)), 27.89 (C(3)), 24.46 (C(4)); IR (CCl_4) 3054 (w), 2924 (s), 2880 (s), 1632 (s), 1508 (m), 1464 (m), 1424 (s), 1383 (s), 1356 (m), 1290 (w), 1250 (w), 1200 (m), 1115 (s), 1034 (w); MS (70 eV) 313 (M^+, 18), 254 (20), 238 (56), 237 (100), 225 (46), 224 (100), 184 (9), 172 (5), 156 (100), 155 (100), 141 (13), 128 (93), 127 (100), 126 (75), 115 (5), 101 (32), 82 (8), 77 (58), 75 (17), 59 (63), 55 (18), 51 (12), 45 (48), 43 (24); TLC R_f 0.15 (hexane/EtOAc, 1/1). Anal. Calcd for $C_{19}H_{23}NO_3$ (313.40): C, 72.82; H, 7.40; N, 4.47. Found: C, 72.78; H, 7.41; N, 4.46. HPLC (column C; hexane/*i*-PrOH, 9/1; 2 mL/min) t_R (*S*)-**15**, 30.42 min (>99.9%). Data for (±)-**15**: HPLC (column C; hexane/*i*-PrOH, 9/1; 2 mL/min) t_R (*R*)-**15**, 18.78 min; t_R (*S*)-**15**, 30.13 min.

(*R*)-*N*-(Methoxycarbonyl)-3-amino-1-phenylheptane (11ba). From 147.5 mg (0.363 mmol) of **9ba**, 12 mg (1.729 mmol, 2.38 equiv) of lithium metal and 0.50 g (9.35 mmol, 5.41 equiv) of solid NH_4Cl, the crude product was purified by column chromatography (hexane/EtOAc, 4/1) and Kugelrohr distillation to afford 73.3 mg (81%) of **11ba** as a colorless oil which crystallized on standing. The crude pyrrolidine **12** isolated and then derivatized with 1-naphthoyl chloride as described above. Purification by column chromatography (hexane/EtOAc, 2/1) afforded 32.4 mg (28% from **9ba**) of **15** as a pale yellow oil. Data for **11ba**: bp 80–90 °C (0.0002 Torr (air bath)); mp 35–36 °C; ^1H NMR (300 MHz) 7.30–7.16 (m, 5 H, C_6H_5), 4.47 (br d, *J* = 10.7, 1 H, NH), 3.80–3.75 (m, 1 H, HC(3)), 3.67 (s, 3 H, OCH_3), 2.72–2.58 (m, 2 H, $H_2C(1)$), 1.82–1.18 (m, 8 H, $H_2C(2)$, $H_2C(4)$, $H_2C(5)$, $H_2C(6)$), 0.89 (t, *J* = 6.4, 3 H, $H_3C(7)$); ^{13}C NMR (75.5 MHz) 156.79 (C=O), 141.97, 128.35, 125.80, 124.26, 65.87 (OCH_3), 51.58 (C(3)), 37.47 (C(1)), 35.26 (C(2)), 32.34 (C(4)), 27.92 (C(5)), 22.63 (C(6)), 14.03 (C(7)); IR (CCl_4) 3443 (m), 3355 (w), 3087 (w), 3065 (w), 3029 (m), 2953 (s), 2861 (m), 1727 (s), 1603 (w), 1508 (s), 1455 (s), 1358 (m), 1194 (s), 1152 (m), 1111 (m), 1086 (m), 1046 (m), 924 (w); MS (70 eV) 249 (M^+, 4), 192 (12), 174 (23), 145 (7), 118 (7), 117 (63), 116 (4), 115 (8), 105 (11), 104 (28), 92 (19), 91 (100), 88 (40), 77 (10), 76 (55), 65 (10), 50 (14), 44 (13), 41 (16); TLC R_f 0.70 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{15}H_{23}NO_2$ (249.35): C, 72.26; H, 9.30; N, 5.62. Found: C, 72.04; H, 9.66; N, 5.40. Data for **15**: The spectroscopic and chromatographic characteristics of this material matches those reported for (*S*)-**15** above. HPLC (column C hexane/*i*-PrOH, 9/1; 2 mL/min) t_R (*S*)-**15**, 30.13 min (>99.9%).

(*S*)-*N*-Acetyl-3-amino-5-phenyl-2,2-dimethylpentane (11cb). From 100.2 mg (0.256 mmol) of **9cb**, 8.3 mg (1.196 mmol, 2.33 equiv) of lithium metal, and 0.30 g (5.61 mmol, 4.69 equiv) of solid NH_4Cl, the crude product was purified by column chromatography (hexane/EtOAc, 6/1) to afford 39.3 mg (66%) of **11cb** as white crystals. The crude pyrrolidine **12** was isolated and then derivatized with 1-naphthoyl chloride as described above. Purification by column chromatography (hexane/EtOAc, 2/1) afforded 40.3 mg (50% from **9cb**) of **15** as a pale yellow oil. Data for **11cb**: mp 104–107 °C; ^1H NMR (300 MHz) 7.33–7.16 (m, 5 H, C_6H_5), 5.17 (br d, *J* = 11.1, 1 H, NH), 3.85 (dt, *J* = 11.1, 1 H, HC(3)), 2.69–2.57 (m, 2 H, $H_2C(5)$), 2.02 (s, 3 H, $COCH_3$), 2.00–1.90 (m, 1 H, HC(4)), 1.49–1.36 (m, 1 H, HC(4)), 0.89 (s, 9 H, $(H_3C)_3C(2)$); ^{13}C NMR (75.5 MHz) 170.03 (C=O), 142.21, 128.41, 128.31, 125.84, 57.39 (C(3)), 34.60 (C(5)), 33.40 (C(4)), 32.40 (C(2)), 26.36 (C(1)), 23.57 ($COCH_3$); IR (CCl_4) 3445 (w), 3305 (m), 3065

(w), 3029 (w), 2965 (s), 2869 (m), 1649 (s), 1605 (w), 1551 (m), 1497 (m), 1478 (m), 1455 (m), 1397 (w), 1370 (m), 1293 (w), 1206 (w), 1102 (w), 1030 (w), 968 (w); MS (70 eV) 233 (M^+, 6), 218 (3), 177 (8), 176 (58), 135 (9), 134 (89), 118 (11), 117 (91), 91 (100), 86 (20), 65 (11), 60 (94), 57 (15), 44 (11), 43 (43), 41 (21); TLC R_f 0.33 (hexane/EtOAc, 1/1). Anal. Calcd for $C_{15}H_{23}NO$ (233.36): C, 77.21; H, 9.94; N, 6.00. Found: C, 77.16; H, 9.98; N, 5.97. Data for **15**: The spectroscopic and chromatographic characteristics of this material matched those reported for (*S*)-**15** above. HPLC (column C; hexane/*i*-PrOH, 9/1; 2 mL/min) t_R (*S*)-**15**, 30.25 min (>99.9%).

Representative Procedure for the Cleavage of Carbamates and Enantiomeric Purity Determination. (*R*)-*N*-(3,5-Dinitrobenzoyl)-2-amino-4-phenylbutane (14a). A solution of carbamate **11aa** (52.6 mg, 0.254 mmol) in CH_3CN (2 mL) was treated with iodotrimethylsilane (0.10 mL, 0.703 mmol, 2.77 equiv), and the reaction mixture was stirred at room temperature for 1 h. Methanol (0.05 mL, 5.00 equiv) was added, and the solution was stirred for 20 min. The reaction mixture was diluted with Et_2O (10 mL), and the volatile components were evaporated under reduced pressure. The residue was dissolved in Et_2O (10 mL), acidified with 10% HCl, and extracted with Et_2O (10 mL). The aqueous solution was neutralized with 45% KOH and extracted with Et_2O (3 × 20 mL). The organic extracts were combined, dried (Na_2SO_4), filtered through a pad of Celite, and concentrated in vacuo to afford 31.1 mg (82%) of the crude amine as a pale yellow oil. The crude amine (22 mg, 0.147 mmol) was dissolved in dry CH_2Cl_2 (3 mL), treated with triethylamine (0.10 mL, 0.717 mmol, 4.88 equiv) and 3,5-dinitrobenzoyl chloride (140 mg, 0.607 mmol, 4.13 equiv), and stirred overnight at room temperature. The reaction mixture was poured into H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organic extracts were washed with brine (10 mL), combined, dried (Na_2SO_4), filtered through a pad of Celite, and concentrated in vacuo to afford a clear brown oil. Purification by column chromatography (hexane/EtOAc, 5/1) afforded 48.6 mg (96%) of (*R*)-**14a** as an off-white solid. The spectroscopic and chromatographic behavior matched those of an independently prepared racemic sample. Data for (±)-**14a**: ^{1}H NMR (300 MHz) 9.18 (m, 1 H, HC(4) on 3,5-DNB), 8.80 (s, 2 H, HC(2), HC(6) on 3,5-DNB), 7.21 (m, 5 H, C_6H_5), 6.32 (d, 1 H, J = 8.7, NH), 4.34 (m, 1 H, HC(2)), 2.76 (m, 2 H, $H_2C(4)$), 2.00 (m, 2 H, $H_2C(3)$), 1.36 (d, J = 6.7, 3 H, $H_3C(1)$); TLC R_f 0.43 (hexane/EtOAc, 1/1); HPLC (column A; hexane/*i*-PrOH, 97/3; 2 mL/min) t_R (*S*)-**14a**, 27.64 min; t_R (*R*)-**14a**, 34.01 min. Data for (*R*)-**14a**: HPLC (column A; hexane/*i*-PrOH, 97/3; 2 mL/min) t_R (*S*)-**14a**, 27.33 min (4%); t_R (*R*)-**14a**, 33.26 min (96%).

(*R*)-*N*-(3,5-Dinitrobenzoyl)-3-amino-1-phenylheptane (14b). From 43.2 mg (0.173 mmol) of **11ba** and 80 μL (0.562 mmol, 3.25 equiv) of iodotrimethylsilane was obtained 25.2 mg (76%) of a crude amine. From 23.3 mg (0.122 mmol) of the amine, 70 μL (0.502 mmol, 4.12 equiv) of triethylamine and 122 mg (0.489 mmol, 4.01 equiv) of benzoyl chloride purification by column chromatography (hexane/EtOAc, 5/1) afforded 45.4 mg (92%) of (*R*)-**14b** as a white solid. The spectroscopic and chromatographic behavior matched those of an independently prepared racemic sample. Data for (±)-**14b**: mp 115–116 °C (hexane/CH_2Cl_2); ^{1}H NMR (300 MHz) 9.11 (s, 1 H, HC(4) on 3,5-DNB), 8.76 (d, 2 H, J = 1.79, HC(2), HC(6), on 3,5-DNB), 7.24 (m, 5 H, C_6H_5), 6.10 (d, 1 H, J = 7.04, NH), 4.28 (m, 1 H, HC(3)), 2.75 (m, 2 H, $H_2C(1)$), 1.95 (m, 2 H, $H_2C(2)$), 1.65 (m, 2 H, $H_2C(4)$), 1.35 (br m, 4 H, $H_2C(5)$, $H_2C(6)$), 0.90 (m, 3 H, $H_3C(7)$); ^{13}C NMR (75.5 MHz) 162.07 (C=O), 148.47, 141.51, 138.00, 128.63, 128.19, 126.95, 126.08, 120.87, 51.18 (C(3)), 35.99 (C(1)), 34.83 (C(2)), 32.41 (C(4)), 28.12 (C(5)), 22.54 (C(6)), 13.97 (C(7)); IR (KBr) 3310 (s), 3088 (s), 3028 (m), 1642 (s), 1592 (m), 1545 (s), 1495 (s), 1453 (s), 1347 (s), 1188 (m), 1111 (m), 1076 (m); MS (70 eV) 385 (12), 281 (61), 280 (18), 238 (30), 224 (8), 195 (64), 174 (23), 118 (12), 117 (88), 105 (12), 104 (60), 103 (14), 92 (15), 91 (100), 75 (26); TLC R_f 0.65 (hexane/EtOAc, 1/1). Anal. Calcd for $C_{20}H_{23}N_3O_5$ (385.42): C, 62.33; H, 6.02; N, 10.90. Found: C, 62.21; H, 6.11; N, 10.80. Data for (*R*)-**14b**: HPLC (column B; hexane/*i*-PrOH, 97/3; 1 mL/min) t_R (*S*)-**14b**, 31.97 min (6%); t_R (*R*)-**14b**, 36.12 min (94%).

(*S*)-*N*-(3,5-Dinitrobenzoyl)-3-amino-5-phenyl-2,2-dimethylpentane (14c). Trimethyloxonium tetrafluoroborate (14.9 mg, 0.1007 mmol, 2.00 equiv) was dissolved in dry DME (1.5 mL) in a 25-mL 2-necked round-bottom flask. To this was added a solution of the amide **11cb** (11.8 mg, 0.0506 mmol) in DME (2 mL). The reaction mixture was stirred at room temperature for 1 h and then was quenched with 2 N NaOH (1 mL). The solution was poured into H_2O (3 mL) and extracted with dry Et_2O (3 × 10 mL). The organic extracts were combined, dried (Na_2SO_4), filtered through a pad of Celite, and concentrated in vacuo to afford a yellow oil. The oil was dissolved in methanol (3 mL) and 6 N HCl (1.5 mL) and heated to reflux for 2 h. The reaction mixture was cooled to 0 °C and quenched with solid NaOH. The solution was poured into H_2O (2 mL) and extracted with Et_2O (3 × 10 mL). The organic extracts were combined, dried (Na_2SO_4), filtered through a pad of Celite, and concentrated in vacuo to afford 5.9 mg (61%) of the amine as a yellow oil. The crude amine (5.9 mg, 0.0308 mmol) was derivatized with triethylamine (0.02 mL, 0.0359 mmol, 4.66 equiv) and 3,5-dinitrobenzoyl chloride (28.5 mg, 0.1236 mmol, 4.01 equiv) as described above. Purification by column chromatography (hexane/EtOAc, 5/1) afforded 8.3 mg (70%) of **14c** as a white solid. The spectroscopic and chromatographic behavior matched those of an independently prepared racemic sample. Data for (±)-**14c**: ^{1}H NMR (300 MHz) 9.16 (m, 1 H, HC(4) on 3,5-DNB), 8.75 (m, 2 H, HC(2), HC(6) on 3,5-DNB), 7.19 (m, 5 H, C_6H_5), 5.78 (d, 1 H, J = 9.59, NH), 4.12 (m, 1 H, HC(3)), 2.70 (m, 2 H, $H_2C(1)$), 2.11, 1.63 (2 m, 2 H, $H_2C(2)$), 0.99 (s, 9 H, $(H_3C)_3C(4)$); TLC R_f 0.58 (hexane/EtOAc, 2/1). Data for (*S*)-**14c**: HPLC (column A; hexane/*i*-PrOH, 19/1; 1 mL/min) t_R (*S*)-**14c**, 24.07 min (>99.9%).

(*R*)-*N*-Acetyl-3-amino-1-phenylheptane (11bb) and (*S*)-1-(3,5-Dinitrobenzoyl)-2-(2-methylpropyl)pyrrolidine (16). From 102 mg (0.28 mmol) of **10bb**, 7 mg (1.0 mmol, 1.7 equiv) of lithium metal, and ca. 0.5 g of NH_4Cl was obtained 66 mg (100%) of **11bb** as white crystals. The ^{1}H NMR spectrum and TLC behavior of this material matched those of a racemic sample. Data for (±)-**11bb**: mp 80–81 °C (hexane); ^{1}H NMR (300 MHz) 7.23 (m, 5 H, C_6H_5), 5.31 (d, J = 9.0, 1 H, NH), 3.95 (m, 1 H, HC(3)), 2.64 (t, J = 8.1, 2 H, $H_2C(1)$), 1.95 (s, 3 H, $COCH_3$), 1.82, 1.65 (2 m, 2 H, $H_2C(2)$), 1.50, 1.38 (2 m, 2 H, $H_2C(4)$), 1.26 (m, 4 H, $H_2C(5)$,$H_2C(6)$), 0.88 (m, 3 H, $H_3C(7)$); ^{13}C NMR (75.5 MHz) 169.60 (C=O), 141.95, 128.37, 128.23, 125.80, 49.28 (C(3)), 36.96 (C(2)), 34.98 (C(4)), 32.37 (C(1)), 27.97 (C(5)), 23.50 ($COCH_3$), 22.60 (C(6)), 13.99 (C(7)); IR (KBr) 3310 (s), 3088 (s), 3028 (m), 1642 (s), 1592 (m), 1545 (s), 1495 (s), 1453 (s), 1347 (s), 1188 (m), 1111 (m), 1076 (m); MS (70 eV) 233 (25), 174 (8), 134 (29), 129 (43), 128 (26), 117 (44), 105 (10), 104 (33), 100 (13), 92 (14), 91 (93), 87 (14), 86 (100); TLC R_f 0.10 (EtOAc/hexane, 1/1). Anal. Calcd for $C_{15}H_{23}NO$ (233.36): C, 77.21; H, 9.94; N, 6.00. Found: C, 77.20; H, 9.97; N, 5.95.

The acidic extracts from the above experiment were combined, cooled to 0 °C, and neutralized by the addition of solid NaOH. The amine was extracted with Et_2O (3 × 8 mL), and the extracts were washed with brine (1 × 10 mL), combined, dried (K_2CO_3), filtered through a pad of Celite, and concentrated at aspirator pressure. The residue was dissolved in THF (4 mL) and treated with a solution of K_2CO_3 (100 mg) in H_2O followed by 3,5-dinitrobenzoyl chloride (60 mg). The reaction mixture was stirred for 2 h, extracted with Et_2O (3 × 10 mL), and filtered through a pad of silica gel. Concentration of the ethereal solution afforded **16** as off-white crystals (28 mg, 31%). HPLC analysis of this compound (column A; hexane/EtOAc/*i*-PrOH, 98.3/1.3/0.7; 0.7 mL/min) t_R (*R*)-**16**, 31.6 min (9.5%); t_R (*S*)-**16**, 33.50 min (90.5%). This is identical with the enantiomeric composition of **13** before conversion to the hydrazone (81% ee).

Hydrolysis and Derivatization of 11bb. From 60 mg (0.41 mmol, 1.48 equiv) of trimethyloxonium tetrafluoroborate and 64 mg (0.27 mmol) of **11bb** was obtained a crude amine, as described above. The amine was derivatized with 3,5-dinitrobenzoyl chloride (120 mg, 0.52 mmol, 1.93 equiv) and K_2CO_3 (100 mg) in aqueous THF. Purification by column chromatography (hexane/EtOAc, 8/1) gave 55 mg (52%) of **14b** as white crystals. HPLC analysis (column B; hexane/*i*-PrOH, 97/3; 1 mL/min) indicated a 87.5:12.5 *R*/*S* mixture of enantiomers (75% ee).

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Registry No. 7, 129757-53-5; 8, 129830-34-8; **9aa**, 127222-03-1; **9ba**, 127221-99-2; **9cb**, 129757-50-2; **9da**, 127222-04-2; **10bb**, 129757-51-3; **11aa**, 129757-52-4; **11ba**, 129757-54-6; **11bb**, 129757-56-8; **11cb**, 129757-55-7; (*R*)-**14a**, 129757-61-5; (*R*)-**14b**, 129757-59-1; (*S*)-**14b**, 129757-63-7; (*S*)-**14c**, 129757-62-6; **15**, 129757-57-9; **16**, 129757-58-0; SAMEMP hydrazine, 129757-60-4; $Ph(CH_2)_3Ph$, 1081-75-0.

New Acetylenic Alcohols from the Sponge *Cribrochalina vasculum*

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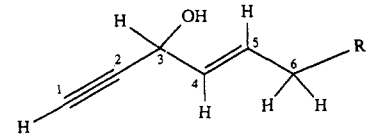
In our continuing search for biologically active compounds from marine organisms, we have isolated five new acetylenic alcohols from a sponge *Cribrochaline vasculum* collected in Belize. These terminal mono acetylenic compounds are simpler in structure and differ from the previously reported polyacetylenic compounds from sponges belonging to genera *Cribrochaline*,[1] *Siphonochaline*,[2] *Petrosia*,[3,4] and *Xestospongia*.[5] We report here their isolation and structure determination.

The methanol–toluene extract of the sponge was partitioned between ethyl acetate and water. The ethyl acetate soluble fraction on chromatography over SiO_2 gel followed by reverse-phase HPLC gave five compounds. These compounds, **1–5**, showed in vitro immunosuppressive activity on MLR assays[6,7] and in vitro antitumor activity against the mouse leukemia P388 cell lines.[8] The molecular formulas for these compounds were established by high-resolution mass spectrometry.

Compound **1**, $C_{20}H_{36}O$, showed infrared absorptions indicative of a terminal alkyne (3295 cm^{-1}) and a hydroxyl group (3590 cm^{-1}). LRFDMS indicated ready loss of 17 mass units (OH group) to give the base peak ion. Homonuclear decoupling experiments and a two-dimensional COSY NMR spectrum identified the spin system in the partial structure A. A long-range coupling of 2.0 Hz was observed between the acetylenic proton at δ 2.54 and the proton attached to the carbon bearing oxygen at δ 4.81. The latter proton was in turn coupled to the two olefinic protons observed at δ 5.59 and 5.89 with coupling constants of 6.1 and 1.4 Hz, respectively. The olefinic protons observed at δ 5.59 and 5.89 are coupled to each other with a coupling constant of 15.3 Hz and to the allylic methylene protons at δ 2.04 with coupling constants of 1.6 and 6.7 Hz, respectively. *E* geometry was assigned to the olefinic double bond based upon the 15.3-Hz vicinal coupling constant. This partial structure A had been reported previously in several metabolites isolated from other sponges.[1,3,5] The compound **1** has only one A unit in contrast to other known compounds which possess two or more of this unit.

The ^1H NMR spectrum further indicated a broad signal (δ 1.33–1.39) integrating to 13 or 14 methylene units and a methyl triplet (δ 0.85, J = 6.5 Hz) for the presense of an alkyl chain in the molecule. The presence of signals equivalent to 14 methylene carbons and a high-field signal for a methyl carbon in the inverse gated[9] ^{13}C spectrum confirmed the presence of a C_{15} alkyl chain. Combination of the above data established the structure **1** for the compound. The structure was confirmed by NMR and mass spectral comparison with a synthetic sample of (±)-3-hydroxyeicos-4(*E*)-en-1-yne.[10] A trace of the next higher homologue was detected in the HREI mass spectrum.

Compounds **2–5** were found to contain the same structural unit A (see the Experimental Section) and differ only in the nature of the alkane chain.



A

1, R = $(CH_2)_{13}$-CH_3

2, R = $(CH_2)_8$-^{15}CH=^{E}CH-$(CH_2)_5$-CH_3

3, R = $(CH_2)_9$-$^{16}CH(CH_3)$-$(CH_2)_3$-$^{20}CH_3$

4, R = $(CH_2)_{12}$-$^{19}CH(CH_3)_2$

5, R = $(CH_2)_8$-^{15}CH=^{E}CH-$(CH_2)_4$-$^{21}CH(CH_3)_2$

Compound **2** has molecular formula $C_{22}H_{38}O$. Comparison with **1** indicated the presence of an additional C_2H_2 unit in **2**. The ^1H NMR spectrum showed in the upper field region a methyl triplet at δ 0.85 and methylene signals around δ 1.3 integrating for 22 protons. Allylic signal integrating for four additional protons in comparison to these of **1** at δ 2.01 and an additional olefinic signal integrating for two protons at δ 5.32 confirmed the presence of an isolated double bond in the alkyl chain. Periodate–permanganate oxidation[11] of **2** at room temperature, followed by methylation of the mixture with CH_2N_2, gave a mixture of products. The mixture was separated, and the major product was identified by ^1H NMR as $(CH_2)_9(COOCH_3)_2$. The position of the isolated double bond was confirmed by the mass spectrum of the hydroxydimethylamino derivative[12] obtained by peroxidation of the double bond with *m*-chlorobenzoic acid followed by heating the epoxide solution in $(CH_3)_2NH$ in a sealed tube. The strongest fragment obtained in the mass spectrum, the ammonium ion $CH_3(CH_2)_5CH{=}N^+(CH_3)_2$ (m/z 142), determined unequivocally the position of the isolated double bond. The geometry of the isolated double bond could not be determined by ^1H NMR, as the two olefinic signals appeared at the same chemical shift value. The assignment of the trans configuration of the isolated double bond was based on the absence of any IR absorptions between 730 and 675 cm^{-1}.

Compound **3**, with the molecular formula $C_{21}H_{38}O$, is the next higher homologue of compound **1**. The ^1H NMR spectrum of **3** was identical with that of **1**, except that the higher field region indicated in addition to the terminal

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