Phenyl(2-naphthyl)acetic acid (14b): mp 141–142 °C (lit.[35] mp 141 °C); ^{1}H NMR (CDCl$_3$) δ 5.11 (s, 1 H), 6.00 (br s, 1 H), 7.12–7.80 (m, 12 H); IR (KBr) 3400–2400 (ν OH), 1712 cm^{-1} (ν CO); MS, *m/e* 262 (M$^+$).

9-Hydroxy-9-fluorenecarboxylic acid (13c): mp 170–172 °C (lit.[36] mp 167 °C); ^{1}H NMR (CDCl$_3$) δ 5.48 (br s, 2 H), 7.20–7.75 (m, 8 H); IR (KBr) 3452 (ν OH), 3300–2500 (ν OH), 1724 cm^{-1} (ν CO); MS, *m/e* 226 (M$^+$).

9-Fluorenecarboxylic acid (14c): mp 222–224 °C (lit.[33] mp 225–227 °C); ^{1}H NMR (CDCl$_3$) δ 4.87 (s, 1 H), 6.01 (br s, 1 H), 7.10–7.85 (m, 8 H); IR (KBr) 3300–2500 (ν OH), 1700 cm^{-1} (ν CO); MS, *m/e* 210 (M$^+$).

IR Measurement of the Intermediates. These experiments were carried out in THF/HMPA solution with a liquid cell under N$_2$. Samples were transferred by a syringe and their spectra were obtained as difference spectra of the samples and the solvents. The results are shown in Figures 1 and 2.

Titration Analysis. A reaction mixture of benzophenone (1 mmol) and Yb (1 mmol) was prepared as described above. The solution was transferred to another vessel by a syringe and the unchanged Yb metal was left. The unchanged metal was dissolved in concentrated HCl and then the amount determined by EDTA (ethylenediaminetetraacetic acid disodium salt) titration with XO (xylenol orange) as an indicator.[37,38] It was 0.07 mmol. The solution was hydrolyzed and the organic products were extracted with ether (3 × 30 mL) and isolated by medium pressure liquid chromatography (silica gel). The products were benzhydrol (**2a**) (174.8 mg, 0.95 mmol) and diphenylmethane (5.0 mg, 0.03 mmol). EDTA titration of the aqueous solution gave Yb^{3+} = 0.90 mmol.

Acknowledgment. This research was supported in part by Grant-In-Aids from the Ministry of Education, Science and Culture, Japan.

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(35) Michael, H. A.; Jeanpretre, J. *Ber.* **1892**, *25*, 1615.

(36) Wislicenus, W.; Mocker, W. *Ber.* **1913**, *46*, 2772.

(37) Kinnunen, J.; Wennerstrand, B. *Chemist-Analyst* **1959**, *46*, 92.

(38) Ueno, K. *Chelatometric Titration (Jpn)*; Nankodo: Tokyo, 1961; pp 327–329.

Synthesis and Photochemistry of Some New Pentacycloundecan-8-ones. Probes for Hydrogen Abstraction in the π-Plane

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A new series of pentacycloundecan-8-ones was prepared to evaluate the reactivity of hydrogen abstraction reactions by excited states of cycloalkanones in the realm perpendicular to the carbonyl plane. Compounds of types 1 and 2 were inert to irradiation at 300 nm (ϕ [–K] $< 10^{-3}$) despite close proximity of oxygen and hydrogen atoms in the ground states (ca. 2.5–2.6 Å). A transition-state model for 2 did not reveal any barriers attributable to unusual steric strain. Estimates of the reactivity of 2 relative to 2-hexanone indicate a decrease in hydrogen abstraction rate of at least 10^3. These studies confirm the importance of stereoelectronic barriers toward hydrogen abstraction in this realm that have been predicted by diverse theoretical models.

Introduction

Hydrogen atom abstraction reactions by photoexcited carbonyl groups are among the most widely studied photoreactions from both experimental as well as theoretical standpoints.[2] A comprehensive body of experimental data exemplifies the dependency of reactivity on a wide variety of parameters, for example: spin multiplicity, electronic configuration, C–H bond strength, physical state, solvent, steric effects, inductive effects, and stereoelectronic factors.

Recent studies of the solid phase have reopened the question of the definition of the optimum transition-state geometry for hydrogen atom abstraction reactions.[3] Earlier workers concluded that hydrogen atom abstraction reactions occur preferentially in the region of space near the n orbital of n,π^* states of simple ketones.[4] Wagner proposed a cos^2 ϕ dependency where ϕ is the C—C=O···H torsion angle.[2] Certain polycyclic ketones were claimed to be "unreactive" because proximate hydrogen did not lie in the plane of the carbonyl group.[5] Scheffer, Trotter, et al.[6] proposed that the ideal stereoelectronic arrangement involves an in-plane interaction of a half-filled n orbital with the abstracted hydrogen at an angle normal to the C=O bond at H···O distances between 2.3 and 2.6 Å. Studies of Norrish type II reactions in the solid state were rationalized in terms of a looser transition state that permitted O···H contacts as long as 3.10 Å and out-of-plane angles as large 62.3°.

Photochemical studies of solid complexes of desoxycholic acid and acetophenone derivatives have provided examples of intermolecular hydrogen abstractions from the perpendicular direction of the carbonyl plane, but it was concluded that molecular motions within the crystal lattice permitted approach of the reactive hydrogen to the locus of the n orbital of the excited ketone.[7]

Several recent theoretical studies have also dealt with the problem of the critical stereoelectronic parameters in hydrogen abstraction reactions.[8] In an ab initio computational analysis of the hydrogen abstraction reaction between methane and the triplet state of formaldehyde, Morrison et al.[9] calculated the following angles for the optimized transition-state geometry: C=O···H = 108.9°;

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(1) Current address: Helwan University, Giza, Egypt.

(2) (a) Wagner, P. J. *Acc. Chem. Res.* **1983**, *16*, 461–467. (b) Wagner, P. J. *Top. Curr. Chem.* **1976**, *66*, 1–52.

(3) Scheffer, J. R. In *Organic Solid State Chemistry*; Desiraju, G. R., Ed.; Elsevier: New York, 1987, Chapter 1.

(4) Dawes, K.; Dalton, J. C.; Turro, N. J. *Mol. Photochem.* **1971**, *3*, 71–78. For an alternate analysis, see ref 2b.

(5) Sugiyama, N.; Nishio, T.; Yamada, K.; Aoyama, H. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1879–1880. Because no data are available on the excited-state lifetimes or quantum yields for the molecules used in this study, no firm conclusions can be drawn on the reactivity in the π-plane.

(6) (a) Scheffer, J. R.; Trotter, J.; Omkaram, N.; Evans, S.; Ariel, S. *Mol. Cryst. Liq. Cryst.* **1986**, *134*, 169–196. (b) Scheffer, J. R.; Dzakpasu, A. A. *J. Am. Chem. Soc.* **1978**, *100*, 2163–2173.

(7) Chang, H. C.; Popovitz-Biro, R.; Lahav, M.; Leiserowitz, L. *J. Am. Chem. Soc.* **1987**, *109*, 3883–3893.

(8) Transition states for type II photoelimination from butanal singlet and triplet states had been calculated by MINDO/3. Dewar, M. J. S.; Doubleday, C. *J. Am. Chem. Soc.* **1978**, *100*, 4935–4941.

(9) Severance, D.; Pandey, B.; Morrison, H. *J. Am. Chem. Soc.* **1987**, *109*, 3231–3233.

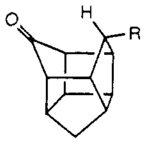
0022-3263/88/1953-6084$01.50/0

H—C=O···H = 25.9°; and O···H···CH_3 = 176.0°. The optimized O···C distance proved to be 2.53 Å. These calculations showed that small deviations from strict "in-plane" approach can be tolerated and that transition-state energy rises rapidly as the H—C=O···H angle increases.

Houk et al.[10] located the transition structures for the intramolecular hydrogen atom abstractions occurring in the butoxy radical and in the triplet and radical cation states of butanal by using ab initio molecular orbital calculations. The calculations highlighted the close structural and energetic similarities among these cyclic transition structures. For the Norrish type II reaction, the optimized transition state had a C=O···H angle of 105° and an O···H···C angle of 153°.

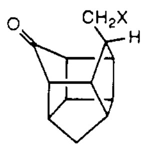
Chandra,[11a] using perturbation theory, concluded that n,π^* triplet states of ketones prefer in-plane geometry for H-atom abstractions and that abstractions by oxygen are forbidden in the π direction. Bigot[11b] extended these ideas by using natural correlation diagrams and ab initio calculations and found that hydrogen capture by the carbon atom of an n,π^* state is a feasible reaction pathway with a variable barrier depending on the initial atomic separations.

Although all of the theoretical studies cited lead to the conclusion that reactions in the π-plane encounter substantial barriers to hydrogen transfers, the available experimental results do not rigorously test this prediction.[12] In view of our interest in stereoelectronic aspects of carbonyl photochemistry, we designed some polycyclic ketones that contain hydrogen atoms fixed in the plane of the π-system with the aim of setting limits on the reactivity of this realm. The synthesis and some photochemical studies of a group of novel pentacycloundecan-8-ones symbolized by formulas **1** and **2** is reported herein.[13]



1a R = H

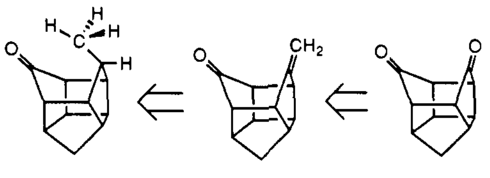
1b R = Phenyl



2 X = H, CH_3, Cl, Br

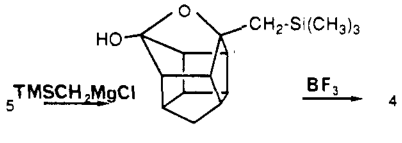
Syntheses

Syntheses of **1a** and **1b** are found in ref 13. Our retrosynthetic scheme for the preparation of 11-*syn*-methylpentacycloundecan-8-one (**3**) is shown in eq 1. Diketone **5** was converted to the methylene ketone **4** by treatment with [(trimethylsilyl)methyl]magnesium chloride to produce cyclic hemiacetal **6**, which was smoothly desilanolized with boron trifluoride (eq 2).[14]



3 4 5

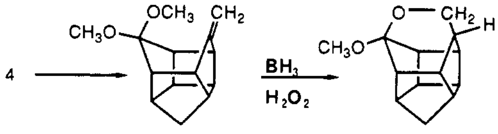
(1)



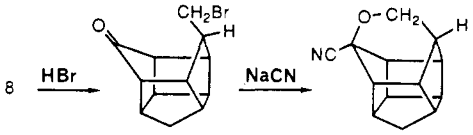
6

(eq 2)

Since functionalization of the methylene group of **4** was to be achieved by hydroboration, it was necessary to protect the carbonyl group by formation of the dimethyl acetal **7**. Treatment of the latter with the dimethyl sulfide complex of diborane followed by oxidation gave a product that did not show hydroxyl or carbonyl absorption in the infrared spectrum. The product showed a single methoxy group at δ 3.20 and a complex methylene multiplet (2 H) at δ 4.0 in the ^1H NMR spectrum. A structure that is consistent with this spectral data is **8**, although it is not clear at what stage the methoxyl group is lost. On the assumption that **8** would liberate hydroxy ketone on acidification, it was treated with HBr in acetic acid with the expectation that keto bromide **9** would be formed. Spectral data (IR 5.78 μm; ^1H NMR δ 3.42 (d, J = 8 Hz, 2 H)) of the product was consistent with this structure, but did not define unambiguously the stereochemistry of the bromomethyl group. This was established by treatment of **9** with cyanide ion to form cyano ether **10** (eq 3). The bromide **9** reacted smoothly with lithium dimethylcuprate to produce ethyl ketone **12**, but was not cleanly reduced with sodium cyanoborohydride. Conversion to the more reactive iodide **11** (sodium iodide–acetone) allowed the preparation of the methyl ketone **3** by selective reduction. Chloride **13** was produced directly from the iodide by an oxidative chlorination procedure.

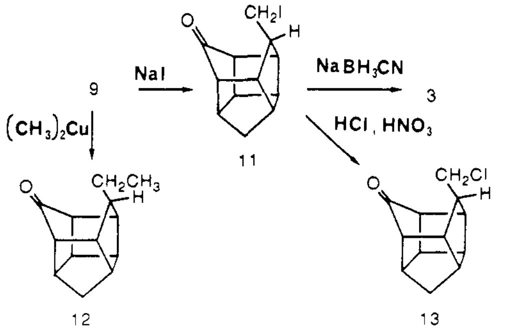


7 8



9 10

(3)



12 13

Treatment of either methylene ketone **4** or hemiacetal **15** with hydrobromic acid produced mixtures of bromo

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[10] Dorigo, A. E.; Loncharich, R. J.; Houk, K. N., private communication. For the triplet formaldehyde–methane system, these workers calculated a value of 9.4 kcal/mol for the energy difference between the transition structure involving the optimized n-orbital geometry and a geometry in which the H—C=O···H bond is rotated by 90°.

[11] (a) Chandra, A. K. *J. Photochem.* **1979**, *11*, 347–360. (b) Bigot, B. *Isr. J. Chem.* **1983**, *23*, 116–123.

[12] A recent report claims to document an out-of-plane hydrogen abstraction reaction by a π,π^* state of an aromatic ketone (Ito, Y.; Matsuura, T.; Fukuyama, K. *Tetrahedron Lett.* **1988**, *29*, 3087–3090). This conclusion must be regarded as highly speculative in the absence of detailed spectroscopic and kinetic data.

[13] (a) For related studies and preliminary work, see: Casal, H. L.; McGimpsey, W. G.; Scaiano, J. C.; Bliss, R. A.; Sauers, R. R. *J. Am. Chem. Soc.* **1986**, *108*, 8255–8259. (b) Sauers, R. R.; Zampino, M.; Stockl, M.; Ferentz, J.; Shams, H. *J. Org. Chem.* **1983**, *48*, 1862–1866.

[14] A similar procedure was recently reported by Marchand and coworkers: Marchand, A. P.; Riza, K. *J. Org. Chem.* **1983**, *48*, 5292–5295. We thank Prof. Marchand for exchange of information concerning this reaction.

Table I. Absorption and Fluorescence Data for Ketones in c-C_6H_{12}

	absorption		fluorescence	
compd	λ_{max} (±2 nm)	ϵ_{max} (±5%)	λ_{max} (±3 nm)	ϕ_f^{rel} (±10%)
1a	297	18	419	1.00[a]
3	296	17	422	0.78
12	295	17	425	0.77
13	298	17	426	0.80
14	296	21	420	1.09
9	298	17	425	0.76

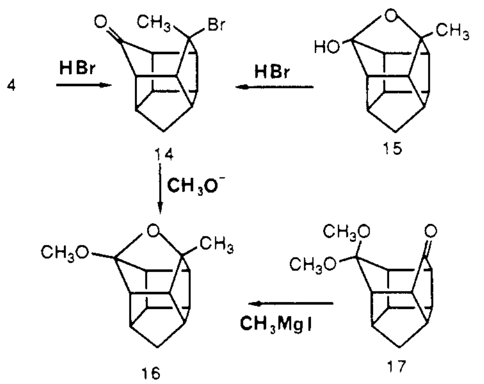
[a] ϕ_f^{abs} = 0.004 05.

Table II. Singlet- and Triplet-State Lifetimes[a,b] of 1a and 1b

ketone	singlet state	triplet state
1a	11.8	9.4
1b	12.3	12.0

[a] In nanoseconds at 25 °C. [b] Isooctane.

ketones. The major isomer was shown to be **14** by its conversion to **16** on treatment with methoxide ion whereas the minor isomer was recovered unreacted. Treatment of ketal **17** with methylmagnesium iodide provided an alternative synthesis of **16** for comparison.



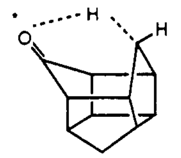
Spectral Data

The absorption and fluorescence data for the compounds used in this study are summarized in Table I. The presence of the substituents causes only minor perturbations in the absorption and fluorescence spectra of the model system **1a**.

Results and Discussion

An analysis of the structures of pentacycloundecan-8-ones by force-field calculations using MM2[15] emphasized the proximity of the γ hydrogen atoms to the carbonyl group. Atomic separations were found to be 3.05 and 2.61 Å for the $O\cdots H$ and $C_\pi\cdots H_\gamma$ distances, respectively. Despite this, the data in Table II show that both the singlet- and triplet-state lifetimes of **1a** vs **1b** are virtually independent of the γ C–H bond strength. In addition, both ketones **1a** and **1b** proved to be highly stable (ϕ [–K] < 0.001) upon irradiation at 300 nm. Thus, there is no significant coupling of electronic and vibrational modes between the excited carbonyl groups and the stretching modes of the γ C–H bonds.[16,17]

Since the reactivity of the excited states of the carbonyl groups of **1a** and **1b** would be expected to be dependent on the transition-state $O\cdots H\cdots C$ bond angles and distances as well as ground-state atomic separations,[18] it was important to model the energetics and geometry of the transition state **18**. One approach to modeling these transition states takes cognizance of the calculated structural and energetic similarities between intramolecular oxy atom hydrogen abstraction reactions and Norrish type II reactions noted by Houk et al.[10] This work pointed out the close resemblance of the bond angles and bond distances in the two transition states and the similarities in the activation enthalpies and entropies. By this analogy we use the oxy system **19** and its precursor oxy radical to model the behavior of the excited carbonyl system.[19] The hydrogen transfer reaction via **19** is expected to be slow becaues there is a large increase in strain energy (5.4 kcal/mol) that attends the molecular reorganization to the new geometry of **19**. Interestingly, a large fraction of this strain is associated with the deviation of the $O\cdots H_\gamma\cdots C$ angle from ideality (145° vs 170.52°), and one can make the argument that a similar problem exists in the carbonyl analogue **18**.[20,21]



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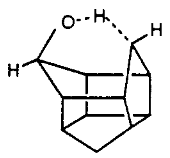

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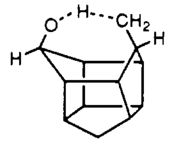
This line of reasoning led us to consider investigation of the homologous systems **2** since the analogous $O\cdots C_\delta\cdots H_\delta$ angle is expected to be significantly larger without sacrificing favorable atomic separations. MM2 calculations showed that the methyl group in **2** exists in a staggered conformation with separations of 2.55 Å ($O\cdots H$) and 2.47 Å ($C\cdots H$) between the closest methyl hydrogen and the carbonyl group atoms. The transition-state model **20**



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showed a more nearly ideal $O\cdots H\cdots C$ angle of 165° and a calculated activation energy of −2.3 kcal/mol. Thus, there are probably no major structural or entropic barriers to

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[15] Burkert, U.; Allinger, N. L. *Molecular Mechanics*; American Chemical Society: Washington, DC, 1982. The carbonyl parameters used were those recently reported: Bowen, J. P.; Pathiaseril, A.; Profeta, S., Jr.; Allinger, N. L. *J. Org. Chem.* **1987**, *52*, 5162–5166.

[16] Yang, N. C.; Elliot, S. P.; Kim, B. *J. Am. Chem. Soc.* **1969**, *91*, 7550–7551. (b) Yang, N. C.; Elliot, S. P. *J. Am. Chem. Soc.* **1969**, *91*, 7551–7553.

[17] Heller, A. *Mol. Photochem.* **1969**, *1*, 257–269.

[18] For an earlier discussion of this problem, see: Lewis, F. D.; Johnson, R. W.; Kory, D. R. *J. Am. Chem. Soc.* **1974**, *96*, 6100–6107.

[19] Dorigo, A. E.; Houk, K. N. *J. Org. Chem.* **1988**, *53*, 1650–1664. It is assumed that the geometry of triplet and singlet states of alkanones is similar.

[20] We are developing similar methodology for reactions of ketone excited states in which account is taken of the nonplanarity of excited carbonyl systems and parameters for various bending modes have been estimated. For a preliminary report, see: Sauers, R. R.; Scimone, A. 12th IUPAC Symposium on Photochemistry, Bologna, Italy, July 1988; Abstract p707.

[21] For discussions of excited-state geometry, see: (a) Turro, N. J.; Dalton, J. C.; Dawes, K.; Farrington, G.; Hautala, R.; Morton, D.; Niemczyk, M.; Schore, N. *Acc. Chem. Res.* **1972**, *5*, 92–101. (b) Lin, C. T.; Moule, D. C. *J. Mol. Spectrosc.* **1971**, *37*, 280–303. (c) Brand, J. C. D.; Wilkinson, D. G. *Adv. Phys. Org. Chem.* **1963**, *1*, 365–423. (d) Krogh-Jesperson, K., unpublished results. (e) Dorigo, A. E.; Pratt, D. W.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 6591–6600.

hydrogen atom transfer in the carbonyl analogues. Nevertheless, ketone **3** was also found to be stable toward irradiation at 300 nm.

Failure to observe photoreaction in this system might be attributable to the highly efficient reversion of triplet hydroxy biradicals to ground-state ketone. This possibility was probed by using methanol-d_4 as solvent with the expectation that the hydrogen-bonding properties of the solvent would inhibit the reversion back to ground-state ketone and encourage forward reactions. In the event, no significant degradation was observed.

The *syn*-ethyl ketone **12** and the *syn*-chloromethyl ketone **13** were examined next with the expectation that the substituents would enhance the reactivity of the adjacent hydrogen atoms. In both cases one of the methylene hydrogens was shown (MM2) to be positioned directly above the carbonyl π-plane about the same distance from the carbonyl group as before. However, neither system showed significant reactivity on irradiation at 300 nm (ϕ [$-$K] $<$ 0.001).

A second attempt to exploit the possible intermediacy of hydroxy biradicals was explored by taking into consideration the results of Wagner and co-workers with δ-halovalerophenones.[22] In these systems generation of triplet biradicals led to loss of halogen in competition with type II processes. Given the disposition of abstractable hydrogen and bromine that exists in **14**, it could react analogously to form **4**. Once again, there was no reaction after long irradiation at 300 nm.

An estimate of the upper limit for the rates of reaction of the singlet states of **3** and **12** is instructive and can be calculated by using the method of Dalton and Turro.[23] The calculated lifetimes for **3** and **12** are ca. 9.2 ns. Maximum rate constants for loss of ketone via singlet-state reactions in these molecules are ca. 10^5 s^{-1}, assuming that the maximum quantum yield of ketone disappearance = 10^{-3}. For comparison, Yang et al. reported values of 1.2×10^7 and 1.2×10^8 s^{-1} for hydrogen abstraction rates from primary and secondary carbon atoms, respectively.[16] The single-state reactivity of ketones **3** and **12** is reduced by factors of 10^2–10^3 relative to acyclic analogues. It is still not clear to what extent the n orbital can be involved in these systems, i.e., how much flexibility is allowable in distorting the framework to permit n-orbital approach. This kind of analysis must take into account the nonplanarity of alkanone excited states as well as the energetics of the molecules as a whole.[20]

Summary and Conclusions

Several sensitive tests for hydrogen abstraction reaction from the π-plane of some cycloalkanones have failed to reveal significant reactivity despite what would otherwise be considered ideal geometric parameters. These results provide experimental verification of the presence of significant stereoelectronic barriers to these reactions. Future studies will attempt to more accurately assess the geometric and energetic limits of this barrier.

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 727 spectrometer. Proton NMR spectra were determined in $CDCl_3$ by using internal tetramethylsilane as a reference. All spectra were determined on a Varian Model T-60 spectrometer. Ultraviolet spectra were obtained from a Perkin-Elmer Model 559 spectrometer or a Cary Model 17-D spectrometer. Fluorescence spectra were determined by using a SLM model 4800 spectrofluorimeter. Elemental analyses were performed by G. Robertson, Florham Park, NJ. Mass spectral data was obtained from a VG Model 7070 EQ high-resolution spectrometer.

Fluorescence. Spectra were determined in spectranalyzed cyclohexane. Concentrations were adjusted to give equal absorbance at the irradiating wavelength (310 nm). Just prior to recording of the spectra, the solutions were deaerated with a stream of nitrogen and securely capped. The areas under the curves were determined by the cut-and-weigh technique, and the results of three determinations were averaged. Because the curves all had essentially identical band shapes, no corrections were applied.

11-Methylenepentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one (4). A solution of 54.0 g (0.44 mol) of (chloromethyl)trimethylsilane in 500 mL of dry ether was added over 1 h to 20.52 g (0.84 g-atom) of magnesium under nitrogen in the presence of a crystal of iodine and 1 mL of 1,2-dibromoethane. The reaction was stirred at 25 °C for an additional 0.5 h and then cooled to 0 °C. Diketone[24] **5** (63 g, 0.36 mol) was added rapidly while the reaction was kept under control with cooling. The resulting mixture was heated at reflux for 2.5 h and stirred for 17 h at 25 °C. The cooled mixture was treated with 1.5 L of saturated aqueous ammonium chloride. The salts were removed by filtration through glass wool, and the organic layer was separated and washed with brine. The dried extract was evaporated to yield 87 g (92%) of 1-hydroxy-6-[(trimethylsilyl)methyl]-12-oxahexacyclo[5.4.1.0^{2,5}.0^{3,10}.0^{4,8}.0^{7,11}]dodecane (**6**): mp 142 °C; IR (CCl_4) 3.03 (br, OH) μm; ^{1}H NMR δ 0.0 (s, 11 H), 1.67 (AB q, J = 10 Hz, 2 H), 2.56 (br s, 8 H), 4.9 (br 1 H). Anal. Calcd for $C_{15}H_{22}O_2Si$: C, 68.65; H, 8.45. Found: C, 68.58; H, 8.67.

A solution of 87 g (0.33 mol) of the alcohol **6** in 1 L of methylene chloride was cooled to 0 °C and treated rapidly with 60 mL of cold boron trifluoride etherate while the reaction temperature was kept below 5 °C. The reaction mixture was stirred at 0–5 °C for 1 h followed by quenching with 1.5 L of saturated aqueous sodium bicarbonate. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give 49 g (87%) of **4**, mp 75 °C after crystallization from petroleum ether (lit.[14] mp 71–72 °C): ^{1}H NMR δ 1.83 (AB q, J = 11 Hz, 2 H), 2.4–3.4 (m, 8 H), 4.78 (d, 2 H). Anal. Calcd for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found: C, 83.73; H, 7.12.

11,11-Dimethoxy-8-methylenepentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (7). A solution of **6** (3.1 g, 1.8 mmol) in 30 mL of anhydrous methanol that contained 2.1 mL (1.9 mmol) of trimethyl orthoformate and 10 mg of *p*-toluenesulfonic acid was heated at reflux for ca. 2 h. The cooled reaction mixture was diluted with ether and water. The water layer was separated and extracted (3×) with ether. The combined extracts were washed with brine and dried (K_2CO_3). The solvents were removed by evaporation, and the residue was distilled at 70 °C (0.007 Torr) to yield 3.77 g (96%) of acetal **7**: ^{1}H NMR δ 1.49 (AB q, J = 12 Hz, 2 H), 2.53 (m, 8 H), 3.05 (s, 3 H), 3.07 (s, 3 H), 4.55 (s, 2 H). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: 76.82; H, 8.44.

6-Methoxy-4-oxahexacyclo[6.4.1.0^{2,7}.0^{3,11}.0^{6,10}.0^{9,12}]tridecane (8). A solution of 4 mL of 10 M borane–dimethyl sulfide complex in 10 mL of dry hexanes and 4 mL of methylene chloride was added over 0.5 h to 16 g (0.073 mol) of **7** in 24 mL of dry hexanes at 0–5 °C. The reaction mixture was stirred for 3 h at 25 °C followed by cautious addition of 35 mL of anhydrous ethanol. This was followed by addition of 12 mL of 3 M aqueous sodium hydroxide. The cooled (0–5 °C) solution was next treated with 12.2 mL of 30% hydrogen peroxide while the temperature was maintained at ca. 25 °C. The resulting mixture was heated at 50 °C for 1 h and then quenched with 250 mL of an ice–water mixture. The aqueous phase was extracted twice with 300-mL portions of ether. The combined extracts were washed with water (2×) and brine (1×) and dried over K_2CO_3. After evaporation of the ether, the residue was distilled at 90° C (0.3 Torr) to yield 12.3 g (82%) of 8: IR (neat) 9.22 μm; ^{1}H NMR δ 1.41 (AB q, J = 16 Hz, 2 H), 1.73 (s, 1 H), 2.49 (m, 8 H), 3.20 (s, 3 H), 4.03

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[22] Wagner, P. J.; Lindstrom, M. J.; Sedon, J. H.; Ward, D. R. *J. Am. Chem. Soc.* **1981**, *103*, 3842–3849.

[23] Dalton, J. C.; Turro, N. J. *J. Am. Chem. Soc.* **1971**, *93*, 3569–3570.

[24] Cookson, R. C.; Crundwell, E.; Hudec, J. *J. Chem. Soc.* **1964**, 3062–3075.

(heptet, 2 H). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.20; H, 8.11.

***syn*-11-(Bromomethyl)pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one (9).** A solution of 12.67 (0.062 mol) of **8** in 114 mL (0.47 mol) of 33% hydrobromic acid in acetic acid was stirred at 25 °C for 3 days and heated at 45 °C for 3 h. Addition of water (250 mL) was followed by ether extraction (3×). The combined extracts were washed with water, 10% aqueous sodium bicarbonate (2×), water, and brine. After drying ($MgSO_4$), the solvents were evaporated to yield a brown oil. The oil was purified by filtration through silica in a solution of 25% ethyl acetate in petroleum ether and followed by crystallization from petroleum ether: yield 11.34 g (72%); mp 59–59.5 °C; IR (CCl_4) 5.78 μm; ^{1}H NMR δ 1.68 (AB q, 2 H), 2.62 (m, 9 H), 3.42 (d, *J* = 8 Hz, 2 H). Anal. Calcd for $C_{12}H_{13}BrO$: C, 56.94; H, 5.18; Br, 31.57. Found: C, 57.00; H, 5.03; Br, 31.80.

6-Cyano-4-oxahexacyclo[6.4.1.0^{2,7}.0^{3,11}.0^{6,10}.0^{9,12}]tridecane (10). A mixture of 450 mg (1.78 mmol) of bromide **9** and 143 mg (2.9 mmol) of sodium cyanide in 50 mL of anhydrous dimethyl sulfoxide was heated at 90–97 °C for 4 h. After cooling, water and ether were added followed by separation of the layers. The organic layer was washed with brine and dried over K_2CO_3. Removal of the solvents by rotary evaporation gave 334 mg (94%) of white needles, mp 124–125 °C after crystallization from methanol: IR 4.49 μm; ^{1}H NMR δ 1.52 (AB q, *J* = 18 Hz, 2 H), 3.90 (heptet, 2 H). Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.14; H, 6.70; N, 6.95.

***syn*-11-(Iodomethyl)pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one (11).** A mixture of 10 g (0.040 mol) of bromide **9** and 41.5 g (0.28 mol) of sodium iodide was heated at reflux in acetone for 3 h. The reaction mixture was diluted with water followed by extraction with ether (4×). The combined extracts were washed with water, aqueous sodium thiosulfate, and brine. The dried ($MgSO_4$) extracts were evaporated to yield 11.9 g (99%) of iodide **11**. The crude product was crystallized from petroleum ether: mp 74 °C; IR (CCl_4) 5.76 μm; ^{1}H NMR δ 1.60 (AB q, *J* = 12 Hz, 2 H), 2.50 (m, 9 H), 3.15 (d, *J* = 8 Hz, 2 H). Anal. Calcd for $C_{12}H_{13}IO$: C, 48.02; H, 4.37; I, 42.28. Found: C, 48.03; H, 4.37; I, 42.08.

***syn*-11-Ethylpentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one (12).** A suspension of 0.38 g (2.0 mmol) of cuprous iodide in 2 mL of dry ether was cooled in a dry ice–chloroform bath and treated with 3.8 mL (4.0 mmol) of a 1.1 M methyllithium solution in ether. One milliliter of ether was added, and the dry-ice bath was replaced by an ice–water bath. When the reaction temperature reached 0 °C, the dry-ice bath was again used to cool the reagents to ~−78 °C. A solution of the bromide **9** (0.253 g, 1.0 mmol) in 2.5 mL of ether was added dropwise. The resulting mixture was stirred at −78 °C for 10 min, 0 °C for 45 min, and 25 °C for 1 h. The reaction mixture was quenched by careful addition of a mixture of 40 mL of saturated aqueous ammonium chloride and 10 mL of concentrated aqueous ammonia to the cooled mixture. The aqueous layer was extracted with ether (3×), and the combined extracts were washed with water (3×), 5% aqueous hydrochloric acid, 5% aqueous sodium carbonate, and brine. The dried extracts ($MgSO_4$) were evaporated to yield 0.16 g (85%) of an oil. Distillation at 68–70 °C (0.025 Torr) afforded 0.14 g (77%) of **12**: IR (neat) 5.76 μm; ^{1}H NMR δ 0.87 (t, 3 H), 1.55 (m, 4 H), 2.63 (m, 9 H). Anal. Calcd for $C_{13}H_{16}O$: C, 76.47; H, 7.84. Found: C, 76.56; H, 7.86.

***syn*-11-Methylpentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one (3).** A mixture of 1.0 g (3.3 mmol) of iodide **11** and sodium cyanoborohydride (0.82 g, 13 mmol) in 16 mL of hexamethylphosphoramide was heated for 2 h at 65 °C. Dilution with water was followed by ether extraction. The combined extracts were washed with water (4×) and brine and dried over $MgSO_4$. Evaporation of the extracts gave 0.53 g (92%) of crude ketone **3**. Purification by sublimation (25 °C, 0.05 Torr) gave a pure sample: mp 84 °C; IR (CCl_4) 5.76 μm; ^{1}H NMR δ 1.00 (d, *J* = 7 Hz, 3 H), 1.69 (AB q, *J* = 10 Hz, 2 H), 2.63 (m, 9 H); exact mass calcd for $C_{12}H_{14}O$ 174.104 465 2, found 174.104 110 0.

***anti*-11-Bromo-*syn*-11-methylpentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one (14).** A mixture of hemiacetal **15** (1.0 g, 5.25 mmol) and 8 mL (33 mmol) of 33% hydrobromic acid in acetic acid was stirred for 24 h at 25 °C. The mixture was diluted with water and extracted with ether (3×). The extracts were washed with water, aqueous sodium bicarbonate, and brine. The dried ($MgSO_4$) extracts were evaporated, and the residue was purified by flash chromatography using 10% ethyl acetate in petroleum ether as eluent. There was obtained 127 mg (9.8%) of **14** as white needles: mp 69 °C; IR (CCl_4) 5.73 μm; ^{1}H NMR δ 1.77 (AB q, 2 H), 1.97 (s, 3 H), 2.9 (m, 8 H). Anal. Calcd for $C_{12}H_{13}BrO$: C, 56.94; H, 5.18. Found: C, 56.65; H, 4.99.

The same compound was obtained in 69% yield upon treatment of alkene **4** with hydrobromic acid under similar conditions.

In both cases a minor product was obtained that was isomeric with **14**: mp 118 °C; IR (CCl_4) 5.75 μm; ^{1}H NMR δ 1.68 (s, 3 H), 1.83 (AB q, 2 H), 2.7 (m, 8 H). Anal. Calcd for $C_{12}H_{13}BrO$: C, 56.94; H, 5.18. Found: C, 56.74; H, 5.35.

1-Methoxy-6-methyl-12-oxahexacyclo[5.4.1.0^{2,5}.0^{3,10}.0^{4,8}.0^{7,11}]dodecane (16). Acetal **17**[25] (2.2 g, 0.010 mol) was added to the Grignard reagent prepared from 5.96 g (0.040 g-atom) of magnesium in ether. After ca. 1 h at reflux, the reaction mixture was quenched by addition of aqueous ammonium chloride. The dried ether layer was evaporated to give a semisolid. Sublimation at ~120 °C (15 Torr) gave the acetal **16** as a colorless oil: IR (neat) no OH absorption; ^{1}H NMR δ 1.44 (s, 3 H), 1.73 (AB q, *J* = 10 Hz, 2 H), 2.7 (m, 8 H), 3.41 (s, 3 H). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.36; H, 7.71.

The same acetal (^{1}H NMR) was obtained on treatment of a mixture of the bromides produced above with sodium methoxide in methanol (17 h, 25 °C).

The isomeric bromide (mp 118 °C) was recovered unchanged.

***syn*-11-(Chloromethyl)pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one (13).**[26] A slurry of 1.5 g (0.005 mol) of iodide **11** in 3 mL of 36–38% aqueous hydrochloric acid was cooled in an ice–salt bath. Nitric acid (>90%, 3 mL) was added with stirring. The resulting solution was warmed to ca. 18 °C and held that at temperature for 2.25 h. The reaction mixture was diluted with water and extracted with methylene chloride (3×). The combined extracts were washed with water, 5% aqueous sodium thiosulfate, wate, and brine. The dried extracts were evaporated to give 0.090 g (86%) of crude chloride. The product was purified by flash chromatography (17% ethyl acetate–benzene) to yield 0.51 g (49%) of pure **13**: mp 45–46 °C; IR 5.78, 7.81 μm; ^{1}H NMR δ 1.70 (AB q, *J* = 14 Hz, 2 H), 2.1–3.2 (br, 9 H), 3.53 (d, *J* = 8 Hz, 2 H); exact mass calcd for $C_{12}H_{13}ClO$ 208.065 492 8, found 208.065 450 0.

1-Hydroxy-6-methyl-12-oxahexacyclo[5.4.1.0^{2,5}.0^{3,10}.0^{4,8}.0^{7,11}]dodecane (15). Diketone **5** (1.16 g, 6.7 mmol) in 5 mL of dry benzene was added rapidly to the Grignard reagent prepared from 1.42 g (10 mmol) of iodomethane and 0.30 g (13 mg-atom) of magnesium in 10 mL of a 1:1 solution of dry ether and benzene. The resulting mixture was stirred at reflux for 1 h and for 17 h at 25 °C. The reaction mixture was quenched by slow addition of ca. 20 mL of saturated aqueous ammonium chloride. The resulting mixture was filtered through glass wool by using methylene chloride to rinse the filtrate. Separation of the layers was followed by washing of the combined organic layers with brine. The dried extracts were evaporated to give 0.93 g (73%) of **15**, mp 99–100 °C (lit.[24] mp 98 °C). The ^{1}H NMR spectral data agreed with that in ref 24.

Irradiations. Typically, 0.1 M solutions of **1a**, **1b**, **3**, **12**, **13**, and **14** in acetonitrile-d_3 were prepared in 5-mm Pyrex NMR tubes. After deaeration with dry nitrogen, the samples were irradiated at 300 nm in a Rayonet reactor. Typically, the samples were irradiated for 20 h, at which time they were monitored by ^{1}H NMR. No new absorptions appeared, and the maximum conversion was estimated from the intensity of the baseline noise. The light intensity was calibrated by actinometry using potassium ferric oxalate.[27] In addition, compound **3** was also irradiated in CD_3OD under similar conditions, and in acetonitrile-d_3 in a quartz tube at 254 nm. Compound **13** was also irradiated at 300 nm as a solid film with no change.

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(25) Barborak, J. C.; Khoury, D.; Maier, W. F.; Schleyer, P. v. R.; Smith, E. C.; Smith, W. F., Jr.; Wyrick, C. *J. Org. Chem.* **1979**, *44*, 4761–4766.

(26) Svetlakov, I. E.; Moisak, I. E.; Averko-Antonovich, I. G. *Zh. Obshch. Khim.* **1969**, *5*, 985.

(27) Sauers, R. R.; Hagedorn, A. A., III; Van Arnum, S. D.; Gomez, R. P.; Moquin, R. V. *J. Org. Chem.* **1987**, *52*, 5501–5505.

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Registry No. **1a**, 69649-19-0; **1b**, 85507-41-1; **3**, 85507-43-3; **4**, 87830-51-1; **5**, 2958-72-7; **6**, 117251-75-9; **7**, 117251-76-0; **8**, 117251-77-1; **9**, 117251-78-2; **10**, 117269-14-4; **11**, 117251-79-3; **12**, 117251-80-6; **13**, 117251-81-7; **14**, 117251-82-8; **15**, 75996-72-4; **16**, 117251-83-9; **17**, 69028-03-1.

N-Hydroxy Amides. 7.[1] Synthesis and Properties of Linear and Cyclic Hexapeptides Containing Three N^5-Acetyl-N^5-hydroxy-L-ornithine Residues as Models for Ferrichrome[2]

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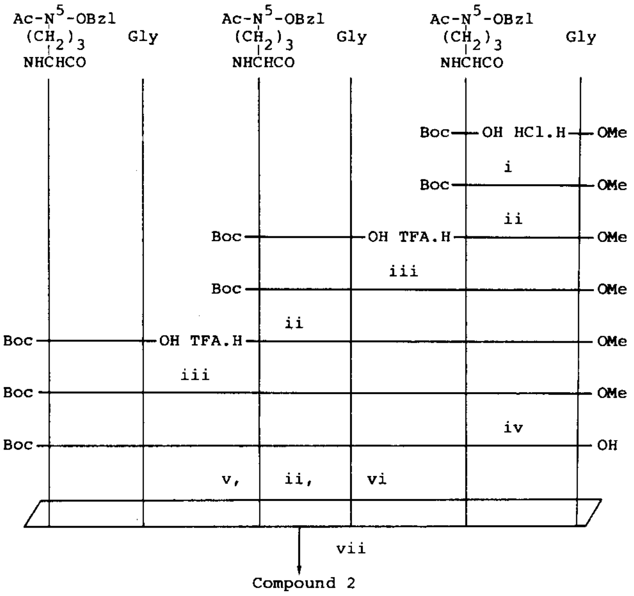
As sequence-modified analogues of desferriferrichrome (**1**), linear and cyclic peptides have been prepared. They are (OrnAH-Gly)$_3$ (**2**), Ac-Gly$_2$-OrnAH$_3$-Gly-OMe (**3**), Ac-(OrnAH-Gly)$_3$-OMe (**4**), and Ac-Gly-OrnAH-(OrnAH-Gly)$_2$-OMe (**5**), where OrnAH stands for an N^5-acetyl-N^5-hydroxy-L-ornithine residue. ^{1}H NMR study in DMSO-d_6 shows that most of the analogues have no particular intramolecular hydrogen bonds and that **2** assumes a C_3 symmetric conformation both in its free state and in a complex with Al(III). The 1:1 molar mixture of these analogues with iron(III) in water forms the 1:3 complex of the metal ion to the hydroxamate unit in a wide pH range. From absorption vs pH curves the stability of the iron complexes is estimated to fall in order of **1** > **4** > **2** > **3** > **5** against H^+ attack and **1** > **4** > **3** > **2** > **5** against OH^- attack. Iron transfer experiments to excess EDTA reveal a better binding of cyclic peptides with the following order of iron holding: **2** > **1** > **4** > **3** > **5**. CD spectra of iron complexes for all the analogues are virtually similar to that of ferrichrome, indicating a predominance of the Λ-cis configuration for the hexapeptides containing three OrnAH residues.

There is continuing interest in synthetic iron sequestering agents for use as drugs or models of naturally occurring compounds.[3,4] Microorganisms excrete metal binding compounds called siderophores to sequester Fe(III) by complexation.[4-7] Ferrichrome is the iron(III) complex of a representative hydroxamate siderophore, first isolated from the fungus *Ustilago sphaerogena* by Neilands.[5,8] It has an octahedrally coordinate Λ-cis configuration held by three ornithyl side chains.[8-10] The iron-free ligand, desferriferrichrome (**1**), is a cyclic hexapeptide composed of the three consecutive residues of glycine and of N^5-acetyl-N^5-hydroxy-L-ornithine. Considerable information has been gathered on microbial iron transport with ferrichrome related compounds.[4-7,11,12] Iron is transferred

Scheme I.[a]



[a] Reagents and conditions: (i) *N*-methylmorpholine/DCC-HOBt; (ii) TFA, 0 °C; (iii) *N*-methylmorpholine/DCC-HOSu; (iv) 1 N NaOH in MeOH at room temperature; (v) DEC·HCl (2 equiv)-HOSu (2 equiv) at -10 °C and then 0 °C; (vi) 3 mM in pyridine at 60 °C (48 h); (vii) 10% Pd-C in MeOH with H_2.

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[1] Part 6: Akiyama, M.; Katoh, A.; Tsuchiya, Y. *J. Chem. Soc., Perkin Trans. 1*, in press.

[2] Abbreviations: OrnAH, N^5-acetyl-N^5-hydroxy-L-ornithine; DMSO, dimethyl sulfoxide; DCC, dicyclohexylcarbodiimide; HOBt, 1-hydroxybenzotriazole; TFA, trifluoroacetic acid; HOSu, *N*-hydroxysuccinimide; EDTA, ethylenediaminetetraacetic acid; DCU, dicyclohexylurea; DEC, 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide.

[3] (a) McMurry, T. J.; Rodgers, S. J.; Raymond, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 3451. (b) Tor, Y.; Libman, J.; Shanzer, A. *J. Am. Chem. Soc.* **1987**, *109*, 6518. (c) Michell, M. S.; Walker, D.-L.; Whelen, J.; Bosnich, B. *Inorg. Chem.* **1987**, *26*, 396. (d) Lee, B. H.; Miller, M. J.; Prody, C. A.; Neilands, J. B. *J. Med. Chem.* **1985**, *28*, 317. (e) Shimizu, K.; Akiyama, M. *J. Chem. Soc., Chem. Commun.* **1985**, 184.

[4] Raymond, K. N.; Müller, G.; Matzanke, B. F. *Top. Curr. Chem.* **1984**, *123*, 49.

[5] Neilands, J. B. *Structure Bonding* **1966**, *1*, 59; **1984**, *58*, 1; *Science* **1967**, *156*, 1443; *Ann. Rev. Biochem.* **1981**, *50*, 715.

[6] Hider, R. C. *Structure Bonding* **1984**, *58*, 25.

[7] Emery, T. *Am. Sci.* **1982**, *70*, 626; *Metal ions in Biological Systems*; Siegel, H., Ed.; Marcel Dekker: New York, 1978; Vol. 7, p 77.

[8] Isolation: Neilands, J. B. *J. Am. Chem. Soc.* **1952**, *74*, 4846. Structure: Rogers, S.; Neilands, J. B. *Biochemistry* **1964**, *3*, 1850.

[9] Crystal structure: van der Helm, D.; Baker, J. R.; Eng-Wilmont, D. L.; Hossain, M. B.; Loghry, R. A. *J. Am. Chem. Soc.* **1980**, *102*, 4224.

[10] Total synthesis: (a) Keller-Schierlein, W.; Maurer, B. *Helv. Chim. Acta* **1969**, *52*, 603. (b) Isowa, Y.; Ohmori, M.; Kurita, H. *Bull. Chem. Soc. Jpn.* **1974**, *49*, 215.

0022-3263/88/1953-6089$01.50/0