Table I. Parameters for AM1 Optimized Geometries of 1 and 2

	1	2[a]
deformation of para-bridged benzene ring		
α,[b] deg	24.2	23.6 (20.5)
β,[c] deg	21.9	21.6 (24.1)
relative geometries between two π systems		
dihedral angle,[d] deg	20.3	18.6 (17.7)
distance,[e] Å	3.12	3.05 (3.03-3.04)

[a] Experimental values determined by X-ray structure analysis of the bismethoxycarbonyl derivative are given in parentheses (ref 6). [b] The out-of-plane bending angle of the para carbons. [c] The out-of-plane bending angle of the benzyl carbons. [d] Angle between the plane C-(12)-C(13)-C(15)-C(16) and the plane C(2)-C(3)-C(8)-C(9) for 1; angle between the plane C(8)-C(9)-C(11)-C(12) and the plane C-(2)-C(3)-C(4)-C(5) for 2. [e] Nonbonded distance C(3)···C(15) or C-(8)···C(16) for 1 and C(3)···C(11) or C(4)···C(12) for 2.

Preparation of benzo-fused propellanone 5 from the enone dichloroethylene photoadducts 4[6] was accomplished using the tetrachlorothiophene dioxide[9] benzoannelation method followed by sequential dechlorination. Ring contraction of 5 afforded acid 6 or ester 7. Although in low yield, chlorinative decarboxylation[10] of 6 gave the expected chloride 8 (9%) and the ring-unopened chloride 9 (7%). The low yield of 8 is due to its lability under the reaction conditions. Dehydrochlorination of 8 proceeded smoothly to give cyclophane 1 as an unstable solid (mp 168-170 °C).[11] Thermal isomerization of 10,[12] a Dewar type valence isomer of 1 prepared by treatment of 9 with excess base, also yielded cyclophane 1 (Scheme I).

As shown in Table I, semiempirical AM1 optimized geometries[13] of 1 and 2 are similar. The only discrepancy is that the bridge π bond of 1 (C(3)-C(8) = 1.41 Å) is considerably longer than that of 2 (C(3)-C(4) = 1.34 Å). Spectroscopic data support this calculation; the coupling constants of the vicinal methylene protons in the ^{1}H NMR spectra of compounds 1 and 2[11] are nearly equal. Additionally, the longest wavelength absorptions (310 nm in cyclohexane) in the UV spectra of both compounds are identical. These data imply that the para-bridged benzene ring of 1 is as deformed as in 2, which contains one of the most severely distorted benzene rings known. Spectroscopically, the only difference between 1 and 2 is the paramagnetic shielding effect exerted by the ortho-bridged ring. In the ^{1}H NMR spectrum of 1, the syn protons (H(15), H(16), δ 6.27) appear at about 1 ppm higher field than the anti protons (H(12), H(13), δ 7.32).

Mutual syn/anti isomerization of the methoxycarbonyl derivatives of [6]paracyclophene 2 took place near room temperature ($\Delta G^{\ddagger}_{25°C}$ = 24.6 kcal/mol), giving an equilibrium mixture composed of equal amounts of the isomers ($K_{25°C}$ = 0.97).[5] In order to investigate the conformational behavior of the [2.2]ortho-paracyclophane system, the methoxycarbonyl-substituted derivatives 3a and 3b were prepared (Scheme I). Heating (dichloroethane, 40 °C, 17 h) the Dewar isomer 11 afforded a mixture of 3a and 3b in a ratio of 2:5 in 47% yield.[11] In contrast to the [6]paracyclophene system, no isomerization was observed when 3a or 3b was heated to 50 °C for 48 h. Higher temperatures only resulted in the rapid decomposition of 3a and 3b. Consequently, benzoannelation of 2 brings about a substantial barrier to this dynamic process, although the most stable conformations of 1 and 2 are similar.[14]

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(11) The spectral properties of 1, 3a, and 3b are given in the supplementary material.
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(14) A similar benzoannelation effect was observed for [2.2]orthometacyclophane (ref 3).

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Supplementary Material Available: Listings of spectral properties for compounds 1, 3a,b, and 5-11 (3 pages). Ordering information is given on any current masthead page.

A New Class of Proteinase Inhibitor. Cyclopropenone-Containing Inhibitor of Papain

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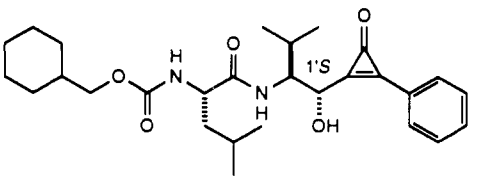
The rational design and synthesis of inhibitors of proteolytic enzymes have recently attracted the attention of bioorganic chemists. We report an entirely new class of molecules that effectively inhibit the action of papain (EC 3.4.22.2), an archetypal cysteine proteinase,[1,2] with a K_i of submicromolar level. The new class of molecules—a cyclopropenone-containing enzyme inhibitor (CCI)—consist of a cyclopropenone structure and a dipeptide moiety connected by a C-C bond as shown in structure 1.



1: 1'*S*
2: 1'*R*-epimer

Cyclopropenone is a highly intriguing system due to its amphiphilic properties: it can act either as an electrophile, owing to the electrophilicity of the olefinic and the carbonyl carbons, or as a proton acceptor, since protonation generates a 2π-aromatic hydroxycyclopropenylium structure.[3] Although the biological properties of a few cyclopropenones have been studied previously,[4] there has been no systematic effort to use the cyclopropenone structure as a design tool in bioorganic chemistry. Here we report the results of our studies in this area[5] on the synthesis of a new and potent papain inhibitor.

The synthesis of 1 was achieved in a straightforward manner as shown in Scheme I. The right-hand side of 1, which may be crucial for the biological activity of the molecule, was synthesized according to the general synthesis of cyclopropenones that we reported recently.[6] Thus, 2-phenylcyclopropenone acetal 3, prepared from 1,3-dichloroacetone in three steps in 76% overall yield, was lithiated,[7] and the resulting vinyllithium reagent was

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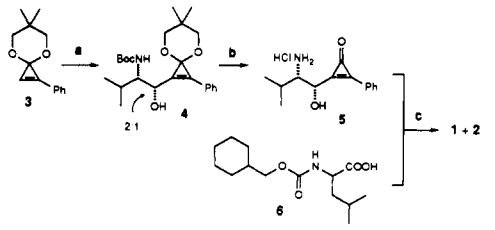
Scheme I[a]



[a] (a) *n*-BuLi/TMEDA/THF and then (*S*)-*N*-Boc-valinal (46%); (b) HCl/H_2O, $AcOEt/Et_2O$ (90%); (c) *i*-BuOCOCl/Et_3N/CH_2Cl_2 (73%).

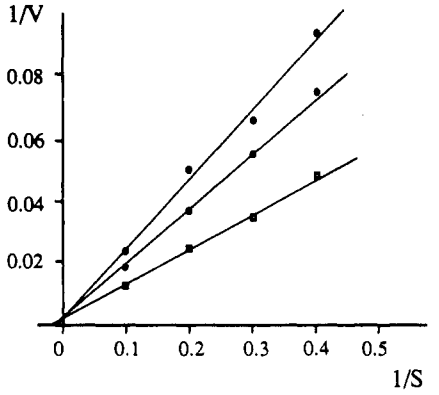


Figure 1. Lineweaver-Burk plot of papain inhibition by compound **1** with Z-Phe-Arg-NMec. The K_m of the substrate is 54.48 μM. Concentrations of the inhibitor are 0 (□), 0.02 μm (●), and 0.05 μM (○). The inhibitor was dissolved in dimethyl sulfoxide and was added to the Na,K-phosphate buffer (pH 6.8) containing papain, EDTA, and dithiothreitol.

added to (*S*)-*N*-(*tert*-butoxycarbonyl)valinal to obtain the alcohol **4** and its 1′*R* epimer as a 2:1 diastereomeric mixture,[8] which was carried through to the final stage without separation. Removal of the acetal and the Boc group was achieved in a single step by the action of HCl in EtOAc-Et_2O. Condensation of the relatively stable amino alcohol hydrochloride (**5**) with the mixed anhydride obtained by the reaction of (*S*)-*N*-(cyclohexylmethoxycarbonyl)leucine **6** with isobutyl chloroformate in the presence of Et_3N then gave the target CCI **1** and its 1′*R* epimer **2** as a ~2:1 mixture readily separable by silica gel chromatography.[9]

The inhibitory activity of **1** and **2** against papain[10] was assayed by using Z-Phe-Arg-NMec[11] as a substrate under the conditions described in the literature.[12] A Lineweaver-Burk plot for **1** is shown in Figure 1, which indicates that this compound is a competitive inhibitor with a K_i value of 0.055 ± 0.021 μM.[13] The 1′*S* isomer **1** is a potent inhibitor of papain, whereas its *R* epimer **2** is a rather weak one as indicated by the IC_{50} values (0.054 and 32 μM for **1** and **2**, respectively, determined under the same conditions). Thus, the configuration at the C1′ carbon bearing a hydroxyl group is very important for inhibitory activity. Most interestingly, unlike typical activated carbonyl inhibitors, **1** exhibits a high level of specificity toward cysteine proteinase. Thus, it was found to be inactive toward serine proteinases (e.g., thrombin, cathepsin G) and carboxyl proteinases (e.g., cathepsin D) at 100 μM.

In summary, we have shown that **1** represents a novel class of inhibitor for papain,[14] and we have demonstrated a new strategy for designing biologically active molecules by combination of a cyclopropenone reactive site and a suitable enzyme recognition site. The mechanism of action of the CCI is unclear at this time owing to the complex reactivities of cyclopropenones (vide supra). Mechanistic studies and further exploration of the concept of CCI are in progress.

Acknowledgment. H.T. thanks JSPS for the predoctoral fellowship.

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(8) The stereochemistry of the C1′ of **4** was assigned to be *S* as indicated, since the minor adduct, which is epimeric at C1′ with **4**, afforded **2**, the single-crystal X-ray analysis of which indicated its 1′*R* configuration. We thank Ms. Nobuko Fukushima and Dr. Takao Matsuzaki for the X-ray analysis.

(9) **1**: mp 85-89 °C; IR (KBr, cm^{-1}) 3330, 1858, 1695, 1658, 1625; ^1H NMR ($CDCl_3$, δ) 0.77 (d, J = 5.0 Hz, 6 H), 0.80-1.05 (m, 2 H), 1.01 (d, J = 6.6 Hz, 3 H), 1.10 (d, J = 6.6 Hz, 3 H), 1.10-1.80 (m, 12 H), 2.40 (m, 1 H), 3.50-3.88 (m, 3 H), 4.09 (m, 1 H), 5.11 (d, J = 4.4 Hz, 1 H), 5.31 (m, 1 H), 7.36-7.62 (m, 4 H), 7.98 (dd, J = 7.5, 1.7 Hz, 2 H). Anal. C, H, N. **2**: mp 148-149 °C; IR (KBr, cm^{-1}) 3350, 3260, 1860, 1825, 1715, 1653, 1625; ^1H NMR ($CDCl_3$, δ) 0.80-1.00 (m, 8 H), 1.08 (d, J = 6.6 Hz, 3 H), 1.15 (d, J = 6.7 Hz, 3 H), 1.10-1.80 (m, 12 H), 2.16 (m, 1 H), 3.68 (m, 1 H), 3.75 (m, 1 H), 4.02-4.22 (m, 2 H), 5.14 (d, J = 2.8 Hz, 1 H), 5.19 (d, J = 6.5 Hz, 1 H), 6.92 (d, J = 6.0 Hz, 1 H), 7.42-7.65 (m, 3 H), 7.99 (dd, J = 6.7, 1.5 Hz, 2 H). Anal. C, H, N.

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Molecular Structure and Electrochemistry of $Ru_2(dpf)_4(C{\equiv}CC_6H_5)_2$ (dpf = *N*,*N*′-Diphenylformamidinate Ion): A Novel Ru(III)-Ru(III) Dimer

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Since the discovery of $Ru_2(OOCCH_3)_4Cl$, numerous Ru_2^{5+} complexes containing a variety of bridging and axial ligands have been reported.[1-5] The electrochemical potentials for the Ru_2^{5+}/Ru_2^{6+} and Ru_2^{5+}/Ru_2^{4+} redox couples vary over a wide range, depending on the σ and π donor ability of the ligands. In most instances, however, the Ru_2^{5+} oxidation state is thermodynamically preferred. A few Ru_2^{4+} complexes have recently been reported,[6-10] but to date no Ru_2^{6+} complex having the tetra-μ-carboxylate type structure has been isolated and structurally characterized. Two diruthenium carboxylate complexes were reported to contain a Ru_2^{6+} core,[11,12] but were later shown by Cotton et al.[13] to be Ru_2^{5+} compounds. The diamagnetic, air-

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