183.8, 125.7, 83.1, 60.2, 51.9, 47.7, 43.5, 29.7; mass spectrum (70 eV), m/e (rel intensity) 268 (M^+, 100), 240 (23), 171 (23), 159 (23), 145 (29), 133 (56), 115 (46), 105 (35), 91 (92), 77 (56), 55 (33).

Continued elution of the column with the same solvent system yielded **29** (25 mg, 20%) and was crystallized from dichloromethane-petroleum ether: mp 215 °C; IR (KBr) ν_{max} 1710, 1630, 1140, 690 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.97 (1 H, d, $J = 1.5$ Hz, $-HC=CH-$), 5.83 (1 H, d, $J = 2.2$ Hz, $-HC=CH$), 5.08 (1 H, d, $J = 4.9$ Hz, $-C=C-HC-O$), 4.5 (1 H, dd, $J_1 = 8.2$ Hz, $J_2 = 4.5$ Hz, $-HC-O-$), 3.62-3.43 (4 H, m), 3.23 (1 H, m), 2.84-2.78 (2 H, m), 2.72 (1 H, td, $J_1 = 14.5$ Hz, $J_2 = 10$ Hz), 2.54 (1 H, m), 2.27 (1 H, dd, $J_1 = 16$ Hz, $J_2 = 3.8$ Hz), 2.16 (1 H, dd, $J_1 = 17$ Hz, $J_2 = 3.2$ Hz), 1.82 (1 H, td, $J_1 = 14.5$ Hz, $J_2 = 6$ Hz); ^{13}C NMR (25.0 MHz, CDCl$_3$) δ 214.8, 208.9, 189.1, 184.8, 125.4, 124.8, 90.8, 84.4, 61.0, 51.3, 50.0, 49.5, 49.0, 43.9, 42.0, 40.9; mass spectrum (70 eV), m/e (rel intensity) 268 (M^+, 100), 169 (12), 158 (13), 131 (42), 115 (28), 91 (50), 79 (23), 77 (44), 65 (25), 53 (22); high-resolution mass spectrum for C$_{17}$H$_{16}$O$_3$. Calcd m/e 268.1099, found m/e 268.1096.

Further elution of the column with 60% benzene-petroleum ether furnished **27** (28 mg, 21%) and was crystallized from dichloromethane-petroleum ether: mp 217 °C dec; IR (KBr) ν_{max} 1705, 1640, 1080, 700 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.86 (2 H, d, $J = 1.2$ Hz, $-HC=C-$), 4.51 (2 H, m, $-HC-O-$), 3.62-3.43 (6 H, m), 2.86 (1 H, d, $J = 7.2$ Hz), 2.82 (1 H, d, $J = 7.2$ Hz), 2.51 (1 H, td, $J_1 = 14$ Hz, $J_2 = 10.5$ Hz); ^{13}C NMR (25.0 MHz, CDCl$_3$) δ 208.9, 186.9, 125.1, 91.4, 60.2, 50.2, 49.3, 42.2, 38.2; mass spectrum (70 eV), m/e (rel intensity) 268 (M^+, 100), 240 (39), 212 (13), 148 (18), 133 (15), 115 (13), 104 (15), 91 (27), 79 (16), 77 (34), 65 (15), 51 (13); high-resolution mass spectrum for C$_{17}$H$_{16}$O$_3$. Calcd m/e 268.1099, found m/e 268.1101.

(1R*,6R*,7S*,9R*,10S*,15R*,16S*,17S*)-8-Oxahexacyclo[13.2.1.0^{2,6}.0^{7,17}.0^{9,16}.0^{10,14}]octadeca-2,13-diene-4,12-dione (31). To a solution of the symmetrical bis-enone **27** (10 mg, 0.06 mmol) in 15 mL of dry dichloromethane was added 10 mg of 1,8-diazabicyclo[5.4.0]undecane (DBU). The reaction mixture was refluxed for 5 h and diluted with 10 mL more of dichloromethane. The organic layer was washed

with 5% HCl, followed by water, and dried. Removal of solvent furnished 10 mg of crude product. A quick filtration through a silica gel (5 g) column furnished the isomerized enone **31** (9 mg, 90%) and was crystallized from dichloromethane-petroleum ether: mp 212-214 °C dec; IR spectrum (KBr) ν_{max} 1710, 1630, 1090, 940 cm^{-1}; ^{1}H NMR (100 MHz, CDCl$_3$) δ 5.76 (2 H, s with st, $HC=C-$), 4.52 (2 H, dd, $J_1 = J_2 = 6$ Hz, $-HC-O$), 3.8-3.3 (4 H, m), 3.1-2.9 (2 H, m), 2.5-2.0 (4 H, m), 2.0-1.6 (2 H, m); ^{13}C NMR (25.0 MHz, CDCl$_3$) δ 209.7, 189.9, 125.6, 81.6, 58.5, 51.3, 46.9, 37.8, 35.5; mass spectrum (70 eV), m/e (rel intensity) 268 (M^+, 100), 240 (33), 212 (12), 148 (12), 132 (12), 115 (12), 105 (15), 91 (21), 77 (20); high-resolution mass spectrum for C$_{17}$H$_{16}$O$_3$ calcd m/e 268.1099, found m/e 268.1101.

(1R*,2S*,6S*,7S*,9R*,10R*,14R*,15S*,16R*,17S*)-8-Oxahexacyclo[13.2.1.0^{2,6}.0^{7,17}.0^{9,16}.0^{10,14}]octadecane-4,12-dione (32). A solution of **31** (8 mg, 0.05 mmol) in 10 mL of dry ethyl acetate was hydrogenated (40-psi H$_2$ pressure) over 10% Pd/C (3 mg) for a period of 6 h. Pd/C was filtered off and the solvent removed to furnish **32** (8 mg, 100%). Crystallization from dichloromethane-petroleum ether furnished an analytically pure sample: mp 150-152 °C; IR (KBr) ν_{max} 1730, 1160, 980 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.39 (2 H, dd, $J_1 = J_2 = 4.39$ Hz, $-HC-O-$), 3.1-3.07 (2 H, m), 3.04-2.91 (4 H, m), 2.70-2.62 (4 H, m), 2.36-2.21 (6 H, m), 1.52-1.47 (1 H, m), 0.94-0.92 (1 H, m); ^{13}C NMR (25.0 MHz, CDCl$_3$) δ 220.2, 87.8, 57.6, 50.1, 43.4, 43.2, 40.5, 38.5, 32.3; mass spectrum (70 eV), m/e (rel intensity) 272 (M^+, 100), 191 (36), 91 (26), 79 (17), 17 (14); high-resolution mass spectrum for C$_{17}$H$_{20}$O$_3$ calcd m/e 272.1412, found m/e 272.1413.

Model Compounds for the Study of Spectroscopic Properties of Visual Pigments and Bacteriorhodopsin

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Contribution from the Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot, Israel. Received May 6, 1985

Abstract: A series of modified retinals bearing nonconjugated positive charges along the polyene were synthesized. It was found that nonconjugated charges shifted the absorption maxima of retinal chromophore as well as protonated retinal Schiff bases. The magnitude of shift observed in bacteriorhodopsin (bR), 5170 cm^{-1}, could be found in our models by the additivity of two factors: (1) interaction through space with a positive charge located in the vicinity of the ring operating in nonprotic solvents, provided that the interaction between the charge and its counteranion is weakened by a homoconjugation effect; (2) weakening the interaction of the Schiff base positively charged nitrogen with its counteranion. A shift of ca. 5000 cm^{-1} can also be achieved by interaction through space with two nonconjugated positive charges. The absorption maximum of protonated retinal Schiff base is influenced significantly by an interaction with a nonconjugated charge located in the vicinity of the ring moiety or carbon 9. The influence of a charge located in the vicinity of carbon 12 and carbon 14 is minor. Nonconjugated positive charges have a remarkable effect on C=C stretching frequencies as well. It is suggested that the different C=C stretching frequencies found in bR, visual pigments, as well as their photochemically induced intermediates, may originate from interaction with external charges. the C=N$^+$ stretching frequency does no exhibit similar sensitivity to external nonconjugated charges, and it is practically unaffected by them.

Color recognition is based on the different absorption maxima of visual pigments which are located in photoreceptors. The human retina contains three types of pigments absorbing at 450, 535, and 650 nm, while other vertebrates have a range of absorptions between 450 and 600 nm.[1] All these visual pigments consist of a chromophore, 11-*cis*-retinal, covalently bound to an apoprotein to the ϵ-amino terminal of a lysine residue via a protonated Schiff base (SBH$^+$) linkage.[2] Protonated 11-*cis*-retinal Schiff base formed from *n*-butylamine absorbs at 440 nm in

methanol. The red shifts from 440 nm found in various visual pigments are due to the effects of the protein environment and were defined as "opsin shifts".[3] A retinal-based pigment, bacteriorhodopsin (bR), was found[4] in the purple membrane of the

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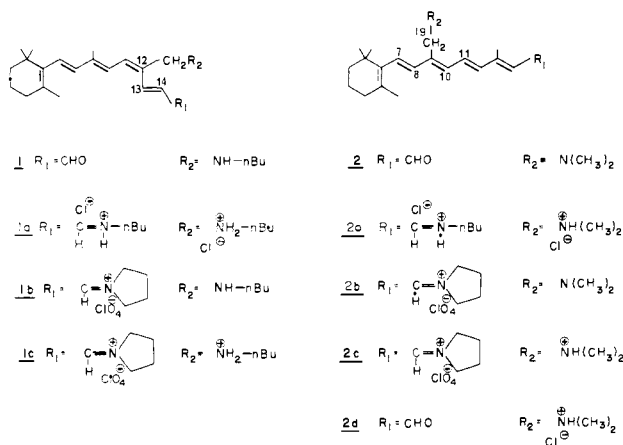
(3) Nakanishi, K.; Balogh-Nair, V.; Arnaboldi, M.; Tsujimoto, K.; Honig, B. *J. Am. Chem. Soc.* **1980**, *102*, 7945–7947.

Study of Spectroscopic Properties of Visual Pigments

J. Am. Chem. Soc., Vol. 107, No. 25, 1985 7525

halophilic microorganism *Halobacterium halobium*. This pigment can, by illumination, generate electrochemical proton gradient across a membrane. As in the photosynthesis process, the energy stored in bR in the electrochemical proton gradient is used by cells to synthesize ATP. Similar to visual pigments, bR consists of a retinal isomer (all-trans) covalently bound to a protein (bacterioopsin) through a protonated Schiff base and exhibits quite a large opsin shift. Its absorption maxima lies at 570 nm (in its light-adapted form), which corresponds to an opsin shift of 5170 cm^{-1}. Different models were suggested in order to explain the red shifts found in the various pigments.[5] Recently, Nakanishi and Honig proposed an external point charge model, which attributes the opsin shift to an interaction through space with a negative charge introduced by the protein, in addition to the Schiff base counteranion. In bovine rhodopsin, in which an opsin shift of 2730 cm^{-1} was found, the negative charge is located in the vicinity of carbons 12–14 of the chromophore.[6] In bacteriorhodopsin (opsin shift of 5170 cm^{-1}) it was suggested that the negative charge is located in the vicinity of the ionone moiety.[3]

Visual pigments, as well as bacteriorhodopsin, under influence of light undergo photochemical cycle, resulting in a number of intermediates possessing different absorption maxima.[7] The various species exhibit different C=C stretching frequencies in resonance Raman spectroscopy, in spite of the fact that all consist of the same chromophore. It was found that the different C=C stretching modes could be correlated with their absorption maxima.[2b,8]

In this study we have prepared retinal analogues possessing nonconjugated positive charges along the polyene skeleton in various locations and investigated their influence on the absorption maxima of retinal chromophore, protonated retinal Schiff base (SBH$^+$), and their C=C and C=N$^+$ frequencies.[9] These studies shed light on the sensitivity of SBH$^+$ to external charges in various locations and suggest possibilities to mimic in solution the magnitude of shifts observed in bacteriorhodopsin and visual pigments. The results also propose that the change in the C=C stretching mode observed for visual pigments, bR, and the various photocycle intermediates may originate from electrostatic interaction with nonconjugated charges introduced by the protein.

Results

A series of retinal analogues was synthesized carrying nonconjugated positive charge in a distance ca. 3 Å from C-12 and C-14 in **1**, from C-8 and C-10 in **2**, and from carbon 5 in chromophore **3**. Chromophore **4** provides information on the influence of two positive charges and **5** and **6** on the influence of a positive charge located above the plane of the polyene, in contrast to the previous compounds whose polyene and the nonconjugated charges are located approximately in the same plane.
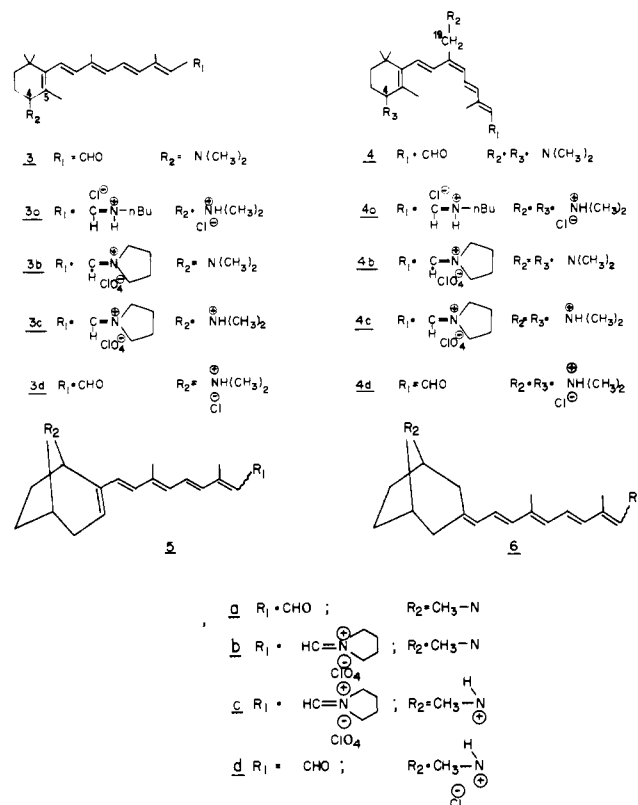
Compounds **7** and **8** provide information on the influence of positive charges on short chromophores, while **9** and **10** bear potential positive charges close to the aldehyde group.

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(7) For review see: Ottolenghi, M. *Adv. Photochem.* **1980**, *12*, 97–200.

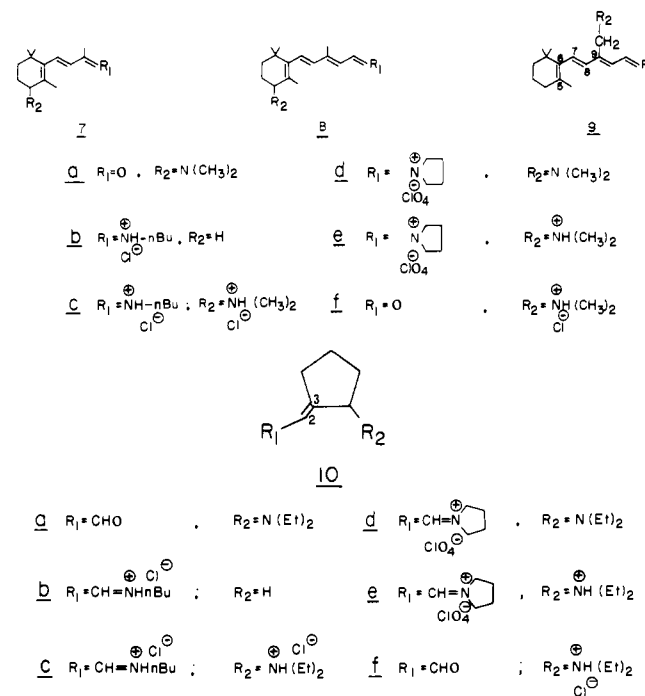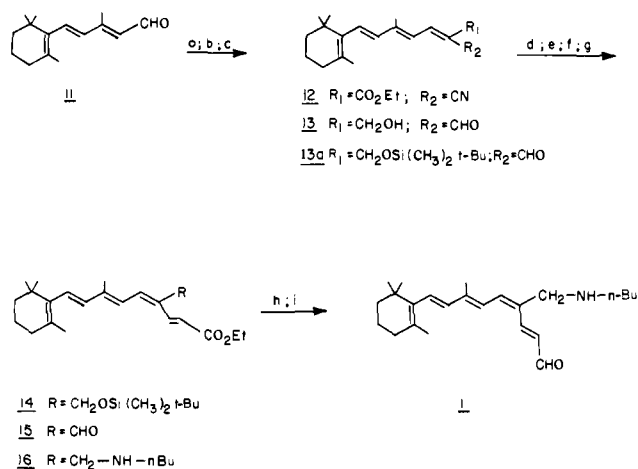(8) Marcus, M. A.; Lewis, A. *Biochemistry* **1978**, *17*, 4722–4735.

(9) For a preliminary report see: (a) Sheves M.; Baasov, T.; Friedman, N. *J. Chem. Soc., Chem. Commun.* **1983**, 77–79. (b) Sheves, M.; Baasov, T. *Tetrahedron Lett.* **1983**, *24*, 1745–1748. (c) Baasov, T.; Sheves, M. *Angew Chem., Int. Ed. Engl.* **1984**, *23*, 803–804.

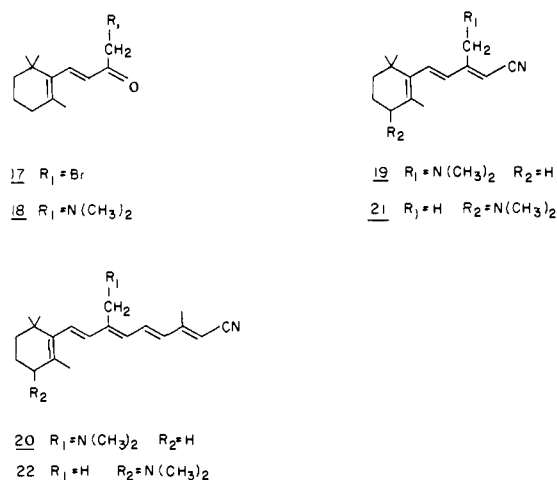**(A) Preparation of Compounds. (1) 11-*cis*-Retinal Analogue 1 (Scheme I).** Aldehyde **11** was condensed with the sodium salt

Scheme I[a]

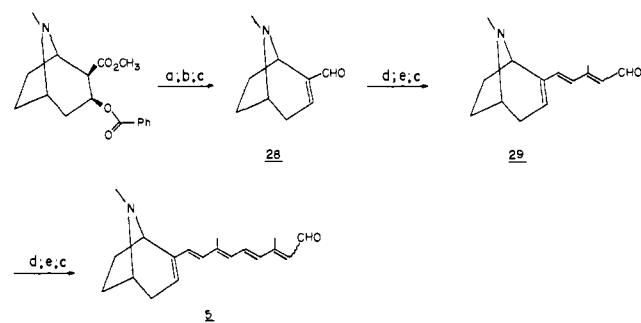
Scheme II[a]

[a] (a) HCl/reflux, 18 h. (b) LiAlH$_4$/THF, 30 min in 0 °C and for 4 h at 25 °C. (c) MnO$_2$/CH$_2$Cl$_2$, 25 °C, 10 h. (d) (EtO)$_2$POCH$_2$C(CH$_3$)=CHCO$_2$Et/NaH/THF, 25 °C, 30 min. (e) DIBAL/hexane, −78 °C, 20 min/silica gel, H$_2$O.

Scheme III[a]
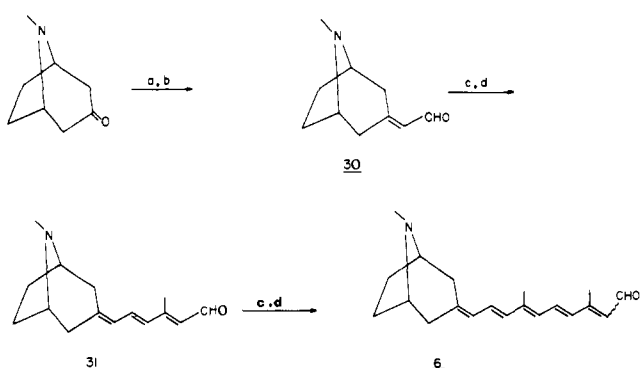
[a] (a) (EtO)$_2$POCH$_2$CN/NaH/THF, 25 °C, 2 h. (b) DIBAL/hexane, −20 °C, 30 min. (c) (EtO)$_2$POCH$_2$C(CH$_3$)=CHCN/NaH/THF, 25 °C, 30 min. (d) DIBAL/hexane, −78 °C, 30 min/silica gel, H$_2$O.

[a] (a) CNCH$_2$CO$_2$Et/NaH/THF-HMPA, −78 °C, 20 min, 25 °C, 1 h. (b) DIBAL/hexane, −78 °C, 1 h. (c) (CH$_3$)$_3$CSi(CH$_3$)$_2$Cl/DMF, imidazole, 25 °C, 2 h. (d) (EtO)$_2$POCH$_2$C(CH$_3$)=CHCO$_2$Et/NaH/THF, 25 °C, 1 h. (e) Bu$_4$NF/THF, 25 °C, 30 min. (f) MnO$_2$/CH$_2$Cl$_2$, 25 °C, 2 h. (g) n-BuNH$_2$/EtOH, 0 °C, 3 h/NaBH$_4$, 25 °C, 3 h. (h) DIBAL/hexane, −78 °C, 1 h. (i) MnO$_2$/CH$_2$Cl$_2$, 25 °C, 2 h.

of ethyl cyanoacetate to give cyano-ester **12** as the only isomer (as was proved by the structure of the hydroxy-aldehyde **13**) probably due to steric reasons. The two electron withdrawing groups enable an easy reduction of the conjugated double bond. However, we succeeded in reducing the nitrile and the ester groups in a reasonable yield and prevented the double bond reduction, using diisobutylaluminum hydride (DIBAL) in hexane at −78 °C, which led to hydroxy-aldehyde **13**. The alcohol group was protected by the *tert*-butyldimethylsilyl group, followed by condensation of the aldehyde group with the sodium salt of triethylphosphonoacetate at 25 °C to give compound **14** (after separation of isomers). Deprotection with Bu$_4$NF in THF and oxidation with MnO$_2$ afforded aldehyde-ester **15**, which was converted to amino-ester **16** with use of reductive-amination with *n*-BuNH$_2$ and NaBH$_4$. Finally, the ester group was transformed to an aldehyde.

mination of **7a** at its C9–Me position leading to ketone **24** which was converted to aldehyde **26** and then to retinal **4**.

(2) 19-(Dimethylamino)-*all-trans*-retinal (2), 4-(Dimethylamino)retinal (3), and 4,19-Di(dimethylamino)-9-*cis*-retinal (4). β-Ionone was brominated at its C9–Me with 5,5-dibromo-2,2-dimethyl-4,6-dioxo-1,3-dioxane[10] and transformed to amino-ketone **18** for the synthesis of **2**. Bromination at the C$_4$ position of β-ionone led to amino-ketone **7a** which served as a precursor to retinal **3**. Both amino-ketones (**18** and **7a**) were transformed to retinals **2** and **3** through intermediates **9a** (for **2**) and **8a** (for **3**). 4,9-Bis(dimethylamino)-9-*cis*-retinal (**4**) was prepared by bro-

(3) Bicyclic Retinals 5 and 6 (Schemes II and III) and Cyclopentanal 10a. The two retinal analogues (**5** and **6**) were prepared from cocaine (for **5**) and tropinone (for **6**). Cocaine was hydrolyzed[11] and transformed to **5** through aldehydes **28** and **29**. Tropinone was converted to **6** with intermediates **30** and **31**. The cyclopentanone derivative (**10a**) was synthesized from cyclopentanone.

(B) Absorption Measurements. We have studied the influence of nonconjugated positive charges on the absorption maximum

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Table I. Absorption Maxima of Protonated Retinal Schiff Bases

chromophore	solvent	λ_{max}/nm	$\Delta\nu^a$/cm⁻¹	chromophore	solvent	λ_{max}/nm	$\Delta\nu^a$/cm⁻¹
SBH⁺ᵇ	EtOH	438		7c	EtOH	305	2846
SBH⁺ᵇ	CHCl₃	456		7c	CHCl₃	308	2969
1a	EtOH	436		8b	EtOH	382	
1a	CHCl₃	456		8b	CHCl₃	390	
2a	EtOH	419	1035	8c	EtOH	335	3672
2a	CHCl₃	423	1710	8c	CHCl₃	330	4662
3a	EtOH	423	810	9c	EtOH	396	925
3a	CHCl₃	432	1218	9c	CHCl₃	406	1010
4a	EtOH	396	2420	10b	EtOH	284	
4a	CHCl₃	398	3200	10b	CHCl₃	290	
7b	EtOH	334		10c	EtOH	269	1963
7b	CHCl₃	339		10c	CHCl₃	268	2830

^{a} Between the chromophore which carries a nonconjugated positive charge and the corresponding chromophore lacking it. ^{b} Protonated retinal Schiff base chloride salt.

Table II. Absorption Maxima of Pyrrolidinium Perchlorate Salts in EtOH and in CHCl₃ (in Parentheses)

chromophore	λ_{max}/nm	$\Delta\nu^a$/cm⁻¹	chromophore	λ_{max}/nm	$\Delta\nu^a$/cm⁻¹
1b	447 (462)		6b	470 (500)	
1c	446 (460)		6c	455 (470)	700 (1270)
2b	447 (476)		7d	(343)	
2c	424 (438)	1215 (1820)	7e	(304)	(3740)
3b	443 (467)		8d	378 (393)	
3c	430 (444)	685 (1110)	8e	337 (345)	3220 (3540)
4b	436 (462)		9d	380 (412)	
4c	404 (418)	1815 (2280)	9e	406 (427)	-1685 (-850)
5b	455 (487)		10d	287 (295)	
5c	460 (455)	650 (1200)	10e	270 (268)	2195 (3415)

^{a} Difference between protonated and nonprotonated (amino groups) species in EtOH and in CHCl₃ (in parentheses).

Table III. Absorption Maxima of Retinal Chromophores in EtOH and in CHCl₃ (in Parentheses)

chromophore	λ_{max}/nm	$\Delta\nu^a$/cm⁻¹	chromophore	λ_{max}/nm	$\Delta\nu^a$/cm⁻¹
2	379 (389)		6	393 (402)	
2d	361 (365)	1315 (1690)	6d	382 (386)	730 (1030)
3	375 (382)		7a	287 (288)	
3d	364 (368)	805 (995)	7f	269 (269)	2330 (2450)
4	370 (377)		9a	325 (327)	
4d	345 (351)	1960 (1965)	9f	336 (349)	-1010 (-1930)
5	386 (390)		10a	243 (-)	
5d	376 (371)	690 (1310)	10f	234 (-)	1580 (-)

^{a} Difference between protonated and nonprotonated (amino groups) species in EtOH and in CHCl₃ (in parentheses).

of protonated retinal Schiff base using two different methods: (1) The corresponding aldehyde was reacted with pyrrolidine perchlorate to give the iminium salt. The absorption maximum was very similar to that of the same chromophore lacking the amino group, indicating that the latter has no marked influence on the absorption maximum. The amino group was protonated with HCl, and the absorption maxima were monitored again. Neutralization with triethylamine shifted the absorption maxima back to its original value. (2) The corresponding aldehyde was treated in EtOH with n-BuNH₂ followed by protonation with HCl. The absorption maxima was compared to that of the same chromophore lacking the amino group (for example, 4-(dimethylamino)retinal Schiff base hydrochloride salt to *trans*-retinal Schiff base hydrochloride salt). The results which are summarized in Tables I and II demonstrate that there is no significant difference between the results obtained by the two methods described above. Note that we did not observe any concentration effect on the absorption maxima either in ethanol or in chloroform in the range of 0.5 × 10⁻¹ to 0.5 × 10⁻⁵ M. Thus, even if some aggregation takes place, it does not affect the absorption maximum. The influence of a nonconjugated positive charge on the absorption maxima of the retinal chromophore itself was studied by comparing the absorption maximum of the corresponding chromophore bearing a dimethylamino group, before and after protonating the nitrogen with HCl (Table III). Note that a similar treatment of *all-trans*-retinal with HCl did not affect the absorption maximum, demonstrating that HCl protonated the amino groups but not the aldehyde function.

The results clearly indicate a change in the absorption maxima of protonated retinal Schiff base due to interaction with a non-conjugated charge, whose location along the polyene is crucial for its influence. This influence is enhanced in nonprotic solvents. Comparable blue shifts were observed in retinal chromophore series, in analogy to previously described[12] interaction between a positive charge and unsaturated ketones.

The magnitude of shifts obtained by us for protonated retinal Schiff bases in solution was significantly smaller than the magnitude of shifts observed in bacteriorhodopsin and various visual pigments. The relatively small shifts were observed both in models **1, 2, 3,** and **4** carrying a nonconjugated positive charge nearly in the plane of the polyene and in models **5** and **6** bearing a positive charge above the plane. The observations demonstrate that similar interactions between the positive charge and the polyene exist in both cases. A major difference between our models and the natural system might be the close proximity of the influencing charge and its counterion in nonprotic solvents, which may weaken the effectiveness of the positive charge. In the protein environment, the charges and their counterions might be separated by a definite distance from each other, allowing an intense interaction between the retinal moiety and the influencing charge. To check this possibility we searched for a system, in which the interaction between the counteranion and the positive charge will be weakened. It is known that excess trifluoroacetic acid (TFA) red shifts the absorption maximum of protonated retinal Schiff base in nonprotic solvents.[13] This was explained by a homoconjugation effect which

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Table IV. Absorption Maxima of Retinal Protonated Schiff Bases Using Various Carboxylic Acids as Protonating Acids

chromo-phore	$\lambda_{max}{}^a$/nm					
	TFA		TCA		BrCH₂CO-OH	
	b	c	b	c	b	c
32	448	513	450	494	446	472
33	423	455	426	448	424	434
34	426	461	429	453	429	442
35	405	406	402	404	400	406
36	484^d	497	484^d	491		
37	500^d	561	500^d	531		

^{a} All measurements were done in CH_2Cl_2. ^{b} One equivalent of the corresponding acid was used for protonation. ^{c} Excess of acid was used up to 1 M solution (concentration of chromophore is 0.5×10^{-4} M). ^{d} This value was observed with use of 0.2×10^{-4} M of the chromophore. The absorption is somewhat sensitive to the chromophore concentration.
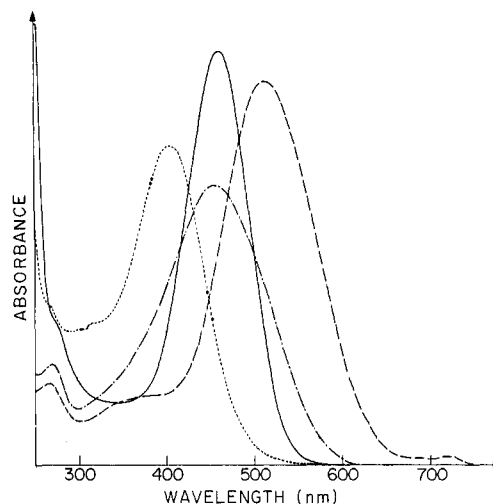
Table V. Shifts in the Absorption Maxima of Retinal Protonated Schiff Bases due to Interaction with Nonconjugated Positive Charges in CH_2Cl_2

| chromo-phore	$\Delta\nu^a$/cm^{-1}					
	TFA		TCA		BrCH₂CO-OH	
	c	d	c	d	c	d
33	1320	2500	1250	2080	1160	1855
34	1150	2200	1090	1830	890	1440
35	2370	5140	2650	4510	2580	3440
37	−660^b	−2300^b	−660^b	−1535^b		

^{a} Difference between the absorption maxima of the corresponding chromophore and that of retinal protonated Schiff base (32) in the same concentration of the corresponding acid. ^{b} Difference between the absorption maxima of 37 and 36 in the same concentration of acid. ^{c} See Table IV, footnote b. ^{d} See Table IV, footnote c.

weakens the interaction between the carboxylate counteranion and the retinal positive iminium nitrogen.[14] We have used this effect by protonating the Schiff bases derived from aldehydes 2, 3, and 4 with excess trifluoroacetic acid. In these systems, the interaction between the counteranion and both positively charged nitrogens (the Schiff base nitrogen and the nonconjugated one) is weakened. However, the effect of the nonconjugated positive charge can be measured by comparing the system to a Schiff base of retinal itself which was protonated with an excess of TFA.

Protonation of the Schiff bases of 2, 3, and 4 in methylene chloride, with 1 equiv of TFA to give 33a, 34a, and 35a reveals blue shift in the absorption maxima relative to 32a, in a similar magnitude to that obtained by protonation with HCl. Excess TFA caused significant red shift in the absorption of 32a but minor changes in the chromophores 33a, 34a, and 35a (Table IV and Figure 1). By comparing the absorption maxima of the latter chromophores to that of 32a (using excess TFA), we could isolate the effect of the nonconjugated positive charge using excess TFA. Thus 33a, 34a, and 35a (0.5×10^{-4} M) with 1 M TFA (CH_2Cl_2) reveal blue shifts of 2500, 2200, and 5140 cm^{-1}, respectively, relative to a solution of retinal 32a (using a 1 M concentration of TFA) (Table V). A positive charge in the vicinity of the Schiff base nitrogen causes a red shift in the absorption maximum.[15] Thus, it is expected that a homoconjugation effect would increase this red shift. Compound 37 prepared from *all-trans*-retinal and methylpiperazine trifluoroacetate salt, exhibited a red shift from 500 to 561 nm with excess TFA (Table IV). Comparing 36 to

(14) (a) Kolthoff, I. M.; Chantooni, M. K.; Bhoyomik, S. *J. Am. Chem. Soc.* 1966, 88, 5430–5439. (b) Pattaroni, Ch.; Lauterwein, J. *Helv. Chim. Acta* 1981, 1969–1984. (c) Sheves, M.; Kohne, B.; Mazur, Y. *J. Chem. Soc., Chem. Commun.* 1983, 1232–1234.
(15) (a) Tabushi, I.; Kuroda, Y.; Shimokawa, K. *J. Am. Chem. Soc.* 1979, 101, 4759–4760. (b) Tabushi, I.; Shimokawa, K. *J. Am. Chem. Soc.* 1980, 102, 5400–5402.

Figure 1. Absorption maxima of protonated retinal Schiff bases (0.5×10^{-4} M) in methylene chloride and 1 M trifluoro acetic acid: (---) retinal 32, (—) 4-(dimethylamino)retinal 34, (-·-) 19-(dimethylamino)retinal 33, (···) 4,19-bis(dimethylamino)retinal 35.

37 (using excess TFA) reveals a shift of 2300 cm^{-1} (Table V) due to the effect of a nonconjugated positive charge in the vicinity of the positively charged nitrogen.

32 R₁=R₂=H

33 R₁=(CH₃)₂$\overset{\oplus}{N}H$; R₂=H

34 R₁=H; R₂=(CH₃)₂$\overset{\oplus}{N}H$

35

36

37
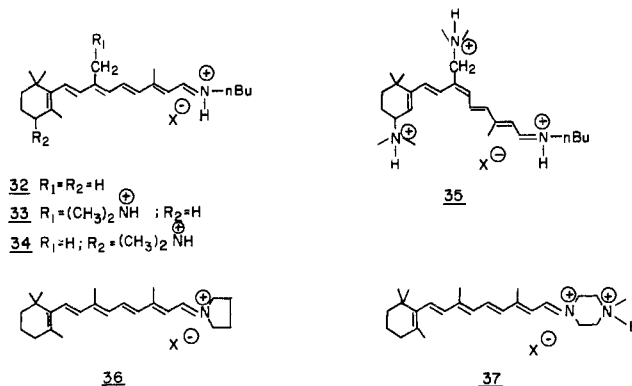
a X=CF₃COO
b X=CCl₃COO
c X=BrCH₂COO
d X=ClO₄

Cancellation or weakening the homoconjugation effect will reduce the effect of the nonconjugated positive charge. Thus, the effects of excess TFA disappeared, using MeOH instead of CH_2Cl_2. Carboxyl acids, bearing weaker electronegative groups than trifluoroacetic acid, such as trichloroacetic acid or bromoacetic acid, reduced the effects of the nonconjugated positive charges relative to TFA (Table V).

(C) Stretching Frequencies. We have studied the influence of nonconjugated positive charges on the C=C and C=N$^+$ stretching frequencies of retinal (pyrrolidinium perchlorate salts) 2b, 3b, 4b and chromophore 37d, possessing amino groups along the polyene skeleton, using FT–IR.

Protonation of these amino groups shifted the C=C stretching band to higher frequencies in case of 2c, 3c, and 4c (Table VI). Chromophore 37d exhibits a positive charge in the vicinity of the iminium nitrogen. Comparison of 37d to 36d reveals a shift of the C=C stretching band of 37d to a lower frequency. The C=N$^+$ bands did not change significantly in all these cases. In analogy to the well-known correlation between the C=C stretching of various visual pigments, bR, and the photochemically induced intermediates and their absorption maxima,[7,8] the C=C bands of our models can be correlated with their absorption maxima. Namely, a blue shift of the absorption spectrum is accompanied by a higher frequency of the C=C band (Figure 2).

Table VI. Stretching Frequencies of Pyrrolidinium Perchlorate Salts in CH_2Cl_2

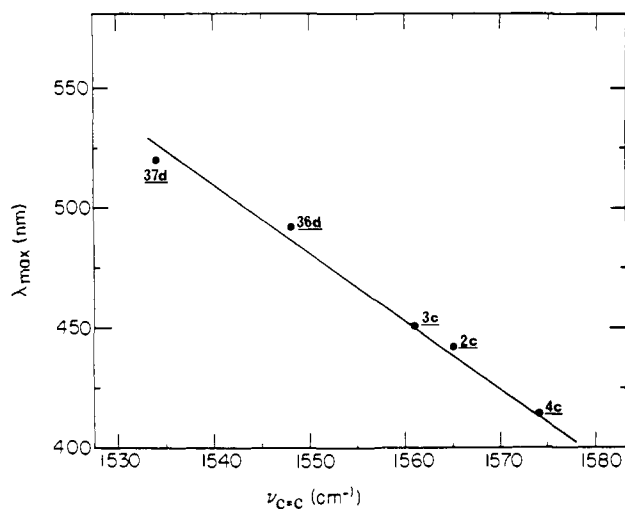| chromophore	λ_{max}/nm	C=C/cm^{-1}	C=N/cm^{-1}	chromophore	λ_{max}/nm	C=C/cm^{-1}	C=N/cm^{-1}
36d	490	1548	1626	37d	520	1534	1620
2b	487	1550	1627	2c	442	1565	1629
3b	469	1552	1626	3c	446	1561	1626
4b	465	1559	1627	4c	414	1574	1629

Figure 2. Stretching frequencies of C=C bonds vs. absorption maxima of pyrrolidinium perchlorate salts.

Discussion

(a) Absorption Maxima. The results described above reveal that nonconjugated positive charges along the polyene skeleton of the SBH$^+$ shift the absorption maxima. The location of these charges is crucial for their influence. Charges located in the vicinity of the ring or close to the edge of the polyene chain cause a significant blue shift, while those located in the vicinity of carbon 12 did not affect the spectra at all. Introducing a positive charge close to the positively charged nitrogen caused a red shift. These different influences reflect the different charge delocalization along the polyene. Migration of a positive charge toward the ring is pronounced in the excited state (relative to the ground state).[7] Therefore, a nonconjugated charge in the vicinity of the ring will interact stronger with the excited state, resulting in a decreased charge delocalization and excited state destabilization. The effect is reflected in a blue shift in the absorption maximum. The influence of two charges on the absorption maximum is close to the sum of each one separately. Another interesting aspect is the influence of the polyene length. The interaction of a nonconjugated positive charge in the vicinity of the ring with the polyene is stronger in the case of a shorter chromophore. The polyene's positive charge is spread over fewer carbons in a short chromophore, resulting in a high density of charge at carbon 5. This situation will lead to a large blue shift due to the interaction with a nonconjugated charge in the vicinity of carbon 5.

The insensitivity of the absorption maxima to the influence of a charge in the vicinity of C_{12} (compound 1) points to a similar influence, both on the ground and the excited states. This observation is supported by the results obtained in compounds 9 and 10. The blue shift obtained in 10 points to a higher density of a positive charge at carbons close to the external charge (carbons 2 and 3) in the excited state relative to the ground state. The situation has changed in 9, due to its longer polyene. The positive charge tends to migrate, in the excited state, toward the edge of the chromophore, leaving a higher density of a positive charge at carbon 9 in the ground state relative to the excited state. This situation will lead to a strong destabilization of the ground state, causing a red shift.

Chromophores 5 and 6, bearing a positive charge above the polyene plane, exhibited a similar trend to chromophore 3. This result reveals a similar influence of the nonconjugated positive charge if the charge is located either nearly in the same plane of

the polyene or above it. The retinal chromophore itself is affected by a nonconjugated positive charge as well. The blue shift observed for a retinal bearing a positive charge in the vicinity of the ring or carbon 9 indicates a migration of a positive charge toward the ring in the excited state. The magnitudes of shifts and their direction are comparable to those observed for a protonated retinal Schiff base. Shifts in the absorption maxima of nonprotonated retinal species were found in the pre-pigment of bacterio-rhodopsin[16] and in M_{412} intermediate which contains a non-protonated retinal Schiff base.[7] Similarly, bR at pH $\sim$12.5 is converted to a nonprotonated retinal Schiff base absorbing at 460 nm.[17] All the absorption maxima of these species are markedly shifted, relative to that of retinal Schiff base in solution ($\sim$360 nm). Our results support the possibility that the shifts in the absorption maxima originate from interaction through space with charges introduced by the protein.

The magnitudes of shifts discussed above were considerably smaller than those found in bacteriorhodopsin or various visual pigments. The shifts are even smaller in protic solvents due to a weaker interaction between charges. However, the effect of a nonconjugated positive charge is markedly enhanced by weakening the interaction between the latter and its counterion, creating a "naked" positive charge. The effect is achieved by a homoconjugation effect which originates from hydrogen bond interaction between the trifluorocarboxylate counteranion and an excess of trifluoroacetic acid. The enhanced interaction between the "naked" positive charge and the retinal chromophore is clearly observed in compounds 33 to 36, using excess TFA as the protonating acid.[18] The large excess of TFA needed for obtaining the effect is probably due to the possibility of hydrogen bonding between carboxyl molecules instead of hydrogen bonding between carboxyl and carboxylate.

Thus, the magnitudes of shifts observed for the absorption maxima of various visual pigments and bacteriorhodopsin, as well as their photochemically induced intermediates, can be successfully mimicked in solution (although opposite in direction) by interaction through space with a positive charge located close to the end of the polyene chain or in the vicinity of the ring moiety of the retinal, operating in a nonprotic solvent, and by weakening the interaction of the operating charge with its counteranion. These conditions led to a shift of ca. 2500 cm^{-1}. An additional shift of ca. 2800 cm^{-1} can be achieved by changing the interaction of the Schiff base positively charged nitrogen with its counteranion. Excess TFA, which weakens this interaction due to a homoconjugation effect, caused a red shift in the spectrum up to 2800 cm^{-1}. Recently we have shown[19] that interaction between the Schiff base positively charged nitrogen and its counteranion can play an important role in determining the absorption maxima of artificial bacteriorhodopsin pigments. Alternatively, a shift of ca. 5000 cm^{-1} can be achieved by interaction of two nonconjugated charges located near the ring and close to carbon 9 (chromophore 4) operating in nonprotic solvent and with excess TFA.

It should be noted that the effect of a nonconjugated positive charge should be similar in magnitude (only the direction of influence is opposite) to a nonconjugated negative charge. Support for this conclusion is found by the comparison of compound 10

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(18) It should be noted that no incorporation of deuterium into the retinal molecule (besides the nitrogen proton) was observed.

(19) Sheves, M.; Albeck, A.; Friedman, N.; Ottolenghi, M. *Biochemistry* **1985**, *24*, 1260–1265.

to a similar compound, previously synthesized, bearing nonconjugated negative charge.[20]   Both compounds exhibit similar magnitude of shifts but opposite in direction.

(b) Stretching Frequencies. The absorption maxima of bacteriorhodopsin, visual pigments, and their photochemically induced intermediates can be correlated with the C=C stretching frequencies found in resonance Raman spectroscopy. A red shift of ca. 60 nm in the λ_{max} is comparable to a shift of ca. 20 cm^{-1} to a lower frequency of the C=C mode. Rimai and co-workers[21] pointed out that the line position of the C=C stretching mode is a sensitive indication of an electron delocalization. A decreased bond alternation results in a shift to higher frequency of the C=C bond. A nonconjugated positive charge in the vicinity of the polyene retinal skeleton will decrease charge delocalization, causing a shift in the C=C stretching to a higher frequency. A positive charge in the vicinity of the positively charged Schiff base nitrogen will cause the opposite effect by increasing charge delocalization. The change in the C=C stretching was not accompanied by a shift in the C=N$^+$ stretching band. Visual pigments and their photochemical induced intermediates do not exhibit a correlation between λ_{max} and C=N$^+$ stretching (similarly to our model compounds). This insensitivity might be explained by coupling of C=N$^+$ stretching with that of N—H.[22]   However, recently a correlation between λ_{max} and C=N$^+$ stretching was found in bacteriorhodopsin and its photochemically induced intermediates.[23] This difference between visual pigments and bacteriorhodopsin needs future investigation. The magnitude of C=C stretching frequencies shifts observed in our synthetic models is close to that found in the natural systems. Thus, our results support the assumption that interaction through space with nonconjugated charges might be responsible for the different C=C stretching mode of different pigments and intermediates. The results clearly point to an influence of external charges on charge distribution along SBH$^+$ in the ground state and not only on the excited state as could be concluded from the absorption maxima measurements. Recently we have shown[24] that external positive charges regulate the rate of thermal isomerization of 13-*cis*-SBH$^+$ to all-trans. The influence of these charges on the C=C stretching frequency clearly supports this regulation.

Conclusions

Synthetic modified retinals bearing nonconjugated positive charges along the polyene provide valuable information on their influence on the absorption maxima, C=C and C=N$^+$ stretching frequencies of the polyene: (a) The magnitude of shift observed in bR (5170 cm^{-1}) can be mimicked in solution by a combination of two factors: (1) interaction through space with a positive charge located in the vicinity of the ring operating in nonprotic solvents, provided that the interaction between this charge and its counteranion is considerably weakened by a homoconjugation effect; (2) weakening the interaction of the Schiff base positively charged nitrogen with its counteranion. Alternatively, a blue shift of ca. 5000 cm^{-1} can be achieved by interaction through space with two nonconjugated positive charges located in the vicinity of the ring and around carbon 9. (b) Recently, a planar s-trans ring chain conformation of the retinal chromophore was suggested by Harbison et al.[25] for bR, based on NMR evidence. The s-trans planarity should contribute significantly to the opsin shift. Thus, the ion pair situation in the vicinity or the ring in bR is probably closer to our models in methylene chloride with use of 1 equiv

of TFA (tied ion pair), rather than the situation in excess TFA, which creates a very weak interaction between the nonconjugated positive charge and its counteranion. Thus, the opsin shift in bR probably originates from a combination of factors which include the following: (1) weak hydrogen bonding with the positively charged Schiff base nitrogen; (2) s-trans chain-ring conformation and an interaction with a nonconjugated charge in the vicinity of the ring. The exact contribution of the latter two factors needs further investigation. (c) The absorption maximum of protonated retinal Schiff base is influenced significantly by an interaction with a nonconjugated charge located in the vicinity of the ring or carbon 9. The influence of a charge located in the vicinity of carbons 12 and 14 (close to the Schiff base nitrogen) is minor. (d) The absorption maxima of the retinal chromophore is influenced as well by nonconjugated positive charges in magnitudes comparable to protonated retinal Schiff base (SBH$^+$). (e) The effect of nonconjugated positive charges located close to the edge of the polyene is more pronounced on short chormophores (protonated Schiff bases as well as aldehydes). (f) The different C=C stretching frequencies found in bR, visual pigments, as well as their photochemically induced intermediates may originate from interaction with external charges.

Experimental Section

The spectroscopic measurements were carried out with the following instruments: UV, Kontron 810; FTIR Nicolet MX-I; NMR, Bruker 270 MHz, chemical shifts were reported in ppm on the δ scale relative to an Me$_4$Si internal standard; MS, Varian Mat 731 and Finnigan 4500. Chromatographies were performed with use of the flash column technique with Merck silica gel 60 (230–400 mesh ASTM) with the solvents mentioned. NaH used was 80% in white oil.

Cyano-Ethyl-Ester 12. NaH (135 mg, 4.5 mmol) was dissolved in 50 mL of a 4:1 solution of THF:HMPA. The mixture was stirred under argon atmosphere at 25 °C and 508 mg (4.5 mmol) of ethyl cyanoacetate were added dropwise. After 15 min the reaction mixture was cooled to −78 °C and 880 mg (4 mmol) of aldehyde **11** were added. The cooling bath was removed and the solution was warmed to room temperature. After 1 h water was added and the product was extracted with ether. Usual workup and chromatography with ether–hexane (5:95) gave 1.07 g of cyano-ester **12** (85% yield). λ_{max} (EtOH) 385 nm (ϵ 20000); NMR (CDCl$_3$) δ 1.06 (s, 6, 1-Me), 1.36 (t, 3, J = 7 Hz, ester methyl), 1.75 (s, 3, 5-Me), 2.17 (s, 3, 9-Me), 4.33 (q, 2, J = 7 Hz, ester methylene), 6.31 (d, 1, J = 16 Hz, 8-H), 6.57 (d, 1, J = 12.7, 10-H), 6.75 (d, 1, J = 16 Hz, 7-H), 8.27 (d, 1, J = 12.7 Hz, 11-H). CI-MS 314 (M + 1)$^+$.

Alcohol-Aldehyde 13. Cyano-ester **12** (870 mg, 2.8 mmol) was dissolved in 100 mL of dry hexane. The mixture was cooled to −78 °C under argon atmosphere and 12 mL of a 1 M solution in hexane of diisobutylaluminum hydride were added dropwise. After 30 min 3 mL of ethyl acetate was added and the reaction mixture was warmed to room temperature followed by addition of 20 mL of water and stirring for 3 h. Filtration through Celite, extraction with ether, and chromatography with ether–hexane 3:7 afforded 300 mg of aldehyde-alcohol **13** (39% yield). λ_{max} (EtOH) 340 nm (ϵ 17000). NMR (CDCl$_3$) δ 1.04 (s, 6, 1-Me), 1.73 (s, 3, 5-Me), 2.06 (s, 3, 9-Me), 4.36 (s, 2, alcohol methylene), 6.20 (1, d, J = 16 Hz, 8-H), 6.54 (1, d, J = 16 Hz, 7-H), 6.96 (1, d, J = 12.8 Hz, 10-H), 10.32 (1, s, aldehyde proton). CI-MS 275 (M + 1)$^+$.

Aldehyde-Silyl Ether 13a. Aldehyde **13** (230 mg, 0.84 mmol) was dissolved in 20 mL of DMF and mixed with 50 mg of imidazole and 226 mg (1.5 mmol) of tert-butyldimethylsilyl chloride at 25 °C for 2 h in the dark. Usual workup with ether and water and chromatography with ether:hexane (1:18) gave 250 mg (88% yield) of **13a**. λ_{max} (EtOH) 350 nm (ϵ 20000). NMR (CDCl$_3$) δ 0.08 (s, 6, silyl methyl), 0.93 (s, 9, *t*-Bu), 1.02 (s, 6, 1-Me), 1.71 (s, 3, 5-Me), 2.04 (s, 3, 9-Me), 4.43 (s, 2, CH$_2$-O), 6.16 (d, 1, J = 16 Hz, 8-H), 6.45 (d, 1, J = 16 Hz, 7-H), 6.96 (d, 1, J = 12 Hz, 10-H), 7.59 (d, 1, J = 16 Hz, 11-H), 10.29 (s, 1, aldehyde proton). **13a** (50 mg) was dissolved in 15 mL of ether and a catalytic amount of I$_2$ was added. The solution was stirred for 15 min in day light. Extraction with water and ether and chromatography with ether–hexane (1:18) afforded 30 mg (60% yield) of E isomer and 20% yield of starting material (isomer Z). E isomer: λ_{max} (EtOH) 356 nm (ϵ 25000). NMR (CDCl$_3$) δ 0.08 (s, 6, silyl methyls), 0.89 (s, 9, *t*-Bu), 1.05 (s, 6, 1-Me), 1.72 (s, 3, 9-Me), 2.10 (s, 3, 9-Me), 4.51 (s, 2, CH$_2$-O), 6.21 (d, 1, J = 16 Hz, 8-H), 6.52 (d, 1, J = 16 Hz, 7-H), 6.77 (d, 1, J = 12 Hz, 10-H), 7.32 (d, 1, J = 12 Hz, 11-H), 9.46 (s, 1, aldehyde proton).

Ester-Silyl Ether 14. Triethylphosphonoacetate (134 mg, 0.6 mmol) was dissolved in 30 mL of dry THF, under argon atmosphere. The solution was cooled to 0 °C and 18 mg (0.6 mmol) of NaH was added.

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The mixture was stirred for 30 min at 0 °C and then 188 mg (0.48 mmol) of aldehyde **13a** (*Z* isomer) dissolved in 5 mL of dry THF was added. The solution was brought to room temperature and stirred for 1 h. Ether and water were added. Chromatography with ether–hexane (1:19) afforded 150 mg of pure 11-cis isomer (67% yield). λ_{max} (EtOH) 365 nm (ϵ 25 000). NMR (CDCl₃) δ 0.09 (s, 6, silyl methyls), 0.89 (s, 9, *t*-Bu), 1.03 (s, 6, 1-Me), 1.30 (t, 3, *J* = 7 Hz, ester methyl), 1.72 (s, 3, 5-Me), 2.00 (s, 3, 9-Me), 4.21 (q, 2, *J* = 7 Hz, ester methylene), 4.48 (s, 2, silyl ether methylene), 6.06 (d, 1, *J* = 16 Hz, 14-H), 6.12 (d, 1, *J* = 16 Hz, 8-H), 6.37 (d, 1, *J* = 16 Hz, 7-H), 6.46 (d, 1, *J* = 12 Hz, 11-H), 6.84 (d, 1, *J* = 12 Hz, 10-H), 7.36 (d, 1, *J* = 16 Hz, 13-H).

Ethyl 11-*cis*-12-Formylretinoate 15. To a 80 mg (0.17 mmol) of silyl ether **14** dissolved in 20 mL of dry THF under argon atmosphere were added 0.2 mL of a 1 M solution of tetrabutylammonium fluoride. The mixture was stirred for 30 min at 25 °C and then ether and water were added. The organic layer was washed with water and brine and dried over MgSO₄. The ether was evaporated and the residue oil was dissolved in 20 mL of methylene chloride and stirred for 2 h at 25 °C with 150 mg of MnO₂. Filtration through Celite, evaporation of the solvent, and chromatography with hexane–ether (19:1) as eluent mixture afforded 50 mg (84% yield) of ester **15**. λ_{max} (EtOH) 395 nm (ϵ 28 000), NMR (CDCl₃) δ 1.07 (s, 6, 1-Me), 1.31 (t, 3, ester methyl), 1.76 (s, 3, 5-Me), 2.17 (s, 3, 9-Me), 4.25 (q, 2, ester methylene), 6.33 (d, 1, *J* = 16 Hz, 8-H), 6.67 (d, 1, *J* = 16 Hz, 7-H), 6.74 (d, 1, *J* = 12 Hz, 10-H), 7.00 (d, 1, *J* = 16 Hz, 13-H), 7.44 (d, 1, *J* = 12 Hz, 11-H), 7.66 (d, 1, *J* = 16 Hz, 14-H), 9.62 (s, 1, aldehyde proton). CI–MS 343 (M + 1)⁺.

Reductive Amination of Ester-Aldehyde 15 To Give Amino-Ester 16. Ethyl retinoate **15** (40 mg, 0, 12 mmol) was dissolved in 5 mL of absolute ethanol and cooled to 0 °C. Freshly distilled *n*-butylamine was added (22 mg, 0.3 mmol) and the mixture stirred at 0 °C for 3 h. The solvent and an excess of butylamine were evaporated and the residue was dissolved in 5 mL of absolute ethanol and treated for 3 h at 25 °C with 12 mg of NaBH₄. Addition of ether and water, usual workup, and chromatography with ether–hexane (2:3) afforded 30 mg (63% yield) of amino-ester **16**. λ_{max} (EtOH) 368 nm (ϵ 25 000). NMR (CDCl₃) δ 0.95 (t, 3, 4′-Me), 1.03 (s, 6, 1-Me), 1.31 (t, 3, ester methyl), 1.73 (s, 3, 5-Me), 2.00 (s, 3, 9-Me), 2.61 (t, 2, 2′-H), 3.48 (s, 2, 20-H), 4.24 (q, 2, methylene of ester group), 6.02 (d, 1, *J* = 15.7 Hz, 14-H), 6.26 (s, 2, 7-H, 8-H), 6.58 (d, 1, *J* = 11.8 Hz, 10-H), 6.85 (d, 1, *J* = 11.8 Hz, 11-H), 7.91 (d, 1, *J* = 15.8 Hz, 13-H).

11-*cis*-Aminoretinol 1. Amino-ester **16** (30 mg, 0.075 mmol) was dissolved in 10 mL of dry THF under argon atmosphere. The mixture was cooled to –78 °C and 0.4 mL of 1 M diisobutylaluminum hydride were added dropwise. The mixture was stirred at –78 °C for 30 min, and the excess of the reagent was destroyed with 2 mL of ethyl acetate. Warming to 25 °C was followed by addition of water and ether, and the reaction mixture was filtered through Celite. The Celite was washed with ethyl acetate and the organic layer was separated and washed with water and brine and after drying over MgSO₄ evaporated to dryness. The residue was dissolved in 5 mL of methylene chloride and 150 mg of active manganese dioxide were added. The mixture was stirred for 1 h at 25 °C and filtered over Celite. Evaporation of solvent and chromatography with ether–hexane (1:2) afforded 15 mg (57% yield from **16**) of 11-*cis*-20-(*n*-butylamine)retinal (**1**). λ_{max} (EtOH) 377 nm (ϵ 32 000), λ_{max} (CHCl₃) 386 nm (ϵ 31 000). NMR (CDCl₃) δ 0.95 (t, 3, 4′-Me), 1.04 (s, 6, 1-Me), 1.73 (s, 3, 5-Me), 2.04 (s, 3, 9-Me), 2.61 (t, 2, 2′-H), 3.51 (s, 2, 20-H), 6.04–7.08 (m, 5, 7-H, 8-H, 10-H, 11-H, 14-H), 7.65 (d, 1, *J* = 15.8 Hz, 13-H), 10.2 (d, 1, *J* = 8 Hz, 15-H). CI–MS 356 (M + 1)⁺.

Bromo-β-ionone 17. β-Ionone (5 g, 26 mmol) was dissolved in 200 mL of dry THF and was reacted under argon atmosphere with 9 g (29.8 mmol) of 5,5-dibromo-2,2-dimethyl-4,6-dioxo-1,3-dioxane at 25 °C for 2 h. Extraction with ether and water and chromatography with ether–hexane (3:97) afforded 4.9 g of **17** (70% yield) and a small amount (0.4 g) of dibromo product. λ_{max} (EtOH) 300 nm (ϵ 18 000). NMR (CDCl₃) δ 1.07 (s, 6, 1-Me), 1.84 (s, 3, 5-Me), 4.02 (s, 2, CH₂-Br), 6.33 (d, 1, *J* = 16 Hz, 8-H), 7.58 (d, 1, *J* = 16 Hz, 7-H).

(Dimethylamino)-β-ionone 18. Bromo-β-ionone (**17**) was added (2.5 g in 10 mL of THF) into a solution containing 100 mL of THF, 10 mL of dimethylamine (25% w/v in water), and 300 mg of sodium carbonate. The mixture was stirred for 1 h at 25 °C followed by addition of water and ether. The organic layer was washed three times with a 10% solution of HCl. Neutralization of the aqueous solution with sodium bicarbonate and extraction with ether followed by chromatography over neutral alumina (grade III), using ether–hexane (3:7), afforded 1.8 g (84% yield) of the keto-amino **18**. λ_{max} (EtOH) 280 nm (ϵ 19 000). NMR (CDCl₃) δ 1.05 (s, 6, 1-Me), 1.78 (s, 3, 5-Me), 2.24 (s, 6, N-Me), 3.28 (s, 2, CH₂-N), 6.31 (d, 1, *J* = 16 Hz, 8-H), 7.41 (d, 1, *J* = 16 Hz, 7-H).

(Dimethylamino)-Nitrile 19. Ketone **18** (750 mg, 3.2 mmol) was reacted with the sodium salt of diethyl cyanomethylphosphonate (620 mg,

3.5 mmol) in THF for 1 h at 25 °C under argon atmosphere. The reaction mixture was extracted with ether and water, and the organic layer was washed three times with a 10% HCl solution. The combined aqueous solutions were neutralized with sodium carbonate and extracted three times with ether. Chromatography with 1:4 ether–hexane afforded two isomers, trans and cis in a 1:1 ratio, in which the less polar one was the trans isomer (90% yield of the two isomers). λ_{max} (EtOH) 270 nm (ϵ 21 000) NMR (CDCl₃) δ 1.02 (s, 6, 1-Me), 1.72 (s, 3, 5-Me), 2.26 (s, 6, N-Me), 3.38 (s, 2, N-CH₂), 5.26 (s, 1, 10-H), 6.05 (d, 1, *J* = 16 Hz, 8-H), 7.04 (d, 1, *J* = 16 Hz, 7-H). Cis isomer: NMR δ 1.04 (s, 6, 1-Me), 1.75 (s, 3, 5-Me), 2.24 (s, 6, N-Me), 3.17 (s, 2, N-CH₂), 5.46 (s, 1, 10-H), 6.57 (d, 1, *J* = 16 Hz, 8-H), 6.85 (d, 1, *J* = 16 Hz, 7-H). The two isomers were differentiated by NOE experiment. Irradiation of 8-H caused a 25% enhancement of 10-H signal in the trans isomer and almost none in the cis isomer. Irradiation of 10-H resulted in a 20% increase of the CH₂-N signal of the cis isomer and a small change in the trans.

Dimethylamino-Aldehyde 9a. The trans isomer of **19** (450 mg, 1.75 mmol) was reduced in dry hexane at –78 °C for 1 h with diisobutylaluminum hydride (4 mL of a 1 M solution). Excess of reagent was destroyed with 2 mL of ethyl acetate, and the product was hydrolyzed by stirring with 5 g of 5% aqueous silica for 30 min at –78 °C and for 5 h at 25 °C. Usual workup and chromatography over basic alumina (activity grade III) with ether–hexane (1:1) afforded aldehyde **9a** (327 mg, 72% yield). λ_{max} (EtOH) 330 nm (ϵ 22 000), NMR (CDCl₃) δ 1.04 (s, 6, 1-Me), 1.73 (s, 3, 5-Me), 2.26 (s, 6, N-Me), 3.48 (s, 2, CH₂-N), 6.02 (d, 1, *J* = 8 Hz, 10-H), 6.16 (d, 1, *J* = 16 Hz, 8-H), 6.98 (d, 1, *J* = 16 Hz, 7-H), 10.22 (d, 1, *J* = 8 Hz, 11-H). High resolution mass spectrum calcd for C₁₇H₂₇NO 261.2086, found 261.2089.

(Dimethylamino)-Nitrile 20. Aldehyde **9a** (290 mg, 0.8 mmol) was reacted with 1 mmol of the sodium salt of diethyl 3-methyl-4-phosphonocrotononitrile in dry THF at 25 °C under argon atmosphere for 30 min. The product was extracted with ether and water, and the organic layer was washed with 10% HCl solution. The acidic solution was neutralized with sodium carbonate and extracted with ether. The two isomers (13-cis and all-trans, in a 3:7 ratio, total yield 75%) were separated by chromatography with ether–hexane (1:4). The less polar isomer (161 mg) was the trans isomer. λ_{max} (EtOH) 357 nm (ϵ 35 000). NMR (CDCl₃) δ 1.02 (s, 6 H, 1-Me), 1.71 (s, 3, 5-Me), 2.22 (s, 6, N-Me), 2.22 (s, 3, 13-Me), 3.22 (s, 2, CH₂-N), 5.18 (s, 1, 14-H), 6–6.8 (m, 5). Cis isomer: NMR δ 1.03 (s, 6, 1-Me), 1.72 (s, 3, 5-Me), 2.06 (s, 3, 13-Me), 2.22 (s, 6 H, N-Me), 3.22 (s, 2, CH₂-N), 5.07 (s, 1, 14-H), 5.9–6.9 (m, 5).

19-(Dimethylamino)-*all-trans*-retinal 2. Nitrile **20** (75 mg, 0.23 mmol) was reduced under argon with 1 mL of 1 M diisobutylaluminum hydride in dry hexane at –78 °C for 30 min. Excess reagent was destroyed with ethyl acetate and the product was hydrolyzed as was described for **9a**. Filtration through Celite, extraction with ether, and chromatography over basic alumina (activity grade III) afforded 60 mg of retinal **2** (79% yield). λ_{max} (EtOH) 380 nm (ϵ 39 000). NMR (CDCl₃) δ 1.03 (s, 6, 1-Me), 1.73 (s, 3, 5-Me), 2.25 (s, 6, N-Me), 2.32 (s, 3, 13-Me), 3.25 (s, 2, CH₂-N), 5.98 (d, 1, *J* = 8 Hz, 14-H), 6.11 (d, 1, *J* = 16 Hz, 8-H), 6.30 (d, 1, *J* = 11.5 Hz, 10-H), 6.39 (d, 1, *J* = 15 Hz, 12-H), 6.62 (d, 1, *J* = 16 Hz, 7-H), 7.28 (dd, 1, *J₁* = 15 Hz, *J₂* = 11.5 Hz, 11-H), 10.11 (d, 1, *J* = 8 Hz, 15-H). High resolution mass spectrum calcd for C₂₂H₃₃NO 327.2554, found 327.2541.

4-(Dimethylamino)-β-ionone 7a. β-Ionone (5 g, 26 mmol) was dissolved in 200 mL of carbon tetrachloride. The mixture was boiled and 5.75 g of *N*-bromosuccinimide (32.3 mmol) was added followed by reflux for 1 h. The reaction was cooled to 0 °C and 50 mL of hexane were added. The mixture was filtered into a solution of 200 mL of THF, 10 mL of dimethylamine solution (w/v 35% in water), and 1 g of sodium carbonate and was stirred for 5 h at room temperature. The solvents were removed by evaporation and the residue was dissolved in 200 mL of ether and washed three times with 100 mL of 5% HCl. The combined water layers were basified with sodium carbonate and extracted with ether. Usual workup and chromatography with ether–hexane (1:4) afforded 4.2 g of 4-(dimethylamino)-β-ionone (68% yield). λ_{max} (EtOH) 283 nm (ϵ 18 000). NMR (CDCl₃) δ 1.05 (s, 6, 1-Me), 1.78 (s, 3, 5-Me), 2.3 (s, 3, 9-Me), 2.21 (s, 6, N-Me), 3.08 (t, 1, *J* = 8 Hz, 4-H), 6.10 (d, 1, *J* = 16.5 Hz, 8-H), 7.25 (1, d, *J* = 16.5 Hz, 7-H). High resolution mass spectrum calcd for C₁₅H₂₅NO 235.1930, found 235.1927.

4-(Dimethylamino)-Nitrile 21. The sodium salt of diethyl cyanomethylphosphonate in THF, formed from 885 mg (5 mmol) of the phosphonate and 150 mg of NaH, was reacted with 1 g of ketone **7a** at 25 °C under argon for 1 h. Workup with ether–water and chromatography with ether–hexane (1:9) gave the less polar cis isomer of **21** (373 mg, 34% yield) and a trans isomer (439 mg, 40% yield). Cis isomer: NMR (CDCl₃) δ 1.02 (s, 3, 1-Me), 1.03 (s, 3, 1-Me), 1.78 (s, 3, 5-Me), 2.06 (s, 3, 9-Me), 2.22 (s, 6, N-Me), 3.08 (t, 1, 4-H), 5.12 (s, 1, 10-H),

6.65 (s, 2, 7-H, 8-H). Trans isomer: NMR (CDCl₃) δ 1.01 (s, 6, 1-Me), 1.73 (s, 1, 5-Me), 2.22 (s, 6, N-Me), 2.22 (s, 3, 9-Me), 3.08 (t, 1, 4-H), 5.19 (s, 1, 10-H), 6.10 (d, 1, J = 16 Hz, 8-H), 6.57 (d, 1, J = 16 Hz, 7-H).

4-(Dimethylamino)-C₁₅-Aldehyde 8a. Nitrile 21 (200 mg, 0.78 mmol) was dissolved in 30 mL of dry hexane and cooled under argon to -78 °C. DIBAL (3 mL) was added dropwise and after 30 min at -78 °C the excess of the reagent was destroyed with 2 mL of ethyl acetate. The reaction was stirred with 3 g of 5% aqueous silica at -78 °C for 30 min and 3 h at 25 °C. Filtration through Celite followed by the usual extraction with ether and water and chromatography with ether-hexane (3:7) afforded 157 mg (78% yield) of aldehyde 8a. λ_max (CHCl₃) 320 nm (ε 24 000) NMR (CDCl₃) δ 1.03 (s, 6, 1-Me), 1.75 (s, 3, 5-Me), 2.23 (s, 6, N-Me), 2.32 (s, 3, 9-Me), 3.09 (t, 1, J = 8 Hz, 4-H), 5.95 (d, 1, J = 8 Hz, 10-H), 6.16 (d, 1, J = 16 Hz, 7-H), 6.75 (d, 1, J = 16 Hz, 8-H), 10.13 (d, 1, J = 8 Hz, 11-H). High resolution mass spectrum calcd for (C₁₇H₂₇NO) 261.2086, found 261.2081.

4-(Dimethylamino)retinyl-Nitrile 22. The sodium salt of diethyl 3-methyl-4-phosphonocrotononitrile in THF formed from 175 mg (0.8 mmol) of the phosphonate and 30 mg of NaH was reacted with 150 mg (0.57 mmol) of aldehyde 8a at 25 °C under argon atmosphere for 1 h. Extraction with ether-water and chromatography with ether-hexane (3:20) afforded after separation of isomers 90 mg of trans-isomer 22 (55% yield of trans isomer). λ_max (CHCl₃) 320 nm (ε 35 000). NMR (CDCl₃) δ 1.02 (s, 6, 1-Me), 1.75 (s, 3, 5-Me), 2.01 (s, 3, 9-Me), 2.23 (s, 6, N-Me), 2.23 (s, 3, 13-Me), 3.07 (t, 1, 4-H), 5.18 (s, 1, 14-H), 5.98-6.46 (m, 5, 7-H, 8-H, 9-H, 10-H, 12-H), 6.96 (dd, 1, J_1 = 16 Hz, J_2 = 12 Hz, 11-H).

4-(Dimethylamino)retinal 3. Nitrile 22 (75 mg, 0.23 mmol) was dissolved in dry hexane and reduced under argon at -78 °C with 2 mL of diisobutylaluminum hydride (1 M solution in hexane). The reaction mixture was stirred for 30 min and then an excess of the reducing reagent was destroyed with ethyl acetate and the product hydrolyzed as was described for 8a. The mixture was filtered through Celite followed by the usual workup and chromtography with ether-hexane (3:17) to give 59 mg (78% yield) of trans-isomer 3. λ_max (EtOH) 375 nm (ε 40 000). NMR (CDCl₃) δ 1.023 (s, 3, 1-Me), 1.024 (s, 3, 1-Me), 1.76 (s, 3, 5-Me), 2.03 (s, 3, 9-Me), 2.23 (s, 6, N-Me), 2.33 (s, 3, 13-Me), 3.08 (t, 1, J = 7 Hz, 4-H), 5.97 (d, 1, J = 8.1 Hz, 14-H), 6.14 (d, 1, J = 16 Hz, 8-H), 6.20 (d, 1, J = 11.8 Hz, 10-H), 6.35 (d, 1, J = 16 Hz, 7-H), 6.38 (d, 1, J = 15.1 Hz, 12-H), 7.13 (dd, 1, J_1 = 11.8 Hz, J_2 = 15.1 Hz), 10.11 (d, 1, J = 8.1 Hz, 15-H). High resolution mass spectrum calcd for C₂₂H₃₃NO 327.2554, found 327.2564.

4-(Dimethylamino)bromo-β-ionone 23. 4-(Dimethylamino)-β-ionone (7a) (500 mg, 2.13 mmol) was dissolved in dry THF and reacted at 25 °C with 1.5 g (5 mmol) of 5,5-dibromo-2,2-dimethyl-4,6-dioxo-1,3-dioxane for 24 h. The reaction was quenched with water and ether and the organic layer was washed three times with 10% HCl solution. The combined acidic solutions were neutralized with sodium carbonate and extracted three times with ether. The ether was washed with water and brine and dried over MgSO₄ and the solvent was evaporated. The residue was chromatographed over basic alumina (activity grade III), with methylene chloride-hexane (3:7) to afford 400 mg (60% yield) of mono-bromo 23. λ_max (EtOH) 302 nm (ε 23 000). NMR (CDCl₃) δ 1.07 (s, 6, 1-Me), 1.84 (s, 3, 5-Me), 2.23 (s, 6, N-Me), 3.10 (t, 1, J = 7 Hz, 4-H), 4.02 (s, 2, CH₂-Br), 6.33 (d, 1, J = 16 Hz, 8-H), 7.58 (d, 1, J = 16 Hz, 7-H).

Bis(dimethylamino)-β-ionone 24. Bromo-β-ionone (23) (200 mg, 0.64 mmol) in 5 mL of THF was added at 25 °C to a solution of 5 mL of dimethylamine (25% w/v in water) and 50 mL of THF containing 50 mg of sodium carbonate. The mixture was stirred at 25 °C for 1 h and then quenched with ether and water. The product was extracted as was described for 23 and then chromatographed over basic alumina with 3:7 methylene chloride-hexane to give 163 mg of 24 (92% yield). λ_max (EtOH) 291 nm (ε 19 000). NMR (CDCl₃) δ 1.05 (s, 6, 1-Me), 1.80 (s, 3, 5-Me), 2.22 (s, 6, N-Me), 2.31 (s, 6, N-Me), 3.28 (s, 2, CH₂-N), 6.30 (d, 1, J = 16.3 Hz, 8-H), 7.44 (d, 1, J = 16.3 Hz, 7-H).

Bis(dimethylamino)-Nitrile 25. Ketone 24 (245 mg, 0.88 mmol) was reacted under argon atmosphere at 25 °C in dry THF with 1 mmol of the sodium salt of diethyl cyanomethylphosphonate for 1 h. The reaction was quenched with ether and water and worked up as was described for 20. Chromatography over basic alumina with 1:4 methylene chloride: hexane afforded nitrile 25 as a mixture of trans and cis isomers (235 mg, 88% yield). λ_max (EtOH) 300 nm (ε 25 000). Trans isomer: NMR (CDCl₃) δ 1.01 (s, 6, 1-Me), 1.74 (s, 3, 5-Me), 2.24 (s, 6, N-Me), 2.26 (s, 6, N-Me), 3.08 (t, 1, J = 8 Hz, 4-H), 3.39 (s, 2, CH₂-N), 5.49 (s, 1, 10-H), 6.05 (d, 1, J = 16 Hz, 8-H), 7.04 (d, 1, J = 16 Hz, 7-H). Cis isomer: NMR (CDCl₃) δ 1.01 (s, 6, 1-Me, 1-Me), 1.78 (s, 3, 5-Me), 2.22 (s, 12, N-CH₃), 3.08 (t, 1, J = 8 Hz, 4-H), 3.16 (s, 2, CH₂-N), 5.28 (s, 1, 10-H), 6.57 (d, 1, J = 16.4 Hz, 8-H), 6.85 (d, 1, J = 16.4 Hz, 7-H).

Bis(dimethylamino)-Aldehyde 26. Nitrile 25 (250 mg, 0.8 mmol) was reduced with 1.5 mL of diisobutylaluminum hydride (1 M solution) in dry hexane at -78 °C for 30 min. The reaction was worked up as was described for retinal 3. The cis isomer was separated by chromatography over basic alumina with ether-hexane (1:1) to give 100 mg (40% yield) of 9-cis-26. λ_max (EtOH) 310 nm (ε 26 000). NMR (CDCl₃) δ 1.04 (s, 6, 1-Me), 1.80 (s, 3, 5-Me), 2.24 (s, 12, N-Me), 3.08 (t, 1, J = 8 Hz, 4-H), 3.20 (s, 2, CH₂-N), 6.07 (d, 1, J = 8 Hz, 10-H), 6.80 (s, 2, 7-H, 8-H), 10.16 (d, 1, J = 8 Hz, 15-H). High resolution mass spectrum calcd for C₁₉H₃₂N₂O 304.2507, found 304.2492.

Bis(dimethylamino)-9-cis-retinal 4. Aldehyde 26 (70 mg, 0.23 mmol) was reacted under argon at 25 °C for 30 min with the sodium salt of diethyl-3-methyl-4-phosphonocrotononitrile (0.25 mmol). The reaction was worked up as was described for 20 to give bis(dimethylamino)-9-cis-retinonitrile (27) (mixture of 13-cis and 13-trans isomers). The crude product was dissolved in dry hexane and reduced with 0.5 mL (1 M solution) of diisobutylaluminum hydride at -78 °C under argon for 20 min. The reaction mixture was worked up as was described for 3 to give 30 mg of 9-cis-retinal 4 and 8 mg of its 13-cis isomer. 9-Cis-13-trans isomer 4: λ_max (EtOH) 370 nm (ε 30 000). NMR (CDCl₃) δ 1.04 (s, 6, 1-Me), 1.82 (s, 3, 5-Me), 2.23 (s, 6, N-Me), 2.26 (s, 6, N-Me), 2.30 (s, 3, 13-Me), 3.10 (t, 1, J = 8 Hz, 4-H), 3.12 (s, 2, CH₂-N), 5.98 (d, 1, J = 8.1 Hz, 14-H), 6.26 (d, 1, J = 11.8 Hz, 10-H), 6.39 (d, 1, J = 15.4 Hz, 12-H), 6.51 (d, 1, J = 16 Hz, 8-H), 6.62 (d, 1, J = 16 Hz, 7-H), 7.03 (dd, 1, J_1 = 15.4 Hz, J_2 = 11.8 Hz, 11-H), 10.11 (d, 1, J = 8.1 Hz, 15-H). High resolution mass spectrum calcd for C₂₄H₃₈N₂O 370.2975, found 370.2979.

Bicyclic-Enal 28. Cocaine (400 mg, 1.32 mmol) was refluxed with 9 mL of concentrated HCl for 18 h. The mixture was washed with ether and the water layer was lyophilyzed. The residue was suspended in 50 mL of dry THF, cooled to 0 °C, and treated under argon with 100 mg of lithium aluminum hydride. After 30 min the mixture was warmed to 25 °C and stirred at this temperature for 4 h. The mixture was treated with a concentrated solution of sodium sulfate, filtered, and evaporated to dryness. The residue was dissolved in methylene chloride and was treated with 800 mg of active MnO₂ which was added in portions (100 mg every 20 min). The mixture was stirred for 10 h at 25 °C, filtered through Celite, evaporated, and chromatographed on neutral alumina (activity grade III) with 3:7 ether-hexane to give 134 mg of aldehyde 28 (75% yield from cocaine). λ_max (EtOH) 228 nm (ε 14 000) NMR (CDCl₃) δ 2.37 (s, 3, N-Me), 6.68 (dt, 1, J_1 = 3.5 Hz, J_2 = 1.2 Hz, vinylic proton), 9.40 (s, 1, aldehyde proton). IR (CHCl₃) 1680, 1630 cm⁻¹. CI-MS 152 (M + 1)⁺.

Bicyclic-Aldehyde 29. Aldehyde 28 (100 mg, 0.66 mmol) was reacted in dry THF under argon at 25 °C for 30 min with the sodium salt of triethyl-3-methyl-4-phosphonocrotonate. The reaction was quenched by addition of water and ether, and the organic layer was washed with water and brine, dried over MgSO₄, and evaporated to dryness. The product (obtained after chromatography over alumina with 1:4 ether-hexane) was dissolved in 30 mL of dry THF and reduced with 2 mL of diisobutylaluminum hydride (1 M solution) at -78 °C under argon atmosphere for 20 min. Excess of the reducing reagent was destroyed with ethyl acetate and the product was hydrolyzed by stirring with wet silica. The mixture was filtered through Celite and the organic layer was washed a few times with water and brine. The solvent was evaporated and the residue was dissolved in methylene chloride and treated with 350 mg of active MnO₂ at 25 °C for 5 h. The mixture was filtered through Celite and the solvent was evaporated. The residue, which contained trans and cis isomers in a ratio of 7:3, was chromatographed over neutral alumina (activity grade III) to give trans isomer 29 (73 mg, 51% yield). λ_max (EtOH) 321 nm (ε 18 000). NMR (CDCl₃) δ 2.21 (s, 3, 9-Me), 2.30 (s, 3, N-Me), 5.82 (t, 1, J = 8.5 Hz, 5-H), 5.98 (d, 1, J = 8 Hz, 10-H), 6.17 (d, 1, J = 15 Hz, 7-H), 6.61 (d, 1, J = 15 Hz, 8-H), 10.11 (d, 1, J = 8 Hz, 11-H). High resolution mass spectrum calcd for C₁₄H₁₉NO 217.1462, found 217.1469.

Bicyclic-Aldehyde 5. Aldehyde 5 was prepared from 29 as a mixture of two isomers (all-trans and 13-cis in a ratio of 7:3) in a similar way as was described for 29 (67% yield). λ_max (EtOH) 386 nm (ε 30 000). NMR (CDCl₃) δ 2.00 (s, 3, 9-Me), 2.32 (s, 3, 13-Me), 2.39 (s, 3, N-Me), 5.65 (t, 1, J = 3.5 Hz), 5.98 (d, 1, J = 8 Hz, 14-H), 7.11 (dd, 1, J_1 = 15 Hz, J_2 = 11.5 Hz, 11-H), 6.21-6.39 (m, 4-H), 10.01 (d, 1, 15-H). IR (CH₂Cl₂) 1657, 1569 cm⁻¹. High resolution mass spectrum calcd for C₁₉H₂₅NO 283.1930, found 283.1917. (For convenience the olefinic carbons were numbered in a way similar to that of the retinal skeleton.)

Bicyclic-Aldehyde 30. Tropinone (1.33 gr, 7.5 mmol) was reacted with the sodium salt of diethyl cyanomethylphosphonate (8 mmol) in THF under argon atmosphere at 25 °C. The mixture was stirred for 2 h and then quenched with water and ether. The organic layer was extracted three times with 10% HCl solution and the water solution was basified with sodium carbonate and extracted three times with ether. The com-

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bined organic solvent was washed with water and brine and evaporated, and the residue was chromatographed over neutral alumina with 3:7 ether–hexane to give 980 mg of bicyclic nitrile. The nitrile was dissolved in dry hexane and cooled under argon to -20 °C. Diisobutylaluminum hydride (10 mL, 1 M solution) was added dropwise and the mixture was stirred for 30 min. Excess of reagent was destroyed with ethyl acetate and the product was hydrolyzed by stirring with wet silica at -78 °C for 30 min and 4 h at 25 °C. Water and ether were added and the mixture was filtered through Celite, and the organic layer was chromatographed over neutral alumina with ether–hexane (1:1) to give 890 mg (75% yield from tropinone) of aldehyde **30**. λ_{max} (EtOH) 233 nm (ϵ 16 000). NMR (CDCl$_3$) δ 2.40 (s, 3, N-Me), 5.92 (d, 1, J = 8 Hz, vinylic proton), 9.97 (d, 1, J = 8 Hz, aldehyde proton). IR (CH$_2$Cl$_2$) 1671, 1627 cm^{-1}. CI-MS 166 (M + 1)$^+$.

Bicyclic-Aldehyde 31. Aldehyde **31** was prepared from **30** in 77% yield similarly to the previously described route for aldehyde **29**. The trans and cis isomer mixture of 7:3 was separated by chromatography over neutral alumina (activity grade III) with ether–hexane (1:1). Trans isomer: λ_{max} (EtOH) 335 nm (ϵ 22 000). NMR (CDCl$_3$) δ 2.32 (s, 3, N-CH$_3$), 2.36 (s, 3, Me), 5.93 (d, 1, J = 8 Hz, 10-H), 6.13 (d, 1, J = 11.3 Hz, 6-H), 6.37 (d, 1, J = 15 Hz, 8-H), 7.12 (dd, 1, J_1 = 11.3 Hz, J_2 = 15 Hz, 7-H), 10.05 (d, 1, J = 8 Hz, 11-H). Cis isomer: λ_{max} (EtOH) 331 nm (ϵ 18 000). NMR (CDCl$_3$) δ 2.13 (s, 3, N-CH$_3$), 2.36 (s, 3, Me), 5.82 (d, 1, J = 8 Hz, 10-H), 6.18 (d, 1, J = 11 Hz, 6-H), 7.00 (dd, 1, J_1 = 15 Hz, J_2 = 11 Hz, 7-H), 7.32 (d, 1, J = 15 Hz, 8-H), 10.15 (d, 1, J = 8 Hz, 11-H). IR (CH$_2$Cl$_2$) 1655, 1596 cm^{-1}. CI-MS 232 (M + 1)$^+$.

Bicyclic-Retinal 6. Bicyclic-retinal **6** was prepared (as a mixture of two isomers, all-trans and 13-cis, in a ratio of 7:3) from aldehyde **31** in a similar route as that described for the preparation of **31** (72% yield). λ_{max} (EtOH) 393 nm (ϵ 29 000). NMR (CDCl$_3$) δ 2.00 (s, 3, 9-Me), 2.32 (s, 3, 13-Me), 2.37 (s, 3, N-Me), 5.8–5.89 (m, 1), 5.98–6.13 (m, 2), 6.21–6.44 (m, 3), 6.56–6.75 (m, 1). IR (CH$_2$Cl$_2$) 1657, 1565 cm^{-1}. High resolution mass spectrum calcd for C$_{20}$H$_{27}$NO 297.2086, found 297.2098.

(Diethylamino)cyclopentanone 32. Cyclopentanone (16.8 g, 0.2 mole) was dissolved in 200 mL of dry CCl$_4$ and was refluxed for 3 h with 35.6 g (0.2 mol) of N-bromosuccinimide in the presence of a catalytic amount of benzoyl peroxide. The reaction mixture was filtered and the solvent was evaporated. The residue was dissolved in 10 mL of THF and was added to a solution of 100 mL of THF and 0.6 mL of diethylamine. The mixture was stirred for 2 h at 25 °C, extracted with methylene chloride, and washed with water and brine. The solvent was evaporated and the residue was distilled (50–57 °C (0.2 mmHg) to give 11.6 g of **32** (60% yield). NMR (CDCl$_3$) δ 1.01 (t, 6, methyls), 2.3–2.6 (m, 4, N-CH$_2$), 3.31 (t, 1, 1-H).

Diethylamino-Aldehyde 10a. The diethylamino ketone (5 g, 32.3 mmol) was condensed with the sodium salt of diethyl cyanomethyl-phosphonate (34 mmol) in dry THF under argon atmosphere at 25 °C for 1 h. Usual workup followed by chromatography over neutral alumina with 1:9 methylene chloride–hexane afforded the nitrile product as one isomer. The nitrile was dissolved in dry hexane and was reduced with 34 mL (1 M solution) of diisobutylaluminum hydride at -78 °C under argon as was described for aldehyde **30**. Chromatography over neutral alumina with 1:4 methylene chloride–hexane gave 4.4 g (75% yield) of diethylamino-aldehyde **10a**. λ_{max} (EtOH) 243 nm (ϵ 18 000). NMR (CDCl$_3$) δ 1.02 (t, 6, J = 7 Hz, methyl groups), 2.32–2.63 (m, 4, N-CH$_2$), 3.7 (m, 1, 4-H), 6.18-6.31 (m, 1, 2-H), 9.95 (d, 1, J = 8 Hz, 1-H). High resolution mass spectrum calcd for C$_{11}$H$_{19}$NO 181.1462, found 181.1453.

Absorption Maxima and Stretching Frequency Measurements. (A) The corresponding aldehyde was dissolved in dry ethanol, cooled to 0 °C, and condensed with 1.2 equiv of pyrrolidine perchlorate for 3 h. The reaction was monitored by following the disappearance of aldehyde absorption and formation of the red-shifted absorption maximum of the pyrrolidinium perchlorate salt. The ethanol was evaporated under high vacuum, and the absorption maximum of the product was measured in the required solvent (EtOH or CHCl$_3$), followed by protonation of the amino group with a solution (EtOH or CHCl$_3$) saturated with HCl and absorption maximum measurement. Neutralization of the acidic solution by addition of triethylamine shifted the absorption maximum to its original value. The C=N$^+$ and C=C stretching frequencies were taken in a similar way.

(B) The corresponding aldehyde was dissolved in dry ethanol and n-BuNH$_2$ (1.2 equiv) was added at 25 °C. The reaction mixture was stirred for 30 min. followed by evaporation of the ethanol and excess of n-BuNH$_2$ under high vacuum. The Schiff base was dissolved in the required solvent (EtOH or CHCl$_3$) and was protonated with solution (CHCl$_3$ or EtOH) saturated with HCl. The samples had a concentration of 0.5 × 10^{-4} M. The experiments with various carboxylic acids were carried out by dissolving the Schiff base in a 1 M solution of the corresponding acid in methylene chloride, to form 0.5 × 10^{-4} M Schiff base in a 1 M solution of carboxylic acid. (C) The amino groups of the aldehyde chromophores were protonated by titration with a solution saturated with HCl. The titration was followed by recording the new absorption maxima.