Pergamon

Tetrahedron Letters, Vol. 35, No. 18, pp. 2865-2868, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0452-4

Effects of Trialkylsilyl Protecting Groups on the Photolysis of 1α-Hydroxy-Provitamin D3

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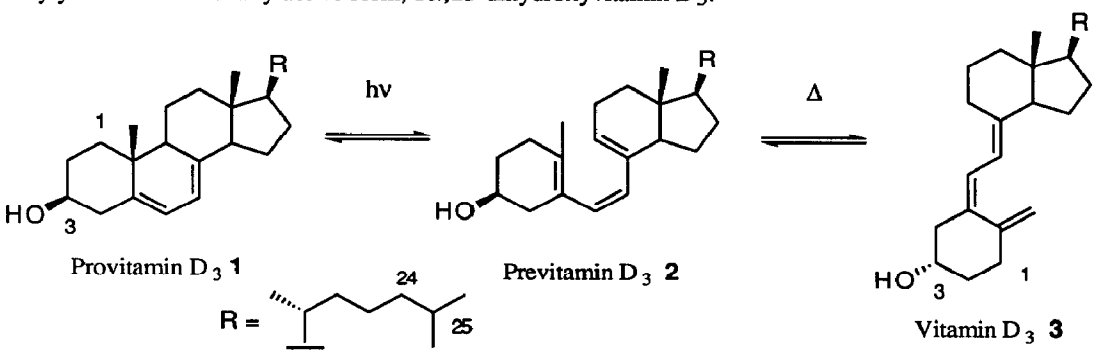
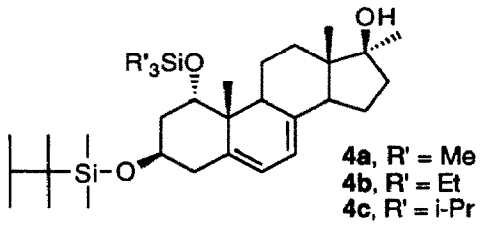
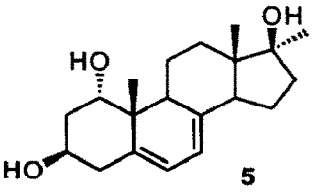
Abstract: *The quantum yield of the photolytic opening of the diene ring of a 1α-hydroxyprovitamin D3 analog decreased with an increase in the size of the trialkylsilyl group on the 1α-hydroxy group. When the 1α-hydroxy group was protected as a triisopropylsilyl ether (4c), the quantum yield of the photochemical ring-opening reaction was found to be about one-third of that of the parent compound (5).*

The conversion of provitamin D3 (**1**) into vitamin D3 (**3**) is of importance not only as a fundamental biological process in the skin,[1] but also in the syntheses of biologically active metabolites and analogs.[2] In both cases, the first step is photolytic opening of the diene ring of **1**[3] to form previtamin D3 (**2**),[4] followed by thermal conversion of **2** into **3** via a formal [1,7]-sigmatropic hydrogen shift.[5] Metabolism of **3** in the liver and kidney yields its hormonally active form, 1α,25-dihydroxyvitamin D3.[1]



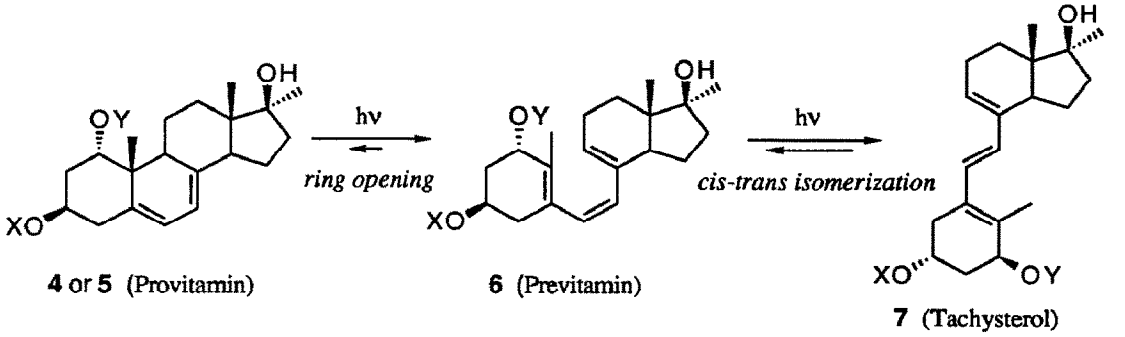
In the course of multi-gram preparations of 1α-hydroxyvitamin D3 analogs, we observed that protection of the 1α-hydroxy group of a provitamin D3 analog has a significant effect on the quantum yield of photolytic opening of the ring B diene; when the hydroxy group was protected with a bulky trialkylsilyl group, longer irradiation periods were required to obtain reasonable conversions than those instances with substrates lacking large substituents or without any protecting groups at all. The unfortunate consequence of these extended photolyses was to increase the formation of by-products. In order to clarify this effect (whether steric or electronic), several 1α-trialkylsilyloxy-provitamin D3 analogs (**4a-c**) were prepared, and the quantum yields of the photochemical ring opening of **4a-c** were compared with that of the parent compound **5**.





The requisite provitamin D3 analog **4**[6] was prepared by treating the corresponding bis-silylated androsta-5,7-dien-17-one[2a,b] with the methylcerium reagent in THF.[7] Compound **5**[8] was obtained by deprotection of **4** with Bu_4NF in THF. The direct methylation of 1,3-dihydroxy-5,7-dien-17-one with the cerium reagent was not satisfactory due to the formation of the corresponding deconjugated diene (presumably via hydrogen abstraction). Fortunately, this was not observed when the 1α-hydroxy group was protected.

The unprotected diene **5** was employed as an internal standard in order to probe the differences in the photolyses of **4a-c**. Variation of decomposition rates, if any, of **4a-c**, **6a-c**, and **7a-c** (X = thexyldimethylsiliyl, Y = SiR'3: R' as defined for compound **4**) are assumed to be negligible since only the alkyl substituents on the silicon differ. Photolyses of mixtures of **4** and **5** were followed simultaneously in solution in order to exclude various extraneous factors. Irradiation of a solution of **4** and **5** (2.5×10^{-5} M each) in t-BuOMe (0°C) with a low pressure Hg lamp (principal emission at 254 nm, 3.5 watts) gave a mixture of the previtamin **6**, the tachysterol **7**, and the remaining starting provitamins **4** and **5**.[3] Under these conditions, the formation of the corresponding lumisterol (i.e. the reverse ring-closure reaction) is negligible.[3c,d]



After irradiating for a certain period, the photoproducts were partitioned between hexane and 95% methanol. The silylated compounds, **4** and its photoproducts **6** and **7**, were in the hexane phase, and the triols, **5**, **6**, and **7**, were obtained from the methanol layer. Each phase was washed twice with either hexane or 95% methanol to avoid cross-contamination and was concentrated to dryness. Base line separation of ^1H NMR signals of olefinic protons in **4** -**7** as well as the characteristic C-1 equatorial proton in **4** and **5** allows quantitative analyses of the photoproducts.[9] Percent conversion of **4a-c** to **6** and **7** was plotted against that measured for **5** (Figure 1). The ratio of photoproducts **6** and **7** depends upon the conversion, being 1:1.5 at 25% conversion and 1:2 at 50% conversion. In the photolysis of provitamin D2 or D3, it is reported to be 1:3.5 when the photostationary state at 254 nm is reached.[3c,d,10]

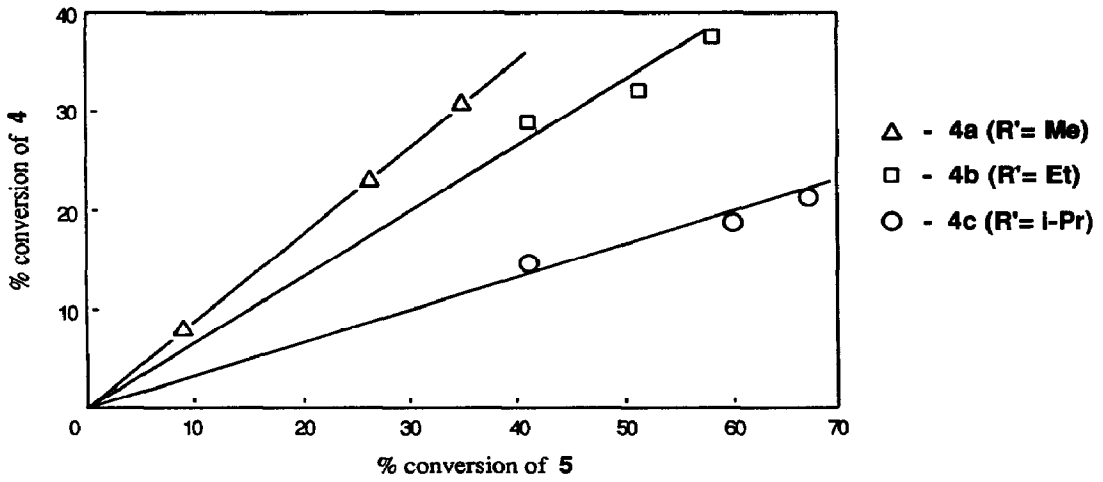


Figure 1. Percentages of conversion of **4a-c** plotted against percentages of **5** converted.

As shown in Figure 1, the quantum yield of the photolytic opening of **4** clearly decreases with an increase in the size of the protecting group. Conversion of **4b** to the ring-opened photoproducts **6** and **7** is much less efficient than that for **4a** and **5**, and **4c** is even less reactive by about a factor of 3. Since there is no significant difference between **4a** and **5**, any electronic effect, if any, due to the silyl group is negligible. The observed steric effect is consistent with the mechanistic scenario recently offered by Bernardi et al.[11] After photoexcitation, the energy barrier that the excited system must overcome to form the previtamin is the $CI_{c/t}^{+}$ conical intersection on the excited-state surface where a fully efficient radiationless decay from the excited state to the ground state of the photoproduct becomes possible.[11] Usually, this barrier (a value of 21 Kcal/mol is reported for a model system[11]) is easily overcome since the system initially arrives at a high-energy region of the excited-state surface after absorption of a photon. The conical intersection is described as tetraradicaloid and, for the ergosterol photochemical reaction network, the MM-VB optimized geometry of the hexatriene unit is twisted and the C-1α hydrogen is directed toward the C-D ring.[11] Such a conformation, when applied to our system, apparently causes a severe steric interaction between a bulky trialkylsilyl protecting group at C-1α and the C-D ring as depicted in Figure 2 below. This additional steric interaction (i.e. extra energy barrier) in the $CI_{c/t}^{+}$ conical intersection makes $CI_{c/t}^{+}$ less accessible and consequently leads to lower relative quantum yields observed in substrates having bulky protecting groups.

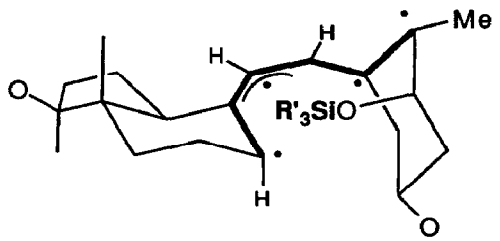


Figure 2. Simulated 1α-Trialkylsilyloxy-substituted $CI_{c/t}^{+}$ Conical Intersection.

In conclusion, the relative quantum yield of the photolytic opening of the diene ring decreases with an increase in the size of the trialkylsilyl protecting group on the 1α-hydroxy group. For the production of 1α-hydroxyvitamin D3 analogs, it is therefore advisable to remove the protecting group prior to photolysis. Furthermore, provitamin analogs with bulky groups on the 1α-hydroxy group may be useful in studying the excited states of substrates undergoing electrocyclic ring-opening reactions.

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6. **4a:** mp 58-62°C; UV (EtOH) λ_{max} 260sh (ε 6830), 270 (ε 10100), 280 (ε 11080), 293 (ε 6530) nm; ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 6H), 0.15 (s, 9H), 0.80 (s, 3H), 0.84 (s, 6H), 0.89 (d, J = 6.8 Hz, 6H), 0.92 (s, 3H), 1.25 (s, 3H), 1.31 (s, 1H), 1.32 (m, 1H), 1.51 (m, 1H), 1.65 (m, 6H), 1.86 (m, 3H), 2.09 (m, 1H), 2.37 (m, 2H), 2.72 (m, 1H), 3.74 (bs, 1H), 4.03 (m, 1H), 5.37 (m, 1H), 5.63 (m, 1H).

   4b: mp 54-58°C; UV (EtOH) λ_{max} 260sh (ε 6420), 270 (ε 9700), 280 (ε 10600), 293 (ε 6300) nm.

   4c: mp 80-81°C; UV (EtOH) λ_{max} 260sh (ε 6940), 270 (ε 10370), 280 (ε 11450), 293 (ε 6830) nm.
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8. **5:** mp 167-175°C; UV (EtOH) λ_{max} 260sh (ε 7100), 270 (ε 10400), 280 (ε 11200), 293 (ε 6500) nm; ^{1}H NMR ($CDCl_3$) δ 0.81 (s, 3H), 0.97 (s, 3H), 1.25 (s, 3H), 1.34 (s, 1H), 1.45 (d, J = 5.6 Hz, 1H), 1.47 (m, 1H), 1.50 (d, J = 3.5 Hz, 1H), 1.65 (m, 6H), 1.86 (m, 2H), 2.13 (m, 2H), 2.35 (m, 1H), 2.53 (m, 1H), 2.72 (m, 1H), 3.80 (bs, 1H), 4.07 (m, 1H), 5.39 (m, 1H), 5.63 (m, 1H).
9. The following ^{1}H NMR signals were used for the analyses: at 3.8 (bs) and 5.4 (m) ppm for **4** and **5**; 5.5 (m) and 5.9 (d) for **6**; 6.1 (d) and 6.6 (d) for **7**.
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(*Received in USA* 13 *May* 1993; *revised* 24 *February* 1994; *accepted* 25 *February* 1994)