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ONE STEP AND CONVENIENT PREPARATIONS OF 4-HYDROXYRETINAL AND 4-OXORETINAL

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Treatment of all-*trans*-retinal with one and two equivalents of NBS in a mixture of CH_3CN-CH_2Cl_2-H_2O provide 4-hydroxyretinal and 4-oxoretinal, respectively, in good yields.

In the study vision, the ability to prepare 4-oxygenated retinoids has become very important. 4-Hydroxyretinal was isolated as one of visual pigments of bioluminescent squid.[1] Additionally, 4-oxoretinal has been used for the photoaffinity labeling of rhodopsion.[2,3] Although many synthetic protocols for those retinoids already have been reported, those procedures required several chemical manipulations.[4-6] Here, we would like to disclose a convenient preparation of 4-hydroxyretinal and 4-oxoretinal from retinal in one step.

It was found that oxidation of NBS of all-*trans*-retinal **1** employing one equivalent in the presence of H_2O provided 4-hydroxyretinal **2** in 66% yield when it was performed at -15 °C. Before working up the reaction, *N,N*-diethylaniline was added into the reaction mixture to neutralize HBr which had been generated during the procedure. A small amount of 5,6-epoxyretinal **3** was also observed

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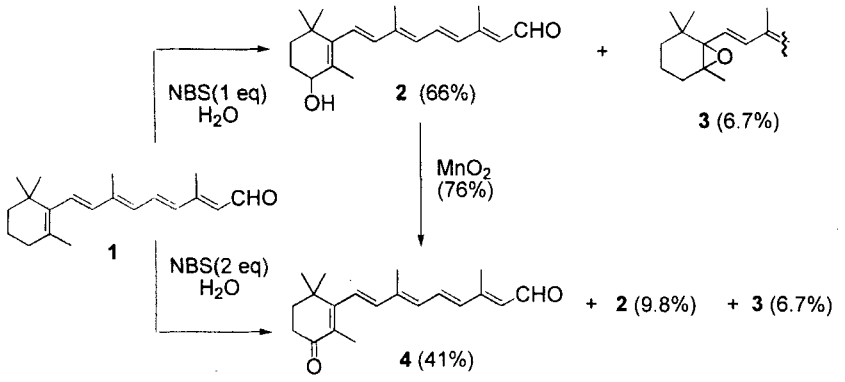

under these conditions. In order to dissolve the less polar all-*trans*-retinal in the presence of H_2O at low temperature (-15 °C), it was necessary to use a mixture of CH_3CN-CH_2Cl_2-H_2O as the solvent. For the preparation of 4-hydroxyretinal **2**, only stepwise transformations via the formate or acetate were reported in literature.[2-7]

Interestingly, employing two equivalent of NBS under similar conditions, 4-oxoretinal **4** was obtained as the major product (41%) along with 4-hydroxyretinal **2** (9.8%) and 5,6-epoxyretinal **3** (6.7%). Further selective oxidation of the allylic C4-carbon by NBS lead to the derived product. This molecule has been typically prepared by oxidation of **2** employing MnO_2 or PCC.[3,7] For confirmation of the 4-oxoretinal **4** thus obtained, 4-hydroxyretinal **2** was converted into **4** by MnO_2 treatment. The ^{1}H-NMR spectra of **3** by both protocols were identical.

EXPERIMENTAL

4-Hydroxy-all-*trans*-retinal (2)

To a solution of all-*trans*-retinal (172 mg, 605 μmol, containing 7% of 13-*cis*-retinal) in a mixture of CH_3CN (15 mL), CH_2Cl_2 (1.0 mL) and H_2O (100 μL), NBS (110 mg, 617 μmol) was added at -15°C under red dim light. After 5 min, *N,N*-diethylaniline (100 μL) was added. The reaction mixture was stirred an additional 5 min, poured into 5% aqueous $Na_2S_2O_3$ solution, and extracted with ether (×3). The combined organic solution was washed with 1 M aqueous HCl

solution, H_2O, and brine successively. After drying with $MgSO_4$, the extract was concentrated under reduced pressure. Silica gel column chromatography by successive elution with 3% and 12% AcOEt:hexane gave 5,6-epoxy-all-*trans*-retinal (**3**) (12.2 mg, 40.7 μmol, 6.7%) and 4-hydroxy-*all-trans*-retinal (**2**) (120 mg, 400 μmol, 66%), respectively. These obtained products contained 7-9% of the corresponding 13-*cis*-isomer.

4-Hydroxy-all-*trans*-retinal (**2**) ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.04, 1.07 (each 3H, s), 1.45 (1H, ddd, J = 3.3, 7.2, 13.5 Hz), 1.73 (3H, m), 1.86 (3H, s), 1.92 (2H, m), 2.05 (3H, s), 2.35 (3H, d, J = 0.9 Hz), 4.04 (1H, br), 6.00 (1H, d, J = 8.2 Hz), 6.20 (1H, d, J = 16.2 Hz), 6.23 (1H, d, J = 11.1 Hz), 6.32 (1H, d, J = 16.2 Hz) 6.41 (1H, d, J = 15.3 Hz), 7.14 (1H, dd, J = 11.1, 15.3 Hz), 10.13 (1H, d, J = 8.2 Hz), The peaks corresponding to the minor 13-*cis*-isomer were observed at 2.16 (d, J = 0.9 Hz), 5.87 (d, J = 8.2 Hz), 7.16 (dd, J = 11.0, 15.3 Hz), and 10.21 (d, J = 8.2 Hz).

5,6-epoxy-all-*trans*-retinal (**3**) CIMS (NH_3) m/z = 318 ($M+NH_3$), 301, ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.13, 1.17 1.45 (each 3H, s), 1.82 (3H, d, J = 0.9 Hz), 2.32 (3H, d. J = 0.9 Hz). 5.15, 5.27 (each 3H, d, J = 17.0 Hz), 5.98 (1H, d, J = 8.1 Hz), 6.36 (1H, d, J = 0.7), 6.39 (1H, d, J = 15.2 Hz), 7.03 (1H, dd, J = 11.1, 15.2 Hz), 10.09 (1H, d, J = 8.1 Hz). The peaks corresponding to the minor 13-*cis*-isomer were observed at 2.14 (d, J = 0.9 Hz), 5.87 (d, J = 8.1 Hz), 6.90 (dd, J = 11.1, 15.3 Hz), and 10.20 (d, J = 8.1 Hz).

4-oxo-all-*trans*-retinal (4)

To a solution of all-*trans*-retinal (143 mg, 503 μmol, containing 7% of 13-*cis*-retinal) in a mixture of CH_3CN (10 mL), CH_2Cl_2 (1.0 mL) and H_2O (1.0 mL), NBS (178 mg, 1.00 mmol) was added at -15°C under red dim light. After 5 min, *N,N*-diethylaniline (100 μL) was added and the reaction mixture was stirred additional 5 min, poured into 5% aqueous $Na_2S_2O_3$ solution, and extracted with ether (×3). The combined organic solution was washed with 1M aqueous HCl solution, H_2O, and brine successively. After drying with $MgSO_4$, the extract was concentrated under reduced pressure. Silica gel column chromatography by successive elution with 2%, 6%, and 8% AcOEt:benzene gave 5,6-epoxy-all-*trans*-retinal (**3**) (11.3 mg, 38 μmol, 6.7%), 4-oxo-all-*trans*-retinal (**4**) (61.1 mg, 205 μmol, 41%), and 4-hydroxy-all-*trans*-retinal (**2**) (14.0 mg, 49.3 μmol, 9.8%), respectively. These obtained products contained 7-9% of corresponding 13-*cis*-

isomer. After chromatography, **4** was crystallized, but recrystallization could not remove the minor isomer completely. A small amount of 13-*cis*-isomer was still observed (ca. 5%). The ^{1}H-NMR spectra of **2** and **3** were identical with those of authentic sample as described above. (**4**) ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.21 (6H, s), 1.87 (3H, s), 1.88 (2H, m), 2.07 (3H, d, J = 1.0 Hz), 2.35 (3H, d, J = 1.2 Hz), 2.53 (2H, dd, J = 6.6, 7.2 Hz), 6.01 (1H, d, J = 8.1 Hz), 6.31 (1H, d, J = 11.7 Hz), 6.35, 6.40 (each 1H, d, J = 16.2 Hz), 6.45 (1H, d, J = 15.3 Hz), 7.13 (1H, dd, J = 11.7, 15.3 Hz), 10.15 (1H, d, J = 8.1 Hz). The peaks corresponding to the minor 13-*cis*-isomer were observed at 2.17 (d, J = 1.2 Hz), 5.90 (d, J = 8.1 Hz), and 10.20 (d, J = 8.1 Hz). EIMS m/z = 298 (M^+), 283 (M-CH_3^+), 269 (M-CHO^+). EIHRMS obsd m/z = 298.1928, calcd for $C_{20}H_{26}O_2$: M^+ 298.1933.

4-oxo-all-*trans*-retinal (4) by MnO_2

A solution of **2** (17.0 mg, 56.7 μmol) in CH_2Cl_2 (2.0 mL) was stirred with MnO_2 (50 mg, excess) at room temperature under red dim light. After 2 h, the mixture was filtered through Celite pad, and the filtrate was concentrated under reduced pressure. The crude residue was purified with silica gel column chromatography. Elution with AcOEt:hexane (16:84) gave **4** (13.0 mg, 43.6 μmol, 76%) which contains 7% of the corresponding 13-*cis*-isomer. ^{1}H-NMR spectrum was identical to the authentic sample as mentioned above.

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