Modification of the Intact Retinoid Structure in the Cyclohexenyl Region: Alkylation of Methyl 4-Oxoretinoate

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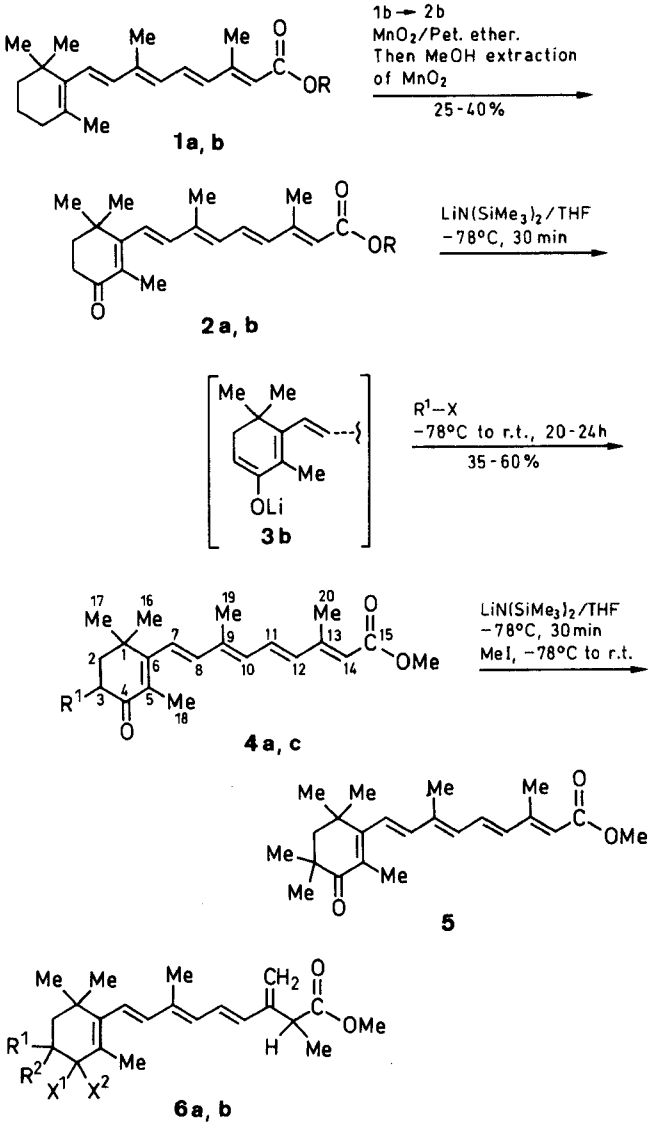
Alkylation of methyl 4-oxoretinoate under kinetic-control conditions gives predominantly 3-alkyl-4-oxoretinoates. 3,3-Disubstituted 4-oxoretinoates are obtained similarly from the 3-monosubstituted derivatives, although introduction of the second substituent is more difficult. Evidence has been obtained for a much slower rate of alkylation α to the ester group.

Certain retinoids (compounds of the vitamin A group, their derivatives, and their analogues) prevent carcinogen-induced malignancies in animals[1] and suppress or reverse certain human premalignant conditions.[2] 4-Hydroxyretinoic acid and 4-oxoretinoic acid (4-oxo-RA, **2a**) are two of the metabolites[3-5] of retinoic acid (RA, **1a**), a natural retinoid. Although it has been postulated that these metabolites are catabolic deactivation products of RA,[5,6] they are active in several bioassays for cancer chemopreventive activity.[7-12] These activities constituted the rationale for the synthesis of analogues of 4-oxo-RA. Because of the sensitivity of the conjugated double-bond system, most retinoids that retain the 2,6,6-trimethylcyclohexenyl group of the natural retinoids are synthesized by constructing the side chain in stages.[13] Analogues in which the trimethylcyclohexenyl group is replaced by other groups have been synthesized by similar stepwise routes.[13-15] Very few retinoids modified in the cyclohexenyl group have been synthesized by modification of the intact retinoid structure.[16] We report herein the synthesis of 3-substituted 4-oxo-RA and 3,3-disubstituted 4-oxo-RA esters by direct introduction of the substituents at position 3.

It might be expected that base-catalyzed alkylation of methyl 4-oxo-RA (**2b**) could occur at the α'-position (carbon 3) of the cyclohexenone group or at the α-position (carbon 14), at the γ-position (carbon 20), or at a more remote position relative to the ester group. Because of precedents among simpler cyclohexenones,[22] it was postulated that alkylation at the α'-position of the cyclohexenone group might be achieved under kinetic-control conditions even though **2b** possesses the extended conjugated ester system. Treatment of methyl 4-oxo-RA (**2b**) with lithium hexamethyldisilazide (1.1–1.2 equivalents) in anhydrous tetrahydrofuran at −78 °C followed by the addition of methyl iodide (2 equivalents) did indeed produce predominantly methyl 3-methyl-4-oxo-RA (**4a**). The yields of isolated **4a** that assayed ≥ 90% by HPLC were 72–84%; purified **4a** could be obtained in 60% yield. Methyl 3-ethyl-4-oxoretinoate (**4b**) and methyl 3-cinnamyl-4-oxoretinoate (**4c**) were obtained similarly. Evidence (MS and HPLC) was obtained for the formation of small amounts of dialkylation products during alkylations according to the method outlined above. Deliberate methylation of **4a** under similar conditions afforded a mixture of methyl 3,3-dimethyl-4-oxo-RA (**5**),



1–3	R
a	H
b	Me

4a–c	R^1
a	Me
b	Et
c	$PhCH{=}CHCH_2$

6a, b	X^1, X^2	R^1	R^2
a	$X^1 + X^2 = O$	Me	H
b	$X^1 = X^2 = H$	H	H

4a, and several other components (cf., below); the dimethyl derivative **5** was isolated by flash chromatography on silica gel.

In addition to the mass spectral, UV, and other data that support structures **4a–c**, these structures were confirmed by ^{1}H NMR studies. The hydrogen chemical shift assignments for **4a–c** and **5** can be made by comparison with methyl retinoate (**1b**). In addition, the cyclohexenyl region of **4a** was assigned by NOE difference spectroscopy. A positive NOE effect for the signals corresponding to H-2e (δ = 1.76, % NOE = 1.7) and H-3a (δ = 2.56, % NOE = 7.6) was obtained on irradiation of the signal produced by the methyl group 16*a*-CH_3 (δ = 1.24). These NOE results indicate a 1,3-diaxial relationship between 16*a*-CH_3 and H-3a and, consequently, the quasi-equatorial position of the group 3*e*-CH_3. The coupling constant of $^3J_{2a,3a}$ = 13.1 Hz for **4a** shows that H-3*a* and H-2*a* are in a 1,2-*trans*-diaxial relationship, a further indication of the quasi-equatorial position of the group 3*e*-CH_3. The observed coupling constants for **4b** and **4c** indicate that these retinoids adopt similar conformations.

Analyses by HPLC and ^{1}H NMR of the total crude products of the methylation of **4a** and of a small fraction that was isolated after **5** and other components had been separated, showed that the product **6a** of α-methylation of the ester group had also been formed. Evidently, the slower rate of the introduction of a second substituent at position 3 resulted in a higher, but still relatively low, degree of alkylation α to the ester group. Further support for this assignment was obtained by subjecting methyl retinoate (**1b**) to methylation under the same conditions. The crude material isolated from this reaction was a mixture of the α-methyl derivative **6b** and **1b** (about 1 : 1). The ^{1}H NMR spectra of the α-methyl (14-methyl) methyl esters, **6a** and **6b**, confirm their structures; the significant hydrogen NMR shifts of the side-chain hydrogens of **6a** and **6b** in comparison with the shifts arising from corresponding positions of the parent retinoids (**2b** and **1b**, respectively) are shown in the Table. The signals from the methyl groups at position 14 of **6a** and **6b** are seen as doublets and the hydrogen at that position produces a quartet. The geminal hydrogens on C-20 produce singlets and show little or no coupling[23] (Table). Further investigations of the methylation of methyl 4-oxo-RA (**2b**) showed that **6a** is also a component of the total crude product, in addition to other minor components, **5**, and the predominant product **4a** (78–90 %). The formation of **6a** and **6b** is consistent with prior demonstrations of α-alkylation of lithium enolates of α,β-unsaturated esters.[24]

Compounds **4a–c** and **5** represent new types of retinoids with potential uses in the prevention or treatment of malignancies. These retinoids and the corresponding retinoic acids are active in a spectrum of bioassays for cancer chemopreventive activity.

All operations involved in the preparation, isolation, purification, and transfer of retinoids were performed in an atmosphere, or under a current, of N_2 or Ar. All such operations were also performed in dim light or photographic dark-room light and, insofar as possible, with containers wrapped with aluminum foil or with black cloths.

Table. Proton NMR Data (δ) of Methyl 14-Methylretinoates **6a**, **6b** and The Parent Methyl Retinoates[a] **4a**, **1b**

Assignment	4a	6a	1b	6b
14-CH_3 (3H)	–	1.39 (d)	–	1.38 (d)
C-19 (3H)	2.03 (s)	1.98 (s)	2.00 (s)	1.94 (d)
C-20	2.36 (d, 3H)	5.17 (s, 1H)	2.36 (d, 3H)	5.11 (s, 1H)
		5.25 (s, 1H)		5.19 (s, 1H)
C-14 (1H)	5.81 (m[b])	3.52 (q)	5.78 (m[b])	3.53 (q)
C-11 (1H)	6.98 (dd)	6.72 (dd)	7.00 (dd)	6.72 (dd)

[a] δ of the protons of C-2, C-3, C-7, C-8, C-10, C-16, C-17, C-18 of **4a** and **6a** are similar as are δ of these protons and the C-4 protons in **1b** and **6b**. The close agreement of these signals from **4a** and **6a** shows that the structure of **4a** and **6a** in the cyclohexenyl and C-7 to C-10 regions are the same. Likewise, the cyclohexenyl and C-7 to C-10 regions of **1b** and **6b** are shown to be identical by the proximity of the signals from the protons in these regions.

[b] Unresolved multiplets.

During the alkylation reactions, the inert atmosphere in the reaction apparatus was maintained with the aid of a Firestone valve. The THF solution of $LiN[SiMe_3]_2$ was purchased from Aldrich Chemical Co. All retinoids were stored in an atmosphere of Ar or N_2 in hermetically sealed containers at – 20 °C or – 80 °C. Melting points were determined in capillary tubes heated in a Mel-Temp apparatus. UV spectra (EtOH) were recorded on a Perkin-Elmer Lambda 9 UV-Visible-NIR spectrophotometer. MS data were taken from low-resolution, electron-impact spectra determined at 70 eV with a Varian/MAT Model 311A spectrometer.

^{1}H NMR spectra were determined at 300.65 MHz with a Nicolet NT 300NB NMR spectrometer in $CDCl_3$ using TMS as the internal standard. Assignments of chemical shifts are designated by the position numbers shown on structure **4**. The NOE experiments were conducted on non-degassed solutions of $CDCl_3$. To minimize the effects of magnetic perturbations with the sample non-spinning, eight FID's (free reduction decays) were acquired with the decoupler set at a desired frequency, and eight FID's were recorded with the decoupler off-resonance. The process was repeated until 400 FID's had been accumulated. Subsquent subtraction of the two spectra afforded the net enhancement.

HPLC was performed with Waters Associates components systems and a Hewlett-Packard Model 3380-S integrator or with a Hewlett-Packard Model 1084B system. HPLC was performed on columns packed with octadecylsilylated silica (Spherisorb ODS), 5μ particle size; unless indicated otherwise, the eluting solvent was 85:15 acetonitrile – 1 % aqueous ammonium acetate, isocratic, 1 mL/minute flow rate; and elution was monitored by UV absorption at 340 nm. Deactivated Al_2O_3 for column chromatography was prepared by thoroughly mixing activated neutral Al_2O_3 (Brockman No. 1) and H_2O with the ratio of 10 : 1. All new compounds gave satisfactory elemental analyses: C ± 0.32, H ± 0.17.

Methyl 3-Methyl-4-oxoretinoate (4a):

A solution of $LiN[SiMe_3]_2$ (17 mmol) in THF [prepared from anhydr. THF (24 mL) and a 1 M solution (17 mL) of the hexamethyldisilazide in THF] was chilled to – 78 °C. A solution of **2b** (5.0 g, 15.2 mmol) dissolved in anhydr. THF (48.3 mL) was added during 10 min to the stirred, cold (– 78 °C) hexamethyldisilazide solution. After the resulting mixture was stirred at – 78 °C for 30 min, MeI (1.86 mL, 30 mmol) was added, the temperature was allowed to rise to r.t., and the mixture stirred overnight and then concentrated under reduced pressure. A sat. aq solution (40 mL) of NH_4Cl was added to the residue, the mixture extracted with EtOAc (2 × 30 mL), the combined EtOAc extracts were dried by adding $MgSO_4$ and Al_2O_3 and stirring the mixture. The mixture was filtered, the filtrate concentrated under reduced pressure to a solid (4.69 g), and the

residue was triturated with petroleum ether (bp 35–60 °C); yield: 4.05 g (77 %); mp 121–123 °C; purity, 90.5 % (HPLC).

A second (306 mg) was obtained by crystallizing the filtrate residue from Et_2O/pentane. The two portions were combined and subjected to chromatography on a column of silica gel; elution by heptane/EtOAc (9:1) was monitored by TLC. Fractions that contained only **4a** were combined and recrystallized from Et_2O/pentane; yield: 3.126 g (60 %); yellow crystals; mp 125–126 °C; purity, 98.1–99.6 % (HPLC).

UV: λ_{max} (ε) = 361 (53000), 285 (12300), 231 nm (7900).

^{1}H NMR: δ = 1.13 (s, 3H, 17*e*-CH_3), 1.14 (d, 3H, 3-CH_3), 1.24 (s, 3H, 16a-CH_3), 1.71 (t, 3H, $J_{2e,2a}$ = 13.2 Hz, $J_{2a,3a}$ = 13.1 Hz, H-2*a*), 1.76 (dd, 1H, $J_{2e,3a}$ = 5.6 Hz, H-2*e*), 1.85 (s, 3H, 18-CH_3), 2.03 (s, 3H, 19-CH_3), 2.36 (d, 3H, J = 1.0 Hz, 20-CH_3), 2.56 (m, 1H, J = 6.6 Hz, H-3a), 3.72 (s, 3H, OCH_3), 5.81 (m, 1H, H-14), 6.25 (d, 1H, $J_{10,11}$ = 11.5 Hz, H-10), 6.32 (s, 2H, H-7,8), 6.35 (d, 1H, $J_{11,12}$ = 15.2 Hz, H-12), 6.98 (dd, 1H, $J_{10,11}$ = 11.5 Hz, $J_{11,12}$ = 15.2 Hz, H-11).

MS: m/z = 342 (M^+), 327 ($M - CH_3$), 295 ($M^+ - CH_3 - CH_3OH$), 283 ($M^+ - CO_2CH_3$).

Methyl 3-Ethyl-4-oxoretinoate (4b):

Compound **4b** was prepared from **2b**, lithium $LiN[SiMe_3]_2$ and EtI in anhydr. THF by the procedure described for **4a**. The crude product was purified by preparative TLC (silica gel; pentane/EtOAc, 8:2) or column chromatography and then by recrystallization from Et_2O/pentane or Et_2O/hexane; yield: 35 %; mp 97–99 °C; purity, 99.7–100 % (HPLC).

UV: λ_{max} (ε) = 360 (54000), 284 (12700), 230 nm (8200).

^{1}H NMR: δ = 0.94 (t, 3H, J = 7.3 Hz, CH_2CH_3), 1.16 (s, 3H, 17*e*-CH_3), 1.23 (s, 3H, 16*a*-CH_3), 1.39 (m, 1H, CH_2CH_3), 1.69 (t, 1H, $J_{2a,2e}$ = 13.2 Hz, $J_{2a,3a}$ = 13.9 Hz, H-2*a*), 1.80 (dd, 1H, $J_{2e,3a}$ = 4.8 Hz, H-2*e*), 1.85 (s, 3H, 18-CH_3), 1.97 (m, 1H, CH_2CH_3), 2.03 (s, 3H, 19-CH_3), 2.36 (d, 3H, J = 0.9 Hz, 20-CH_3), 2.36 (m, 1H, H-3), 3.72 (s, 3H, OCH_3), 5.82 (m, 1H, H-14), 6.25 (d, 1H, $J_{10,11}$ = 11.3 Hz, H-10), 6.33 (s, 2H, H-7,8), 6.36 (d, 1H, $J_{11,12}$ = 15.0 Hz, H-12), 6.94 (dd, 1H, $J_{10,11}$ = 11.3 Hz, $J_{11,12}$ = 15.0 Hz, H-11).

MS: m/z = 356 (M^+), 341 ($M^+ - CH_3$), 297 ($M^+ - CO_2CH_3$).

Methyl 3-Cinnamyl-4-oxoretinoate (4c):

A solution of **2b** (3.0 g, 9.13 mmol) in anhydr. THF (29 mL) was added to a THF solution of $LiN[SiMe_3]_2$ (9.13 mmol) at −78 °C, prepared as described for **4a**. After the mixture was stirred for 30 min, a solution of cinnamyl bromide (2.70 g, 13.7 mmol) in anhydr. THF (3 mL) was added to the cold, stirred mixture. The temperature of the mixture was allowed to rise slowly to r.t., and the mixture was stirred overnight. The reaction mixture was worked up as described for **4a**, and the EtOAc extract was dried ($MgSO_4$) and evaporated under reduced pressure to a solid. The crude product was chromatographed on a column of silica gel with gravity elution by heptane/EtOAc (9:1). TLC indicated that the first fraction (1.29 g) contained cinnamyl bromide as well as **4c**; the second fraction (3.18 g) consisted of **4c** and minor impurities. The first fraction was separated into two fractions by flash chromatography on a column of silica gel with pentane/EtOAc (9:1) as the eluent. The second fraction was contaminated by cinnamyl bromide and subjected to flash chromatography in the same way. The first fractions (0.28 g and 0.33 g) from the two flash chromatography columns were combined with the second fraction (3.18 g) from the gravity column, and the total product, which was free of cinnamyl bromide, was purified further by gravity chromatography on a column of silica gel with elution successively by heptane and by heptane containing 1, 2, 5, or 10 % EtOAc. Fractions containing almost pure **4c** were combined and concentrated to a solid residue (3.53 g; yield, 87 %) that was recrystallized from Et_2O/pentane; yield: 2.17 g (53 %); mp 74–75 °C. A polymorphic form was obtained by evaporating the solvent from an EtOH solution of **4c**: mp 84–85 °C; purity, 98–99.5 % (HPLC).

UV: λ_{max} (ε) = 362 (53900), 292 (sh), 284.5 (13700), 252 nm (23700).

^{1}H NMR: δ = 1.14 (s, 3H, 17*e*-CH_3), 1.23 (s, 3H, 16*a*-CH_3), 1.70 (t, 1H, $J_{2a,2e}$ = 13.4 Hz, $J_{2a,3a}$ = 14.0 Hz, H-2a), 1.83 (dd, 1H, $J_{2e,3a}$ = 4.8 Hz, H-2*e*), 1.87 (s, 3H, 18-CH_3), 2.03 (s, 3H, 19-CH_3), 2.31 (m, 2H, CH=CHC$\underline{H}_2$), 3.72 (s, 3H, OCH_3), 5.82 (m, 1H, H-14), 6.21 (m, CH=C$\underline{H}$CH$_2$), 6.25 (d, 1H, $J_{10,11}$ = 11.4 Hz, H-10), 6.33 (s, 2H, H-7, 8), 6.35 (d, 1H, $J_{11,12}$ = 15.0 Hz, H-12), 6.43 (d, 1H, J = 15.6 Hz, C$\underline{H}$=CHCH$_2$); 6.98 (dd, 1H, $J_{10,11}$ = 11.4 Hz, H-11), 7.17–7.38 (m, 5H, C_6H_5).

MS: m/z = 444 (M^+), 429 ($M^+ - CH_3$), 388, 327 (M^+ – cinnamyl group), 117 (cinnamyl group).

Methyl 3,3-Dimethyl-4-oxoretinoate (5):

A THF solution of **4a** was treated with $LiN[SiMe_3]_2$ (1.2 equiv) and MeI (1.2 equiv) by the procedure described for the preparation of **4a**. The mixture resulting from the addition of sat. aq NH_4Cl solution to the concentrated reaction mixture was extracted with Et_2O (3 × 25 mL), and the ethereal extract was dried ($MgSO_4$) and concentrated under reduced pressure. The residue (0.83 g from 962 mg of **4a**) was dissolved in EtOAc and subjected to flash chromatography on a column of silica gel; the eluting solvents used successively were pentane and pentane/EtOAc (97:3, 94:6, 85:15). The eluate portions were combined into three fractions, and the first fraction was recrystallized from Et_2O/pentane; yield: 289 mg; purity by HPLC: 94 % **5**. Recrystallization from Et_2O/pentane furnished **5**; mp 101–102 °C; purity by HPLC: 98.8 %.

UV: λ_{max} (ε) = 361 (51700), 286 (12300), 230 nm (8000).

^{1}H NMR: δ = 1.18 (s, 6H, 2 × CH_3 at C-3), 1.22 (s, 6H, 17*a*-CH_3, 16*a*-CH_3), 1.8 (s, 2H, H-2*a*,*e*), 1.88 (s, 3H, 18-CH_3), 2.03 (d, 3H, J = 0.8 Hz, 19-CH_3), 2.36 (d, 3H, J = 1.1 Hz, 20-CH_3), 3.72 (s, 3H, OCH_3), 5.82 (m, 1H, H-14), 6.25 (d, 1H, $J_{10,11}$ = 11.4 Hz, H-10), 6.35 (s, 2H, H-7,8), 6.36 (d, 1H, $J_{11,12}$ = 15.0 Hz), 6.99 (dd, 1H, $J_{10,11}$ = 11.4 Hz, $J_{11,12}$ = 15.0 Hz, H-11).

MS: m/z = 356 (M^+), 341 ($M^+ - CH_3$), 324 ($M^+ - CH_3OH$), 309 ($M^+ - CH_3 - CH_3OH$), 297 ($M^+ - COOCH_3$).

The second and third fractions from the chromatographic column may also be recrystallized from Et_2O/pentane. HPLC analyses of the recrystallized fractions indicate that each contains four components; the major component is **4a** (62 % and 52 %, respectively).

Methylation at C-14:

(A). Methylation of **4a** was performed according to the method described for the preparation of **4a** with the following modifications to the procedure: (1) a small amount of the solution of **4a** (5.0 g, 14.6 mmol) in THF (46.6 mL) was added to the cold, stirred solution of the base (prepared from 16.2 mL of a 1 M THF solution of the base plus 23 mL of anhydr. THF); (2) a small part of a solution of MeI (58.4 mmol) in anhydrous toluene (10.9 mL) was added from a second addition funnel; and (3) the two solutions were then added simultaneously. The reaction apparatus (fitted with a stirrer and two addition funnels) was closed except for the flow of dry Ar controlled by a Firestone valve. The reaction mixture was stirred at −78 °C for 2 h, allowed to warm to r.t., and stirred overnight. HPLC analysis (monitored at 340 nm) of the unfractionated crude product (obtained as described for **4a**) revealed four major components and three minor components (peak, retention time in min, %): A, 4.5, 0.4; B, 5, 0.6; C, 5.4; 12.8; D, 5.7, 24.6; E, 6.2, 17.4; F, 6.6, 43.9; G, 8.9, 0.3. Further analyses by HPLC by co-injection of the crude product with **4a** or **5**, as well as subsequent fractionation, showed that components E and F are **4a** and **5**, respectively. The ^{1}H NMR spectrum of the crude product included the expected peaks arising from **4a** and **5**; in addition, well-separated peaks at δ = 1.40d (C-14-CH_3), 3.54q (1H, C-14), 5.19s and 5.26s (2H, C-20), 6.72dd (1H, C-11) revealed the presence of components with a methyl group at C-14. The crude product was dissolved in EtOAc/heptane and poured onto a flash-chromatography column of silica gel. Eluent portions from elution successively with heptane and heptane/EtOAc mixtures (95:5, 9:1, 85:15) were combined into three fractions, all of which were shown by HPLC to contain components C-F in different amounts: fraction 1, 2.75 g, 66 % **5**; fraction 2, 2.03 g, mixture of C-F ion amounts ranging from 21–30 %; fraction 3, 230 mg, 44 % C and 24 % D. Further fractionation of fractions 1 and 2 yielded 1.89 g of

material containing 85–86% **5**, which may be purified further. Fraction 3 was subjected to preparative TLC (silica gel, 85:15 pentane–EtOAc). The material (120 mg) isolated from the leading band was predominately component C and **4a**; FAB-MS, $m/z = 357$ ($M^+ + H$ of a dimethylation product). The ^1H NMR data (Table) from the spectrum of this material showed that component C was **6a**; the ratio of **6a**:**4a** (estimated from the integrals of the C-20 hydrogens of **6a** and the C-3 hydrogens of **6a** + **4a**) was approximately 57:43. The HPLC analysis (monitored at 340 nm) was similar (50% C, 45% **4a**, and minor components).

(B). In three separate experiments, methylation of **2b** as described immediately above and analyses of the total crude products by HPLC and by ^1H NMR showed the presence of **6a** and **5** in addition to **4a** (78–90% by HPLC). Compound **6a** was identified by the hydrogen signals (C-14-CH_3, C-20, C-14, C-11) listed in the Table.

(C). Methyl retinoate (**1b**) was treated with MeI by the procedure outlined above, and the total crude product was analyzed by HPLC (peak, retention time in min, %): A, 8.3, 40; B, 9.2, 14; C, 10.5, 41; minor components. Co-injection of this material with **1b** indicated that component C was **1b**, and the FAB-MS spectrum included peaks corresponding to the molecular ions of **1b** ($m/z = 314$), **6b** ($m/z = 328$), and the introduction of two methyl groups ($m/z = 342$). The ^1H NMR data (Table) showed that component A was **6b** and confirmed the presence of **1b** (ratio of integrals **1b**:**6b** is approximately 1:1).

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(15) See, also, Mayer, H. et al., ref. 1 and Loeliger, P. et al., ref. 1.
(16) Oxo and hydroxyl groups have been introduced by allylic oxidation at position 4 of retinoids and the 4-oxo group has been reduced to the 4-hydroxy group.[14,17,18] Retinoids with substituents at position 4 have been prepared via allylic halogenation and subsequent replacement reactions,[19] and 4,4-difluororetinoids have been prepared via the action of diethylaminosulfur trifluoride on the 4-oxo group.[20] 3,4-Didehydroretinoids have been prepared from the 4-bromo or 4-hydroxy derivatives.[18] Retinoids with oxygen functional groups at position 3 have been prepared from the 3,4-didehydroretinoids.[21]
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