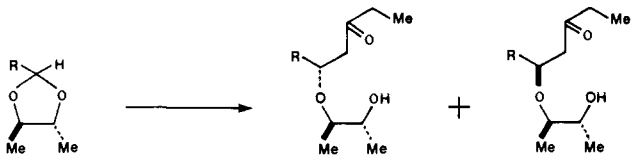
Table I



8 9 10

substance	conditions	products[14,15]
8a, R = C_6H_5	$MeCH_2COCH_2Si(CH_3)_3$/ $SnCl_4$/MeCN/−40 °C	9a-10a (16:1)
8a, R = C_6H_5	CH_2=$CHCH_2Si(CH_3)_3$/ $SnCl_4$/MeCN/−15 °C	9a'-10a' (5:1)
8b, R = $Me(CH_2)_8$	$MeCH_2COCH_2Si(CH_3)_3$/ $SnCl_4$/MeCN/−40 °C	9b-10b (3.1:1)
8c, R = $(Me)_2C$=CH	same	9c-10c (2.3:1)
8d, R = $(Me)_2CH$	same	9d-10d (ca. 1:1)

°C (double melting points); α_D +202° (*c* 0.38, $CHCl_3$)] and **7** [mp 178–180 °C; α_D +180° (*c* 0.15, $CHCl_3$)] in a ratio of 1.3:1.0[10] in 95% combined yield. Acidic hydrolysis of **6** (TFA/−78 °C → room temperature),[11] followed by chromatographic purification, afforded optically active aklavinone [**1**; mp 170–172 °C; α_D +150° (*c* 0.21 $CHCl_3$)][12] in 84% yield. Thus, by utilization of this asymmetric crossed aldol reaction, our synthetic route now provides optically active natural[13] aklavinone in 23% overall yield in six steps from bromojuglone.

Encouraged by the successful asymmetric transformation of **3** to **4**, we subjected four additional acetals, **8a–d** to the crossed aldol reaction (Table I). The absolute configuration of major aldol products **9a**, **9a'**, and **9b** were established by correlating them with known substances.[14] It is worth noting that optically active β-hydroxy ketones were easily obtained from the major aldol products in about 70% overall yield in three steps, i.e., (1) Swern or PCC oxidation, (2) Baeyer–Villiger oxidation (MCPBA/CH_2Cl_2/room temperature), and (3) methanolysis (*p*-TSA·py/CH_3OH/60 °C). As this procedure seems to have good potential for solving other synthetic problems, we are currently engaged in further developments of this reaction.

Acknowledgment. Financial support from the National Cancer Institute (Grant CA 22215) is gratefully acknowledged.

Supplementary Material Available: Experimental details and ^1H NMR spectra (13 pages). Ordering information is given on any current masthead page.

(10) Note that the ratio of **4** to **5** was improved compared with that of the corresponding two diastereomers in the racemic series; however, recycling of **7** was not applicable for the optically active series.

(11) Swenton, J. S.; Anderson, D. K.; Jackson, D. K.; Narasimhan, L. *J. Org. Chem.* **1981**, *46*, 4825.

(12) The absolute configuration of natural aklavinone is as shown in structure **1**. The specific rotation of natural aklavinone was found to be +151° in $CHCl_3$. An authentic sample of aklavinone was prepared by hydrolysis of natural aclacinomycin A. We are indebted to Professor Umezawa, Institute of Microbial Chemistry, and Dr. Oki, Sanraku-Ocean, Inc., for a generous gift of a sample of aclacinomycin A. We thank Dr. M. R. Uskokovic, Hoffmann-La Roche, Inc., for a generous gift of aklavinone, isolated from fermentation broths.

(13) If desired, this synthetic route is applicable for synthesis of the antipode of natural aklavinone by using L(+)- instead of D(−)-2,3-butanediol.

(14) The absolute configuration of **9a'** was established by its successful conversion to known (*S*)-(−)-*n*-PrCH(OH)Ph (Yamaguchi, S.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 1870) in four steps: (1) H_2/Pd–Pb–$CaCO_3$; (2) PCC oxidation; (3) MCPBA; (4) *p*-TSA·py/MeOH. Aldol product **9a'** was correlated with the PCC oxidation product of **9a** in three steps: (1) O_3; (2) EtMgBr; (3) PCC oxidation, establishing the absolute configuration of **9a**. According to the procedure given in the text, the β-hydroxy ketone was prepared from **9b**, which was then treated with (1) 3,5-$(NO_2)_2C_6H_3CO_3H$, (2) $LiAlH_4$, and (3) Ac_2O/py, to yield (*R*)-(−)-$Me(CH_2)_8CH(OAc)$-CH_2CH_2OAc. An authentic sample was prepared by using Sharpless' asymmetric epoxidation (Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974) and Red-Al reduction of the resultant epoxide (Finan, J. M.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2719), followed by acetylation.

(15) Compounds **9a'** and **10a'** have a CH_2=$CHCH_2$– group instead of a $MeCH_2COCH_2$– in the structure shown in Table I.

Practical Asymmetric Syntheses of 11-Deoxydaunomycinone and Related Compounds

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Received August 2, 1982

In the preceding paper we reported a practical synthesis of optically active aklavinone using an asymmetric crossed aldol reaction.[1] Encouraged by this success, we explored the possibility of extending our approach to asymmetric syntheses of daunomycinone, adriamycinone, and related compounds. Modification of the functional groups at the C10, C11 and C13 positions are required to realize this plan (cf. the structures in Table I). In this communication we describe a solution that achieves the required functionalization at C10 and C13 and also present a practical asymmetric synthesis of the aglycones of recently discovered 11-deoxydaunomycinone and related anthracycline antibiotics (Table I).[2-6]

The synthesis of **10** demonstrates a general method for modifying the C10 functional group. Analogous to our synthesis of aklavinone,[7] benzofuran **5a** (mp 168–169 °C, Chart I)[8] was synthesized in 70–75% yield from bromojuglone (**3**)[7] and furandiene **4**[9] ($SrCO_3$/radical scavenger/C_6H_6/reflux, followed by air oxidation in $CHCl_3$ containing *i*-Pr_2EtN). Ozonolysis of **5a**, followed by acetalization [L(+)-2,3-butanediol[10]/*p*-TSA·py/toluene/reflux/4 h] gave acetal **6** [mp 121–122 °C; α_D +49° (*c* 0.10, 1:1 $CHCl_3/CH_3OH$)] in 80–85% yield. Asymmetric aldol reaction of **6** with excess $CH_3CH_2COCH_2Si(CH_3)_3$ (3.0 equiv $SnCl_4/CH_3CN$/−20 °C/2 h) produced an approximately 17:1 mixture of two products, which were separated by using silica gel chromatography to yield **7** [85–90% yield; mp 81–83 °C; α_D +63° (*c* 0.10, 1:1 $CHCl_3/CH_3OH$)] and its C7 epimer (~5% yield).

During the aklavinone synthesis, we noticed that base-induced cyclization of a keto methyl ester similar to **7** in aprotic solvents yielded exclusively a product with the same relative stereochemistry

†National Institutes of Health Trainee at Harvard University, 1979–1982.

(1) McNamara, J. M.; Kishi, Y., *J. Am. Chem. Soc.*, preceding paper in this issue.

(2) For recent reviews on the chemistry of anthracycline antibiotics, see ref 3 of the preceding paper.

(3) For asymmetric syntheses of daunomycinone, see: (a) Terashima, S.; Jew, S.-s.; Koga, K. *Tetrahedron Lett.* **1978**, 4937; *Chem. Pharm. Bull. (Tokyo)* **1979**, *27*, 2351. (b) Terashima, S.; Tanno, N.; Koga, K. *Tetrahedron Lett.* **1980**, *21*, 2753.

(4) For syntheses of 11-deoxydaunomycinone and related compounds, see: (a) Gesson, J.-P.; Jacquesy, J. C.; Mondon, M. *Tetrahedron Lett.* **1980**, *21*, 3351. (b) Bauman, J. G.; Barber, R. B.; Gless, R. D.; Rapoport, H. *Ibid.* **1980**, *21*, 4777. (c) Krohn, K. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 576. (d) Kimball, S. D.; Walt, D. R.; Johnson, F. *J. Am. Chem. Soc.* **1981**, *103*, 1561. (e) Yadav, J.; Corey, P.; Hsu, C.-T.; Perlman, K.; Sih, C. J. *Tetrahedron Lett.* **1981**, *22*, 811. (f) Kende, A. S.; Rizzi, J. P. *Ibid.* **1981**, *22*, 1779. (g) Kende, A. S.; Boettger, S. D. *J. Org. Chem.* **1981**, *46*, 2799. (h) Alexander, J.; Flynn, D. L.; Mitscher, L. A.; Veysoglu, T. *Tetrahedron Lett.* **1981**, *22*, 3711. (i) Gesson, J.-P.; Mondon, M. *J. Chem. Soc., Chem. Commun.* **1982**, 421. (j) Rao, A. V. R.; Deshpande, V. H.; Reddy, N. L. *Tetrahedron Lett.* **1982**, *23*, 775. (k) Rao, A. V. R.; Mehendale, A. R.; Reddy, K. B. *Ibid.* **1982**, *23*, 2415.

(5) Arcamone, F.; Cassinelli, G.; DiMatteo, F.; Forenza, S.; Ripamonti, M. C.; Rivola, G.; Vigevani, A.; Clardy, J.; McCabe, T. *J. Am. Chem. Soc.* **1980**, *102*, 1462.

(6) Cassinelli, G.; Rivola, G.; Ruggieri, D.; Arcamone, F.; Grein, A.; Merli, S.; Spalla, C.; Casazza, A. M.; DiMarco, A.; Pratesi, G. *J. Antibiot.* **1982**, *35*, 176.

(7) Pearlman, B. A.; McNamara, J. M.; Hasan, I.; Hatakeyama, S.; Sekizaki, H.; Kishi, Y. *J. Am. Chem. Soc.* **1981**, *103*, 4248.

(8) Satisfactory spectroscopic data were obtained for all new compounds in this paper.

(9) An approximately 3:1 mixture of deconjugated and conjugated esters was prepared from 3-furanyl methyl ketone in two steps: (1) $(EtO)_2P(O)$-$CH_2CO_2CH_2CH_2Si(CH_3)_3$/NaH/THF/50 °C; (2) LDA/THF/−78 °C, followed by quenching with phenol. The Diels–Alder reaction was carried out by using 2.7 equiv of the mixture.

(10) This substance was prepared from L(+)-tartaric acid in five steps: (1) $MeC(OMe)_2Me$/MeOH/*p*-TSA/cyclohexane/Δ (Carmack, M.; Kelley, C. J. *J. Org. Chem.* **1968**, *33*, 2171); (2) $LiAlH_4/Et_2O$/room temperature; (3) TsCl/py/0 °C; (4) EtOH/*p*-TSA/Δ; (5) $LiAlH_4/Et_2O$/Δ. We thank Professor Still, Columbia University, for the procedure of steps 2–5.

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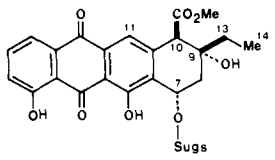
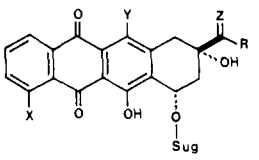
Table I



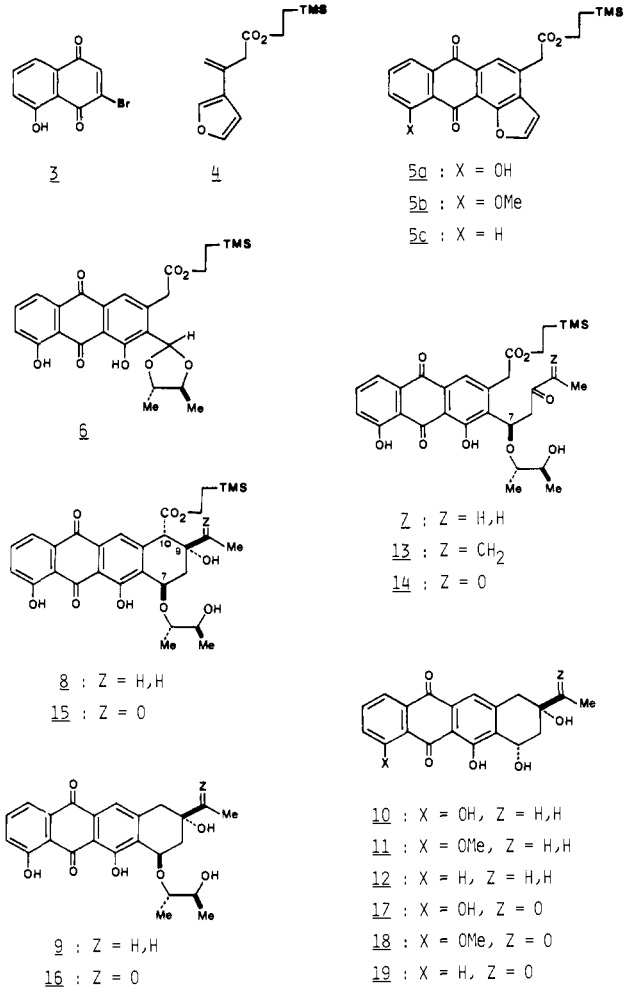
1 : aclacinomycin A



2

	X	Y	Z	R
2a, OMe	OH	O	Me (daunomycin)	
b, OMe	OH	O	CH_2OH (adriamycin)	
c, OMe	H	O	Me	
d, OMe	H	O	CH_2OH	
e, OMe	H	OH, H	Me	
f, OMe	H	H, H	Me	
g, OH	H	O	Me	
h, OH	H	O	CH_2OH	
i, OH	H	OH, H	Me	
j, OH	H	H, H	Me	

Chart I



at C7, C9, and C10 as **8**.[7] Thus, cyclization of **7** (DBN/THF/room temperature/6 h) yielded **8** [70–75% yield; mp 117–118 °C; α_D −230° (*c* 0.053, 1:1 $CHCl_3/CH_3OH$)] in addition to a small amount of its C10 epimer (~10% yield; mp 187–189 °C). The key transformation of **8** to **9** was achieved in one step by treatment with excess *n*-Bu_4NF in THF at room temperature.[11]

The product **9** [mp 139–141 °C; α_D −113° (*c* 0.053, 1:1 $CHCl_3/CH_3OH$)] was isolated in 75–80% yield. The same product was obtained from the minor product of the cyclization in comparable yield, establishing them as C10 epimers. Therefore, for practical purposes, it was possible to carry out the transformation of **7** to **9** in about 65–70% overall yield without isolation and separation of the intermediates.

Trifluoroacetic acid treatment[12] of **9** furnished an approximately 8:1 mixture of **10**[13] [75% yield; mp 189–191 °C; α_D +148° (*c* 0.10, 1:1 $CHCl_3/CH_3OH$)] and its C7 epimer (9% yield; mp 170–171 °C). This seven-step synthesis provided the natural or unnatural antipode of **10** in 24% overall yield from **3**.[14] In the same manner, optically active **11**[13] [40% overall yield from **5b**; mp 213–216 °C; α_D +132° (*c* 0.10, 1:1 $CHCl_3/CH_3OH$)] and **12** [33% overall yield from **5c**; mp 186–188 °C; α_D +81° (*c* 0.10, CH_3OH)] were synthesized from the corresponding benzofurans **5b** (mp 124–125 °C)[15] and **5c** (mp 101–103 °C).[16]

The synthesis of **17** demonstrates a general method for incorporating the C13 functional group. Asymmetric crossed aldol reaction of **6** with excess $CH_3C(=CH_2)COCH_2Si(CH_3)_3$[17] was not effected under the conditions used for the previous cases but was effected in toluene containing gaseous BF_3 at −78 °C to give an approximately 13:1 mixture of **13** and its C7 epimer in 80–85% combined yield. Separation of the products at this stage was difficult but was easily performed in the next step. Ozonolysis of this mixture [O_3/CH_3OH/−78 °C, followed by $(CH_3)_2S$ workup] gave a mixture of **14** [75% overall yield from **6**; yellow oil; α_D +61° (*c* 0.087, 1:1 $CHCl_3/CH_3OH$)] and its C7 epimer (6% overall yield from **6**; yellow oil).

Cyclization of **14** (5 equiv DBN/THF/room temperature/10 min) gave an approximately 5:2 mixture of **15** [61% yield; mp 108–109 °C; α_D −26° (*c* 0.10, 1:1 $CHCl_3/CH_3OH$)] and its C10 epimer (24% yield; mp 167–170 °C). On treatment with *n*-Bu_4NF [8 equiv (1 M in THF)/DMF/room temperature], both products yielded **16** [mp 138–140 °C; α_D −49° (*c* 0.10, 1:1 $CHCl_3/CH_3OH$); 79% yield from **15** and 61% yield from its C10 epimer], establishing that they were C10 epimers. Again, for practical purposes, it was possible to convert **14** to **16** in about 65% overall yield without isolation and separation of the intermediates. Acidic hydrolysis of **16** (TFA/−78 °C → room temperature[12]) furnished an approximately 8:1 mixture of **17**[13] [74% yield; mp 173–176 °C; α_D +195° (*c* 0.10, 1:1 $CHCl_3/CH_3OH$)] and its C7 epimer (8% yield). This eight-step synthesis provided the natural or unnatural antipode of **17** in 25% overall yield from **3**.[14] In the same manner, optically active **18**[13] [23% overall yield from **5b**; mp 215–219 °C; α_D +174° (*c* 0.10, 1:1 $CHCl_3/CH_3OH$)] and **19**[18] [23% overall yield from **5c**; mp 201–203 °C; α_D +124° (*c* 0.10, CH_3OH)] were synthesized from the corresponding benzofurans **5b** and **5c**, respectively. Since methods for transforming daunomycinone into adriamycinone are well established,[2] this synthesis should be able to provide optically active 11-deoxyadriamycinone and related compounds as well.

Acknowledgment. Financial support from the National Cancer

(11) Although it is a low-yielding process, C10 demethoxycarbonylation of aclacinomycin and related antibiotics is known; see (a) Tanaka, H.; Yoshioka, T.; Shimauchi, Y.; Matsuzawa, Y.; Oki, T.; Inui, T. *J. Antibiot.* **1980**, *33*, 1323. (b) Essery, J. M.; Doyle, T. W. *Can. J. Chem.* **1980**, *58*, 1869.

(12) Swenton, J. S.; Anderson, D. K.; Jackson, D. K.; Narasimhan, L. *J. Org. Chem.* **1981**, *46*, 4825. Under the $BF_3{\cdot}Et_2O$ conditions used in our aklavinone synthesis,[7] a substantial amount of dehydrated product was observed.

(13) We are indebted to Dr. Arcamone, Farmitalia, for a generous gift of a sample and NMR spectra of this substance.

(14) With D(−)- instead of L(+)-2,3-butanediol, the unnatural antipode was also synthesized.

(15) This substance was prepared by methylation of **5a** (CH_3I/Ag_2O/$CHCl_3$/50 °C) in 92% yield.

(16) This substance was prepared by the Diels–Alder reaction of 1,4-naphthoquinone and 4 under cation-radical conditions (Bellville, D. J.; Wirth, D. D.; Bauld, N. L. *J. Am. Chem. Soc.* **1981**, *103*, 718. Bellville, D. J.; Bauld, N. L. *Ibid.* **1982**, *104*, 2665), followed by air oxidation in $CHCl_3$ containing i-Pr_2EtN.

(17) This substance [bp 67–72 °C (1.5 mmHg)] was prepared by treatment of $MeC(=CH_2)CO_2Me$ with $LiCH_2Si(CH_3)_3$ in refluxing pentane.

(18) This substance is not the aglycone of naturally occurring antibiotics but was previously synthesized in racemic form: Umezawa, H.; Takahashi, Y.; Kinoshita, M.; Naganawa, H.; Tatsuta, K.; Takeuchi, T. *J. Antibiot.* **1980**, *33*, 1581.

Institute (Grant CA 22215) is gratefully acknowledged.

Supplementary Material Available: Experimental details and ^1H NMR spectra (39 pages). Ordering information is given on any current masthead page.

Inactivation of Bovine Opsin by *all-trans*-Retinoyl Fluoride

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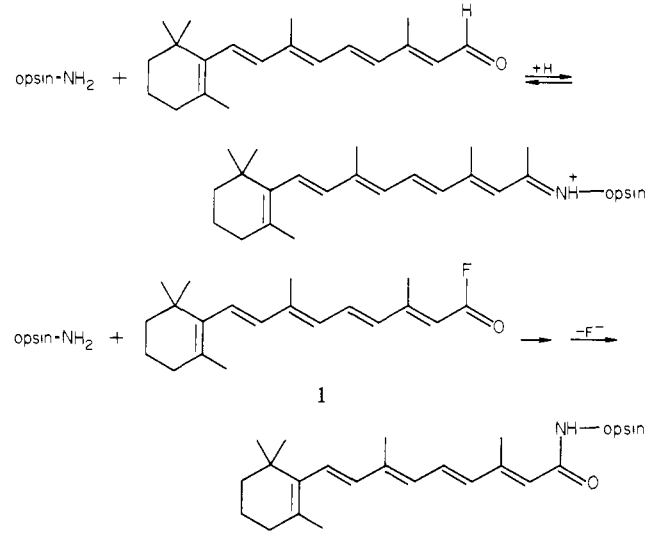
Received June 1, 1982

The initial step in vertebrate visual transduction involves the absorption of a photon by rhodopsin with the subsequent isomerization of the chromophoric 11-*cis*-retinal Schiff's base to the all-trans isomer.[1] This photochemical isomerizatioon occurs within picoseconds and within seconds is followed by a series of conformational changes of the protein resulting in the eventual hydrolysis of the Schiff's base to *all-trans*-retinal and opsin.[2] The protein conformational changes, which begin the cascade of events leading to the hyperpolarization of the rod outer segment membranes, occur on the μs–ms time scale, and a great deal of attention has been focused on them.[3] An approach to studying the role of conformational changes of rhodopsin in visual transduction is to design specific, irreversible inactivators of opsin that could freeze it in either the activated or unactivated states. Although opsin is not generally perceived as being an enzyme, it nevertheless is the agent of nonphotochemical processes such as Schiff's base formation and hydrolysis (Scheme I). This being the case, it seemed likely that *all-trans*-retinoyl fluoride **1**, a close structural analogue of *all-trans*-retinal, would be a specific inactivator of opsin, because subsequent to the attack of the active-site lysine residue on the carbonyl group, fluoride ion would leave and result in the formation of a peptide bond rather than a Schiff's base (Scheme I). In this communication, we report the synthesis of *all-trans*-retinoyl fluoride and show that it specifically inactivates bovine opsin. To our knowledge, this is the first specific inactivator reported for opsin. In addition we are also introducing the substitution of acyl fluorides for aldehydes as potential active-site-directed irreversible inhibitors.

all-trans-Retinoyl fluoride **1** was prepared from *all-trans*-retinoic acid by using the fluoridating agent prepared from the condensation of hexafluoropropylene with diethylamine.[4] Purification of **1** as a light yellow powder was accomplished just prior to use via preparative silica plate chromatography in 7:3 diethyl ether/hexane as solvent. The structure proof of **1** rested on its quantitative conversions to *all-trans*-methyl retinoate by methanol and to *all-trans*-retinol by lithium aluminum hydride. In addition, the ^1H NMR, ^{13}C NMR, ^{19}F NMR infrared, and ultraviolet spectral properties of the compound were entirely in accord with the assigned structure. The compound, being a highly conjugated acyl fluoride, is not enormously reactive toward water. For example, incubation of **1** for 23 h in 10% water/isopropanol led only to the formation of approximately 38% *all-trans*-retinoic acid.

When digitonin-solubilized bovine opsin was treated with **1**, it was irreversibly inhibited as determined by both the rates and extent of rhodopsin regeneration upon addition of 11-*cis*-retinal. The data on this inactivation process are shown in Figure 1. Control bovine opsin (3.2 μM) treated with 11-*cis*-retinal rapidly

Scheme I. Inactivation of Opsin by 1



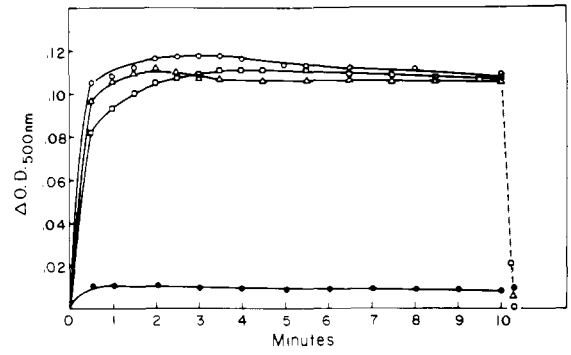


Figure 1. Inactivation of digitonin-solubilized bovine opsin by **1**. The assay for rhodopsin regeneration in 1% digitonin/66 mM KH_2PO_4, pH 6.5, after pretreatment at room temperature in the dark either with *all-trans*-retinoyl fluoride dissolved in isopropanol or with isopropanol as control followed the procedure of Hubbard et al.,[6] except that NH_2OH was added before regeneration with 11-*cis*-retinal.[8b,9] Final concentrations of *all-trans*-retinoyl fluoride, rhodopsin, hydroxylamine, and 11-*cis*-retinal are 105 μM, 3.2 μM, 66 mM, and 39 μM, respectively. (●) Retinoyl fluoride in isopropanol is incubated with bleached opsin in the dark at room temperature for 20 min before addition of NH_2OH and 11-*cis*-retinal. (□) As a control isopropanol is incubated with bleached opsin under the identical conditions as above. (△) As another control retinoyl fluoride in isopropanol is incubated with unbleached rhodopsin in the dark at room temperature for 20 min followed by addition of NH_2OH. Bleaching is followed by addition of 11-*cis*-retinal. (○) As a third control retinoyl fluoride in isopropanol is added to bleached opsin in 1% digitonin/66 mM KH_2PO_4, 66 mM NH_2OH, pH 6.5, and then incubated at room temperature in the dark for 20 min before the addition of 11-*cis*-retinal.

forms rhodopsin as measured by following the optical density increases at 500 nm (□). If the opsin (3.2 μM) is treated first with 105 μM **1** for 20 min, regeneration in the presence of 11-*cis*-retinal (39 μM) does not take place to any significant extent (○). Even after an overnight incubation with 11-*cis*-retinal, no specific regeneration was observed. Two controls are noteworthy in Figure 1. First, incubation of unbleached rhodopsin with 105 μM **1** for 20 min followed by the addition of hydroxylamine and subsequent bleaching resulted in full regeneration upon the introduction of 11-*cis*-retinal (△). Second, when bovine opsin was pretreated with hydroxylamine prior to the addition of **1**, no inactivation occurred presumably because **1** is converted to the hydroxymate under these conditions (○). It should be noted that the inactivation of opsin appears specific for **1**, since another potential acylating agent, *all-trans*-methyl retinoate, at concentrations up to 440 μM had no effect, presumably because it is not active-site directed. Furthermore, we have found that **1** is also not an inactivator of horse liver alcohol dehydrogenase even though

(1) Wald, G. *Science (Washington, D.C.)* **1968**, *162*, 230–239.
(2) Hayward, G.; Carlsen, W.; Siegman, A.; Stryer, L. *Science (Washington, D.C.)* **1981**, *211*, 942–944.
(3) (a) Hubbell, W. L.; Bownds, M. D. *Ann. Rev. Neurosci.* **1979**, *2*, 17–34. (b) Hagins, W. A. *Ann. Rev. Biophys. Bioeng.* **1972**, *1*, 131–158.
(4) Takaoka, A.; Iwakiri, H.; Ishikawa, N. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3377–3380.

0002-7863/82/1504-7374$01.25/0