ents,[17] one of them again being Na in liquid NH_3.[18] In fact treatment of **6** with this reagent furnishes **4** in 32% yield.[16]

Hydrocarbon **4**, isolated as a colorless solid (mp 27–30 °C) by preparative GLC on SE 30 at 50 °C, is characterized by its mass spectrum (very similar to that of cubane[19]) [*m/e* 104 (15), 103 (43), 102 (10), 78 (100), 77 (44), 63 (18), 52 (45), 51 (67), 50 (51), 39 (83), 38 (23)], by its simple IR spectrum [3088, 3016, 1434, 1411, 1120 cm^{-1} (in CCl_4)], and by its unique NMR spectra: ^1H NMR ($CDCl_3$, 250 MHz) δ = 2.19 and 1.87 (multiplets of 4 H each); coupling constants obtained by simulation: $J_{1,2}$ = 4.9, $J_{1,3}$ = 0.1, $J_{1,5}$ = −0.6, $J_{1,6}$ = 5.4, $J_{1,7}$ = 2.8, $J_{3,4}$ = 11.3, $J_{3,7}$ = 0.0, $J_{3,8}$ = 0.0; ^{13}C NMR ($CDCl_3$) δ = 35.09 (d, ^1J = 160 Hz, C-1) and 9.58 (d, ^1J = 206 Hz, C-3). **4** is thermally inert up to 140 °C (in pyridine-d_5). A study on reactivity and properties of **4** in relation to bicyclo[1.1.0]butane and to other $(CH)_8$ isomers is in progress.

Appropriate starting materials for a path A access to the octabisvalene framework, functionalized tetracyclo[4.1.1.$0^{2,4}$.$0^{3,5}$]-octanes or tricyclo[3.1.1.$1^{2,4}$]octanes, are now available by addition of nucleophiles to **3**.[3] Thus attack of the divalent nucleophiles Na_2Se and Na_2Te on **3** in MeOH/THF furnishes the selenide **7** and the telluride **8** (89% and 87% yield, respectively, Scheme III), which upon treatment with excess *n*-butyllithium in THF undergo metalation and double intramolecular ring-closing substitution to afford **3** (64% and 83%, respectively).[20]

Acknowledgment. Support from the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, BASF AG, and Shell AG is gratefully acknowledged. We thank Prof. H. Prinzbach for critical discussions, Prof. H. Fritz and Dr. D. Hunkler for NMR, and Dr. J. Wörth for mass spectroscopic measurements.

(17) Fatiadi, A. J. In *The Chemistry of Triple-Bonded Functional Groups*; Patai, S., Rappoport, Z., Ed.; Wiley: 1983; pp 1057–1303.
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(19) Kybett, B. D.; Carroll, S.; Natalis, P.; Bonnell, D. W.; Margrave, J. L.; Franklin, J. L. *J. Am. Chem. Soc.* **1966**, *88*, 626.
(20) All new compounds gave spectral and analytical data consistent with the proposed structures.

ClO_2 Oxidation of Amines: Synthetic Utility and a Biomimetic Synthesis of Elaeocarpidine[1]

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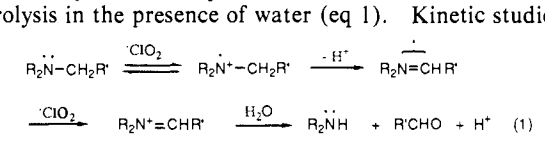
Chlorine dioxide (ClO_2)[2] is a gaseous free radical that is readily generated and stored in moderate concentrations (ca. 0.25 M at 0–5 °C) in either aqueous or selected organic solvents. ClO_2 reacts with tertiary amines to produce iminium ions which undergo hydrolysis in the presence of water (eq 1). Kinetic studies by

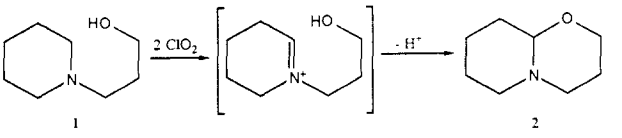


(1)

Rosenblatt and co-workers[3] have determined that the oxidation of tertiary amines by ClO_2 occurs via an electron abstraction route similar to that involved in the electrochemical oxidation of amines.[4]

Surprisingly, the synthetic utility of ClO_2 has hardly been explored.[2] We report here the use of ClO_2 to generate and trap iminium ions in situ with both internal and external nucleophiles, yielding a variety of α-substituted amines and nitrogen heterocycles.

Tertiary aminoalcohols react with ClO_2 in basic media to give moderate yields of bicyclic oxazolidines and tetrahydro-1,3-oxazines (Table I). Yield optimization studies using 1-piperidinepropanol (**1**) as a model substrate (eq 2) indicated that the



(2)

1 2

maximum yield (62–67%) of the desired bicyclic product **2** was obtained in the range of pH 9–11. In a typical oxidative cyclization a solution of ClO_2 was slowly added to a solution of the amine; sodium borate buffer, along with simultaneous addition of aqueous NaOH, was used to maintain the pH in the range 9.0 ± 0.2. Cyclizations of 2-methyl-substituted 1-piperidinepropanol and 1-piperidineethanol (Table I) show that there is a distinctly greater regiochemical tendency for ring closure to take place at the less-substituted α-carbon of the piperidine moiety. On the other hand, the mechanistically different $Hg(OAc)_2$ oxidations of the same compounds[5] yield products resulting from oxidation and ring closure predominately at the more-substituted piperidine α-carbon.

Reaction of tertiary amines with ClO_2 in the presence of 5–7 mol-equiv of aqueous sodium cyanide as an external nucleophile affords 53–83% yields of α-cyano-substituted tertiary amines (Table II).[5,6]

In the case of oxidative α-cyanation of *N*-methylpyrrolidine a high ratio of ring cyanation to methyl cyanation (>8:1) was observed. This same observation in the electrochemical cyanation has been explained as an electrode effect.[4] However, a stereoelectronic requirement for periplanarity of an α C–H bond with the partially occupied orbital on the nitrogen of the intermediate aminium radical cation in the second step of the oxidation (loss of a proton from the 2-carbon), may, at least in part, offer a better explanation for the observed results.[7]

α-Cyano-substituted tertiary amines can provide masked carbonyl anion equivalents in basic media[8,9] and iminium ion salts through loss of cyanide ion in acidic media.[10] This versatility makes the N,N-disubstituted α-aminonitriles available directly from fully formed tertiary amines by ClO_2-mediated cyanation (as well as $Hg(OAc)_2$ oxidation[5,6] and the three-step "one-pot" modified Polonovski procedure[10]) excellent intermediates for synthetic purposes.[8]

(1) Dedicated to Professor E. J. Corey on the occasion of his 60th birthday.
(2) Masschelein, W. J. In *Chlorine Dioxide*; Ann Arbor Science Publishers Inc: MI, 1979.
(3) (a) Rosenblatt, D. H.; Hayes, A. J., Jr.; Harrison, B. L.; Streaty, R. A.; Moore, K. A. *J. Org. Chem.* **1963**, *28*, 2790. (b) Rosenblatt, D. H.; Hull, L. A.; De Luca, D. C.; Davis, G. T.; Weglein, R. C.; Williams, H. K. R. *J. Am. Chem. Soc.* **1967**, *89*, 1158. (c) Hull, L. A.; Rosenblatt, D. H.; Davis, G. T.; Mann, C. K. *J. Phys. Chem.* **1969**, *73*, 2142. (d) Hull, L. A.; Davis, G. T.; Rosenblatt, D. H. *J. Am. Chem. Soc.* **1969**, *91*, 6247 and references cited.
(4) Chiba, T.; Takata, Y. *J. Org. Chem.* **1977**, *42*, 2973. For a review, see: Shono, T. *Tetrahedron* **1984**, *40*, 811.
(5) Leonard, N. J.; Musker, W. K. *J. Am. Chem. Soc.* **1960**, *82*, 5148.
(6) (a) Leonard, N. J.; Hay, A. S. *J. Am. Chem. Soc.* **1956**, *78*, 1984. (b) Leonard, N. J.; Hauck, F. P., Jr. *Ibid.* **1957**, *79*, 5279.
(7) This periplanarity requirement has already been suggested earlier by Chow et al. (Chow, Y. L.; Danen, W. C.; Nelsen, S. F.; Rosenblatt, D. H. *Chem. Rev.* **1978**, *78*, 243). Lack of periplanarity of the α hydrogens of aminium radical cations in sterically hindered tertiary amines has been shown to lead to a sufficient increase in the lifetime of the aminium radical cations to allow cyclic voltametry experiments to be performed: Nelsen, S. F.; Ippoliti, J. T. *J. Am. Chem. Soc.* **1986**, *108*, 4879.
(8) (a) Stork, G.; Jacobson, R. M.; Levitz, R. *Tetrahedron Lett.* **1979**, 771. (b) Stork, G.; Ozorio, A. A.; Leong, A. Y. W. *Tetrahedron Lett.* **1978**, 5175. (c) Bosch, J.; Bonjoch, J.; Diez, A.; Linares, A.; Moral, M.; Rubiralta, M. *Tetrahedron* **1985**, *41*, 1753. See, also: ref 9.
(9) Arseniyadis, S.; Kyler, K. S.; Watt, D. S. *Org. React.* **1984**, *31*, 55.
(10) Bonin, M.; Romero, J. R.; Grierson, D. S.; Husson, H.-P. *J. Org. Chem.* **1984**, *49*, 2392 and references cited; Groutas, W. C.; Essawi, M.; Portoghese, P. S. *Synth. Commun.* **1980**, *10*, 495. Lounasmaa, M.; Koskinen, A. *Tetrahedron* **1983**, *39*, 1627 and *Heterocycles* **1982**, *19*, 2115. The regiochemistry of the modified Polonovski reaction (in the absence of specific directing influences) appears similar to that of $Hg(OAc)_2$ oxidations of *N*-alkyl cyclic amines in favoring the more thermodynamically stable endocyclic product to the near exclusion of the exocyclic product.

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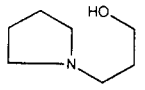
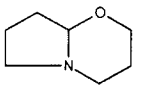
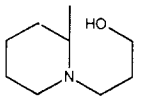
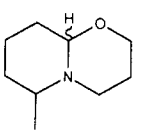
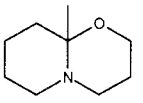
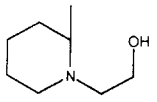
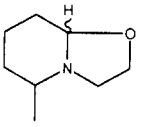
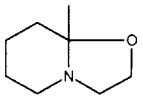
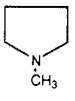
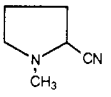
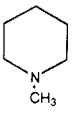
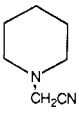
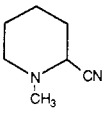
Table I. ClO_2 Oxidation of 3-Aminopropanols and 2-Aminoethanols

amine[a,b]	product	ClO_2 (at pH 9.0) (%)	$Hg(OAc)_2$[5] (%)
1	**2**	67	25
		61	34
	  A,A′ (3:1)[c] B	48 (6:1)	57 (1:1 [98°])[d] 56 (1:9 [60°])
	  A,A′ (3:1)[c] B	52 (5:2)	58 (1:20)[d] (at both 65° and 90°)

[a] Similar results were obtained for additional cyclic aminoalkanol analogues (Chen, C.-K., unpublished). In no case was any attempt made to determine the relative percentage of oxidation occurring at the acyclic N-CH_2 group in the aminoalcohol series. [b] ClO_2 oxidation of the acyclic prototype, 3-dimethylamino-1-propanol, afforded 3-methyl-1,3-tetrahydrooxazine in 60% yield. [c] Products A and A′ in both the third and fourth entries are equilibrating diastereomers which coincidently equilibrate to a 3:1 ratio in each case. [d] The yields and A,A′:B ratios for $Hg(OAc)_2$ cited in ref 5 have also been confirmed experimentally in this laboratory (NMR assay).

Table II. ClO_2 Oxidative Cyanation of Amines

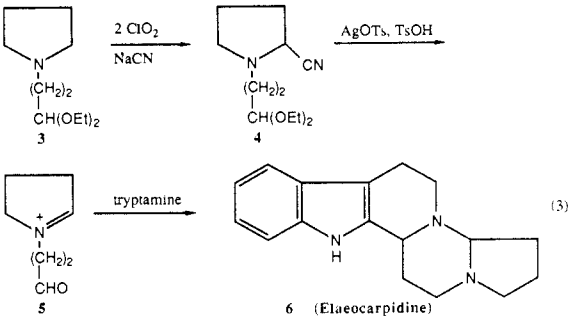
amine	product	yield (isolated)[a]	anodic ox[e]
$(CH_3)_3N$	$(CH_3)_2NCH_2CN$	67[b]	53
$(Et)_3N$	$(Et)_2NCH(CN)CH_3$	69[b]	38
$(n\text{-Prop})_3N$	$(n\text{-Prop})_2NCH(CN)Et$	53[b]	
$(n\text{-Bu})_3N$	$(n\text{-Bu})_2NCH(CN)(n\text{-Prop})$	83[b]	
	 	73[c] (11:89)[d] (13:87) crude	48 (19:81)
	 	68[c] (35:65)[d]	57 (38:62)

[a] The yields were based on ClO_2 as the limiting reagent. Slightly lower yields (5–10%) were obtained when the amine was the limiting reagent. Acetonitrile was used as a co-solvent in the case of water-insoluble tertiary amines. [b] The pH of the reaction mixture was maintained at 12.0 ± 0.3. [c] No pH control. [d] The ratios were for distilled products and were determined by ^1H NMR integration. [e] See ref 4.

Our results indicate that the oxidative cyanation of tertiary amines with ClO_2 is a potentially useful alternative to electrochemical, $Hg(OAc)_2$, and modified Polonovski oxidations from several points of view, viz., convenience, regioselectivity, and chemoselectivity. The ClO_2 oxidations of tertiary amines are conducted in mildly basic media at 0–25 °C by simple addition of a near-stoichiometric amount of ClO_2 to the amine. In contrast, $Hg(OAc)_2$ oxidations require acidic media, a large excess of the oxidant, and elevated temperatures,[5,6] and the modified Polonovski procedure requires strong oxidizing agents (peroxide or peroxyacid) and acylating conditions.[10]

The advantageous chemoselectivity of the ClO_2-based oxidative cyanation procedure is nicely demonstrated in the following biogenetically patterned synthesis of elaeocarpidine (**6**) which was facilitated by the ability to prepare acid-sensitive **4** from **3** under the nonacidic conditions which prevail in ClO_2-mediated oxidative cyanations.

The *Elaeocarpus* alkaloids[11] comprise a large family of indolizidine alkaloids for which the iminium ion **5** (or its biological equivalent) has been suggested as a common precursor.[12] Treatment of **3** with ClO_2–NaCN afforded an 88–92% yield of two monocyanated products (9:1). The major product, acetal **4**,[13] represents a synthetic equivalent of **5**. Addition of a solution of **4** (1 mol-equiv), tryptamine (1 mol-equiv), and TsOH (2 mol-equiv) in EtOH–H_2O to a solution of AgOTs (1 mol-equiv) in refluxing EtOH–H_2O afforded chromatographically pure (mplc) (±)-elaeocarpidine (**6**) in 38% yield based on **4** (eq 3). The yield compares favorably with that obtained in a previous biomimetic synthesis of **6** reported by Gribble.[14]



Acknowledgment. This work was supported in part by BRSG S07 RR07054-17 awarded by the Biomedical Research Support Grant Program, Division of Research Resources, National Institutes of Health. The assistance of the Washington University High Resolution NMR facility, funded in part through NIH 1S10R02004, and of the Washington University Mass Spectrometry Resource, funded through NIH RR00954, is also gratefully acknowledged.

Registry No. 3, 24299-78-3; **4**, 114583-15-2; **6**, 20069-07-2; ClO_2, 10049-04-4; $(CH_3)_2N(CH_2)_3OH$, 3179-63-3; $(CH_3)_3N$, 75-50-3; $(CH_3)_2NCH_2CN$, 926-64-7; $(Et)_3N$, 121-44-8; $(Et)_2NCH(CN)CH_3$, 82215-74-5; $(n\text{-prop})_3N$, 102-69-2; $(n\text{-prop})_2NCH(CN)Et$, 114583-14-1; $(n\text{-Bu})_3N$, 102-82-9; $(n\text{-Bu})_2NCH(CN)(n\text{-prop})$, 103229-71-6; 1-pyrrolidinepropanol, 19748-66-4; hexahydro-2*H*-pyrrolo[2,1-*b*][1,3]oxa-

(11) For recent syntheses of *Elaeocarpus* alkaloids, see: (a) Flann, C.; Malone, T. C.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6097. (b) Shono, T.; Matsumura, Y.; Uchida, K.; Tsubata, K.; Makino, A. *J. Org. Chem.* **1984**, *49*, 300 and references cited.

(12) See, e.g.: (a) Johns, S. R.; Lamberton, J. A. In *Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1973; Vol. 14, p 325. (b) Cordell, G. A. In *Introduction to Alkaloids: A Biogenetic Approach*; Wiley-Interscience: New York, 1981; p 222.

(13) Purified by flash chromatography on neutral alumina: ^{13}C NMR ($CDCl_3$), 117.96 (s), 100.83 (d), 61.26 (t), 61.00 (t), 53.76 (t), 51.18 (t), 48.23 (t), 32.58 (t), 29.61 (t), 21.93 (t), 15.32 (q). Mass spectra and detailed ^1H NMR (including COSY and ^1H J-correlated) spectra are also in agreement with the proposed structure.

(14) Gribble, G. W.; Soll, R. M. *J. Org. Chem.* **1981**, *46*, 2433.

zine, 5860-49-1; 2-methyl-1-piperidinepropanol, 94-88-2; *cis*-hexahydro-6-methyl-2*H*,6*H*-pyrido[2,1-*b*][1,3]oxazine, 114583-09-4; *trans*-hexahydro-6-methyl-2*H*,6*H*-pyrido[2,1-*b*][1,3]oxazine, 114583-10-7; hexahydro-9a-methyl-2*H*,6*H*-pyrido[2,1-*b*][1,3]oxazine, 110423-48-8; 2-methyl-1-piperidineethanol, 17719-74-3; *cis*-hexahydro-5-methyl-5*H*-oxazolo[3,2-*a*]pyridine, 114583-11-8; *trans*-hexahydro-5-methyl-5*H*-oxazolo[3,2-*a*]pyridine, 114583-12-9; hexahydro-8a-methyl-5*H*-oxazolo-[3,2-*a*]pyridine, 114583-13-0; 3-methyl-1,3-tetrahydrooxazine, 21635-18-7; *N*-methylpyrrolidine, 120-94-5; 1-pyrrolidineacetonitrile, 29134-29-0; 1-methyl-2-pyrrolidinecarbonitrile, 20297-37-4; *N*-methylpiperidine, 626-67-5; 1-piperidineacetonitrile, 3010-03-5; 1-methyl-2-piperidinecarbonitrile, 18747-95-0; tryptamine, 61-54-1.

A New Method for the Formation of Nitrogen-Containing Ring Systems via the Intramolecular Photocycloaddition of Vinylogous Amides. A Synthesis of Mesembrine†,[1]

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Searle Chemistry Laboratories, Department of Chemistry The University of Chicago, Chicago, Illinois 60637

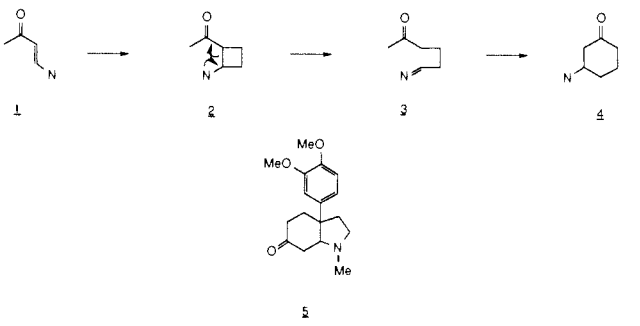
Received January 26, 1988

We report herein our preliminary results with the intramolecular photocycloaddition of vinylogous amides, which leads to a new and general method for the synthesis of nitrogen-containing ring systems. Several groups have reported on the intramolecular photocycloaddition of vinylogous amides and imides.[5-7] However, in none of the previously reported cases has the chemistry of the ketoimine **3**, which results from retro-Mannich fragmentation of the photoadduct **2**, been exploited (Scheme I). The intramolecular photocycloaddition of *suitably substituted* vinylogous amides begins a cascade of reactions that terminates in the formation of a new carbon–carbon bond via Mannich closure of the intermediate ketoimine, i.e., **3** → **4** (Scheme I). We report herein the application of this photoaddition–retro-Mannich–Mannich sequence to a synthesis of the alkaloid mesembrine, **5**.[8-10]

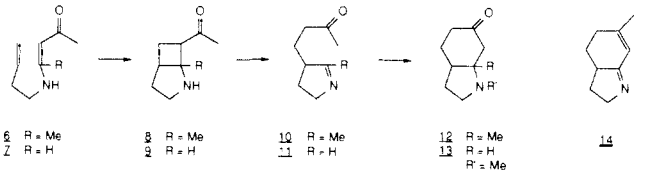
To establish the viability of the sequence outlined in Scheme I, the reaction of vinylogous amides **6** and **7** (Scheme II), resulting from the condensation of 3-butenylamine with acetyl acetone and sodio formyl acetone, respectively, was examined.[11] Irradiation of a 0.026 M solution of **6** in acetonitrile through Pyrex, using a medium-pressure mercury lamp, led to the formation not of **8** but instead to **10**,[12] the product of photoaddition and retro-Mannich fragmentation, consistent with results obtained by Schell in a related system.[5] On treatment with base, or simply on standing at room temperature in chloroform solution, the ketoimine was converted to the unsaturated imine, **14**, via tautomerization of the imine to enamine, addition to the carbonyl group, and elimination of water. The conversion of **10** (or the corresponding iminium ketone, obtained on reaction of **10** with trimethyloxonium tetrafluoroborate in methylene chloride) to **12**, the desired Mannich product, could not be accomplished under either acidic or basic reaction conditions. However, irradiation of **7**, lacking the methyl group of **6** and therefore precluding the formation of products analogous to **14**, led to the formation of the ketoimine **11**. Reaction of **11** with 1 equiv of trimethyloxonium tetrafluoroborate in methylene chloride, followed by treatment of the derived iminium ketone with 15% aqueous hydrochloric acid, led to the formation of the photocycloaddition–retro-Mannich–Mannich product **13**, isolated as its DNP derivative in 50% overall yield.

The utility of ketoimines such as **3** in the synthesis of alkaloids has already been demonstrated,[8] and we describe herein the application of this methodology to an efficient synthesis of mesembrine, **5** (Scheme III). The requisite photosubstrate **18** was prepared as outlined below. Reaction of veratrole with 3-bromopropionyl chloride led to the formation of **15** in 82% yield, which on treatment with the Tebbe reagent[13] led to the formation of styryl bromide **16** in 93% yield. Treatment of **16** with ammonia led to the formation of amine **17** in 89% yield. Condensation with 4-chloro-3-buten-2-one[14] led to the formation of the photosubstrate **18** in 77% yield. Irradiation in the usual manner led, via **19**, to

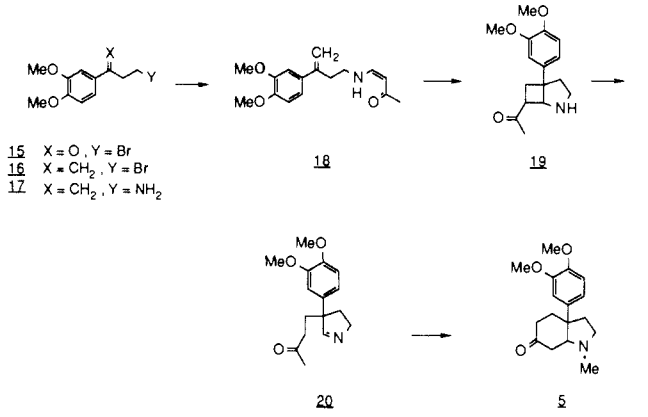
Scheme I



Scheme II



Scheme III



† Dedicated to Professor E. J. Corey on the occasion of his 60th birthday.

(1) Presented in part at the 194th National Meeting of the American Chemical Society, New Orleans, LA, August 30–September 4, 1987; ORGN 118.

(2) Fellow of the Alfred P. Sloan Foundation, 1987–1989. Recipient of a National Institutes of Health Career Development Award, 1988–1993, and a Merck Grant for Faculty Development, 1985–1986.

(3) Fellow of the National Institutes of Health Predoctoral Training Program (GM07183).

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