Synthesis of a New Tyrosine Analogue Having χ_1 and χ_2 Angles Constrained to Values Observed for an SH2 Domain-Bound Phosphotyrosyl Residue

Bin Ye, Zhu-Jun Yao, and Terrence R. Burke, Jr.*,†

Laboratory of Medicinal Chemistry, Division of Basic Sciences, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892

Received January 15, 1997[⊗]

Synthesis is reported of a new tricyclic amino acid, (±)-(*rel*-2*S*,3*R*)-2-carboxy-1,2,3,4,5,6-hexahydro-8-hydroxy-1,5-methano-3-methyl-3-benzazocine (**2**), which contains within its structure the elements of a tyrosine moiety having χ_1 and χ_2 angles (168° and −95°, respectively) constrained to values observed for a phosphotyrosyl (pTyr) residue bound to the 56[lck] SH2 domain (χ_1 and χ_2 values of 163° and −94°, respectively). Additionally, the ϕ angle of N-acylated **2** correlates well with the ϕ angle of the SH2 domain-bound pTyr residue. Compound **2** represents a unique, highly constrained amino acid which may be of value in signal transduction studies.

Phosphorylation of key tyrosyl residues in proteins by protein-tyrosine kinases (PTKs) provides the "phosphotyrosyl pharmacophore" (pTyr) which is required for recognition and binding by secondary signaling proteins through their Src homology 2 (SH2) or phosphotyrosine binding (PTB) domains. Such protein−protein associations subsequently establish the basis for further signal transduction.[1] Because of the central role played by pTyr residues, its analogues have become important tools for developing SH2 domain-binding antagonists.[2] In order to enhance binding affinities of flexible ligands, one useful approach has been to reduce entropy penalties by constraining ligands to conformations approximating those required for binding. A number of conformationally restricted amino acids, including analogues of phenylalanine[3] and tyrosine,[4] have been devised for these purposes. In the case of SH2 domain ligands, the availability of X-ray and solution structures of ligated SH2 domains has provided a clear definition of relevant binding geometries which would be required for the preparation of conformationally constrained pTyr analogues.[5] Utilizing the previously reported X-ray structure of a pTyr-containing peptide bound to the p56[lck] SH2 domain,[5b] we have designed tricyclic methanobenzazocine analogue **2**, which contains within its structure a tyrosine moiety having χ_1 and χ_2 torsion angles (168° and −95°, respectively for the N-acylated form) closely approximating those of the SH2 domain-bound pTyr residue **1** (163° and −94°, respectively, Figure 1). Additionally, as can be seen from Figure 1, ϕ angles are also quite similar, such that the *N*-acyl carbonyl groups are in close alignment. This carbonyl oxygen participates in hydrogen bonding to the SH2 domain.[5] Amino acid analogue **2** is unusual in simultaneously constraining three torsion angles to biologically relevant values displayed by the

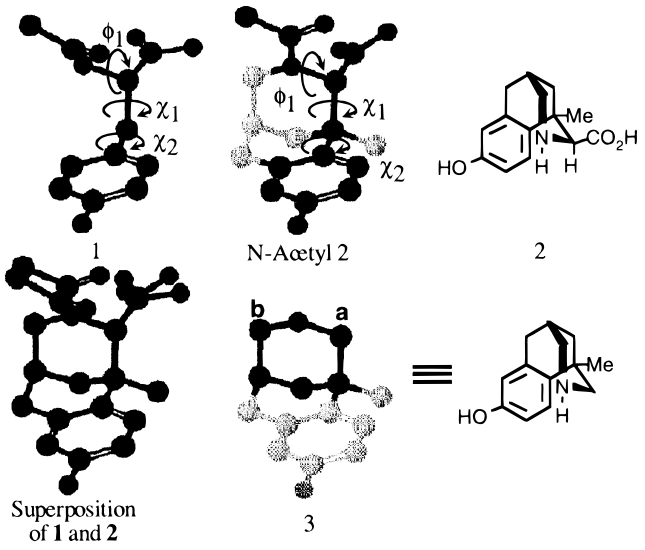


Figure 1. Comparison of p56[lck]-bound pTyr residue **1** with the N-acetylated form of conformationally constrained tyrosyl mimetic **2**. The *N*-acyl group of **1** is held in the conformation observed for the SH2 domain-bound Gln−pTyr amide bond, while *N*-acetyl **2** represents an energy-minimized structure. Shading of **2** and **3** is intended to highlight important structural features.

† Author to whom correspondence should be addressed at Building 37, Room 5C06, National Institutes of Health, Bethesda, MD 20892. Phone: (301) 496-3597. Fax: (301) 402-2275. E-mail: tburke@helix.nih.gov.

⊗ Abstract published in *Advance ACS Abstracts,* July 1, 1997.

(1) Panayotou, G.; Waterfield, M. D. *Bioessays* **1993**, *15*, 171−177.

(2) (a) Burke, T. R., Jr.; Smyth, M. S.; Otaka, A.; Nomizu, M.; Roller, P. P.; Wolf, G.; Case, R.; Shoelson, S. E. *Biochemistry* **1994**, *33*, 6490−6494. (b) Gilmer, T.; Rodriquez, M.; Jordan, S.; Crosby, R.; Alligood, K.; Green, M.; Kimery, M.; Wagner, C.; Kinder, D.; Charifson, P.; Hassell, A. M.; Willard, D.; Luther, M.; Rusnak, D.; Sternbach, D. D.; Mehrotra, M.; Peel, M.; Shampine, L.; Davis, R.; Robbins, J.; Patel, I. R.; Kassel, D.; Burkhart, W.; Moyer, M.; Bradshaw, T.; Berman, J. *J. Biol. Chem.* **1994**, *269*, 31711−31719. (c) Ye, B.; Akamatsu, M.; Shoelson, S. E.; Wolf, G.; Giorgetti-Peraldi, S.; Yan, X.; Roller, P. P.; Burke, T. R., Jr. *J. Med. Chem.* **1995**, *38*, 4270−4275. (d) Shahripour, A.; Plummer, M. S.; Lunney, E. A.; Para, K. S.; Stankovic, C. J.; Rubin, J. R.; Humblet, C.; Fergus, J. H.; Marks, J. S.; Herrera, R.; Hubbel, S. E.; Saltiel, A. R.; Sawyer, T. K. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1209−1214.

(3) Josien, H.; Lavielle, S.; Brunissen, A.; Saffroy, M.; Torrens, Y.; Beaujouan, J. C.; Glowinski, J.; Chassaing, G. *J. Med. Chem.* **1994**, *37*, 1586−1601.

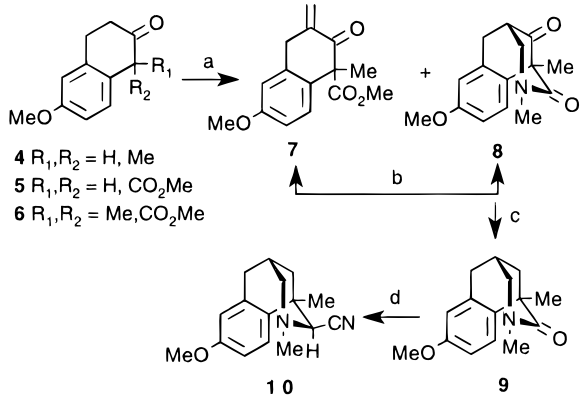
(4) (a) Jiao, D.; Russell, K. C.; Hruby, V. J. *Tetrahedron* **1993**, *49*, 3511−3520. (b) Mosberg, H. I.; Lomize, A. L.; Wang, C. G.; Kroona, H.; Heyl, D. L.; Sobczykkojiro, K.; Ma, W. L.; Mousigian, C.; Porreca, F. *J. Med. Chem.* **1994**, *37*, 4371−4383. (c) Obrecht, D.; Lehmann, C.; Ruffieux, R.; Schonholzer, P.; Muller, K. *Helv. Chim. Acta* **1995**, *78*, 1567−1587. (d) Burke, T. R., Jr.; Barchi, J. J., Jr.; George, C.; Wolf, G.; Shoelson, S. E.; Yan, X. *J. Med. Chem.* **1995**, *38*, 1386−1396.

(5) (a) Waksman, G.; Shoelson, S. E.; Pant, N.; Cowburn, D.; Kuriyan, J. *Cell* **1993**, *72*, 779−790. (b) Eck, M. J.; Shoelson, S. E.; Harrison, S. C. *Nature* **1993**, *362*, 87−91.

(6) Carruthers, W.; Williams, M. J. *J. Chem. Soc., Chem. Commun.* **1986**, 1287−1288.

S0022-3263(97)00078-9 This article not subject to U.S. Copyright. Published 1997 by the American Chemical Society

Scheme 1[a]



[a] (a) $MeNH_2$·HCl, 36% CH_2O, AcOH, reflux, overnight; 1 N NaOH, MeOH, room temperature, 2 h; (b) $MeNH_2$, 1 N NaOH, dioxane, room temperature, 1 h, 90%; (c) NH_2NH_2·H_2O, 88% KOH, diethylene glycol, reflux, 14 h, 98%; (d) DIBAL-H, THF, −78 °C, 1 h, TMSCN, $ZnCl_2$, CH_2Cl_2, room temperature, 2 h, 74%.

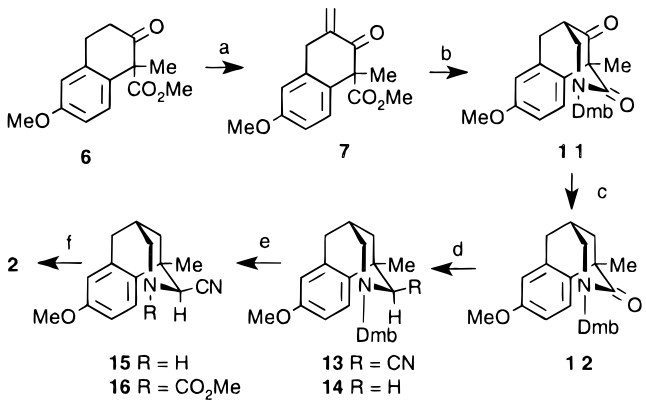
parent on which it is modeled and may be of potential value as a conformationally constrained tyrosine analogue for signal transduction studies.

Synthesis

We have previously reported the preparation of the simplified, constrained, partial tyrosine analogue **3**.[4d] In relation to this structure, preparation of **2** would entail selectively introducing the carboxyl functionality at carbon "a" rather than carbon "b" while maintaining proper relative stereochemistry at this center. In contrast to our previous synthesis of **3** where the amine-containing ring was prepared in a one-pot manner by Mannich-type condensation of methylamine and 2 equiv of formaldehyde onto tetralone **4**, our synthesis of **2** utilized a stepwise ring construction which introduced oxygen functionality at the "a" carbon, which was subsequently transformed into the desired carboxyl group.

The incipient oxygenated "a" carbon was first introduced onto starting 6-methoxy-2-tetralone[7] by carbomethoxylation to yield **5**,[8] which was then methylated to yield **6**. Methylation was required to prevent further reaction at this center. While it was anticipated that sequential Mannich reaction/intramolecular ring closure[9] would yield the desired lactam **8**, it was found that usual Mannich conditions ($MeNH_2$, HCHO, ACOH, reflux, 5 h) gave only a 10% yield of desired **8** directly (Scheme 1). It was necessary to treat the crude reaction product with aqueous NaOH to obtain a 31% yield of lactam **8** along with a 16% yield of highly unstable α,β-unsaturated keto ester **7**. Isolation of **7** and treatment with methylamine (room temperature, 1 h) resulted in 1,4-Michael-type addition,[10] followed by intramolecular amidation to provide additional lactam **8** in 90% yield. The methanobenzazocine 11-oxo carbonyl was then removed via Wolff−Kishner reduction (KOH, diethylene glycol, reflux, 4 h)[4d] to provide **9** (98% yield). Sequential reduction of lactam **9** with DIBAL-H, followed by treatment with TMSCN in the presence of $ZnCl_2$ (room temperature, 1.5 h), then gave **10** in 74% yield as a single isomer, bearing the desired relative stereochemistry as determined by X-ray crystallography.[11]

Scheme 2[a]



[a] DMBz = dimethoxybenzyl; (a) LDA, HMPA, THF, −78 °C, 1 h; Eschenmoser's salt, room temperature, overnight, 52%; (b) $DMBzNH_2$, 1 N NaOH, room temperature, 4 h; DBU, toluene, reflux, overnight, 38%; (c) NH_2NH_2·H_2O, 88% KOH, diethylene glycol, reflux, 5 h, 71%; (d) DIBAL-H, THF, −78 °C, 2 h, TMSCN, $ZnCl_2$, CH_2Cl_2, room temperature, 1.5 h, 78%; (e) TFA, anisole, 65 ± 5 °C, 3 h; MeOCOCl, Et_3N, CH_3CN, room temperature, 4 h, 93%; (f) 6 N HCl, reflux, 6 days, 88%.

Surprisingly, attempted N-demethylation by a variety of techniques failed, providing in each case recovered starting **10**. This potentially indicated severe steric crowding which prevented reaction at the nitrogen center. To circumvent this obstacle, the nitrogen bearing a 2,4-dimethoxybenzyl group (DMBz) was introduced, which could be removed by chemical modification distal to the nitrogen itself. Because of its acid lability, formation of lactam **11** was done under basic conditions by treating α,β-unsaturated keto ester **7** with 2,4-dimethoxybenzylamine using DBU as a catalyst (refluxing toluene, 5 h, 38% yield) (Scheme 2). Keto ester **7**, which had previously been obtained in low yield as a byproduct during the synthesis of methylamine adduct **8**, was prepared in 54% yield by treatment of **6** with Eschenmoser's salt (*N*,*N*-dimethylmethyleneammonium iodide), using LDA as a base.[12] Wolff−Kishner reduction of **11** afforded lactam **12** (71% yield), with subsequent DIBAL-H reduction and treatment with TMSCN and $ZnCl_2$ giving nitrile-containing *N*-2,4-dimethoxybenzylated compound **13** (77% yield).

Initial attempts at direct conversion of **13** to **2** by simultaneous acid-catalyzed debenzylation, O-demethylation, and nitrile hydrolysis (6 N HCl, reflux) resulted in loss of the nitrile group with formation of the corresponding imine. Alternatively, treatment of **13** under moderately alkaline conditions (NaOH, MeOH, reflux)[13] gave no reaction, while harsher treatment (KOH, diethylene glycol, reflux)[14] resulted in reductive displacement of the nitrile to yield **14** (76% yield). The bulky benzyl group was therefore replaced with a smaller carbamate functionality, which both reduced steric crowding and tied up the nitrogen lone electron pair, preventing its

(7) Kidwell, R. L.; Darling, S. D. *Tetrahedron Lett.* **1966**, *5*, 531−535.
(8) Colvin, E. W.; Martin, J.; Parker, W.; Raphael, R. A.; Shroot, B.; Doyle, M. *J. Chem. Soc., Perkin Trans. 1* **1972**, 860−870.
(9) Tramontini, M. *Synthesis* **1973**, 703.
(10) Elz, S.; Heil, W. L. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 667−672.
(11) Relative configurations were confirmed by single-crystal X-ray crystallography.
(12) Marshall, J. A.; Flynn, G. A. *J. Org. Chem.* **1979**, *44*, 1391−1397.
(13) Ezzitouni, A.; Barchi, J. J.; Marquez, V. E. *J. Chem. Soc., Chem. Commun.* **1995**, 1345−1346.
(14) Christopfel, W. C.; Miller, L. L. *J. Org. Chem.* **1986**, *51*, 4169−4175.

participation in intramolecular elimination of the nitrile group. Although oxidative debenzylation worked well (DDQ),[15] ease of workup favored the use of TFA (65 °C, 3 h)[16] to provide **15** in 92% yield. Subsequent treatment with methyl chloroformate in the presence of Et_3N gave carbamate **16** in 85% overall yield from benzylamine **13**. Finally, treatment of **16** with 6 N HCl (reflux, 3 days), followed by a propylene oxide quench,[17] gave final target **2** in 87% yield.

Experimental Section

General Methods. ^{1}H NMR data are reported in ppm relative to TMS and referenced to the solvent in which they were run. Solvent was removed by rotary evaporation under reduced pressure and silica gel chromatography was performed using Merck silica gel 60 with a particle size of 40−63 μm. Anhydrous solvents were obtained commercially and used without further drying. Preparative HPLC were conducted using a Vydac preparative C_{18} peptide and protein column. Energy minimization of *N*-acetyl **2** was achieved with the CAChe mechanics program (version 3.9) using augmented MM2 parameters in a conjugate gradient method with convergence at 0.001 kcal/mol.

(±)-3,4-Dihydro-1-carbomethoxy-6-methoxy-1-methyl-2(1*H*)-naphthalen-2-one (6). A mixture of (±)-3,4-dihydro-1-carbomethoxy-6-methoxy-2(1*H*)-naphthalen-2-one (**5**)[18] (17.8 g, 76.1 mmol), potassium carbonate (52.5 g, 381 mmol), and iodomethane (13 g, 91.2 mmol) in acetone (500 mL) was heated to reflux (3 h). The reaction mixture was cooled to room temperature and filtered and the filter cake washed with ether. The combined filtrate was taken to dryness and then diluted with EtOAc (200 mL), washed with brine (3 × 30 mL), and dried ($MgSO_4$), and the solvent was removed to provide crude **6**. Purification by silica gel chromatography (hexanes:EtOAc 4:1) afforded pure **6** (12.3 g, 65%) as a syrup: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.15 (d, J = 8.6 Hz, 1 H), 6.81 (dd, J = 8.6, 2.6 Hz, 1 H), 6.73 (d, J = 2.6 Hz, 1 H), 3.8 (s, 3 H), 3.61 (s, 3 H), 3.2−2.54 (m, 4 H), 1.67 (s, 3 H); IR (film) 3020, 1715, 1504, 1216 cm^{-1}; FABMS (*m*/*z*) 249 (M + H)$^+$. Anal. Calcd ($C_{14}H_{16}O_4$): C, 67.73; H, 6.5. Found: C, 67.88; H, 6.57.

(±)-3,4-Dihydro-1-carbomethoxy-6-methoxy-1-methyl-3-methylene-2(1*H*)-naphthalen-2-one (7) and (±)-1,3-Dimethyl-1,2,3,4,5,6-hexahydro-1,5-methano-8-methoxy-3-benzazocine-2,11-dione (8). A mixture of **6** (1.176 g, 4.78 mmol), $MeNH_2$·HCl (355 mg, 5.26 mmol), and aqueous 37% $(CH_2O)_n$ (158 mg) in AcOH (10 mL) was heated to reflux (3 h). The reaction mixture was cooled to room temperature and AcOH reduced in volume nearly to dryness. To the resulting residue was added 1 N NaOH (to pH 12−13), the reaction mixture was stirred (1 h) and then extracted with $CHCl_3$ (3 × 50 mL), washed with brine (2 × 20 mL), and dried ($MgSO_4$), and the solvent was removed to provide crude product containing a mixture of **7** and **8**. Purification by silica gel chromatography (hexanes:EtOAc gradient from 20% to 90%) afforded **7** (198 mg, 16%) and **8** (387 mg, 31%). **7**: ^{1}H NMR (250 MHz, DMSO-d_6) δ 7.19 (d, J = 9.0 Hz, 1 H), 6.89 (s, 1 H), 6.86 (m, 1 H), 6.08 (s, 1H), 5.63 (d, J = 1.3 Hz, 1H), 3.87 (d, J = 17.8 Hz, 1 H), 3.76 (s, 3 H), 3.74 (d, J = 17.8 Hz, 1 H), 3.60 (s, 3 H), 1.63 (s, 3 H); IR (film) 2953, 1733, 1661, 1615, 1505, 873 cm^{-1}. **8**: ^{1}H NMR (250 MHz, $CDCl_3$)δ 7.3 (d, J = 8.7 Hz, 1 H), 6.8 (dd, J = 8.7, 2.6 Hz, 1 H), 6.62 (d, J = 2.6 Hz, 1 H), 3.76 (s, 3 H), 3.67−3.49 (m, 3 H), 3.28 (m, 2 H), 2.85 (s, 3 H), 1.65 (s, 3 H); IR (film) 2987, 1715, 1655, 1029 cm^{-1}; FABMS (*m*/*z*) 260 (M + H)$^+$. Anal. Calcd ($C_{15}H_{17}NO_3$·$^1/_4H_2O$): C, 68.31; H, 6.64; N, 5.31. Found: C, 68.62; H, 7.04: N, 4.94.

Conversion of Compound 7 to Compound 8. To a solution of **7** (102 mg, 0.39 mmol) in dioxane (1 mL) at room temperature under argon were added 40% methylamine (39.5 mg, 0.51 mmol) and 1 N NaOH (0.51 mL, 0.51 mmol). The reaction mixture was stirred (1 h) and then diluted with H_2O (5 mL), extracted with $CHCl_3$ (3 × 20 mL), washed with brine (2 × 5 mL), and dried (Na_2SO_4), and the solvent was removed to provide crude **8**. Silica gel chromatography (hexanes:EtOAc 2:8) afforded pure **8** (92 mg, 90%).

(±)-1,3-Dimethyl-1,2,3,4,5,6-hexahydro-1,5-methano-8-methoxy-3-benzazocin-2-one (9). A mixture of **8** (292 mg, 1.1 mmol), NH_2NH_2·H_2O (450 mg, 9 mmol), and 88% KOH (381 mg, 6.8 mmol) in diethylene glycol (6 mL) was heated to reflux (14 h). The reaction mixture was cooled to room temperature, diluted with H_2O (20 mL), extracted with EtOAc (3 × 50 mL), washed with brine (2 × 5 mL), and dried (Na_2SO_4), and solvent was removed to provide crude **9**. Silica gel chromatography (hexanes:EtOAc 3:7) afforded pure **9** (272 mg, 98%): ^{1}H NMR (250 M Hz, $CDCl_3$) δ 7.39 (d, J = 8.7 Hz, 1 H), 6.71 (dd, J = 8.7, 2.8 Hz, 1 H), 6.60 (d, J = 2.8 Hz, 1 H), 3.74 (s, 3 H), 3.65 (dd, J = 12.5, 6.7 Hz, 1 H), 3.25 (dd, J = 17.6, 6.7 Hz, 1 H), 3.15 (d, J = 12.5 Hz, 1 H), 2.79 (d, J = 17.6 Hz, 1 H), 2.77 (s, 3 H), 2.56 (m, 1 H), 2.1 (dd, J = 13.3, 3.5 Hz, 1 H), 1.97 (dd, J = 13.3, 3.5 Hz, 1 H), 1.58 (s, 3 H); IR (film) 3420, 1651, 1031 cm^{-1}; FABMS (*m*/*z*) 246 (M + H)$^+$. Anal. Calcd ($C_{15}H_{19}NO_2$): C, 73.47; H, 7.76; N, 5.71. Found: C, 73.69; H, 7.86; N, 5.47.

(±)-(*rel*-2*S*,3*R*)-2-Cyano-1,3-dimethyl-1,2,3,4,5,6-hexahydro-1,5-methano-8-methoxy-3-benzazocine (10). To a solution of **9** (1.43 g, 5.82 mmol) in THF (15 mL) at −78 °C under argon was added dropwise DIBAL-H, 1 M in hexanes (5.82 mL, 5.82 mmol), and the reaction mixture was stirred at −78 °C (1 h). The reaction mixture was quenched at −78 °C with 2 N NaOH (50 mL) and then warmed to room temperature and extracted with $CHCl_3$ (3 × 100 mL), washed with brine (2 × 50 mL), and dried (Na_2SO_4), and the solvent was removed to provide crude **10**, which was placed under high vacuum (3 h). The material was taken up in CH_2Cl_2 (116 mL), and to this solution at room temperature under argon was added TMSCN (1.154 g, 11.6 mmol) followed by $ZnCl_2$, 1 M in CH_2Cl_2 (5.82 mL, 5.82 mmol). The reaction mixture was stirred (2 h) and then quenched with saturated aqueous $NaHCO_3$ (30 mL), extracted with $CHCl_3$ (3 × 70 mL), washed with brine (2 × 50 mL), and dried (Na_2SO_4), and the solvent was removed to provide crude **10**. Purification by silica gel chromatography afforded pure **10** as a crystalline solid (1.1 g, 74%): mp 105 °C; ^{1}H NMR (250 M Hz, $CDCl_3$) δ 7.16 (d, J = 8.6 Hz, 1 H), 6.67 (dd, J = 8.6, 2.6 Hz, 1 H), 6.6 (d, J = 2.6 Hz, 1 H), 3.76 (s, 3 H), 3.32 (s, 1 H), 3.13 (dd, J = 17.6, 6.9 Hz, 1 H), 2.77 (d, J = 17.6 Hz, 1 H), 2.69 (d, J = 11.8 Hz, 1 H), 2.57 (dd, J = 11.8, 2.5 Hz, 1 H), 2.19 (s, 3 H), 2.06 (d, J = 13.8 Hz, 1 H), 1.85 (dd, J = 12.3, 2.3 Hz, 1 H), 1.69 (d, J = 12.3 Hz, 1 H), 1.5 (s, 3 H); IR ($CHCl_3$) 2922, 2364, 1544, 1134 cm^{-1}; FABMS (*m*/*z*) 257 (M + H)$^+$. Anal. Calcd ($C_{16}H_{20}N_2O$): C, 74.97; H, 7.86; N, 10.93. Found: C, 74.68; H, 7.88; N, 10.66.

Preparation of Compound 7 Using Eschenmoser's Salt. To a solution of **6** (12 g, 48.4 mmol) in THF (300 mL) containing HMPA (20 mL) at −78 °C under argon was dropwise added LDA, 2 M in THF (29 mL, 58.1 mmol), and the reaction mixture stirred at −78 °C (1 h). To this was added Eschenmoser's salt (*N*,*N*-dimethylmethyleneammonium iodide) (17.9 g, 97 mmol) quickly in one portion, the dry ice−acetone bath was then removed, and the reaction mixture was allowed to come to room temperature (overnight). The reaction mixture was quenched with 1 N HCl (70 mL), diluted with brine (150 mL), extracted with EtOAc (2 × 200 mL), washed with brine (2 × 100 mL), and dried (Na_2SO_4), and the solvent was removed to provide crude **7**. Purification by silica gel chromatography (hexanes:EtOAc; 8:2) afforded pure **7** (6.6 g, 52%). (See also above.)

(±)-1-(2,4-Dimethoxybenzyl)-1,2,3,4,5,6-hexahydro-1,5-methano-8-methoxy-3-methyl-3-benzazocine-2,11-dione (11). To a solution of **7** (400 mg, 1.54 mmol) in dioxane (8 mL) at room temperature under argon was added 2,4-dimethoxybenzylamine, prepared by the reaction of 2,4-dimethoxybenzylamine hydrochloride (344 mg, 1.7 mmol) with 1 N NaOH (1.7 mL, 1.7 mmol). The reaction mixture was stirred (4 h) and then diluted with brine, extracted with $CHCl_3$ (3 × 50 mL), washed with brine (2 × 5 mL), and dried

(15) Matteson, D. S.; Kandil, A. A. *J. Org. Chem.* **1987**, *52*, 5121−5124.
(16) Buckle, D. R.; Rockell, C. J. M. *J. Chem. Soc., Perkin Trans. 1* **1982**, 627−630.
(17) Langolis, N.; Rojas, A. *Tetrahedron* **1993**, *49*, 77−82.
(18) Colvin, E. W.; Martin, J.; Parker, W.; Raphael, R. A.; Shroot, B.; Doyle, M. *J. Chem. Soc., Perkin Trans. 1* **1972**, 860−870.

(Na_2SO_4), and the solvent was removed to provide crude **11**. This was dried under high vacuum (4 h) and then dissolved in toluene (80 mL) containing DBU (23 mg) and stirred at reflux (overnight). The reaction mixture was concentrated and then purified by silica gel chromatography (hexanes:EtOAc 7:3) to afford pure **11** (232 mg, 38%): ^{1}H NMR (250 M Hz, $CDCl_3$) δ 7.34 (d, J = 8.8 Hz, 1 H), 6.81 (dd, J = 8.8, 6.1 Hz, 1 H), 6.7 (d, J = 8.4 Hz, 1 H), 6.58 (d, J = 2.5 Hz, 1 H), 6.35 (d, J = 2.3 Hz, 1 H), 6.28 (dd, J = 8.3, 2.5 Hz, 1 H); 4.62 (d, J = 14.7 Hz, 1 H), 4.3 (d, J = 14.7 Hz, 1 H), 3.77 (s, 3 H), 3.75 (s, 3 H), 3.62 (s, 3 H), 3.59−3.4 (m, 3 H), 3.2−3.0 (m, 2 H), 11.48 (s, 3 H); IR (film) 2952, 1738, 1651, 1155, 931 cm^{-1}. Anal. Calcd ($C_{23}H_{25}NO_5 \cdot {}^1/_2H_2O$): C, 68.32; H, 6.94; N, 3.47. Found: C, 68.26; H, 6.62; N, 3.38.

(±)-1-(2,4-Dimethoxybenzyl)-1,2,3,4,5,6-hexahydro-1,5-methano-8-methoxy-3-methyl-3-benzazocin-2-one (12). A mixture of **11** (870 mg, 2.2 mmol), $NH_2NH_2 \cdot H_2O$ (890 mg, 17.6 mmol), and 88% KOH (739 mg, 13.2 mmol) in diethylene glycol (6 mL) was heated to reflux (5 h) and then cooled to room temperature. The reaction mixture was diluted with H_2O (20 mL), extracted with EtOAc (3 × 50 mL), washed with brine (2 × 5 mL), and dried (Na_2SO_4), and the solvent was removed to provide crude **12**. Purification by silica gel chromatography (hexanes:EtOAc 3:7) afforded pure **12** (582 mg, 71%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.44 (d, J = 8.6 Hz, 1 H), 6.73 (brd, J = 8.4 Hz, 1 H), 6.6 (brs, 1 H), 6.55 (d, J = 8.4 Hz, 1 H), 6.34 (brs, 1 H), 6.23 (d, J = 8.3 Hz, 1 H), 4.6 (d, J = 14.8 Hz, 1 H), 4.18 (d, J = 14.8 Hz, 1 H), 3.76 (s, 3 H), 3.73 (s, 3 H), 3.62 (s, 3 H), 3.6 (m, 1H), 3.21 (dd, J = 17.6, 6.5 Hz, 1 H), 3.06 (d, J = 12.5 Hz, 1 H), 2.66 (d, J = 17.6 Hz, 1 H), 2.49 (m, 1 H), 2.11 (d, J = 13.4 Hz, 1 H), 1.98 (d, J = 13.4 Hz, 1 H), 1.64 (s, 3 H); IR (film), 2931, 1675, 1208, 935 cm^{-1}; FABMS (m/z) 382 (M + H)$^+$. Anal. Calcd ($C_{23}H_{27}NO_4$): C, 72.42; H, 7.13; N, 3.67. Found: C, 72.48; H, 7.21; N, 3.72.

(±)-(*rel*-2*S*,3*R*)-2-Cyano-1-(2,4-dimethoxybenzyl)-1,2,3,4,5,6-hexahydro-1,5-methano-8-methoxy-3-methyl-3-benzazocine (13). To a solution of **12** (115 mg, 0.3 mmol) in THF (1 mL) at −78 °C under argon was added dropwise DIBAL-H, 1 M in hexane (0.45 mL, 0.45 mmol), and the reaction mixture was stirred at −78 °C (2 h). The reaction mixture was quenched at −78 °C with 2 N NaOH (10 mL) and then allowed to warm to room temperature. The mixture was extracted with $CHCl_3$ (3 × 30 mL), washed with brine (10 mL), and dried (Na_2SO_4), and the solvent was removed to provide crude product, which was dried under high vacuum (3 h). The residue was dissolved in CH_2Cl_2 (6 mL), and to this solution was added at room temperature under argon, TMSCN (60 mg, 11.6 mmol) followed by $ZnCl_2$, 1 M in CH_2Cl_2 (0.33 mL, 0.33 mmol). The reaction mixture was stirred (1.5 h) and then quenched with saturated aqueous $NaHCO_3$ (10 mL), extracted with $CHCl_3$ (3 × 20 mL), washed with brine (2 × 50 mL), and dried (Na_2SO_4), and the solvent was removed. Purification by silica gel chromatography afforded pure **13** as a white crystalline solid (92 mg, 78%): mp 98 °C; ^{1}H NMR (250 M Hz, $CDCl_3$) δ 7.04 (d, J = 9.34 Hz, 1 H), 6.67−6.65 (m, 2 H), 6.31−6.27 (m, 2 H), 6.14 (dd, J = 8.4, 2.3 Hz, 1 H), 3.79 (s, 3 H), 3.73 (s, 3 H), 3.55 (s, 3 H), 3.5 (d, J = 17.6 Hz, 1 H), 3.44 (d, J = 17.6 Hz, 1 H), 3.26 (brs, 1 H), 3.12 (dd, J = 17.4, 6.7 Hz, 1 H), 2.85−2.7 (m, 3 H), 2.19 (m, 1 H), 1.93 (dd, J = 13.1, 2.1 Hz, 1 H), 1.75 (brd, J = 13.1 Hz, 1 H), 1.45 (s, 3 H); IR ($CHCl_3$) 2920, 2218, 1612, 933 cm^{-1}; FABMS (m/z) 392 (M + H)$^+$. Anal. Calcd ($C_{24}H_{28}N_2O_3 \cdot {}^1/_4H_2O$): C, 72.64; H, 7.19; N, 7.06. Found: C, 72.63; H, 7.39; N, 6.94.

(±)-(*rel*-2*S*,3*R*)-1-Carboxymethoxy-2-cyano-1,2,3,4,5,6-hexahydro-1,5-methano-8-methoxy-3-methyl-3-benzazocine (16). A mixture of **13** (140 mg) and anisole (0.5 mL) in TFA (6 mL) was heated to 65 ± 5 °C (3 h) and then cooled to room temperature and TFA removed under vacuum. The resulting residue was diluted with $CHCl_3$ (10 mL), treated with saturated aqueous $NaHCO_3$ (5 mL), extracted with $CHCl_3$ (3 × 20 mL), washed with brine (2 × 5 mL), and dried (Na_2SO_4), and the solvent was removed. The resulting residue was purified by silica gel chromatography (hexanes:EtOAc 8:2) to afford intermediate amine **15** (77.2 mg, 91%). This residue (72.7 mg, 0.31 mmol) was reacted with methyl chloroformate (148 mg, 1.57 mmol) in the presence of Et_3N (162 mg, 1.57 mmol) in acetonitrile (6.3 mL) at 0 °C. After addition of reagents at 0 °C, the reaction mixture was warmed to room temperature and stirred (4 h). The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL), extracted with $CHCl_3$ (3 × 20 mL), washed with brine (2 × 5 mL), and dried (Na_2SO_4), and the solvent was removed to provide crude **16**. Purification by silica gel chromatography (hexanes:EtOAc 8:2) afforded pure **16** (84 mg, 93%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.22 (m, 1 H), 6.69 (dd, J = 8.7, 2.9 Hz, 1 H), 6.56 (brs, 1 H), 4.82 (brs, 0.4 H), 4.63 (brs, 0.6 H), 4.27−4.03 (m, 1 H), 3.74 (s, 3 H), 3.52 (s, 1.2 H), 3.33 (s, 1.8 H), 3.25 (m, 1H), 3.11 (brd, J = 16.3 Hz, 1 H), 2.78 (m, 1 H), 2.23 (m, 1 H), 2.05 (d, J = 15.1 Hz, 1 H), 1.82 (d, J = 15.1 Hz, 1 H), 1.54 (s, 3 H); IR ($CHCl_3$) 2923, 1684, 2200 (weak), 1216 cm^{-1}. Anal. Calcd ($C_{17}H_{20}N_2O_3$): C, 67.98; H, 6.71; N, 9.33. Found: C, 67.72; H, 6.90; N, 9.05.

(±)-(*rel*-2*S*,3*R*)-2-Carboxy-1,2,3,4,5,6-hexahydro-8-hydroxy-1,5- methano-3-methyl-3-benzazocine (2). A suspension of compound **16** (51 mg) in 6 N HCl (6 mL) was heated to reflux (3 days). The reaction mixture was cooled to room temperature, and the main portion of 6 N HCl was removed under vacuum. The resulting solid was treated with propylene oxide (1 mL) in EtOH (3 mL) and then taken to dryness. The resulting residue was shown by ^{1}H NMR to be relatively pure **2**. Further purification by HPLC (solvent A = 0.05% TFA in H_2O, solvent B = 0.5% TFA in acetonitrile; linear gradient 0% B to 100% B over 30 min) provided target **2** as a solid (38 mg, 88%): mp 64 °C; ^{1}H NMR (250 MHz, D_2O) δ 7.39 (d, J = 8.67 Hz, 1 H), 6.83 (dd, J = 8.67, 2.4 Hz, 1 H), 6.72 (d, J = 2.4 Hz, 1 H), 4.0 (dd, J = 12.7, 4 Hz, 1 H), 3.83 (brs, 1 H), 3.27−3.18 (m, 2 H), 2.81 (d, J = 18 Hz, 1 H), 2.5 (m, 1 H), 2.05 (d, J = 13.6 Hz, 1 H), 1.76 (d, J = 13.6 Hz, 1 H), 1.51 (s, 3 H); IR 3700−2400, 2960, 1716, 1501, 1024 cm^{-1}; FABMS (m/z) 360 (M + TFA$^-$)$^-$, 246 (M − H)$^-$. Anal. Calcd ($C_{14}H_{17}NO_3 \cdot CF_3CO_2H \cdot {}^9/_4H_2O$): C, 47.82; H, 5.6; N, 3.49. Found: C, 47.79; H, 5.77; N, 3.42.

Acknowledgment. Appreciation is expressed to Dr. Clifford George of the Naval Research Laboratory, Washington, DC, for X-ray crystallographic analysis and to Ms. Pamela Russ and Dr. James Kelley of the LMC for mass spectral analysis.

JO9700787