Table V. MM2 Energies of Ketonization Transition States[a]

proton donor distance, Å	tricyclic enol exo energy	tricyclic enol endo energy	cyclohexane enol exo energy	cyclohexane enol endo energy
2.0	142.33	148.99	101.27	102.69
2.2	101.24	110.45	60.99	62.75
2.4	77.11	88.45	37.41	39.48
2.6	62.74	75.28	23.79	26.11
2.8	54.26	67.77	16.03	18.52
3.0	49.11	63.06	11.70	14.27
3.2	45.87	59.97	9.38	11.91
3.4	43.70	57.69	8.24	10.58
3.6	42.17	55.80	7.76	9.80
3.8	41.02	54.06	7.66	9.29
4.0	40.13	52.36	7.75	8.92
5.0	38.37	43.29		

[a] Energy units are kcal.

mg (0.057 mmol) of dimer, 9-*endo*-acetyl-9-[1-(9'-*anti*-tricyclo-[4.2.1.1^{2,5}]decanylidene)ethoxy]-*anti*-tricyclo[4.2.1.1^{2,5}]decane, in 150 mL of isopropyl alcohol containing 1.5 mL of cyclohexane, was irradiated for 10 min. Analysis by NMR showed conversion to be about 4%. Analysis by GC gave an *endo*-acetyl- to *exo*-acetyltricyclic ratio of 91:1.

Molecular Mechanics Calculations. MM2 calculations were carried out by using MM2[16] as incorporated in a variation of TRIBBLE.[17] Optimized geometries for the tricyclic, cyclohexane, and 2-phenylcyclohexane exocyclic enols were calculated and are tabulated in Table IV. A proton donor was simulated by a bromine atom with a +1 charge, and a series of calculations were carried out in which the position of the proton donor was brought toward the enol along both exo and endo perpendicular approaches. The positions of the proton donor and the two sp^2 hybridized carbons of the enol were fixed, and the geometry was optimized for the rest of the system. The results of these calculations for the tricyclic and cyclohexyl exo enols are summarized in Table V. Due to excessive computational time, the transition-state energies of the 2-phenylcyclohexane exo enols were only calculatred at a single (3.0 Å) distance of the proton donor to the α-carbon. This was the distance that showed the largest endo–exo difference in the other cases studied.

Acknowledgment. Support of this research by the National Science Foundation and National Institutes of Health Grant GM07487 is gratefully acknowledged. The synthetic aspects of this research was supported by NIH while the mechanistic portions were supported by NSF. Appreciation is due to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for a grant which permitted purchase of the VAX/750 used in quantum mechanical and molecular mechanics calculations. We acknowledge with thanks the efforts of Mr. David Greenberg with synthetic assistance on the early portions of this research and Dr. Kenneth Haller for assistance with X-ray determination.

Registry No. 1, 95693-86-0; 2, 95693-87-1; 2 (lithium enolate), 95693-99-5; 3a, 95693-84-8; 3b, 95782-18-6; 4a, 95693-85-9; 4b, 95782-16-4; 5, 95694-02-3; 6, 95693-91-7; 7, 66953-28-4; 8, 66953-29-5; 9, 95693-93-9; 10, 95693-88-2; 11, 95693-94-0; 12, 95693-89-3; 13a, 95693-95-1; 13b, 95782-17-5; 14a, 95693-90-6; 14b, 95782-15-3; 15, 95693-96-2; 16, 95693-92-8; 18, 95694-01-2; 19, 95693-98-4; 21, 95723-87-8; 22, 95694-00-1; 22 (R = Ph), 95693-97-3; O_2, 7782-44-7; $PhCH_2OCH_3$, 538-86-3; cyclopentadiene, 542-92-7; 2-chlorocyclopentanone, 694-28-0; acetylcyclohexane enol, 95694-03-4; 1-acetyl-2-phenylcyclohexane *cis*-enol, 95694-04-5; 1-acetyl-2-phenylcyclohexane *trans*-enol, 95694-05-6.

Metal-Catalyzed Organic Photoreactions. Iron(III) Chloride Catalyzed Photooxidation of Cyclic Olefins and Its Application to the Synthesis of *exo*-Brevicomin

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Photooxidation of 1,ω-disubstituted cyclic olefins gave α,ω-dichloro ketones or α-chloro 1,ω-diketones, depending upon the reaction conditions. The reaction was applied to the synthesis of the pheromone *exo*-brevicomin in three steps. Starting from 1-ethyl-6-methylcyclohexene, the synthesis was achieved in an overall yield of 51%.

We reported in our previous papers that iron(III) chloride exhibited a characteristic effect on the photooxidation of olefin 1 in pyridine and induced the production of either α-chloro ketone 3 (type A), ω,ω-dichloro ketone 4 (type B), or α,ω-dichloro ketone 5 (type C) as shown in Scheme I.[1] It has been assumed, and in some cases confirmed, that the primary product of the photooxidation is a β-chloro hydroperoxide, 2. We have illustrated the formation of the β-chloro hydroperoxide as involving a photoinduced interligand electron transfer from the chlorine ligand to molecular oxygen through the metal ion and olefin molecule, for which we proposed the term "long-range electron transfer" (Scheme II). The reaction type is dependent on the substitution pattern of the starting olefins: olefins in which R^2 and R^3 are hydrogen undergo the type A reaction through dehydration of the intermediate secondary hydroperoxides, while olefins in which R^2 is alkyl undergo the ring cleavage at either the a- or b-position to afford the type B or type C reaction products, respectively. The position of the bond cleavage was also dependent on the substitution pattern, the cleavage occurring always on the bond to the carbon atom carrying the alkyl group (R^1 or R^3 in Scheme I). Both type B and type C reactions are characteristic in that they afford a chain compound of any length having two functionalities on both ends of the chain by starting from a cyclic olefin having appropriate substituents and ring size. In our previous paper,[1] we demonstrated the utility of the type B reaction as a synthetic method by applying the reaction to the synthesis of some natural products. In the present study, we will demonstrate the synthetic utility of the type C reaction.

(1) A. Kohda, K. Nagayoshi, K. Maemoto, and T. Sato, *J. Org. Chem.*, 48, 425 (1983).

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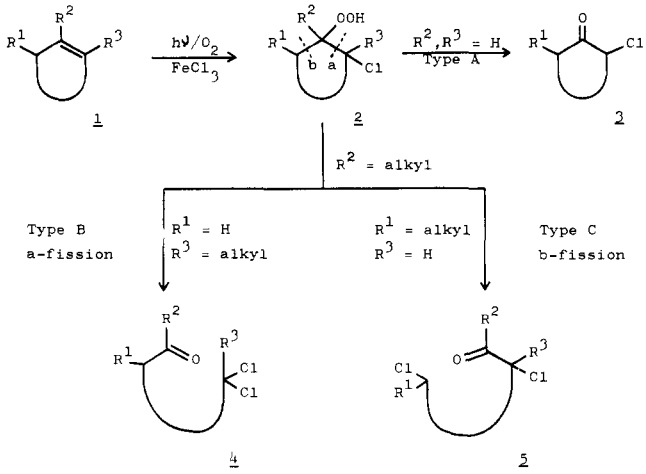
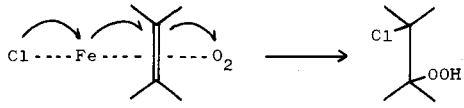
Scheme I

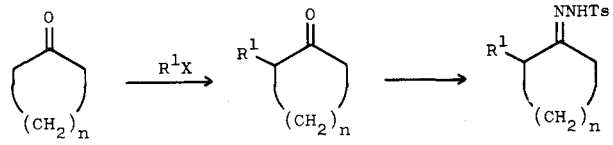


Scheme II

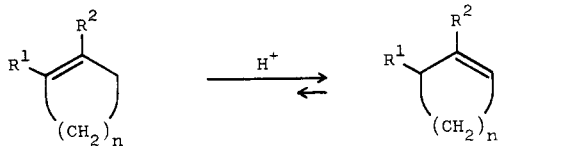


Scheme III

Route A



Route B



The starting olefins **6**, which have a typical substitution pattern for the type C reaction, are generally available by introducing appropriate substituents into cyclic ketones through a reaction sequence shown in Scheme III, route A[2] or, in particular cases, by equilibrating the disubstituted unsaturated cyclic olefins with acid (Scheme III, route B). In order to explore the synthetic utility of the type C reaction, we investigated the chemical behavior of the β-chloro hydroperoxides **7** under various conditions.

Iron(II) induced a smooth decomposition of **7** to produce dichloro ketones **8-Cl** (Chart I) when the reaction system contained a chloride anion. In the same way, other halide and thiocyanate ions were successively introduced into **8-X** as ω-substituents as shown in Table I. However, the reactions with other anions shown in the table were complicated, and no expected products were identified in the reaction mixture.

In contrast to the catalytic activity of iron(II) for the hydroperoxide decomposition, iron(III) chloride did not induce any decomposition of **7a** in the dark, irrespective of the presence or absence of molecular oxygen, while it induced decomposition under irradiation. When the irradiation was carried out in the absence of oxygen, the product was dichloro ketone **8a-Cl**, while diketone **11a** was obtained when the irradiation was carried out with oxygen. We confirmed that **8a-Cl** did not produce **11a** under the present conditions and that, in the absence of iron(III), no decomposition of **7a** was observed upon irradiation even in the presence of oxygen.

Notably the overall reaction from the olefins to the diketones involves two consecutive oxidation steps to and from the intermediate β-chloro hydroperoxides **7**, both steps proceeding under the same conditions requiring the cooperation of light, metal compound, and molecular oxygen. Expectedly, the prolonged irradiation (4 h) of olefins **6a** and **6b** under the present conditions produced the diketones **11a** and **11b** exclusively in a single operation in yields of 83% and 64%, respectively, while photooxidation

(2) A. R. Chamberlin, J. E. Stemke, and F. T. Bond, *J. Org. Chem.*, **43**, 141 (1978); L. A. Paquette, W. E. Fristad, D. S. Dime, and T. R. Bailey, *J. Org. Chem.*, **45**, 3017 (1980).

Chart I

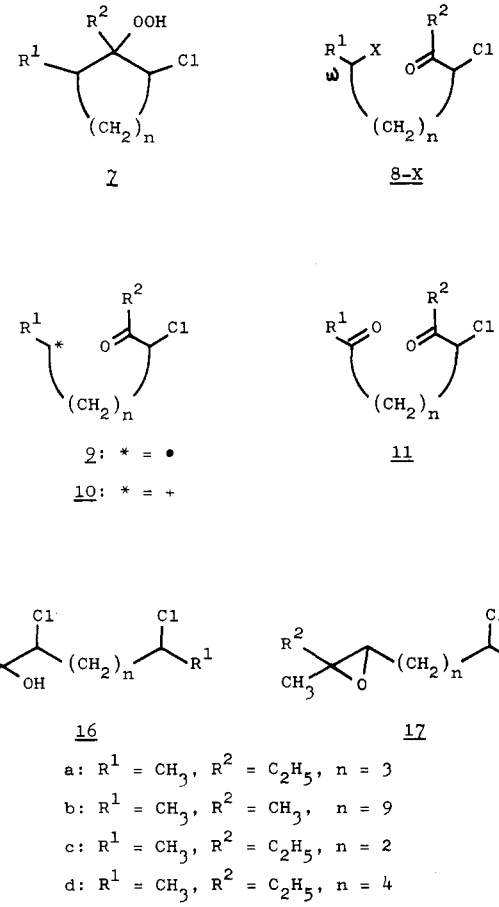
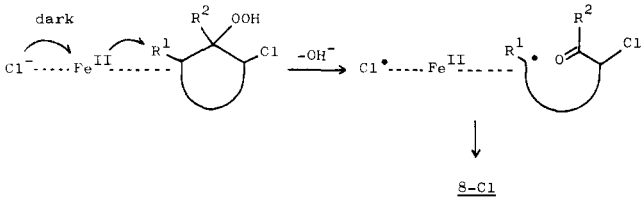


Table I. Iron(II)-Catalyzed Decomposition of 7 in the Presence of X^-

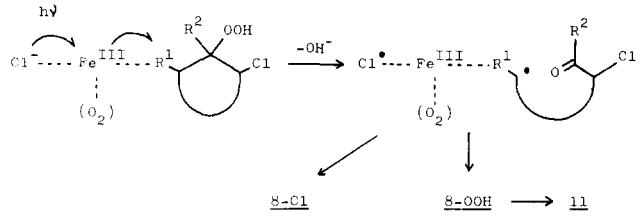
hydroperoxide	anion (X^-)	product (yield, %)[a]
7a	Br	**8a-Br** (55)
7a	I	**8a-I** (52)
7a	SCN	**8a-SCN** (50)
7a	CN	**8a-CN** (5)
7a	N_3	**8a-N_3** (5)
7a	OTs	**8a-OTs** (0)
7a	OAc	**8a-OAc** (0)
7a	OCH_3	**8a-OCH_3** (0)
7b	Br	**8b-Br** (66)
7c	Br	**8c-Br** (49)
7d	Br	**8d-Br** (52)

[a] Overall yield from olefin.

Scheme IV



Scheme V



for a shorter period (1 h) was sufficient for the preparation of the corresponding hydroperoxides.

The iron(II)-catalyzed decomposition of cyclic tertiary hydroperoxide has been documented as initiated by an electron transfer from iron(II) to the hydroperoxide to produce iron(III) and a radical species such as **9**.[3] Although the subsequent oxidation of **9** to **10** by the resulting iron(III) followed by the coupling of **10** with the anions X might be a reasonable pathway for the formation of **8-X**, it is unlikely that a cationic species intervenes in the reaction, in view of the failure of the reaction with tosylate, acetate, or methoxyl ion as X. As a possible alternative, we could conceive a scheme in which the iron(III) oxidized X anions to the corresponding radicals, followed by the cross coupling between the resulting X radicals and **9**. Although it might seem unlikely for the two radicals to survive long enough to undergo cross coupling, this reaction path would be reasonable if we assume that the whole process occurs simultaneously within the coordination sphere of the iron(II), as shown in Scheme IV. This is a nonphotochemical version of our long-range electron-transfer mechanism,[1] which involves an interligand electron transfer from a donor to an acceptor, followed by the coupling of the two species as soon as they are furnished with radical character.

The iron(III)-catalyzed photoreaction from **7** to **8** could also be shown by the long-range electron-transfer mechanism as depicted in the Scheme V. Presumably the ability as a promoter for the electron transfer is greater with iron(II) than with iron(III), and hence the iron(II)-mediated interligand electron transfer proceeds without the assistance of photoexcitation, in contrast to the iron(III)-mediated reaction which requires photoassistance, although we have not confirmed whether the light energy is used for promoting the electron-transfer process or merely for the reduction of iron(III) to the more reactive iron(II). When molecular oxygen exists in the reaction system, it might also be activated on the metal ion, producing hydroperoxides **8-OOH**, which then dehydrate to the final products **11**. In view of the fact that the reaction in the presence of oxygen produces the diketone **11** as an exclusive product even when the reaction system contains a chloride ion, we assume that molecular oxygen is activated on the metal ion to such an extent as to surpass the reactivity of the chlorine ligand in the present reaction system.[4]

(3) G. Sosnovsky and D. J. Rawlinson, "Organic Peroxides", Vol. II, D. Swern, Ed., Wiley-Interscience, New York, 1971, p 153.

Table II. Reduction of ω-Halo α-Chloro Ketone 8-X

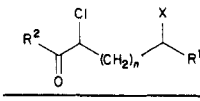
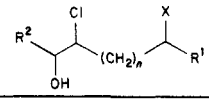
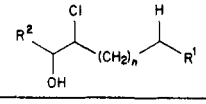
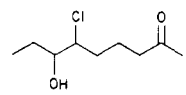
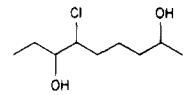
starting material	product (yield, %)	
		
8a-Cl	**12a-Cl** (80)	**13a** (0)
8a-Br	**12a-Br** (87)	**13a** (0)
8a-I	**12a-I** (59)	**13a** (20)
8b-Cl	**12b-Cl** (70)	**13b** (0)

Table III. Reduction of Diketone 11a

conditn			product and yield, %	
				
solvent	temp,[a] °C	time, min	**14**	**15**
CH_3OH	rt	15	0	80
n-C_4H_9OH	rt	15	0	89
n-C_4H_9OH	−30	30	47	19
n-C_4H_9OH	−40	30	61	0
n-C_4H_9OH	−50	45	76	0
n-C_4H_9OH	−70	120	41	0

[a] rt = room temperature.

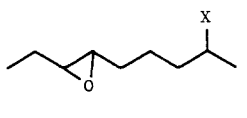
In order to demonstrate the potentiality of the present reaction as a synthetic method, we further explored the chemoselective manipulation of these functional groups.

When the dihalo compounds **8-X** were treated with lithium aluminum hydride, the reduction occurred predominantly at the carbonyl group producing the corresponding ω-halo chlorohydrins **12-X**, although a minor extent of reductive elimination of iodine was also observed with iodo compound **8a-I**. The results are shown in Table II. The chemoselective reduction of one of the two carbonyl groups in **11** required more critical conditions. As shown in Table III, both carbonyl groups in **11a** were reduced by sodium borohydride in methanol or in 1-butanol at room temperature producing **15**, while the selective reduction at the carbonyl group having an α-chlorine was accomplished at temperatures lower than −40 °C using 1-butanol as solvent. The best result was obtained at −50 °C, which afforded **14** in 76% yield as a single product.

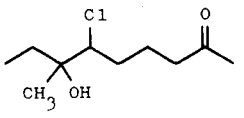
A Grignard reagent reacted with α,ω-dichloro ketones **8a–Cl** and **8b-Cl** exclusively at the carbonyl group and gave the corresponding tertiary alcohols **16a** and **16b** in yields of 90% and 60%, respectively. As observed in the chemoselective reduction of the α-chloro carbonyl group, the diketone **11a** reacted with the Grignard reagent preferentially at the carbonyl group having the α-chlorine atom, but neither the yield nor the chemoselectivity for the formation of **19** and **20** was satisfactory for synthetic purposes. The heterogeneity of the reaction system might be responsible for these results, and further elaboration of the reaction conditions should be necessary before good selectivity is achieved.

In contrast to the preferential reaction at the α-chloro carbonyl group mentioned thus far, the reaction of **8a-I** with silver tosylate or mercury(II) acetate occurred exclusively at the ω-position producing **8a-OTs** or **8a-OAc**, respectively. Although the reaction might be attractive since it affords compounds which were not accessible through the selective reduction of the diketone **11** or through the iron(II)-catalyzed decomposition of the β-chloro hydroperoxide **7**, extensive optimization should be

(4) The activation of molecular oxygen by iron(III) chloride was recently reported; S. Ito, K. Aihara, and M. Matsumoto, *Tetrahedron Lett.*, **25**, 3891 (1984).



18-X



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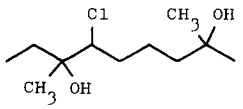

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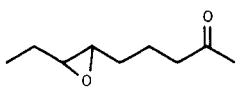

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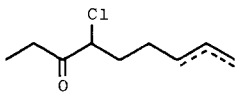

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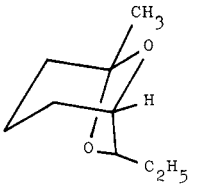
necessary for the reaction to become a preparative method, because the yields were usually poor (27–36%) and the products were always accompanied by a mixture of olefins **22**.

It has been well documented that the nucleophilic addition to the carbonyl group having the α-halogen atom proceeds via a dipolar model[5] In the present study the stereoselectivity of the reduction was investigated by converting the chlorohydrins **12a-Cl** and **12a-Br** into the corresponding epoxides **18-Cl** and **18-Br**, since no information concerning the stereochemistry was obtained with **12** from GLC and NMR analyses. The NMR spectrum of **18-Cl** showed two multiplets centered at δ 2.72 and 2.50 with a ratio of 3:1, each ascribable to the protons on the epoxide ring of either the cis or trans isomer. Since the major peak at δ 2.72 shifted to the lower field more extensively than the minor peak upon addition of a shift reagent, Eu(fod), we assigned the cis structure to the major product, speculating that the cis isomer would coordinate to the shift reagent more effectively. The assignment is consistent with previous observations that the protons on an epoxide ring having two cis substituents resonate at a lower field than those in the trans isomer.[6] The results are also consistent with the proposed reaction path via the dipolar model at the stage of reduction. The GC–MS analysis of **18-Cl** showed two peaks with relative intensities of 3:1 on the gas chromatogram, both indicating similar mass spectra. In the same way the bromo epoxy derivative **18-Br** was also found to be a 3:1 mixture of cis and trans isomers, the *cis* isomer being the major product.

The stereoselectivity at the reduction of the carbonyl group in the diketone **11a** was also investigated by converting the primary product **14** into the corresponding epoxide **21**, which proved to be a 93:7 mixture of stereoisomers by GC–MS analysis. Although the NMR analysis did not afford any information on the stereochemistry, we assigned the cis structure for the major component on the analogy of previous observations. The assignment of the stereochemistry was finally confirmed by deriving a mixture of these epoxy ketones into a stereochemically definite phromone, brevicomin.

Brevicomin is an attractant pheromone produced by the western pine beetle, *Dendroctonus brevicomis*. Silverstein[7] established the structure of the active constituent as *exo*-7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane (**23**).



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Notably, the endo isomer is also found in nature, but is inactive. Most of the reported stereoselective syntheses of the pheromone utilize either stereoselective formation of C1–C7 bond[8a] or stereoselective epoxidation of cis or trans olefin in order to introduce two oxygen functions at C1 and C7.[8b] We expected that the high stereoselectivity observed in the chemoselective reduction of the diketone **11a** would make the reaction a key step for the synthesis of the pheromone. The *exo*-brevicomin was actually prepared in a 51% overall yield from the olefin **6a** by a three-step sequence involving (1) iron(III) chloride catalyzed photooxidation to **11a** (2) chemo- and stereoselective reduction of **11a** to chlorohydrin **14**, and (3) treatment of **14** with a base and then with an acid. Since the reaction step 3 was fairly clean, the tandem cyclization–rearrangement was performed without intermediate purification. Column chromatography of the final reaction product afforded *exo*-brevicomin which contained 6% of the endo isomer as a sole contaminant as revealed by GC–MS and NMR analyses. The mass spectrum of each component coincided completely with the reported datum of the respective isomer.[7] The NMR spectrum of the product was identical with that of *exo*-brevicomin.[7]

Experimental Section

General Procedures. GLC experiments were carried out on a 2.5 m × 6 mm (for preparative) or 2.5 m × 3 mm (for analytical) stainless steel column packed with silicone SE30 or Carbowax 20M on silanized Chromosorb W. Preparative TLC was carried out on a silica gel plate using solvents as indicated. Unless otherwise stated, all the spectroscopic data were determined on pure samples obtained by either distillation, preparative TLC, or GLC, and CCl_4 solutions were used for NMR spectral determination, and neat film was used for IR.

The photooxidation was carried out on a pyridine solution of olefin (0.025 M) and $FeCl_3 \cdot 6H_2O$ (0.025 M) in a Pyrex tube while oxygen gas was bubbled through. A medium-pressure mercury lamp (Ushio UM452 (450 W)) was used as a light source.

Starting Materials. 1-Ethyl-6-methylcyclohexene (**6a**) and 1,12-dimethylcyclododecene (**6b**) were prepared in the same way as described.[1] 1-Ethyl-5-methylcyclopentene (**6c**) and 1-ethyl-7-methylcycloheptene (**6d**) were prepared from the corresponding 2-methylcycloalkanone tosylhydrazones according to the method for the preparation of **6a**.

β-Chloro Hydroperoxides 7. The olefins **6a–d** were photooxidized according to the general method for 1 h, and the irradiated solutions were neutralized with 4 M HCl solution. The mixture was extracted with CH_2Cl_2, passed through a short column of Florisil, and dried over Na_2SO_4. Evaporation of the solvent in vacuo gave the corresponding hydroperoxides, which were analyzed directly by NMR without further purification. The yields were determined from the integrated area of the proton attached to the carbon carrying the chlorine atom at δ 4.0–4.7, using 1,1,2,2-tetrachloroethane as an internal reference.

ω-Substituted α-Chloro Ketones 8. The crude hydroperoxides **7a–d** obtained from the corresponding olefins **6** were added to the reagent solutions which had been prepared as described

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below. The amount of reagent solution was adjusted so that the amount of iron(II) in the solution is equivalent to that of the starting olefin. The mixture was stirred at room temperature for 4 h, an equal volume of water was added, and the whole solution was shaken with $CHCl_3$. After being washed with water and dried over Na_2SO_4, the extract was concentrated in vacuo, and the products were isolated through column chromatography or preparative TLC (silica gel/benzene). For **8a-Cl**:[1] exact mass (EI), *m/e* 210.0568 ($C_9H_{16}Cl_2O$ (M), *m/e* 210.0578). For **8a-Br**: exact mass (EI), *m/e* 254.0062 ($C_9H_{16}BrClO$ (M), *m/e* 254.0073); IR ν_{max} 2925, 2875, 1720, 1450, 1378, 1350, 1260, 1100, 740 cm^{-1}; NMR δ 1.07 (3 H, t, *J* = 7 Hz), 1.71 (3 H, d, *J* = 7 Hz), 1.43–2.23 (6 H, m), 2.66 (2 H, q, *J* = 7Hz), 3.7–4.3 (2 H, m). For **8a-I**: bp 150–160 °C (0.7 mmHg Kugelrohr); exact mass (CI), *m/e* 302.9969 ($C_9H_{17}ClIO$ (M + H), *m/e* 303.0015); NMR δ 1.04 (3 H, t, *J* = 7 Hz), 1.91 (3 H, d, *J* = 7 Hz), 1.4–2.2 (6 H, m), 2.64 (2 H, q, *J* = 7 Hz), 3.7–4.4 (2 H, m). For **8a-SCN**: exact mass (CI); *m/e* 234.0715 ($C_{10}H_{17}ClNOS$ (M + H); *m/e* 234.0719); IR ν_{max} 2930, 2155, 1715, 1455, 1380, 1105 cm^{-1}; NMR δ 1.08 (3 H, t, *J* = 7 Hz), 1.50 (3 H, d, *J* = 7 Hz), 1.35–2.2 (6 H, m), 2.4–2.9 (2 H, q, *J* = 7 Hz), 3.0–3.55 (1 H, sextet, *J* = 7 Hz), 4.14 (1 H, t, *J* = 7 Hz). For **8b-Br**: IR ν_{max} 2920, 2845, 1712, 1450, 1348 cm^{-1}; NMR δ 1.1–1.5 (14 H, b s), 1.5–1.8 (4 H, m), 1.67 (3 H, d, *J* = 7 Hz), 2.28 (3 H, s), 3.85–4.25 (2 H, m). For **8c-Br**: IR ν_{max} 1712, 1450, 1380, 790 cm^{-1}; NMR δ 1.05 (3 H, t, *J* = 7 Hz), 1.74 (3 H, d, *J* = 7 Hz), 1.8–2.2 (4 H, m), 2.75 (2 H, q, *J* = 7 Hz), 3.8–4.45 (2 H, m). For **8d-Br**: IR ν_{max} 2930, 1718, 1460, 1380 cm^{-1}; NMR δ 1.08 (3 H, t, *J* = 7 Hz), 1.68 (3 H, d, *J* = 7 Hz), 1.3–2.1 (8 H, m), 2.65 (2 H, q, *J* = 7 Hz), 3.85–4.2 (2 H, m). For **8a-CN**: IR ν_{max} 2930, 2870, 2150, 1718, 1455, 1380, 1350, 1100 cm^{-1}; NMR δ 1.07 (3 H, t, *J* = 7 Hz), 1.32 (3 H, d, *J* = 7 Hz), 1.4–2.1 (7 H, m), 2.65 (2 H, q, *J* = 7 Hz), 4.12 (1 H, t, *J* = 7 Hz). For **8a-N_3**: IR ν_{max} 2930, 2875, 2100, 1715, 1450, 1220, 920 cm^{-1}; NMR δ 1.08 (3 H, t, *J* = 7 Hz), 1.26 (3 H, d, *J* = 7 Hz), 1.5–2.0 (7 H, m), 2.65 (2 H, q, *J* = 7 Hz), 4.13 (1 H, t, *J* = 7 Hz).

The reagent solutions were prepared by dissolving 4 equiv of the following salts of X and 1 equiv of $FeSO_4 \cdot 7H_2O$ (956 mg) in a mixture of 7% H_2SO_4 (24 mL) and methanol (29 mL). The salts were LiBr for X = Br, NaI for X = I, NaOAc for X = OAc, LiOTs for X = OTs, NH_4SCN for X = SCN, NaN_3 for X = N_3, and KCN for X = CN.

α-Chloro 1,ω-Diketones 11. The olefins **6a** and **6b** were photooxidized according to the general procedures for 4 h. The irradiated solutions were neutralized with 4 M HCl and extracted with $CHCl_3$. The solutions were passed through a short column of Florisil to remove iron compounds, and the solvent was removed. The residues were analyzed by NMR to determine the yields by using 1,1,2,2-tetrachloroethane as an internal reference. Distillation (for **11a**) or column chromatography (for **11b**, silica gel/$CHCl_3$) gave pure samples. For **11a**: bp 95–98 °C (1.2 mmHg); exact mass (EI); *m/e* 155.1055 ($C_9H_{15}O_2$ (M – Cl), *m/e* 155.1071); IR ν_{max} 2930, 1718, 1540, 1462, 1413, 1359, 1220, 1159, 960 cm^{-1}; NMR δ 1.05 (3 H, t, *J* = 7 Hz), 1.5–199 (4 H, m), 2.08 (3 H, s), 2.43 (2 H, t, *J* = 6 Hz), 2.65 (2 H, q, *J* = 7 Hz), 4.14 (1 H, t, *J* = 6 Hz). For **11b**: exact mass (EI); *m/e* 260.1525 ($C_{14}H_{25}ClO_2$ (M); *m/e* 260.1543); IR ν_{max} 2923, 2852, 1717, 1460, 1414, 1358, 1225, 1160 cm^{-1}; NMR δ 1.2–1.7 (16 H, m), 2.1–2.5 (2 H, dist t, *J* = 6 Hz), 2.02 (3 H, s), 2.21 (3 H, s), 4.07 (1 H, t, *J* = 6 Hz).

Reduction of 4,8-Dichloro-3-nonanone (8a-Cl). An ether solution (6 mL) of **8a-Cl** (230 mg) was added dropwise to an ether solution (6 mL) of $LiAlH_4$ (39 mg), and the mixture was refluxed for 1 h. To the solution was added 4 M HCl, and the product was extracted with ether. The extract was dried over Na_2SO_4, and the solvent was removed. The remaining oil (213 mg) was almost pure chlorohydrin **12a-Cl** by GLC analysis: MS (CI), 213 (M + H); IR ν_{max} 3560–3300, 2930, 1460, 1380, 1040 cm^{-1}; NMR δ 0.98 (3 H, t, *J* = 6 Hz), 1.53 (3 H, d, *J* = 8 Hz), 1.2–1.9 (8 H, m), 2.13 (1 H, b), 3.2–3.6 (1 H, m), 3.6–4.2 (2 H, m).

Preparation of 2-Chloro-6,7-epoxynonane (18-Cl). The crude **12a-Cl** (213 mg) obtained above was dissolved in a methanol solution (10 mL) of KOH (0.2 g), and the solution was refluxed for 2 h. Water was added, and the product was extracted with CH_2Cl_2. The extract was washed with NaCl solution and dried over Na_2SO_4. The yellow oil (206 mg), which remained after the evaporation of the solvent, was distilled with a Kugelrohr to give **18-Cl** (177 mg): bp 70–80 °C (0.3 mmHg); exact mass (CI), *m/e* 177.1039 ($C_9H_{18}ClO$ (M + H); *m/e* 177.1046); IR ν_{max} 2950, 1455, 1378, 1258, 903, 890 cm^{-1}; NMR δ 0.97 (3 H, t, *J* = 6 Hz), 1.55 (3 H, d, *J* = 6 Hz), 1.2–1.8 (8 H, m), 2.4–2.6 ($^1/_4 \times 2$ H, m, for trans isomer), 2.6–2.8 ($^3/_4 \times 2$ H, m, for cis isomer), 4.10 (1 H, d of t, *J* = 6 Hz).

Upon addition of $Eu(fod)_3$, the multiplet at δ 2.6–2.8 shifted downfield more extensively than that at δ 2.4–2.6. GC–MS analysis showed two peaks with a relative ratio of 3:1 on the gas chromatogram. Both peaks showed identical mass spectra, which had no parent peaks: *m/e* (relative intensity) 147 (1.0, M – 29), 149 (0.3, M + 2 – 29), 116 (9.0), 99 (12), 91 (4.1), 89 (13), 85 (24), 83 (100), 82 (29), 81 (30), 69 (25), 67 (67).

Reduction of 4-Chloro-8-bromo-3-nonanone (8a-Br). In the same way as described above, **12a-Br** (302 mg) was obtained by reducing **8a-Br** (300 mg in 5.5 mL of ether) with $LiAlH_4$ (45 mg in 5.5 mL of ether), for 40 min: IR ν_{max} 3550–3100, 2915, 2856, 1460, 1380, 1261, 1115, 1030 cm^{-1}; NMR δ 0.97 (3 H, t, *J* = 7 Hz), 1.66 (3 H, d, *J* = 7 Hz), 1.5–1.9 (8 H, m), 2.40 (1 H, b), 3.2–3.6 (1 H, m), 3.6–4.2 (2 H, m).

Preparation of 2-Bromo-6,7-epoxynonane (18-Br). The crude **12a-Br** (302 mg) obtained as above was dissolved in a methanol solution (12 mL) of KOH (255 mg), and the solution was refluxed for 20 min. The reaction mixture was worked up in the same way as for the chloride. The crude product (247 mg) was obtained as an oil: exact mass (CI), *m/e* 221.0553 ($C_9H_{18}BrO$ (M + H), *m/e* 221.0542); IR ν_{max} 2915, 2840, 1458, 1379, 904, 889, 783 cm^{-1}; NMR δ 1.03 (3 H, t, *J* = 6 Hz), 1.72 (3 H, d, *J* = 7 Hz), 1.25–2.1 (8 H, m), 2.4–2.6 ($^1/_4 \times 2$ H, m, for trans isomer), 2.6–2.85 ($^3/_4 \times 2$ H, m, for cis isomer), 4.04 (1 H, d of t, *J* = 6 Hz).

GC–MS analysis showed two peaks with a relative ratio of 3:1 on the gas chromatogram. Both peaks showed identical mass spectra, which had no parent peaks: *m/e* (relative intensity) 191 (0.3, M – 29), 193 (0.3, M + 2 – 29), 162 (2.7), 160 (2.6), 122 (8.1), 120 (8.0), 99 (13), 85 (16), 83 (100), 81 (27), 67 (30).

Reduction of 4-Chloro-8-iodo-3-nonanone (8a-I). Ar ether solution (1 mL) of **8a-I** (60 mg) was added dropwise to an ether solution (1 mL) of $LiAlH_4$ (8 mg), and the solution was refluxed for 1 h. The work-up was carried out in the same way as described for the reduction of **8a-Cl**. The remaining oil (51 mg) after the evaporation of the solvent was a mixture of **12a-I** and **13a** as revealed from GLC and NMR analyses. For **12a-I**: NMR δ 1.92 (d, *J* = 7 Hz), 3.3–4.4 (m).

Grignard Reaction of 4,8-Dichloro-3-nonanone (8a-Cl). To an ether solution (4 mL) of a Grignard reagent prepared from methyl iodide (175 mg) and magnesium (28 mg) was added an ether solution (2 mL) of **8a-Cl** (173 mg) dropwise at –50 °C, and the solution was stirred at –50 °C for 3 h. After the conventional workup procedure, an oil (167 mg) was obtained which was almost pure **11a** by GLC and TLC analyses. Column chromatography (silica gel/benzene) afforded a pure sample: NMR δ 0.91 (3 H, t, *J* = 7 Hz), 1.17 (3 H, s), 1.52 (3 H, d, *J* = 7 Hz)e, 1.4–1.9 (8 H, m), 2.1 (1 H, b), 3.6–4.1 (2 H, m).

Preparation of 2-Chloro-7-methyl-6,7-epoxynonane (17a). A methanol solution (21.5 mL) of **16a** (376 mg) and KOH (430 mg) was refluxed for 2 h. Water was added and the product was extracted with CH_2Cl_2. After the extract was washed with NaCl solution and dried over Na_2SO_4, the solvent was removed in vacuo. The residual oil (366 mg) was almost pure **17a** by GLC analysis. A pure sample was obtained by distillation with a Kugelrohr: bp 100–105 °C (1 mmHg); NMR δ 0.95 (3 H, t, *J* = 7 Hz), 1.14 (0.3 × 3 H, s), 1.20 (0.7 × 3 H, s), 1.50 (3 H, d, *J* = 7 Hz), 1.3–1.9 (8 H, m), 2.51 (1 H, dist t), 3.5–4.1 (1 H, m).

Grignard Reaction of 3,13-Dichloro-2-tetradecanone (8b-Cl). In the same way as above, **16b** was obtained in 60% yield as a crude oil, which was directly treated with KOH. The resulted epoxy chloride **17b** was purified by distillation: bp 105–110 °C (0.2 mmHg); IR ν_{max} 2930, 2850, 1460, 1380 cm^{-1}; NMR δ 1.15–1.55 (27 H, m), 2.55 (1 H, dist t), 3.88 (1 H, quintet, *J* = 6 Hz).

Reduction of 6-Chloro-2,7-nonanedione (11a). To a methanol or 1-butanol solution (1.5 mL) of the diketone **11a** (50 mg) was added $NaBH_4$ (10 mg) under the conditions specified in Table III. The solution was acidified with 4 M HCl and saturated with NaCl. The products were extracted with ether, and the extract was washed with NaCl solution and dried over Na_2SO_4, and the solvent was removed in vacuo. The remaining oil was mainly **14** and/or **15**, depending upon the reaction conditions. When the

product was a mixture of both components, the ratio was determined from NMR analysis using a singlet at δ 2.11 for **14** and a doublet at δ 1.15 for **15** as probe signals. For **14**: exact mass (CI), *m/e* 193.0970 ($C_9H_{18}ClO_2$ (M + H); *m/e* 193.0995); IR ν_{max} 3100–3600, 2930, 2875, 1720, 1460, 1380, 1240 cm^{-1}; NMR δ 0.98 (3 H, t, *J* = 7 Hz), 1.3–1.9 (6 H, m), 2.11 (3 H, s), 2.46 (2 H, dist t), 2.85 (1 H, b), 3.3–3.7 (1 H, m), 3.6–4.1 (1 H, m). For **15**: IR ν_{max} 3100–3600, 2925, 2875, 1460, 1380, 1120 cm^{-1}; NMR δ 0.98 (3 H, t, *J* = 6 Hz), 1.15 (3 H, d, *J* = 7 Hz), 1.3–2.0 (8 H, m), 3.10 (1 H, b s), 3.3–4.1 (3 H, m).

Preparation of 6,7-Epoxy-2-nonanone (21). A crude sample of **14** (142 mg) was dissolved in a methanol solution (7 mL) containing KOH (133 mg), and the solution was refluxed for 15 min. Water was added, and the product was extracted with CH_2Cl_2. The extract was washed with NaCl solution and dried over Na_2SO_4. The evaporation of the solvent followed by preparative TLC (silica gel/AcOEt-*n*-hexane, 1:1) gave almost a pure sample of **21**. GC–MS analysis showed that the product was a mixture of cis (93%) and trans (7%) isomers. Both isomers showed identical mass spectra: MS, *m/e* (relative intensity) 156 (7.3, M), 127 (8.4), 114 (93), 98 (36), 86 (39), 85 (100), 68 (46); NMR (cis–trans mixture) δ 0.97 (3 H, t, *J* = 7 Hz), 1.2–198 (6 H, m), 2.07 (3 H, s), 2.2–2.85 (4 H, m).

Preparation of *exo*-Brevicomin. The crude epoxy ketone **21** containing 93% of the cis isomer obtained from 142 mg of **14** was dissolved in a mixture of acetone (0.9 mL) and water (0.9 mL). To the solution was added H_2SO_4 (245 mg) with cooling by ice–water, and the mixture was stirred for 1 h at room temperature. The solution was neutralized with $NaHCO_3$ solution and shaken with ether. The ether extract was washed with a saturated NaCl solution and dried over Na_2SO_4. The residue (99 mg) left after the evaporation of the solvent was almost pure brevicomin as revealed from GLC and NMR analyses. GC–MS analysis indicated that the product was *exo*-brevicomin accompanied by 6% of endo isomer, each showing mass spectrum identical with the reported datum of the respective isomer.[7] The NMR spectrum of the product was identical with that reported for *exo*-brevicomin.[7]

Registry No. (±)-**6a**, 95694-10-3; (±)-**6b**, 95782-29-9; (±)-**6c**, 95694-11-4; (±)-**6d**, 95694-12-5; **7a**, 95694-13-6; **7b**, 95694-14-7; **7c**, 95694-15-8; **7d**, 95694-16-9; **8a-Cl**, 84098-65-7; **8a-Br**, 95694-17-0; **8a-I**, 95694-19-2; **8a-SCN**, 95694-23-8; **8a-CN**, 95694-18-1; **8a-N_3**, 95694-20-5; **8a-OTs**, 95694-22-7; **8a-OAc**, 95694-21-6; **8b-Cl**, 81505-12-6; **8b-Br**, 95694-24-9; **8c-Br**, 95694-25-0; **8d-Br**, 95694-26-1; (±)-**11a**, 95694-27-2; (±)-**11b**, 95694-28-3; **12a-Cl**, 95694-30-7; **12a-Br**, 95694-29-4; **12a-I**, 95723-90-3; **12b-Cl**, 95694-31-8; **13a**, 95694-32-9; **14**, 95694-33-0; **15**, 95694-34-1; **16a**, 95694-35-2; **16b**, 95694-36-3; **17a**, 95694-37-4; **17b**, 95694-38-5; **18-Cl**, 95694-40-9; **18-Br**, 95694-39-6; (±)-*cis*-**21**, 89188-46-5; (±)-*trans*-**21**, 89188-45-4; (±)-*exo*-**23**, 60018-04-4; (±)-*endo*-**23**, 62532-53-0.

2′-Chloropentostatin,[1] a New Inhibitor of Adenosine Deaminase[2]

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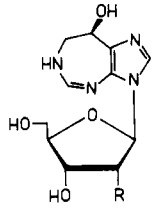
A new inhibitor of adenosine deaminase was isolated from the fermentation broths of an unidentified actinomycete, ATCC 39365. The inhibitor was shown by spectroscopic analysis to be a 2′-chloro analogue of pentostatin. Acetolysis of the glycosylic linkage gave 1,3,5-tri-*O*-acetyl-2-chloro-2-deoxy-α,β-D-ribofuranoses, thus establishing the structure of the nucleoside as (8*R*)-3-(2-chloro-2-deoxy-β-D-ribofuranosyl)-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepin-8-ol (2′-chloropentostatin). An unambiguous synthesis of the sugar moiety, along with its D-*arabino* isomer, was developed.

Inhibitors of adenosine deaminase (adenosine aminohydrolase, EC 3.5.4.4) have been of interest as possible codrugs to enhance the activity of adenine nucleosides in the treatment of viral diseases and cancer.[3,4] Aside from potentiating the activity of adenosine analogues, these compounds possess potent immunosuppressive activity and represent a new class of agents for modulating the immune function.[4–6] The only compounds of microbial origin known to be potent inhibitors of this enzyme are the nucleosides pentostatin (**1**)[7] and coformycin (**2**),[8] both of which possess the unique 3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepine aglycon. Both compounds, as well as analogues,[9–12] have been the focus of synthetic efforts from these laboratories during the past few years. This report describes the isolation and structure elucidation of the novel component 2′-chloropentostatin (**3**), including the unambiguous synthesis of the carbohydrate moiety.



1: R = -H
2: R = -OH
3: R = -Cl

(1) The chemical name is (8*R*)-3-(2-chloro-2-deoxy-β-D-ribofuranosyl)-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepin-8-ol.

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