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Regioselective Synthesis of 19-Fluorovitamin D via Fluorination of Vitamin D-Sulfur Dioxide Adducts

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Abstract: *19-Fluorovitamin D derivatives are conveniently synthesized by the regioselective electrophilic fluorination of vitamin D-SO_2 adducts followed by desulfonylation and photochemical isomerization.*
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Hormonally active vitamin D_3, 1α,25-$(OH)_2D_3$ (**1a**), elicits its activities by controlling the target gene expression via binding to the nuclear receptor (VDR) specific for **1a**.[1] 1α,25-$(OH)_2D_3$ is a highly flexible molecule where an A-ring, a seco-B-ring, and a side-chain can adopt numerous conformations. To investigate the molecular mechanism for expressing biological responses, we have been studying the conformation-activity relationships of the side chain[2] and the A-ring[3] using conformation restricted vitamin D analogs as tools. As part of our ongoing research, we are synthesizing the A-ring and triene fluorinated analogs of **1a** as probe compounds to monitor the conformation of **1a** binding to VDR by ^{19}F NMR spectroscopy. It is also interesting whether the electron density at the triene part affects the activity.

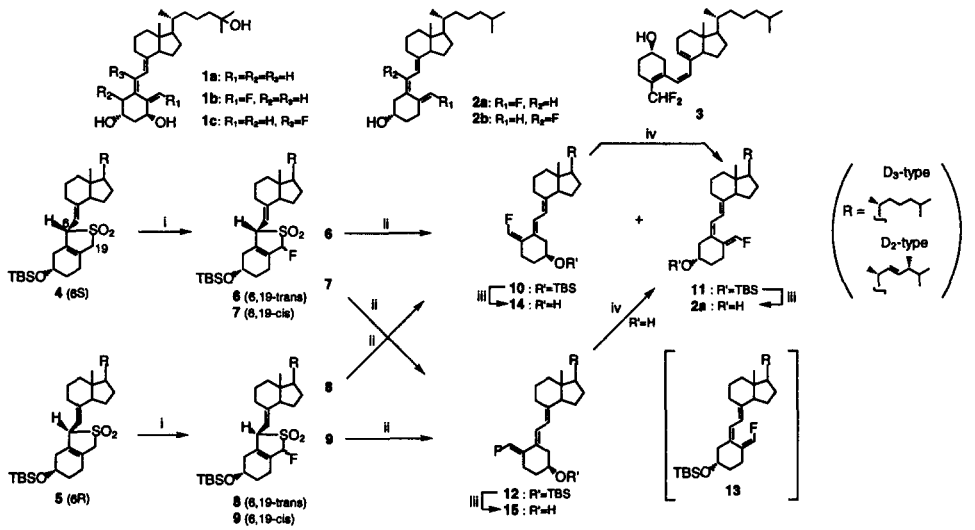
6-Fluorovitamin D_3 (**2b**)[4] is the only known vitamin D analog in which the fluorine atom is introduced into the triene moiety and has been reported to antagonize 1α,25-$(OH)_2D_3$ activity in vivo. The attempted synthesis of 19,19-difluorovitamin D_3 via a photosynthetic route was unsuccessful because thermal conversion of previtamin D (**3**) to vitamin D was inhibited by the electronic effect of the fluorine atoms on C-19.[5]

We report here a new strategy for synthesizing 19-fluorovitamin D_3 in which a fluorine atom was introduced by regioselective fluorination of the vitamin D-SO_2 adduct.

Scheme outlines the synthesis of 19-fluorovitamin D_3. Sulfur dioxide-adducts **4** and **5** were prepared from vitamin D_3 by treatment with liquid SO_2 followed by TBDMSCl. Procedures for the regiocontrolled generation of carbanions from **4** and **5** have been established by Yamada et al.[6] The regioselective 19-fluorination of **4** and **5** was achieved by using electrophilic N-fluorobenzenesulfonimide and bulky lithium hexamethyldisilazide (THF/HMPA, -78 ℃). The 6*S*-SO_2 adducts (**4**) afforded the corresponding 19-fluorinated adduct as a 3:1 mixture of 6,19-*trans*-isomer (**6**) and 6,19-*cis*-isomer (**7**) in 51% yields (based on recovered **4**). Under these conditions, no epimerization at C-6 occurred. A similar result was obtained using the 6*R*-adduct (**5**) (**8**:**9** = 3:1; 52% based on recovered **5**). In both reactions, 6,19-*trans* products predominated. This indicates that the bulky base abstracts the protons located *trans* to the substituent at C-6 and the resulting 19-carbanion reacted with the cationic fluorine before equilibration to the *cis* anion is attained. The stereochemistry of **6**, **7**, **8** and **9** was assigned by their ^1H NMR spectra.[7] The proton at C-6 of the *trans*-isomers (**6** and **8**) appeared downfield (ca. 0.2 ppm) compared with those of the *cis*-isomers (**7** and **9**) due to the 1,3-*syn*-dipsuedoaxial effect of F-19. Further evidence comes from a study of the stereochemistry of the cheletropic extrusion of SO_2 from the fluorinated adducts. Four diastereoisomers (**6**, **7**, **8** and **9**) were desulfonylated by heating (80 ℃) in the presence of $NaHCO_3$. Both 6,19-*trans*-adducts **6** and **8** gave (5*E*,10*Z*)-vitamin D (**10**) and (5*Z*,10*E*)-isomer **11** (5-8 : 1 ratio, total yield 94%), whereas both of the *cis*-

isomers **7** and **9** afforded **12** (80%) as a single product and no trace of the sterically unfavorable isomer (**13**) was detected. It is clear that the desulfonylation preceded exclusively in a suprafacial manner. These results indicate that in contrast with precedents of simple sulfolenes[8] and 19-alkylated vitamin D-SO_2 adducts,[9] no *cis-trans* isomerization (**6** $\rightleftarrows$ **7** $\rightleftarrows$ **8** $\rightleftarrows$ **9**) occurred under these conditions. Desilylation of **10** and **12** with n-Bu_4NF provided **14** and **15**, respectively. Dye-sensitized (anthracene) photoisomerization of both **14** and **15** gave (10*E*)-19-fluorovitamin D_3 (**2a**) as the sole isomer. It is interesting to note that in the photoreaction of **14**, isomerization of both the 5- and 10(19)-bonds converged to (5*Z*,10*E*)-vitamin D. In the UV spectrum, 19-fluorovitamin D_3 (**2a**) absorbs at the shorter wavelength of 260 nm (ε=20900) compared with the parent vitamin D_3 (265 nm), indicating the electronic effect of fluorine substitution. We also synthesized 19-fluorovitamin D_2 by the method described above.

In conclusion, we developed a novel, short synthetic route to 19-fluorovitamin D via the regioselective fluorination of the vitamin D-SO_2 adduct as a key step. The new strategy is currently being applied to the synthesis of the active vitamin D analog (**1b**) having the two hydroxyl groups at C-1 and C-25 which are known to be essential for the optimum binding to the VDR.



Scheme Reagents: i) $(PhSO_2)_2NF$/LiHDMS; ii) Δ/$NaHCO_3$; iii) n-Bu_4NF; iv) hv/Anthracene

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7. The structures of the new compounds were confirmed based on the ^1H and ^{19}F NMR, mass, and UV spectra. The configuration of the fluorinated vitamin D **15**, **16** and **2a** at C-19 was established from the 2D NOESY spectra.
   2a: ^1H NMR ($CDCl_3$) δ 0.53 (3 H, s, H-18), 0.86 and 0.87 (each 3 H, d, *J* =6.6 Hz, H-26, 27), 0.92 (3 H, d, *J* =6.4 Hz, H-21), 2.56 (2 H, m), 2.78 (1 H, m), 3.93 (1 H, m, H-3), 5.93 (1 H, d, *J*=11.1 Hz, H-7), 6.28 (1 H, d, *J* =11.1 Hz, H-6), 6.51 (1 H, d, *J* =87.4 Hz, H-19). ^{19}F NMR δ -132.5 (d, *J* =87.4 Hz). MS *m/z* (%) 402 (M^+, 27), 135 (100).
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