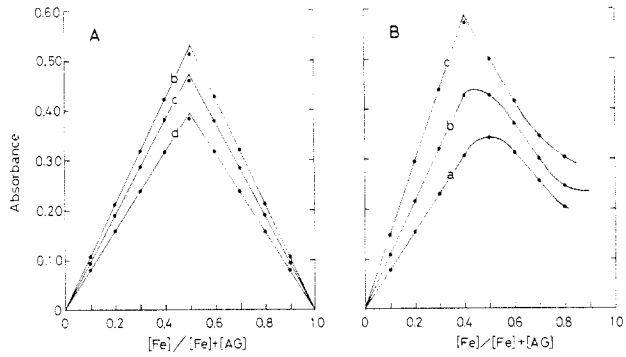

Figure 3. Job's plots of continuous variation method measured at 500 (a), 480 (b), 440 (c), and 420 (d) nm. Experiments were performed with 0.5 mM of alcaligin (AG) and $FeCl_3$ (Fe) at pH 2.0 (A) and 6.0 (B).

imum at 206 nm, while those of ferric alcaligin exhibits maxima at 206 and 426 nm at pH 6.0, which is a typical absorption spectrum for a ferric hydroxamate. As the pH is lowered from 6.0 to 2.0 with HCl, the wavelength of the absorption maximum moves from 426 (ϵ 2432) to 472 (ϵ 2128) nm, and an isosbestic point appears at 450 nm. The red shift at lower pH[8] and the content of bound hydroxylamine[9] indicates that alcaligin has two hydroxamate groups per molecule [IR(KBr) 3420.0 s, 3304.0 vs, 3120.0 s, 2940.0 s, 2832.0 s, 1648.0 vs, 1585.6 s, 1553.6 s, 1478.4 s, 1420.0 s, 1215.7 m, 1174.7 m, 1109.2 m, 1000.1 s, 703.7, 501.0, and 407.4 cm^{-1}]. See ref 10 and 11 for the ^{13}C and ^1H NMR assignments. The chemical shifts were assigned by using results of ^1H homonuclear decoupling, HETCOR, and DEPT experiments. The complete structure determination was given by a single-crystal X-ray crystallography[12] (Figure 1). As shown in Figure 2, alcaligin has a novel structure with a ring dihydroxamate. Hydroxamate siderophores have rarely been found in bacterial species, and ring form trihydroxamates, such as ferrichromes[13] and fusarinines,[14] are all of fungal origin while ferrioxamines[15] occur in actinomycetes. The closest known relative of alcaligin is the very recently described bisucaberin,[16] a cyclic dihydroxamate from the salt water bacterium *Alteromonas haloplanktis*. In alcaligin, the two residues of *N*-hydroxycadaverine of bisucaberin have been replaced by 2 mol of *N*-hydroxyputrescine additionally substituted with an alcohol function in the carbon chain. This type of linker has not been reported previously in the siderophore series.

Analysis of Job's plots of continuous variation method demonstrated that alcaligin chelates ferric iron at a molar ratio of 3:2 at pH 6.0 and 1:1 at pH 2.0. A molecular model shows that intramolecular coordination with iron is sterically capable when two carbonyl oxygens of amide groups other than two hydroxamate groups coordinate to the ferric iron. Unfortunately, we have been unable to crystallize the ferric complex, and elucidation of coordinating atoms remained uncertain. The apparent stability constants were determined by displacement method with EDTA[17] and found them smaller than those of EDTA or known dihydroxamate siderophores.[18] The approximate values of apparent stability constants defined as $K_{Fe_2AG_3} = [Fe_2AG_3]/[Fe]^2[AG]^3$ at pH 6.0 and $K_{FeAG} = [FeAG]/[Fe][AG]$ at pH 2.0 are calculated to be 10^{37} and 10^9, respectively.

Acknowledgment. We thank J. B. Neilands, University of California Berkeley, for kindly providing the siderophore auxotrophs and many helpful suggestions for the experiments and manuscript; Y. Yamamoto, Kyoto University, for the use of mass and NMR analyzer and advice; N. Shiraishi, Faculty of Agriculture, Kyoto University, for the use of IR analyzer; and S. Hara, Faculty of Science, Osaka University, for the use of an amino acid analyzer. This study was supported in part by a grant from the Lake Biwa Research Institute, Shiga Prefecture.

Supplementary Material Available: Precise data for X-ray crystallography, bond angles and distances, and torsion angles and ^1H and ^{13}C NMR spectra (9 pages). Ordering information is given on any current masthead page.

(6) The FABMS was measured on a JEOL JMS-DX303 mass spectrometer. Two major peaks, $[M + H]^+$ *m/z* 405 and $[M + H - 16]^+$ *m/z* 389, were obtained. The latter, which corresponds to the loss of an oxygen from the hydroxylamine group, is typical of a hydroxamate siderophore. Dell, A.; Hider, R. C.; Barber, M.; Bordoli, R. S.; Sedgwick, R. D.; Tyler, A. N.; Neilands, J. B. *Biomed. Mass Spectrom.* **1982**, *9*, 158-161.

(7) Anal. Calcd for $C_{16}H_{28}N_4O_8 \cdot 2H_2O$: C, 43.62; H, 7.34; N, 12.72; O, 36.32. Found: C, 43.64; H, 7.29; N, 12.69; O, 36.23.

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(9) (a) Csáky, T. Z. *Acta Chim. Scand.* **1948**, *2*, 450-454. (b) Gillam, A. H.; Lewis, A. G.; Andersen, R. J. *Anal. Chem.* **1981**, *53*, 841-844.

(10) ^{13}C NMR (100 MHz, CD_3OD) δ 29.015 (C-15 and C-28); 31.497, 31.847, 32.328, and 32.620 (C-19, C-27, C-30, C-26); 45.946, 46.705, 46.938, and 48.033 (C-25, C-13, C-20, C-24); 64.818 and 68.408 (C-16 and C-29); 170.516, 174.953, 175.391, and 175.683 (C-17, C-23, C-21, C-18).

(11) ^1H NMR (400 MHz, CD_3OD, 10 °C) δ 1.24 (tm, 1 H, *J* = 12.8 Hz, 28-H), 1.47 (m, 1 H, 15-H), 1.83 (m, 1 H, 15-H), 2.15 (dt, 1 H, *J* = 13.5 and 3.9 Hz, 27-H), 2.22 (tm, 1 H, *J* = 12.9 Hz, 28-H), 2.36 (ddd, 1 H, *J* = 14.9, 7.1, and 3.7 Hz, 26-H), 2.44-2.58 (m, 4 H, 19-H, 27-H, 20-H, 26-H), 2.67 (ddd, 1 H, *J* = 16.9, 7.1 and 2.9 Hz, 30-H), 2.87-2.98 (m, 3 H, 25-H, 19-H, 30-H), 3.27-3.37 (m 3 H, 25-H, 13-H, 24-H), 3.49 (tm, 1 H, *J* = 10.5 Hz, 29-H), 3.59 (m, 1 H, 16-H), 3.70 (dd, 1 H, *J* = 12.7 and 3.4 Hz, 20-H), 3.98 (td, 1 H, *J* = 12.7 and 2.5 Hz, 24-H), 4.17 (ddd, 1 H, *J* = 14.3, 10.0, and 4.4 Hz, 13-H).

(12) Alcaligin was crystallized in the space group $P2_12_12_1$ with *a* = 11.706 (1) Å, *b* = 16.200 (2) Å, *c* = 11.030 (1) Å. Data collection was performed with an automated diffractometer. Reflections in the two octants were measured within $2\theta = 120°$, with the Cu Kα radiation. The R_{sym} of averaging the equivalent reflections was 0.015. The structure was solved and refined by the automatic structure analysis package for the microcomputer, based on MULTAN 78. The final *R* factor was 0.059, including 32 hydrogen atoms and two water molecules.

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Total Synthesis of (±)-Methyl Homosecodaphniphyllate: A Remarkable New Tetracyclization Reaction

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The *Daphniphyllum* alkaloids are a group of complex, squalene-derived natural products.[1] In this communication, we

(1) (a) Yamamura, S.; Hirata, Y. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic: New York, 1975; Vol. 15, p 41. (b) Yamamura, S.; Hirata, Y. *Int. Rev. Sci., Org. Chem., Ser. 2* **1976**, *9*, 161. (c) Yamamura, S. In *The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1986; Vol. 29, p 265.

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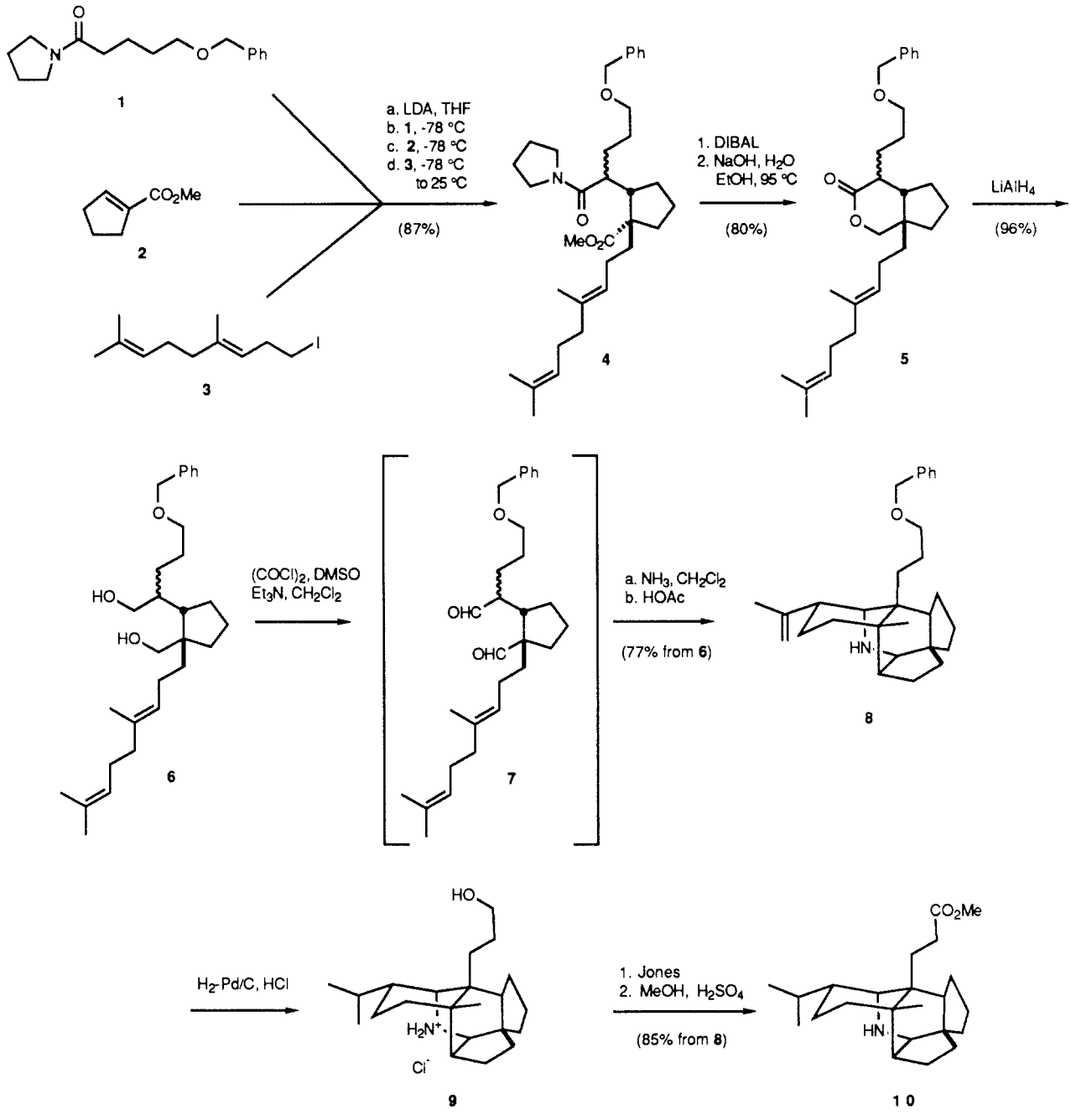
Scheme I



describe a concise, high-yielding total synthesis of (±)-methyl homosecodaphniphyllate (**10**), a representative member of the group (see Scheme I).[2] The key step in the synthesis is an extraordinary new tetracyclization process in which five bonds and four rings are formed.

To the preformed lithium enolate of amide **1**[3] are added α,β-unsaturated ester **2**[4] and homogeranyl iodide (**3**).[5] Compound **4**, obtained in 87% yield, is converted in two steps into lactone **5**, which is reduced to diol **6**. Swern oxidation of **6** provides a methylene chloride solution of dialdehyde **7**. Gaseous ammonia is passed into the solution, the solvent is removed at reduced pressure, the residue is taken up in acetic acid, and the resulting solution is warmed for 1.5 h at 70 °C; pentacyclic unsaturated amine **8** is obtained in 77% yield, based on diol **6**. The isopropenyl double bond is saturated, and the benzyl ether is cleaved by treatment of an ethanolic solution of **8** with hydrogen over Pd/C, first in neutral solution (to saturate the double bond) and then in the presence of added hydrochloric acid (to accomplish hydrogenolysis). Filtration and removal of the solvent provides hydrochloride **9**, which is subjected to Jones oxidation and Fischer esterification to obtain (±)-methyl homosecodaphniphyllate (**10**), identified by comparison of its TLC behavior and ^{1}H NMR spectrum with an authentic sample provided by Professor S. Yamamura.

The tetracyclization process (**6** -> **8**) has been carried out a number of times, on quite practical scales (up to 10 mmol), and proceeds in reproducibly excellent yield. Bicyclic azadiene **11** and tetracyclic imine **12**, intermediates in the process, have both been

(2) For the only previous total synthesis of a *Daphniphyllum* alkaloid, see: Heathcock, C. H.; Davidsen, S. K.; Mills, S.; Sanner, M. A. *J. Am. Chem. Soc.* **1986**, *108*, 5650.

(3) Amide **1** was prepared from δ-valerolactone in two steps in 90% overall yield (1. KOH, benzyl chloride, refluxing toluene; 2. *N,N'*-carbonyldiimidazole, pyrrolidine). Details will be reported in the full paper.

(4) Unsaturated ester **2** was prepared by reduction of 2-(methoxycarbonyl)cyclopentanone with $NaBH_4$ and elimination of the resulting alcohol with *p*-toluenesulfonyl chloride and pyridine. See: (a) Rhoads, S. J.; Chattopadhyay, J. K.; Waali, E. E. *J. Org. Chem.* **1970**, *35*, 3352. (b) Kronenthal, R. L.; Becker, E. I. *J. Am. Chem. Soc.* **1957**, *79*, 1095.

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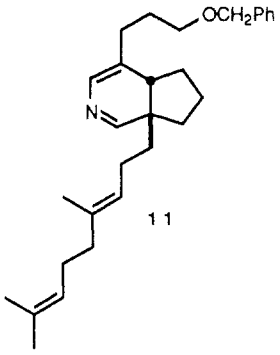

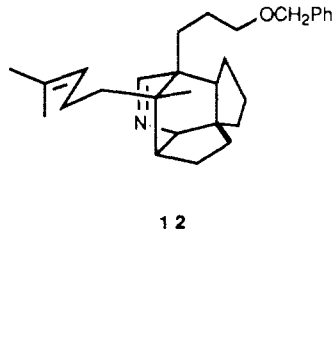

isolated and fully characterized. Chromatographic analysis of the reaction mixture indicates that **12** is produced immediately upon addition of acetic acid to **11**, whereas **8** is produced only upon warming the solution. The conversion of **11** to **12** may be formulated as an intramolecular Diels–Alder reaction of the protonated form of **11**. The Diels–Alder reaction has been demonstrated with **11** itself, but it is slow in toluene at 110 °C.[6] The transformation of **12** into **8** is presumably a π-cyclization of the prenyl double bond onto the immonium moiety of **12**. It is noteworthy that the process is highly stereoselective with respect to the isopropenyl group and delivers **8** with the double bond situated only in the terminal position. We believe that a process such as this may be involved in the biosynthesis of the *Daphniphyllum* alkaloids.

The total synthesis reported here is notable for its brevity and high yield; only nine laboratory operations are required from homogeranyl iodide, and the overall yield from this material is 44%. At the present time, we have prepared more than 3 g of **10** in this manner.

Acknowledgment. This work was supported by a research grant from the National Science Foundation, CHE-8418427, an American Chemical Society Organic Division Graduate Fellowship to R.B.R. from Smith Kline & French Laboratories, and a National Science Foundation Graduate Fellowship to M.M.H. We thank Professor S. Yamamura for supplying us with methyl homosecodaphniphyllate.

Supplementary Material Available: Physical data for compounds **4**, **5**, **6**, **8**, **9** (free base), **10**, **11**, and **12** (4 pages). Ordering information is given on any current masthead page.

(6) Diels–Alder reactions involving 2-azadienes are precedented. See, inter alia: (a) Eddaif, A.; Laurent, A.; Mison, P.; Pellissier, N.; Carrupt, P.-A.; Vogel, P. *J. Org. Chem.* **1987**, *52*, 5548. (b) Cheng, Y.-S.; Ho, E.; Mariano, P. S.; Ammon, H. L. *Ibid.* **1985**, *50*, 5678. (c) Boger, D. L.; Weinreb, S. N. In *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: San Diego, CA, 1987; pp 255–260. (d) Boger, D. L. *Tetrahedron* **1983**, *39*, 2876–2882.

A New and Practical Method of Decarboxylation: Photosensitized Decarboxylation of *N*-Acyloxyphthalimides via Electron-Transfer Mechanism

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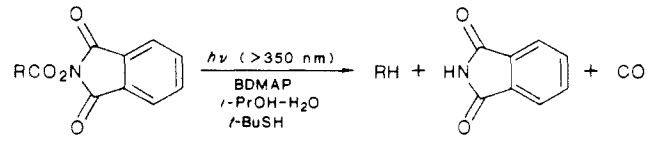
Photosensitized electron-transfer reactions have recently attracted considerable attention in organic photochemistry. Many mechanistic investigations concerning the reactivities of cation and anion radicals have been currently published.[1] However, synthetically useful application based on this methodology has been limited to fewer examples.[2] We report a new and practical method of decarboxylation of carboxylic acids via *N*-acyloxyphthalimides with use of the photosensitized electron-transfer reaction. The decarboxylations of unactivated carboxylic acids were classically achieved by thermolysis of peresters[3] or by two-step conversion via haloalkanes through Hunsdiecker reaction.[4,5] Recently Barton and his co-workers developed an elegant method of decarboxylation which proceeds via radical addition to *O*-ester of thiohydroxamic acid derivatives.[6] More recently Hasebe and Tsuchiya reported a new photolytic method with oxime esters.[7] Although these recently developed methods much improved the yields and the procedures for the decarboxylation reactions, the use of anhydrous conditions and the relatively narrow range of excitation wavelength for its direct photolysis in the latter still place several restrictions. The present photosensitized decarboxylation through *N*-acyloxyphthalimides, which are readily derived from various carboxylic acids and *N*-hydroxyphthalimide by use of DCC and are easily isolated as stable compounds,[8] proceeds in high yields in aqueous solvents with irradiation of visible light (350–450 nm).

Irradiation of a *i*-PrOH–water (95:5) solution of 1,6-bis(dimethylamino)pyrene (BDMAP), *N*-acyloxyphthalimide (**1a**), and

Table I. Photosensitized Decarboxylation of the Esters **1a–c** in Aqueous *i*-PrOH Containing 2% *t*-BuSH[a]



1 2

R; **a**: *t*-Bu—⟨⟩—$(CH_2)_3$—, **b**: $(PhCH_2)_2CH$—, **c**: 9-triptycyl

	hydrocarbon[b] yield (%)	phthalimide[c] yield (%)	sensitizer[c] recovery (%)	ΔG^d (kcal/mol)	k_q^e (M^{-1} s^{-1})
1a	88	92	82	−30.5	7.9×10^9
1b	98	84	84	−31.0	8.3×10^9
1c	84	87	75	−33.0	8.9×10^9

[a] [substrate] = $0.5–3.1 \times 10^{-3}$ M, [sensitizer] = $0.8–1.7 \times 10^{-3}$ M in *i*-PrOH–H_2O (95:5, 100 mL) containing *t*-BuSH (2 mL). Irradiation was performed under argon for 2 h. [b] GC determination. [c] Isolated yield. [d] Calculated from Rehm–Weller equation.[15] [e] From the fluorescence quenching experiment in THF–H_2O (95:5) at [BDMAP] = 6.56×10^{-6} M.[16]

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