C_{19} to C_{24} moiety may be derived biosynthetically from D-glucosamine as is found, for example, in mitomycin C, another aziridine-containing antibiotic.[12]

Spin-echo experiments[13,14] in the ^{13}C NMR of CZ showed positive effects for C_{11}, C_{14}, C_{16}, C_{18}, C_{19}, C_{20}, and C_{24}, confirming that these carbons are directly bonded to zero or two protons, and negative effects for C_{12}, C_{13}, C_{17}, C_{21}, and C_{23}, indicating these carbons are directly bonded to one or three protons, in accord with the assigned structure I.

A zwitterionic form for CZ is anticipated owing to the presence of the carboxyl group at C_{20} and the basic N bridge. Whereas the C_{15}–H appears as a sharp singlet at δ 5.10 in $CDCl_3$, it changes to a triplet ($J = 1.5$ Hz, δ 5.25) upon addition of CF_3COOH (TFA) when the rate of proton exchange from the bridgehead N is slowed. Upon addition of an equivalent of TFA the aziridine rings may be opened selectively while the peptide backbone of the molecule is unaffected. The direction of the aziridine ring opening as evidenced by the contrasting large chemical shift change for H_{24} (δ 2.5 to 4.50) together with the ^{19}F shifts of the resulting CH_2OCOCF_3 groups (q.v.) corresponds to the S_N2 ring opening expected for a monosubstituted aziridine.[15] During this process the geminal $C_{24}H_2$ coupling of <0.9 Hz, characteristic of an aziridine,[16] becomes the normal value of 12 Hz for an open-chain compound. Treatment with TFA also results in γ-lactone formation between the C_{19} carboxyl and the C_{22}–OH, resulting in the disappearance of the signals due to these two protons, observations of vicinal coupling between H_{21} and H_{22} of 3.7 Hz, and appearance of an IR band at 1750 cm^{-1}.[17] Upon treatment with more than 2 equiv of TFA, the C_{20}–OH and C_{22}–OH groups are acylated, and examination of the ^{19}F NMR spectrum confirms three types of OTFA groups at +0.154, –0.218, and –0.396 (relative to $CF_3CO_2CH_3$), corresponding to terminal (C_{24}) in-chain (C_{22}), and in-ring (C_{20}) OTFA ester groups.[18] That structure I and conformation II indicate similarity to the bis-intercalating quinoxaline antitumor antibiotics (echinomycin,[19] triostin,[19] and luzopeptin[20]) immediately suggests a mode of action for CZ. The intrinsic fluorescence of the naphthalene chromophores[21] (excitation at 346 nm, emission at 427 nm) shows a progressive enhancement up to 200% when aliquots of calf thymus DNA are added to the solution. The presence of the two aziridine moieties in close proximity to these chromophores (II) also accounts for the observed specifically acid-promoted interstrand cross-linking of DNA by CZ.[8,9] These and other aspects of the mechanism of action will be reported subsequently.

Acknowledgment. This work was supported by grants from the National Cancer Institute of Canada and the Natural Sciences and Engineering Research Council of Canada.

Registry No. Carzinophilin A, 81553-83-5.

Supplementary Material Available: ^1H and ^{13}C NMR data as well as proton coupling constants and spin-echo and nuclear Overhauser differences on carzinophilin A (7 pages). Ordering information is given on any current masthead page.

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Synthesis and Binding Studies of a Photoaffinity Label for Bovine Rhodopsin

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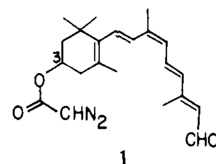
Received January 8, 1982

Our earlier studies with various rhodopsins incorporating synthetic model retinals led to the proposal of the external point-charge model[1-3] which accounted for the variation of the absorption maxima of rhodopsins. In the following we report the synthesis of the photoaffinity labeled retinal **1**, properties of the



bovine rhodopsin formed therefrom, and the fact that the protein binds preferentially to one of the enantiomers at C-3. We believe that such photoaffinity labeling studies[4] will assist in clarifying the positioning of the chromophore within the protein binding site when the apoprotein structure becomes elucidated.[5]

The photoaffinity label should be such that it absorbs light efficiently in a region that overlaps minimally with the pigment absorption, it is introduced at a later stage in the synthesis (for radioactive label studies), and it should be separable from the polyene moiety so that complications arising from double-bond isomerizations etc., are minimized during subsequent sequencing studies. These were the reasons for choosing the diazoacetoxyl group, which had been employed by Westheimer and co-workers in their pioneering studies.[6] The synthesis of the diazoacetate was eventually carried out according to Scheme I. All intermediates and final products were characterized by spectral data.

Dehydro-β-ionone **2**, prepared from β-ionone following known procedures,[7] was converted to 3-hydroxy-β-ionone **3** by hydroboration[8] and then to the 3-hydroxy-9-*cis*-retinal **6** (Scheme I). This was then photoaffinity labeled as follows by slight modification of conventional procedures.

Glyoxylic acid tosylhydrazone[13] (64.5 mg, 0.266 mM) in 300 μL of CH_2Cl_2 and 45 μL of DMF containing (dimethylamino)-pyridine (6.4 mg) was stirred for 15 min at room temperature, and the solution was treated at 0 °C with retinal **6** (80 mg, 0.266

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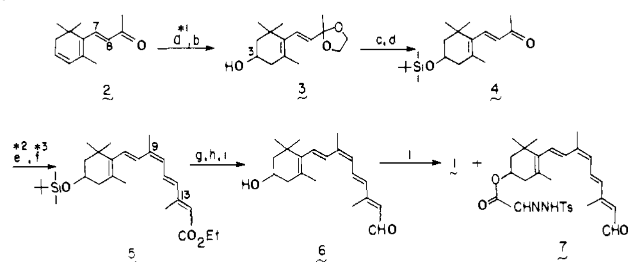
Scheme I



^{a} $HOCH_2CH_2OH/p\text{-}TsOH/PhH$, reflux, 70%. ^{b} (i) 9-BBN, 55-60 °C; (ii) $NaOH/H_2O_2$, 50%. ^{c} TBDMS-Cl/Im·DMF, room temperature, 90%.[9] ^{d} 5% HCl in Me_2CO, 90%. ^{e} (i) $(Me)_3SiCH_2CH{=}N\text{-}t\text{-}Bu/LDA/THF/{-}78$ °C; (ii) HCO_2H/room temperature, 75%.[10] ^{f} $(OEt)_2POCH_2C(CH_3){=}CHCO_2Et/NaH/THF/{-}10$ °C, 85%. ^{g} $n\text{-}Bu_4N^+F^-/THF$, room temperature. ^{h} Dibal/$Et_2O/{-}78$ °C. ^{i} MnO_2/CH_2Cl_2, room temperature.[11] Steps *g*, *h*, *i* combined 50-55% yield. ^{j} $TsNHNCHCO_2H/DCC/DMAP/CH_2Cl_2/DMF$, room temperature, 5-10% for **1**.[12] (*1) When the ketone was not blocked, partial reduction of the 7-ene occurred upon hydroboration. (*2) A 70/30 trans/9-cis mixture is obtained in this two-carbon elongation, 75% yield; the 9-cis isomer is separated by flash chromatography on SiO_2. (*3) The phosphonate reagent was a 3/2 trans/cis mixture and so **6** is also a (65/35) mixture of the trans/13-cis compounds.

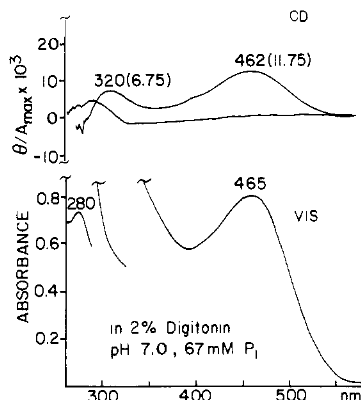


Figure 1. Absorption and circular dichroism spectra of pigment prepared from 3-diazoacetoxy-9-*cis*-retinal and bovine opsin.

mM) in 1 mL of CH_2Cl_2 and then with DCC (54.9 mg, 0.266 mM) in 300 μL of CH_2Cl_2. After 15 min the temperature was raised to room temperature the solution stirred for 4 h, filtered, and concentrated under Ar, and the residue consisting of **1** (major) and tosylhydrazones **7** (syn and anti) was submitted to a three-step purification: (i) flash chromatography separation of the 9-cis esters from the 9,13-dicis esters (ca. 20%) and starting material **6**; (ii) HPLC, Altex Lichrosorb 10 × 250 mm, 12% EtOAc/hexane, separation of **1** from hydrazones **7**; (iii) HPLC, Waters μPorasil 3.9 × 300 mm, 9% EtOAc/hexane. This gave pure 3-diazoacetoxy-9-cis compound **1** in ca. 10% yield from **6**:[14,15] desorption chemical ionization mass spectrum, (NH_3 reactant gas), m/z 369 $(M + H)^+$; UV (hexane) 245 nm (ε 14 280), 357 nm (ε 29 500) (Figure 2); IR (thin film) 2112 cm^{-1} (diazo), 1689 (ester), 1659 (unsaturated aldehyde) cm^{-1}. The 9-cis structure was fully supported by the ^1H NMR data.[16] The Schiff base (SB) and

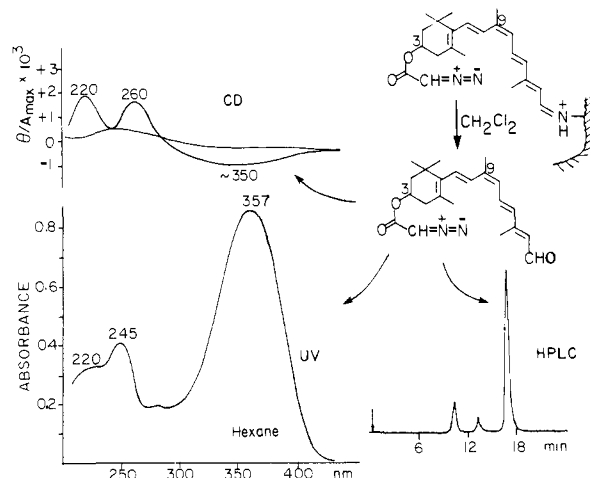


Figure 2. CH_2Cl_2 extraction and HPLC analysis of the chiral opsin-bound 3-diazoacetoxy-9-*cis*-retinal, μPorasil, 12% EtOAc/hexane. The UV and CD were both measured in hexane.

SBH^+ of **1** with *n*-butylamine were made as described previously;[17] UV of SB (MeOH) 350 nm, UV of SBH^+ (MeOH) 425 nm (or 23 525 cm^{-1}).

The pigment was formed[18] by incubating a suspension of bleached rod outer segment membranes (bovine) with a 5-fold optical density (OD) excess of pure chromophore in EtOH at pH 7.0, 67 mM phosphate buffer, 25 °C, and 23 h in the dark, and working up as usual by washing out the excess chromophore and solubilizing in 2% digitonin.[19] The pigment thus formed absorbed at 465 nm (21 505 cm^{-1}) accompanied by CD extrema (Figure 1). As expected the opsin shift[3] of 2020 cm^{-1} (23 525 cm^{-1} for SBH^+ minus 21 505 cm^{-1} for pigment) is similar to that of 9-*cis*-rhodopsin or isorhodopsin (SBH^+ 440 nm or 22 727 cm^{-1}, pigment 485 nm or 20 619 cm^{-1}, opsin shift 2110 cm^{-1}). The pigment was stable in digitonin solution in the dark at 4 °C for at least 9 days, but at 30 °C a 15% decomposition was observed after 80 h; however, it is unstable to 0.05 M NH_2OH and a 50% decomposition is seen after 1 h, pH 7.0, in the dark. Since 9-*cis*-rhodopsin and the photoaffinity-label-bearing rhodopsin absorb at similar wavelengths, the fact that **1** occupies the same binding site as with 9-*cis*-retinal was demonstrated as follows. After reincubation of the hexane-washed pigment with 9-*cis*-retinal for 3 h in 67 mM phosphate buffer, pH 7.0 at 30 °C, the pigment was solubilized in 2% digitonin and was treated with NH_2OH (final concentration 0.05 M), upon which 95% of the 465-nm absorption disappeared. Since 9-*cis*-rhodopsin is far stabler to NH_2OH, if it had been formed, a 95% reduction in absorption maximum would not have been observed.

Application of the CH_2Cl_2 denaturation–extraction procedure[20] followed by HPLC analysis (coinjection) showed that the bulk of the 3-diazoacetoxyretinal remained unchanged after binding (Figure 2); moreover, the chromophore thus extracted produced the same pigment upon reincubation. However, the HPLC peak of the chromophore was now chiral with CD extrema at 220, 260, and 350 nm, in hexane (Figure 2). Despite previous attempts with 6-allenic retinal[21] to show chiral discrimination by the opsin, the reextracted chromophore had never shown optical activity, and

(14) House et al. have prepared diazoacetates in a two-step procedure in 20–30% yields employing TsNHNCHCOCl for esterification and base treatment of the tosylhydrazone esters.[15] This procedure was not used due to the sensitivity of the retinal moiety to acid.

(15) The mechanisms by which this one-step reaction yields diazoacetates can only be hypothesized at this stage, and whether the tosylhydrazone ester itself is an intermediate or not is unclear. Since the 3-diazoacetoxy retinal forms pigment efficiently with bovine rhodopsin, efforts are now under way to increase the efficiency of its production.

(16) ^1H NMR ($CDCl_3$) δ 1.14 (s, 1-Me), 1.77 (s, 5-Me), 2.03 (s, 9-Me), 2.33 (s, 13-Me), 4.75 (s, diazoacetate CH), 5.20 (m, 3-H), 5.99 (d, J = 7.8 Hz, 14-H), 6.13 (d, J = 11.7 Hz, 10-H), 6.26 (d, J = 16.1 Hz, 7-H), 6.33 (d, J = 15.3 Hz, 12-H), 6.66 (d, J = 16.1 Hz, 8-H), 7.20 (dd, J = 15.3 Hz, J = 11.7 Hz, 11-H), 10.12 (d, J = 7.8 Hz, 15-H).

(17) Gawinowicz, M. A.; Balogh-Nair, V.; Sabol, J. S.; Nakanishi, K. *J. Am. Chem. Soc.* 1977, *99*, 7720.

(18) Regeneration of artificial rhodopsins is frequently more difficult than for the natural system owing to the instability of the retinal, lesser binding tendencies, etc. The conditions given here are the optimum for the 3-diazoacetoxy-9-*cis*-retinal chromophore.

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from this and other results, i.e., adamantyl allenic retinal,[22] we had concluded that the β-ionone binding site[23] of bovine opsin is lenient in its steric requirement. The present result is thus the *first indication of chiral discrimination by the opsin.*[24]

Irradiation of the pigment (67 mM phosphate buffer, pH 7.0, 2% digitonin) with >510-nm light[25] resulted in disappearance of the 465-nm band in 4 h. Photolysis of the diazoacetoxy group, λ_{max} 245 nm, was carried out by irradiation of the pigment at 254 nm by using a 4-W[26] Hg lamp and narrow band pass interference filter at 25 °C. Since a 4-h irradiation resulted in only a ca. 10% decrease of the 465-nm peak, we believe that the specific interactions between chromophore and opsin in the binding sites (which are responsible for the characteristic absorption maximum) have not been considerably affected by irradiation at 254 nm. The amount of chromophore extracted by the CH_2Cl_2[27] method diminished successively with time so that after the 4-h irradiation it was only 15–30% of the nonirradiated control. This indicates that the diazoacetoxyl group has been photolyzed efficiently within the binding site. The extent of covalent binding to the protein will be determined quantitatively by ongoing studies with the pigment formed from 3-($O^{14}COCHN_2$)-labeled 9-*cis*-retinal.[28]

Registry No. 1, 81600-84-2; **2**, 14398-35-7; **3**, 81555-36-4; **4**, 81555-37-5; *cis*-**5**, 81555-38-6; *trans*-**5**, 81600-85-3; *cis*-**6**, 81600-86-4; *trans*-**6**, 81600-87-5; *syn*-**7**, 81583-45-1; *anti*-**7**, 81623-37-2.

(22) Blatchly, R. A.; Carriker, J. D.; Balogh-Nair, V.; Nakanishi, K. *J. Am. Chem. Soc.* **1980**, *102*, 2495.
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(24) Studies are in progress to resolve the two enantiomeric retinals and to determine the absolute configuration of the enantiomer accepted by the protein.
(25) 1-kW Ushio projector lamp, 25-cm distance, 510-nm filter, room temperature.
(26) A weak intensity lamp was deliberately used to minimize the loss of the 465-nm absorption.
(27) The hexane-washed (11 times to remove excess unbound chromophore) pigment pellets each prepared from 2 OD opsin were extracted five times with CH_2Cl_2, and the CH_2Cl_2 extracts were combined and submitted to HPLC.
(28) The present studies were supported by NIH grant EY 01253.

Stereocontrol in the Intramolecular Diels–Alder Reaction. 3. A Potentially General Method for the Synthesis of *cis*-Hydrindenes by Use of (*Z*)-Diene Units

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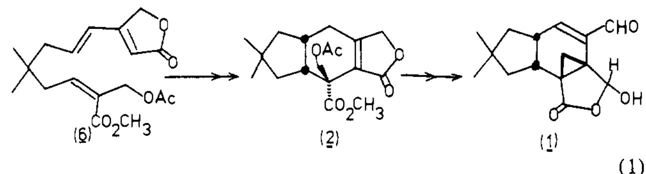
Received December 14, 1981

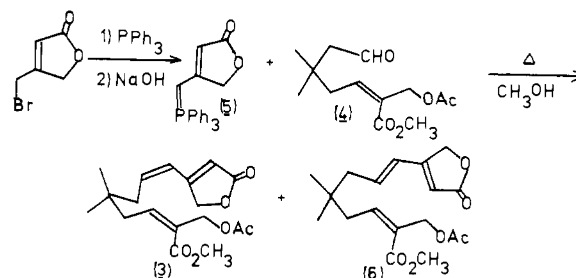
In a previous communication, we reported a convergent synthetic sequence to the unique sesquiterpene antibiotic marasmic acid (**1**), which utilized as the key element of the synthetic strategy an intramolecular Diels–Alder reaction to assemble the required *cis*-hydrindene skeleton (eq 1).[1]



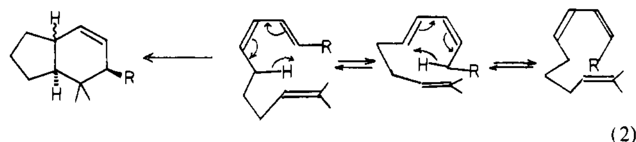
(1)

However, in spite of a large amount of work recorded in this area, especially by Roush[2,3] and ourselves,[1,4] a *general solution* to the problem of construction of *cis*-hydrindene nuclei with complete stereoselectivity via intramolecular cycloaddition has not become available.

Scheme I



We were attracted to the possibility that the use of (*Z*)-diene elements might provide such a solution, since it was apparent that other control elements such as dienophile geometry and stereoelectronic effects were insufficient energetically to impart the required levels of stereocontrol.[4] Bimolecular Diels–Alder reactions of (*Z*)-dienes are effectively unknown, and only two examples of the successful intramolecular cycloaddition of (*Z*)-dienes have thus far been reported.[5,6] These cases were examples of systems that were relatively unsubstituted or possessed highly activated dienophile groups. Consequently, the application to a highly substituted and less activated system such as that described herein would represent a stringent test of the methodology. It was further of interest to have a quantitative comparison of the relative reactivity of a pair of more highly functionalized but not unusually highly activated (*Z*)- and (*E*)-diene systems, since the apparently comparable rates of cyclization for *E* and *Z* isomers observed by House appeared to violate intuition.[5] Most importantly, the studies reported herein examine the validity of concern over a potentially serious limitation on the method indirectly suggested by the studies of Borch.[7] Competition between thermally allowed 1,5 sigmatropic hydrogen shifts and cycloaddition, formally possible in nearly all (*Z*)-diene systems, could result in loss of the geometric or structural integrity of the diene as shown schematically in eq 2.



(2)

We report the successful use of a (*Z*)-diene unit as the control element in the highly substituted triene **3** to the *completely stereoselective* construction of the highly functionalized *cis*-lactone **2**, which has previously been transformed to marasmic acid (**1**). The (*Z*,*Z*,*Z*)-triene **3** was prepared from known precursors as shown in Scheme I.[8] Treatment of the aldehyde **4** (1 equiv) with

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(2) Reviews: (a) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63. (b) Oppolzer, W. *Synthesis* **1978**, 793. (c) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10. (d) Funk, R. L.; Vollhardt, K. P. C. *Chem. Soc. Rev.* **1980**, *9*, 41. (e) Carlson, R. G. *Ann. Rep. Med. Chem.* **1974**, *9*, 270.
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(8) **3**: IR ($CHCl_3$) 1780, 1755, 1725, 1640 cm^{-1}; NMR ($CDCl_3$/400 MHz) δ 6.33 (t, J = 7.8 Hz, 1), 6.21 (d, J = 11.7 Hz, 1), 6.11 (dt, J = 11.7 Hz, J_2 = 7.3 Hz, 1), 5.98 (s, 1), 4.95 (s, 2), 4.75 (s, 2), 3.77 (s, 3), 2.58 (d, J = 7.8 Hz, 2), 2.20 (d, J = 7.3 Hz, 2), 2.07 (s, 3), 1.00 (s, 6). **5**: IR ($CDCl_3$) 1685 cm^{-1}; NMR ($CDCl_3$/90 MHz) δ 7.46 (m, 16 H), 4.73 (s, 2), 4.15 (s, 1).

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