recognized, explored experimentally, and utilized in the experimental design before a satisfactory result could be obtained.

To a solution of the methyl ester of (*S*)-5-HPETE [prepared by reaction of (*S*)-5-HPETE with diazomethane] in 1:1 methylene chloride–ether (75 mg/mL) and 1,2,2,6,6-pentamethylpiperidine[7] (6 equiv), maintained at −110 °C by means of a liquid nitrogen–ethanol bath, was added 2 equiv of trifluoromethanesulfonic anhydride. After 40 min a large volume of pentane containing 1% triethylamine was added and the crude product was isolated by washing with water, drying with sodium sulfate, and removal of solvent in vacuo. The crude product which consisted of a mixture of the desired methyl ester of **3** and the conjugated dienone **4** could not be separated chromatographically and so it was treated with an excess of sodium borohydride in dimethoxyethane at 0 °C to reduce **4** to the corresponding hydroxy ester. Chromatography of the resulting mixture (preparative layer plate of silica gel impregnated with triethylamine using 1:4 ether–pentane containing 1% triethylamine for elution) afforded pure **3** methyl ester, R_f 0.45 (yield ~25%), chromatographically and spectroscopically identical[9] with pure leukotriene A methyl ester prepared by the previously described[4] synthetic route.[9]

Treatment of **3** methyl ester in methanol containing triethylamine with excess glutathione at 23 °C for 5 h, removal of methanol, and isolation as previously described[4] gave the monoester of LTC-1 (**5**) in essentially homogeneous form as determined by reverse-phase high-performance liquid chromatography (Waters Associates C-18 μ-Porasil column using 65% methanol, 35% water containing 0.1% acetic acid buffered to pH 5.6 with ammonium hydroxide). Cochromatography of this product with methyl ester **5** prepared as previously described[4] resulted in one peak, and identity was also indicated by ultraviolet absorption (maximum in CH_3OH at 280 nm (ε 40 000) with shoulders at 270 and 290 nm).[4] Finally hydrolysis of **5** as described previously[4] led cleanly to **1**, identical with authentic LTC-1 by ultraviolet and chromatographic measurements and by bioassay.[5e,10]

The experimental work outlined herein demonstrates a short (five step) and simple route to the primary SRS LTC-1 (**1**) and also the related LTD. It represents a convenient method for the synthesis of small amounts of these SRS's as well as a chemical mimic of the proposed biosynthetic pathway. It is noteworthy, but hardly surprising, that the chemical conversion of 5-HPETE methyl ester into leukotriene A methyl ester is stereospecific and that the newly generated double bonds and oxirane ring are formed in the more stable trans arrangement.[11]

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(8) Found for synthetic **3** methyl ester: UV max (CH_3OH) 278 nm (ε 40 000) with shoulders at 269 and 289 nm; mass spectrum (*m/e*) 332 (M^+), 301 ($M - OCH_3$), 279, 203, 189, 149, 129, 101, 91; ^1H NMR (in C_6D_6, δ) 1.13 (t, J = 7 Hz, 3 H, $-CH_2CH_3$), 1.40–1.70 (br, 12 H, CH_2), 2.34 (m, 2 H, CH_2–COO), 2.75 (t × d, J = 7, 2 Hz, 1 H, =CHHC(O)C*H*), 3.20 (m, 3 H, C=CCH_2C=C, HC(O)C); 3.60 (s, 3 H, $COOCH_3$), 5.5–5.75 (m, 4 H, olefinic at C(7), C(12), C(14), C(15)), 6.15 –7.0 (m, 4 H, olefinic at C(8)–C(11)).
(9) The dienone **4** was also isolated from the reaction mixture by chromatography on untreated silica gel. The product so obtained was identical with conjugated dienone **4** prepared by oxidation of 5-HETE using manganese dioxide in methylene chloride at 23 °C. Found for **4**: IR max (CCl_4) 1580, 1680, 1735 cm^{-1}; UV max (CH_3OH) 276 nm; mass spectrum (*m/e*) 332 (M^+), 301, 231, 129, 101, 79; partial ^1H NMR (in $CDCl_3$, δ) 1.80 (m, 2 H, C(16) H_2), 2.33 (q, 2 H, J = 6 Hz, CH_2COOCH_3), 2.58 (q, 2 H, $COCH_2$), 2.80 (m, 2 H, C(13) H_2), 3.05 (m, 2 H, C(10) H_2), 3.67 (s, 3 H, $COOCH_3$), 5.40 (m, 4 H, olefinic at C(11), C(12), C(14), C(15)), 5.9 –6.25 (m, 3 H, olefinic at C(6), C(8), C(9)), 7.50 (q, J = 16.9 Hz, 1 H, olefinic at C(7)).

(10) We are indebted to Professor Bengt Samuelsson and associates of the Karolinska Institutet, Stockholm, for the biological comparison.
(11) We are grateful to Dr. Shun-ichi Hashimoto for providing (±)-5-HPETE. This study was assisted financially by the National Science Foundation and the National Institutes of Health.

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Electronic Structure of 2-Fe Ferredoxin Models by Xα Valence Bond Theory

Sir:

We report here calculations of $Fe_2S_2(SH)_4^{2-,3-}$, models for the active sites of oxidized and reduced 2-Fe ferredoxin proteins, by the recently developed Xα valence bond (Xα-VB) theory.[1] We believe that these calculations provide the first accurate theoretical description of the much-studied[2-4] antiferromagnetic coupling between the two iron centers. By including the physically most important aspects of electron correlation in our theoretical model, we find much greater similarity between the 2-Fe and 1-Fe[5,6] active sites than was evident from our previous Xα molecular orbital (Xα-MO) calculations on $Fe_2S_2(SH)_4^{2-,3-}$.[7]

Figure 1 shows SCF-Xα-SW-VB energy levels for

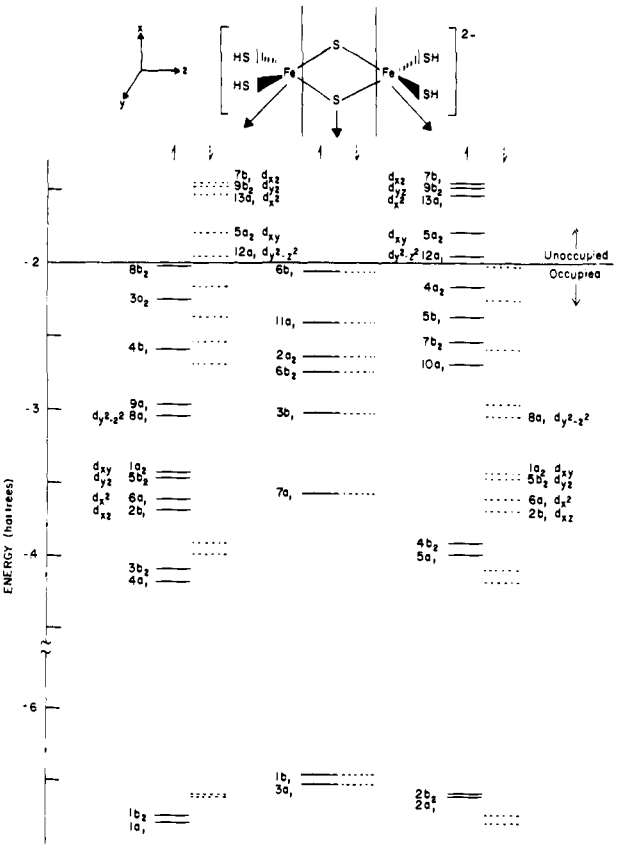

Figure 1. Xα-SW-VB valence levels of $Fe_2S_2(SH)_4^{2-}$. The orbitals are separated according to their localization on the left, center, or right of the molecule. Spin-up levels are depicted with solid lines, spin-down levels with dashed lines. The ten pairs of Fe 3d-like orbitals are indicated.

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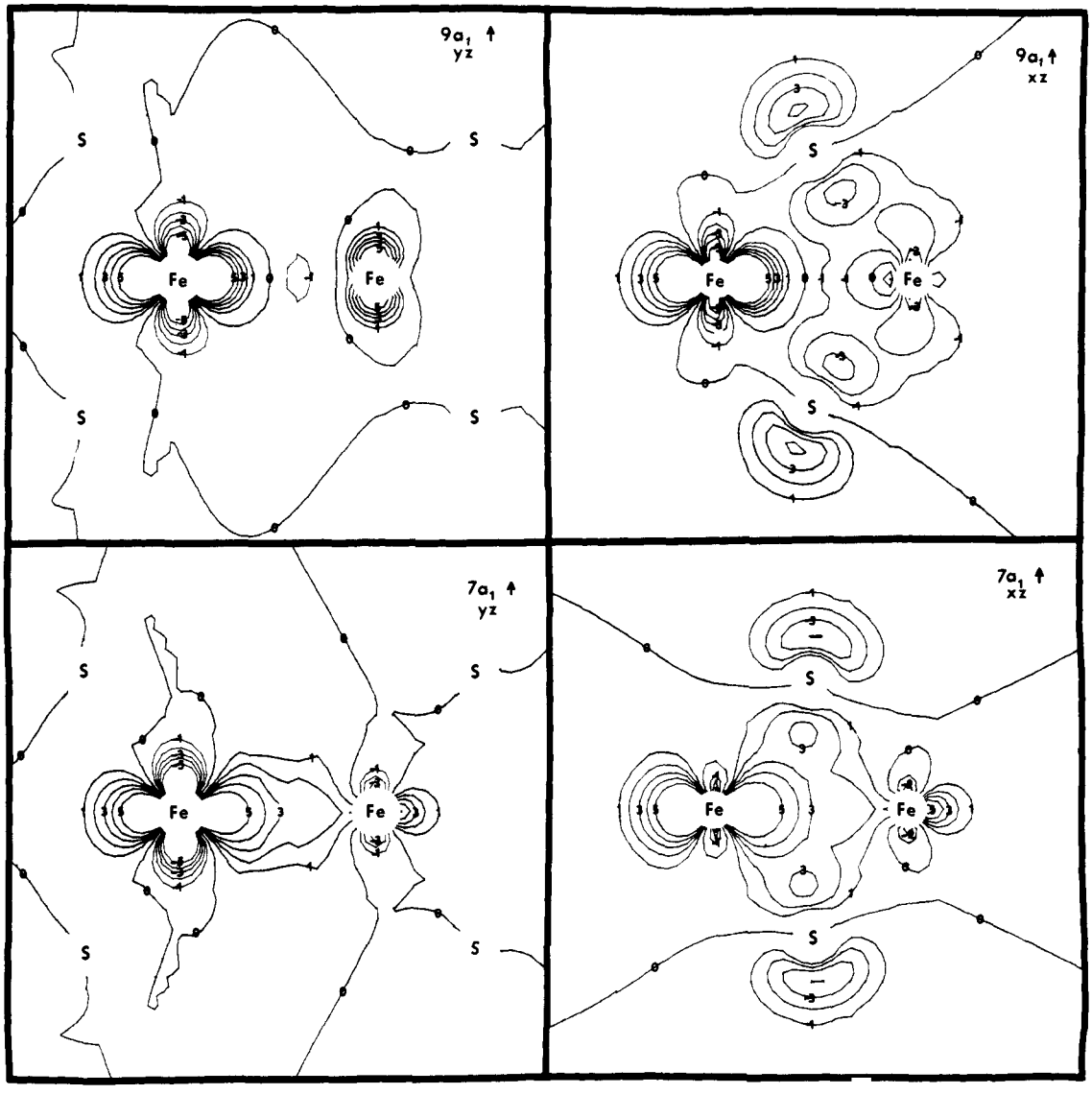

Figure 2. Contour maps of wave functions for the $7a_1\uparrow$ and $9a_1\uparrow$ orbitals of $Fe_2S_2(SH)_4^{2-}$ in the planes both perpendicular to and containing the bridging sulfur atoms. The $7a_1\downarrow$ and $9a_1\downarrow$ orbitals are the mirror images across the Fe-Fe axis of those shown here. The left side of this figure may be compared directly with Figure 2 in ref 7. Contour values here and in Figure 3 are 0, ±1, ±2, ±3, ±4, ±5 = 0, ±0.050, ±0.075, ±0.100, ±0.125, ±0.160 (electrons/bohr^3)$^{1/2}$, respectively.

$Fe_2S_2(SH)_4^{2-}$ in the broken symmetry C_{2v}.[8] The three columns in this spin-polarized diagram show the energies of orbitals localized primarily on the left side, in the center, and on the right side of the ion. A given spin-up orbital on the left is energetically degenerate with its spin-down mirror image on the right. This arrangement makes it easy to view the ion as two coupled *high-spin* monomers. The left monomer, e.g., is assigned all the orbitals in the left column, and a half share in both the spin-up and -down orbitals in the center column. It thus has a net up spin of $5/2$, since there are five empty spin-down orbitals (above −0.2 hartree); similarly the right monomer has a net down spin of $5/2$.

Most orbitals can be grouped in spin-up/spin-down pairs having large overlap, each pair thus resembling a doubly occupied MO. Examples are ($1a_1\uparrow$,$2a_1\downarrow$), a left-side S-H bond; ($3a_1\uparrow$,$3a_1\downarrow$), a bridging-sulfur lone pair; and ($5b_1\uparrow$,$4b_1\downarrow$), a right-side S lone pair. There are ten pairs for which spin-up/spin-down overlap is poor. All have mainly Fe 3d character, and are labeled with d-orbital symbols in Figure 1. Here the natural pairs contain one orbital each from the left and right sides—e.g., ($2b_1\uparrow$,$2b_1\downarrow$). We refer to these as the magnetic orbitals, since they contain the unpaired spins if one considers the monomers as isolated.

In contrast to our previous MO solution,[7] the highest *occupied* orbitals are not mainly Fe 3d. The spin polarization allowed by the symmetry breaking drives the occupied 3d band below Fe-S and S lone-pair orbitals. The 2-Fe active site thus resembles two weakly coupled high-spin ($S = 5/2$) 1-Fe protein active sites: our most important conclusion (subsequently supported by experiment[9]) from spin-polarized Xα-SW-MO calculations on $Fe(SR)_4^-$ was that the five HOMOs (all spin up) are mainly sulfur, while the five LUMOs (all spin down) are mainly iron.[5] The 2-Fe MO solution in this context is like an excited state formed from coupling two low-spin ($S = 1/2$) 1-Fe sites: Fe-Fe σ, σ^*, $\delta_\perp$, $\delta_\perp{}^*$, and $\delta_\parallel$ orbitals are occupied, implying doubly occupied Fe $3d_{z^2}$ and $3d_{xy}$ and singly occupied $3d_{x^2-y^2}$ orbitals in the monomers. Moreover, the detailed Xα-VB charge distribution shows that, of the five magnetic electrons per monomer, ca. four are Fe 3d and one is S 3p. This corresponds to an Fe^{II}-S· monomer ground state, closely resembling the major configuration found for $Fe(SH)_4^-$ by GVB-CI calculations.[6]

Figure 2 shows the spin-up components of the two VB pairs ($7a_1\uparrow,\downarrow$ and $9a_1\uparrow,\downarrow$) which most closely correlate with the MOs ($4a_g$ and $6a_g$, respectively) pictured in our previous paper.[7] As in the MO solution, greater Fe-Fe *overlap* is found in the pair

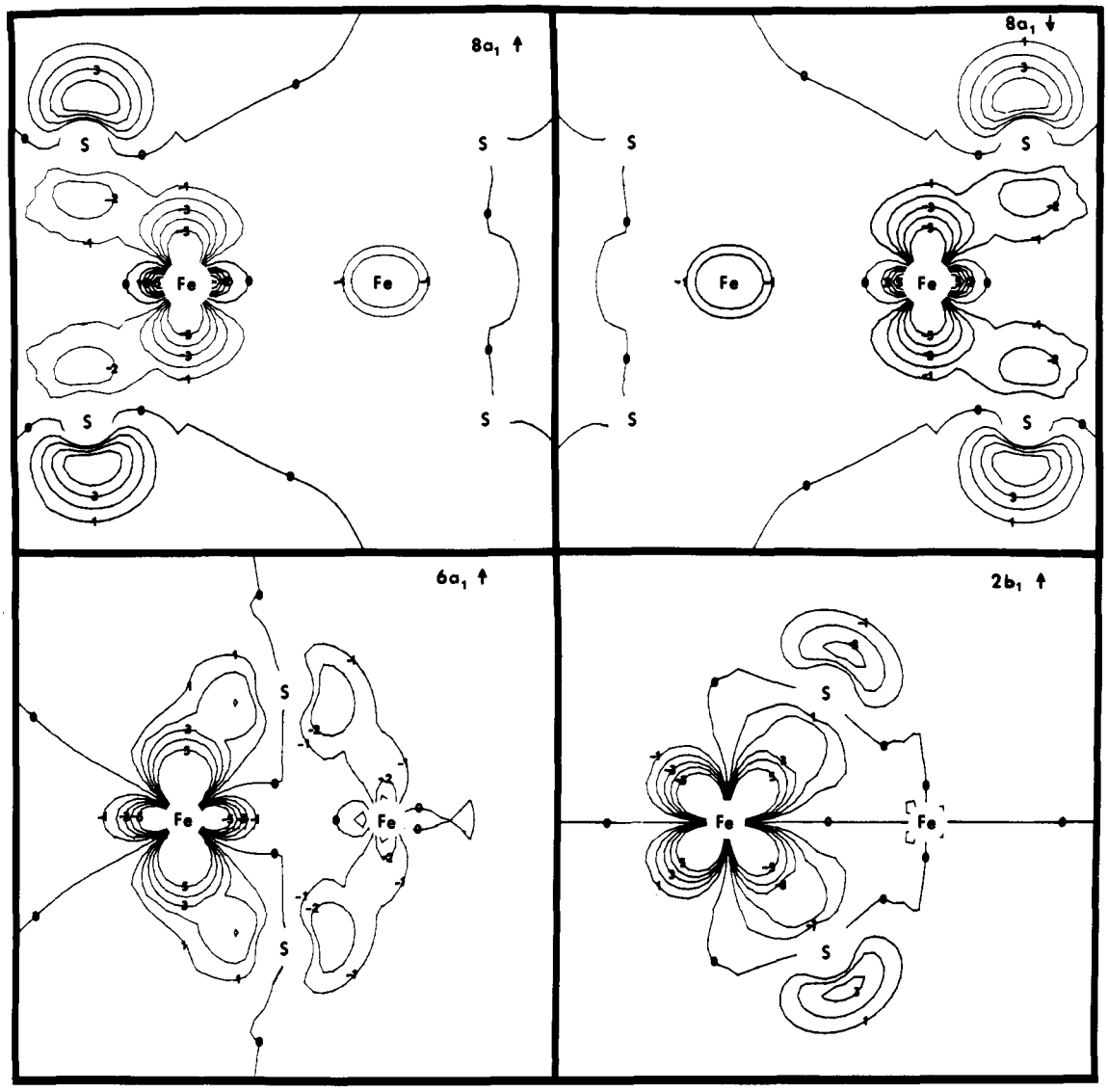

Figure 3. Contour maps of the wave functions for the ($8a_1\uparrow$, $8a_1\downarrow$), $2b_1\uparrow$, and $6a_1\uparrow$ orbitals of $Fe_2S_2(SH)_4^{2-}$. $8a_1$ is shown in the terminal-sulfur plane, while $2b_1\uparrow$ and $6a_1\uparrow$ are in the bridging-sulfur plane.

($7a_1$) having both lower energy and less Fe *character*. Figure 3 shows some of the magnetic orbitals; the small intrapair overlaps are evident. In $8a_1$, we see some of the sulfur-radical character which arises from Fe-S covalency in the magnetic orbitals. The $2b_1\uparrow$ and $6a_1\uparrow$ maps illustrate the dominant superexchange mechanism for the observed antiferromagnetism.

Our Xα-VB calculations of $Fe_2S_2(SH)_4^{3-}$ with both equivalent and distinct iron centers[10] predict that the electron added upon reduction enters the $12a_1\uparrow$ orbital, as would be naively predicted using Figure 1. We label this orbital as $d_{y^2-z^2}$, since its iron character is ca. $-\frac{2}{3}\,d_{z^2} - \frac{1}{3}\,d_{x^2}$. This composition is consistent with experimental spectroscopy of of the reduced protein.[2a]

The detailed Xα-VB theory for extracting energies of pure multiplets from the broken-symmetry SCF state, and for calculating Heisenberg coupling constants J, will be presented separately.[12] For $Fe_2S_2(SH)_4^{2-}$ we predict $J = -265$ cm^{-1} vs. -183 and -149 cm^{-1} determined experimentally for the oxidized protein[2b] and synthetic model,[3] respectively. For $Fe_2S_2(SH)_4^{3-}$ we obtain -76 and -82 cm^{-1} for the equivalent- and distinct-center models, respectively. Experimental values for the reduced protein range from -70 to -110 cm^{-1}.[4] We consider this very good agreement with experiment for these extremely small energy differences.

A subsequent full paper will compare complete Xα-SW-VB results for ground and excited states of 2-Fe models with those being obtained by others[13] for 4-Fe/8-Fe protein active sites.

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(13) Case, D. A., personal communication.
(14) Fellow of the Alfred P. Sloan Foundation, 1978-1980.

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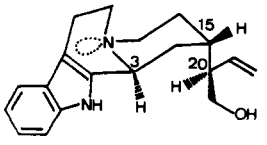
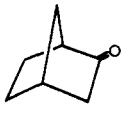
Synthesis of (±)-Antirhine from (±)-Norcamphor

Sir:

Antirhine (**1**),[1] the major alkaloid of *Antirhea putaminosa*, is an unique yohimbonoid variant with cis C/D ring juncture and only two congeners, hunterburnine α- and β-methochlorides[2] (10-hydroxyantirhine α- and β-methochloride), have been isolated so far. Although a structurally simple compound, **1** has not previously been synthesized, probably owing to difficulty in the stereocontrolled construction of the three chiral centers, the centers at C_3 and C_{15} with the less stable anti relationship, and the center at C_{20} bearing vinyl and hydroxymethyl moieties.[3] We describe here the first stereoselective synthesis of (±)-antirhine (**1**), starting from (±)-norcamphor[4] (**2**).



1



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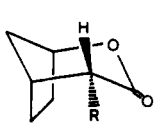
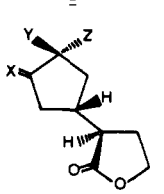


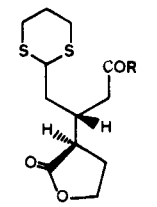
3: R=H
4: R=$CH_2CH=CH_2$
5: R=CH_2CH_2OH



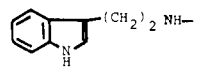
6: X=H_2, Y=H, Z=OH
7: X=H_2, Y=Z=-O-
8: X=-S$(CH_2)_3$S-, Y=Z=-O-

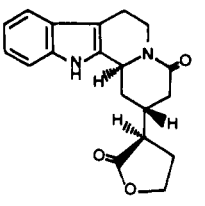
Ozonization of the bicyclic δ-lactone **4** [prepared stereoselectively from (±)-norcamphor (**2**) via **3** (75.4% overall yield)[4c]] in methanol (−78 °C), followed by direct reduction with sodium borohydride in the same flask (−78 °C to room temperature) furnished the oily γ-lactone **6**[5] [79.9% yield; IR (neat) 3400, 1755 cm^{-1}; mass spectrum *m/e* 171 ($M^+ + 1$) 153 (100%)] spontaneously through the δ-lactone **5**. Oxidation of **6** with Jones reagent gave the keto lactone **7**, mp 78-80 °C, in 79.8% yield: IR (Nujol) 1750, 1725 cm^{-1}; mass spectrum *m/e* 168 (M^+), 140 (100%). Regioselective thioketalization was achieved by treatment of the pyrrolidine enamine derived from keto lactone **7** with trimethylene dithiotosylate[6] in the presence of triethylamine, affording the α-diketone monothioketal **8**, mp 142-144 °C, in 51.8% yield: IR (Nujol) 1755, 1720 cm^{-1}; mass spectrum *m/e* 272 (M^+), 272 (100%).

Base cleavage[7] of **8** (KOH-*t*-BuOH, 60 °C, 1 h) and acid workup produced the carboxylic acid **9**, amorphous foam, in quantitative yield: IR (Nujol) 3400-2400, 1758, 1710 cm^{-1}; NMR ($CDCl_3$) δ 3.94-4.55 (3 H, m), 10.36 (1 H, s, disappeared with D_2O); mass spectrum *m/e* 290 (M^+), 119 (100%). Treatment of **9** with ethyl chloroformate in the presence of triethylamine[8] (CH_2Cl_2, room temperature, 4 h) gave the crude mixed anhydride, which on condensation with tryptamine (CH_2Cl_2, room temperature) afforded the secondary amide **10**, amorphous foam, in 76.8% overall yield: IR (Nujol) 3250, 1752, 1640 cm^{-1}; NMR ($CDCl_3$) δ 3.57 (2 H, br t), 4.13 (3 H, m), 6.05-6.50 (1 H, br q, disappeared with D_2O), 6.96-7.90 (5 H, m), 8.88 (1 H, s, disappeared with D_2O); mass spectrum *m/e* 432 (M^+), 143 (100%).



9: R=OH
10: R=





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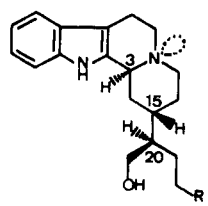
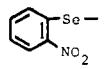


12: R=OH
13: R=



On hydrolysis of the dithiane group, by treatment of **10** with methyl iodide in aqueous acetonitrile at room temperature[9,10] (~48 h), cyclization occurred to furnish the lactam **11**, mp 214-217 °C, in 36.8% yield: IR (Nujol) 3140, 1759, 1608 cm^{-1}; NMR ($CDCl_3$ + CF_3CO_2H) δ 4.00-4.46 (2 H, m), 4.78-5.28 (2 H, m), 7.05-7.70 (4 H, m), 8.72 (1 H, br s); mass spectrum *m/e* 324 (M^+), 184 (100%). Reduction ($LiAlH_4$, boiling THF, 3.5 h) of the lactam **11** gave the aminodiol **12** with the anti C_3-C_{15} relationship, mp 215-218 °C, in 92.5% yield: IR (Nujol) 3170 cm^{-1}; NMR ($CDCl_3$) δ 3.40-3.98 (4 H, m), 4.15 (3 H, br s, 2 H, disappeared with D_2O), 6.90-7.60 (4 H, m), 9.02 (1 H, br s, disappeared with D_2O); mass spectrum *m/e* 314 (M^+), 225 (100%). Support for the assignment of the stereochemistry at C_3 and C_{15} was obtained from spectral examination. As expected, the IR spectrum did not exhibit Bohlmann bands, while the NMR spectrum exhibited the C_3 H as a multiplet centered at δ 4.15, both indicating the cis B/C configuration owing to the anti C_3-C_{15} relationship.[3b,11,12]

Treatment of the diol **12** with 1 molar equiv of *o*-nitrophenyl selenocyanate and tri-*n*-butylphosphine[13] (THF, room temperature, 2 h) allowed selective selenylation at the desired position to give the monoselenide **13**, mp 175-177 °C, in 39.2% yield (64.3% yield based on recovered **12**): IR ($CHCl_3$) 3470, 3280, 1590, 1330 cm^{-1}; NMR ($CDCl_3$) δ 4.21 (1 H, br s), 6.95-7.70 (7 H, m), 8.27 (1 H, d, J = 7.6 Hz), 8.73 (1 H, br s, disappeared with D_2O); mass spectrum *m/e* 498 (M^+), 225 (100%). The selenide **13**, upon oxidation with *m*-chloroperbenzoic acid (1.3 equiv, CH_2Cl_2, −20 °C to room temperature) afforded (±)-antirhine (**1**), mp 100-102 °C (lit.,[1] 112-114 °C), in 71.7% yield, which had R_f values and IR, NMR, and mass spectra identical with those of the natural product.[14] Since chiral norcamphor has been obtained,[15] the present method is potentially useful for a chiral synthesis of antirhine (**1**).

Acknowledgment. We thank the Ministry of Education, Japan, for supporting this work.

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