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NOVEL REGIOSELECTIVE C-6 AND C-19 ALKYLATION OF VITAMIN D_3 VIA ITS SULFUR-DIOXIDE ADDUCTS

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Summary: Vitamin D-sulfur dioxide adducts undergo regioselective methylation at C-6 with sodium hydride used as the base and at C-19 with lithium tetramethylpiperidide. The methylated adducts are converted to the corresponding vitamin D derivatives by extrusion of sulfur dioxide.

In the course of our studies on the chemistry of vitamin D, we have been interested in the reactions of the vitamin with the dienophiles, singlet oxygen[1] in connection with biological oxidation[2] and sulfur dioxide as a potential protecting group of the s-cis diene part of the molecule. In the previous paper,[3,4] we reported that vitamin D (3) reacted quantitatively with sulfur dioxide to afford the adduct (1 and 2) at the s-cis diene part and that the adduct extruded sulfur dioxide easily by thermolysis to give the corresponding 5,6-trans-vitamin D (4) as the major product and vitamin D (3) as the minor product. Since it has been known that selective one-way isomerization of the trans-vitamin D to the corresponding vitamin D is possible by photo-sensitized isomerization,[5] if a sensitizer with appropriate triplet energy was used, sulfur dioxide was proved to be an useful protecting group of the reactive triene chromophore of vitamin D. We now report the structural modification of vitamin D via its sulfur-dioxide adducts.[6]

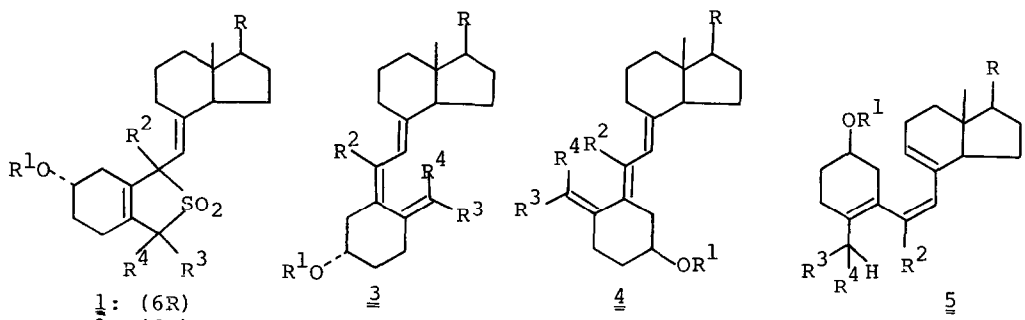
Advantage of sulfur dioxide as protecting group of the diene is that it can also act as activating group of the adjacent C-H bond, making an introduction of an electrophile to the 6- and/or the 19-position of vitamin D possible. All of the C-6 and C-19 protons of the adducts (1a and 2a) were exchanged with deuterium by equilibration with deuterium oxide in DMF in the presence of potassium t-butoxide at room temperature. Thermolysis (DMF, $NaHCO_3$, 90°, 5 hr) followed by photo-sensitized isomerization (Eosin-Y, EtOH, halogen lamp) of the deuterated adducts (1c and 2c) afforded the trideuterated vitamin D_3 (3c) in 60% overall yield. The result demonstrated not only that introduction of an electrophile into the 6- or the 19-position was possible but also that the consecutive reactions of sulfur-dioxide adducts formation, equilibration with deuterium or tritium oxide in the presence of a base, thermolysis, and photochemical isomerization provided a useful method for the synthesis of deuterium or tritium labeled vitamin D derivatives.

Methylation of the adducts (1b and 2b) occured selectively at the 6-posi-

tion when sodium hydride was used as the base. Thus, the reaction of the adducts (1b and 2b)[7] with methyl iodide in the presence of sodium hydride (DMF-benzene, 0° - 5°) gave two isomeric mono-methylated adducts, less polar 1d and more polar 2d, in 65% total yield in the 1:1 ratio. The structures of 1d and 2d were determined to be the C-6 epimers of 6-methylated adducts based on the spectral data [1d: MS m/e 482 ($M^+ - SO_2$); ^1H NMR (C_6D_6) δ 0.82 (3H, s, H-18), 1.47 (3H, s, Me-6), 3.13 (2H, bs, H-19), 4.75 (1H, bs, H-7); IR ($CHCl_3$) 1305, 1120 cm^{-1}, 2d: MS m/e 482 ($M^+ - SO_2$), ^1H NMR (C_6D_6) δ 0.73 (3H, s, H-18), 1.53 (3H, s, Me-6), 3.10 (2H, bs, H-19), 4.82 (1H, bs, H-7); IR ($CHCl_3$) 1305, 1120 cm^{-1}]. The C-6 configuration of 1d and 2d were assigned to be R and S, respectively, from the CD spectra of the corresponding free hydroxy compounds (1e and 2e, respectively) [CD (95% EtOH) 1e: 208 nm ($\Delta\varepsilon = -34.0$), 2e: 212 nm ($\Delta\varepsilon = +17.3$)] based on the assumption previously described for the determination of the stereochemistry of the sulfur-dioxide adducts of vitamin D_2[3] and parent adducts (1a and 2a).[6] Thermolysis (EtOH, $NaHCO_3$, 90°, 25 hr) of either 1e or 2e yielded 6-methylprevitamin D_3 (5e) as the major product (>95%) and 6-methyl-5,6-trans-vitamin D_3 (4e) as the minor product (<5%) in 85% total yield. The spectral properties of 5e and 4e were in good agreement with the assigned structures [5e: MS m/e 398 (M^+), 365, 285; ^1H NMR ($CDCl_3$) δ 0.68 (3H, s, H-18), 1.76 (3H, s, Me-6), 1.54 (3H, s, H-19), 3.90 (1H, m, H-3), 5.50 (2H, m, H-7 and 9); UV (95% EtOH) 248 nm, 4e: MS m/e 398 (M^+), 150, 132; ^1H NMR ($CDCl_3$) δ 0.61 (3H, s, H-18), 1.81 (3H, s, Me-6), 3.85 (1H, m, H-3), 4.74 (1H, bs, H-19), 5.03 (1H, bs, H-19), 5.44 (1H, bs, H-7); UV (95% EtOH) 240 nm].[8] The exclusive formation of the previtamin D (5e) in the thermolysis can be explained as follows: thermal desulfonylation produced sterically less constrained 6-methylvitamin D_3 (3e) predominantly as the primary product which in turn isomerized to the thermodynamically more stable previtamin D (5e) by sigmatropic rearrangement under the reaction conditions.[9] 6-Methylvitamin D_3 (3e) [MS m/e 398 (M^+), 365, 150, 132; ^1H NMR (CD_3COCD_3) δ 0.59 (3H, s, H-18), 1.79 (3H, s, Me-6), 4.64 (1H, bs, H-19), 4.85 (1H, bs, H-19), 5.59 (1H, bs, H-7); UV (hexane) 240 nm (sh)] was obtained by reductive desulfonylation (LAH, Et_2O, reflux, 5 min) of 2e in ~40% yield together with the trans-isomer (4e) (~10% yield). The vitamin (3e) was completely isomerized to the previtamin D (5e) by short refluxing in EtOH (~2 hr) to support the above mechanism.

Regioselective C-19 alkylation was performed using the stronger and bulky base such as lithium tetramethylpiperidide (LiTMP). Treatment of a mixture of the adducts (1b and 2b) and methyl iodide in THF with LiTMP (prepared in pentane at -78°) at -78°[10] yielded 19-methylated adducts (1f and 2f) [MS m/e 482 ($M^+ - SO_2$)] as an unresolvable mixture of the diastereomers at C-6 and C-19 in 70%

total yield. Without separating the isomers, the mixture was subjected to the successive reactions of deprotection of the hydroxyl group and thermal desulfonylation (EtOH, $NaHCO_3$, 90°, 24 hr) to give isomeric two products, less polar 4g and more polar 3g, in approximately 1.4:1 ratio in 60% total yield. The spectral properties of 3g and 4g were quite similar [3g: MS m/e 398 (M^+), 150, 132; ^{1}H NMR ($CDCl_3$) δ 0.54 (3H, s, H-18), 1.72 (3H, d, J = 7 Hz, Me-19), 3.95 (1H, m, H-3), 5.37 (1H, q, J = 7 Hz, H-19), 5.93 (1H, d, J = 11 Hz, H-7), 6.16 (1H, d, J = 11 Hz, H-6), UV (95% EtOH) 268 nm, 4g: MS m/e 398 (M^+), 150, 132; ^{1}H NMR ($CDCl_3$) δ 0.58 (3H, s, H-18), 1.70 (3H, d, J = 7 Hz, Me-19), 3.88 (1H, m, H-3), 5.36 (1H, q, J = 7 Hz, H-19), 5.95 (1H, d, J = 11 Hz, H-7), 6.28 (1H, d, J = 11 Hz, H-6); UV (95% EtOH) 264 nm] and either 19-methylvitamin D_3 or 19-methyl-5,6-trans-vitamin D_3 was compatible as the structures of both compounds. Respective (Z)- and (E)-configurations of the 5(6)-double bond in 3g and 4g were tetatively assigned based on the analysis of the their ^{1}H NMR spectra with the aid of the shift reagent.[11] It has been known that the signal of the C-6 proton of trans-vitamin D (4) appears lower field compared with that of vitamin D (3) by virtue of the anisotropic effect of the 10(19)-double bond. For this reason, the major isomer (4g) which showed lower C-6 proton signal was assigned as the trans-isomer and the minor one (3g) as the cis-isomer. Supporting evidences for the assignment were provided by the LIS method. The respective ratio of the shift value of the C-6 and the C-7 protons to the value of the 3α-proton by the addition of $Eu(dpm)_3$ were 0.19 and 0.12 for 3b and 0.15 and 0.20 for 4g.[12] This results demonstrated that, in the former compound (3g), the C-6 proton was situated closer to the 3β-hydroxyl group than the C-7 proton was, whereas in the latter compound (4g), the situation was reversed, indicating the former to be the cis-isomer and the latter to be the trans-isomer.[13]



1: (6R)
2: (6S)

3

4

5

R:

	a	b	c	d	e	f	g
R^1	H	THP	H	THP	H	THP	H
R^2	H	H	D	Me	Me	H	H
R^3	H	H	D	H	H	Me	Me
R^4	H	H	D	H	H	H	H

Syntheses of a variety of 6- and 19-substituted vitamin D derivatives using the present method are progressing. The mechanism and the stereochemistry of the cheletropic reaction of the 19-substituted vitamin D-sulfur dioxide adducts are currently under investigation and the results will be reported elsewhere.

References and Notes

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6) S. Yamada, T. Suzuki, and H. Takayama, Abstracts of papers, 7th Symposium on Progress in Organic Reactions and Syntheses, Gifu, Nov. 1980, p 120.
7) In the reactions described in this paper, sulfur-dioxide adducts (1 and 2) were used as a mixture of the C-6 epimers.
8) The UV spectra of 3e, 4e, and 5e were nearly identical with those of 6-methyl-vitamin D_3, 6-methyl-trans-vitamin D_3, and 6-methylprevitamin D_3, respectively, reported : M. Scheves and Y. Mazur, J. Chem. Soc. Chem. Commun., 1977, 21.
9) M. Scheves et al.[8] reported that the equilibrium between 3e and 5e lay completely in favor of 5e.
10) LiTMP must be added in one portion to avoid multialkylation.
11) E-configuration of the 10(19)-double bond was assigned based on the examples similar to this case in which cheletropic desulfonylation to give conjugated diene or triene proceeded so as to yield thermodynamically more stable isomer: W. L. Mock, J. Am. Chem. Soc., 97, 3666 (1975).
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13) Similar downfield shift value ratio were observed in vitamin D_3 (0.19 for H-6/H-3 and 0.12 for H-7/H-3) and trans-vitamin D_3 (0.14 for H-6/H-3 and 0.17 for H-7/H-3).

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