Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 5, No. 8, pp. 899-904, 1995

0960-894X/95 $9.50+0.00

0960-894X(95)00137-9

SYNTHESIS OF 6,7-DIAZA-19-NORVITAMIN D COMPOUNDS

Rafal R. Sicinski[1] and Hector F. DeLuca*

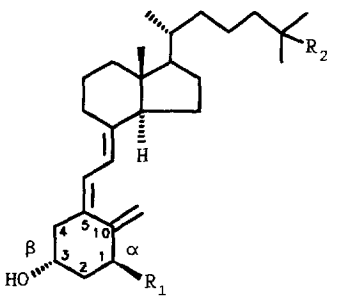
Department of Biochemistry, College of Agricultural and Life Sciences, University of Wisconsin-Madison, 420 Henry Mall, Madison, Wisconsin 53706

Abstract: Two A-ring stereoisomeric 1-hydroxy-6,7-diaza-19-norvitamin D_3 compounds **7a**, **8a** and their 25-hydroxylated analogs, **7c**, **8c** have been prepared starting with enantiomeric trans-3,5-dihydroxycyclohexanones **3c,d** and the CD-ring 8-ketones **4a** and **4c**. 1,25-Dihydroxy azavitamins **7c** and **8c** are essentially devoid of biological activity, demonstrating the importance of the 5,7-diene structure of vitamin D.

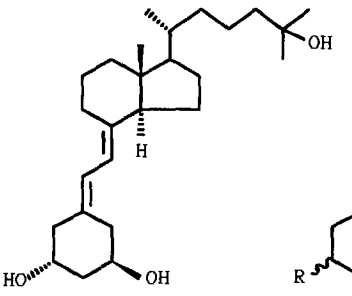
The discovery that the most potent metabolite of vitamin D_3 (**1a**), namely 1α,25-$(OH)_2D_3$ (**1c**), not only regulates the calcium homeostasis in animals[2] but also induces cell differentiation and suppresses cell proliferation,[3] has stimulated vitamin D analog syntheses targeted at establishing structure-activity relationships. Comparisons among structural variants indicated that the presence of the 1α-hydroxy group in vitamin D compounds plays a crucial role in their broad biological functions;[2-4] the synthetic analog 1α-OH-D_3 (**1b**) and natural hormone 1α,25-$(OH)_2D_3$ (**1c**) have already been used in clinical applications. It was also established that some side-chain modifications led to an interesting separation of calcium and cell differentiation activities.[5] In view of the observation that 1α,25-dihydroxy-19-norvitamin D_3 (**2**)[6] recently synthesized in our laboratory, possesses respectable albeit selective biological activity, we became interested in the possibility of modifying the 5,7-diene system. Noting the limited number of the azavitamin analogs[7] described, an intriguing possibility seemed to be synthesis of 19-norvitamin D derivatives with C_5-C_8 diene modified by replacing both carbon atoms C-6 and C-7 by nitrogens.

As a method for the construction of the C_5=N-N=C_8 moiety we applied the condensation of a hydrazone derived from the corresponding cyclohexanone **3** (A-ring fragment) with the appropriate Grundmann's type ketone **4** (contributing the upper CD unit). Before starting the synthesis of the target diazavitamins possessing hydroxylated A-ring we have decided to obtain some model compounds which could clarify the possible stereochemical problems expected in the final products.

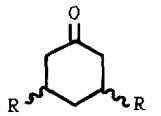
Thus, condensation of 1.3 equiv of a cyclohexanone hydrazone hydrate (obtained from **3a** and hydrazine hydrate in 61% yield)[8] with bicyclic ketone **4a**[9] (Et_2O, over 4Å mol. sieves, rt, 48 h) resulted in the formation of a single azine product **5a** in 44% yield (83% based on recovered **4a**). An analogous reaction of the epimeric 14β-ketone **4b**,[9] obtained by equilibration of **4a** (methanolic NaOH, rt, 1.5 h; 3.7:1 ratio of **4b** and **4a**), afforded a 3:1 mixture of **5b** and **6** in 40% yield[10] after HPLC separation.[11] These experiments clearly showed that



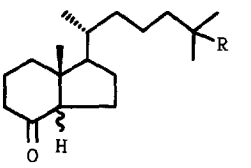
1a. R_1=H, R_2=H
1b. R_1=OH, R_2=H
1c. R_1=OH, R_2=OH



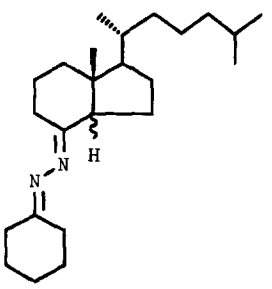
2



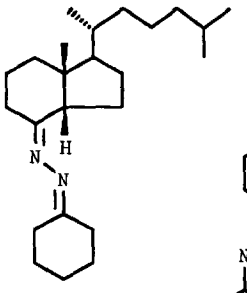
3a. R=H
3b. R=OTBDMS (3S,5S)
3c. R=OH (3S,5S)
3d. R=OH (3R,5R)
3e. R=OH (*cis*)
3f. R=-OB(Ph)O-



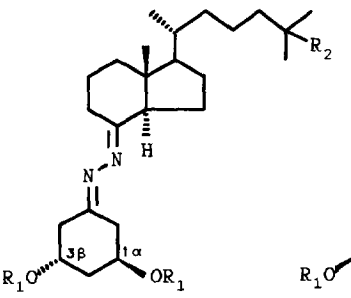
4a. 14α-H, R=H
4b. 14β-H, R=H
4c. 14α-H, R=OH



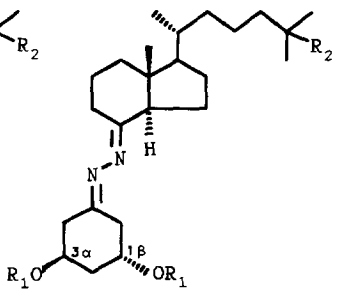
5a. 14α-H
5b. 14β-H



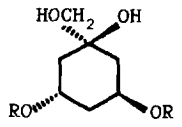
6



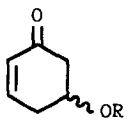
7a. R_1=H, R_2=H
7b. R_1=TBDMS, R_2=H
7c. R_1=H, R_2=OH
7d. R_1=TBDMS, R_2=OH



8a. R_1=H, R_2=H
8b. R_1=TBDMS, R_2=H
8c. R_1=H, R_2=OH
8d. R_1=TBDMS, R_2=OH



9a. R=TBDMS
9b. R=H



10a. R=H
10b. R=COCH(OMe)Ph

epimerization at C-14 did not take place during the azine formation. Structures of the azines were assigned on the basis of their ^{1}H NMR data[12] and mechanistic rationale. Considering the well-known fact that the larger of the two substituents at sp^2 carbon of an azine is better accommodated at the anti site,[13] the predominant formation of the isomers trans to the tertiary C-14 atom could be easily predicted; formation of exclusively one product with 14α-configuration and of both azines in the 14β-series can be rationalized as in the case of oximation of steroidal ketones.[14] The presence of the deshielded signal at δ 2.93, ascribed to the 9β-H, in the ^{1}H NMR spectrum of **5a** also supports the 7E-configuration[16] of the azine moiety. An analogous deshielding effect of the equatorial proton at C-10[19] has not been observed, due to rapid interconversion between both chair

forms of the cyclohexane A-ring; an averaged signal of the four hydrogens at α-carbon atoms C-4 and C-10 appeared as a broad multiplet at δ 2.37. The presence of a deshielded signal of 14β-H at δ 2.98 in the minor condensation product **6** and the striking fact of the absence of any deshielded equatorial proton signal in the ^{1}H NMR spectrum of the isomeric (7E)-azine **5b** can be explained by comparison of the steric energy differences between the corresponding cis-hydrindane azine conformers having equatorially and axially oriented 14β-protons.[20] Besides the E/Z isomerism of the C_8=N_7 double bond of azines **5a,b** and **6**, the possibility of existance of conformers about the N-N single bond should also be considered; literature data seem to indicate that alkyl substituted azines exist primarily in the s-trans and/or gauche form.[13,21]

As an A-ring fragment required for the synthesis of the 6,7-diazaanalogs of **2** the bis-silylated ketodiol **3b**[6b] has been initially used. Thus, treatment of **3b** with 2 equiv of 98% hydrazine hydrate (Et_2O/EtOH, rt, 1 h) afforded the corresponding hydrazone (UV λ_{max} 208.0 nm) which was then subjected to condensation with ketones **4a** and **4c**[22] (2 molar excess of hydrazone, EtOH, over 4Å mol. sieves, 45 °C, 40 h). HPLC purification afforded the pure azines **7b** and **7d** (23 and 15% yield, respectively) in addition to unreacted substrates. Since all attempts to remove the silyl protecting groups from the azines caused decomposition, we decided to synthesize dihydroxy vitamins **7a,c** using the unprotected (3S,5S)-3,5-dihydroxycyclohexanone **3c** as a substrate. The hydrolysis of the TBDMS ethers in **3b** was not possible due to instability of the ketol system. The desired dihydroxy ketone **3c** has been therefore prepared in 25% yield from the known **9a**[6b] by the hydrolysis of the silyl groups (HOAc/H_2O/THF 3:1:1, rt, 24 h) followed by sodium periodate cleavage ($NaIO_4$, CH_3OH/H_2O, 0 °C, 30 min) of the vicinal diol in the resulted tetrahydroxy compound **9b**. Ketone **3c**, in a manner analogous to that described for silyloxy derivative **3b**, was then converted to the hydrazone (UV λ_{max} 205.5 nm) and condensed with CD ring fragments **4a** and **4c** (1.5 molar excess of hydrazone) to give the expected azines **7a** and **7c** in 32 and 30% yield, respectively.[10] The A-ring hydroxyl groups in the compounds **7a,c** can be converted into TBDMS ethers using mild silylating conditions (MTBSTFA, DMF, 45 °C, 1 h, yield of **7b,d** ca. 40%)[23].

Noting the considerable stereochemical differences between conjugated dienes and azines as well as the known fact that the spatial arrangement of the hydroxy functions in vitamin D compounds is crucial for biological activity we have also decided to obtain a set of the isomeric azines with the opposite configurations of both A-ring hydroxyls. The synthesis of 1β,3α-dihydroxy analogs **8a,c** has been completed by using commercially available 1,3,5-cyclohexanetriol (T.C.I., cis- and trans-mixture) as a source of the A-ring synthon. Treatment of the triol with CPA (0.8 M, 2 equiv., 15 °C, 30 min)[24] resulted in oxidation of the single hydroxyl group and formation of cis- and trans-3,5-dihydroxycyclohexanones **3c,d,e** (60% yield after chromatography on silica); unreacted substrate and enone **10a** have been also isolated. Although the keto compounds with trans-oriented hydroxyls accounted only for ca. 7% of the oxidation products[25] their isolation has easily been achieved by treatment of the resulted mixture with phenylboric acid (Et_2O/acetone, rt, 20 min) which converted the cis-diol **3e** into the phenylboronate ester **3f**. Separation by flash chromatography afforded an enantiomeric pair of trans-

dihydroxycyclohexanones **3c,d**. Attempted separation of these enantiomers as their diastereomeric o-methylmandelate esters was unsuccessful; esterification of **3c,d** with the acid chloride (prepared from potassium salt of (S)-(+)-α-methoxyphenylacetic acid and oxalyl chloride) in pyridine for 18 h at rt gave a complex mixture of products; two main components were isolated by HPLC and identified as the diastereomeric pair of o-methylmandelate esters **10b**. Taking into account the instability of β-ketodiol system we decided to complete the azine synthesis using unseparated enantiomers **3c** and **3d**. Analogous to the reaction sequence described above, i.e. conversion of **3c,d** into hydrazones followed by condensation with CD ring synthon **4a** gave a 1:1 mixture of the expected azines **7a** and **8a** whereas the coupling of the enantiomeric hydrazones with 25-hydroxy Grundmann's ketone **4c** led to an equimolar mixture of **7c** and **8c** (yield ca. 30%).[10] The diastereomeric pairs of azines have easily been separated by HPLC and, for further characterization, converted to the corresponding *tert*-butyldimethylsilyl ethers **7b,d** and **8b,d**.

Preliminary biological *in vitro* tests showed that the binding affinity of 1α,25-dihydroxy-6,7-diaza-19-norvitamin D_3 (**7c**) and its isomer **8c** to porcine intestinal nuclear receptor[26] is reduced by four and five orders of magnitude, respectively, as compared with 1α,25-$(OH)_2D_3$ (**1c**) or 1α,25-$(OH)_2$-19-norvitamin D_3 (**2**). Azavitamins **7c** and **8c** are also ca. 1000-fold less active than **1c** in the ability to differentiate of HL-60 cells into monocytes[3] and possess no calcium mobilizing activity or intestinal transport activity *in vivo*.

References and Notes

1. Present address: Department of Chemistry, University of Warsaw, 02-093 Warszawa, Poland.
2. For general reviews, see: (a) Norman, A. W. *Vitamin D, the Calcium Homeostatic Steroid Hormone*; Academic Press: New York, 1979; (b) DeLuca, H. F.; Schnoes, H. K. *Annu. Rep. Med. Chem.* **1984**, *19*, 179; (c) Jones, G. *Steroids* **1987**, *49*, 1; (d) Ikekawa, N. *Med. Res. Rev.* **1987**, *7*, 333; (e) Dickson, I. *Nature*, **1987**, *325*, 18; (f) DeLuca, H. F. *FASEB J.* **1988**, *2*, 224; (g) Reichel, H.; Koeffler, H. P.; Norman, A. W. *N. Engl. J. Med.* **1989**, *320*, 980.
3. (a) Miyaura, C.; Abe, E.; Kuribayashi, T.; Tanaka, H.; Konno, K.; Nishii, Y.; Suda, T. *Biochem. Biophys. Res. Commun.* **1981**, *102*, 937; (b) Tsoukas, C. D.; Provvedini, D. M.; Manolagas, S. C. *Science (Washington, D.C.)* **1984**, *224*, 1438; (c) MacLaughlin, J. A.; Gange, W.; Taylor, D.; Smith, E.; Holick, M. F. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 5409; (d) Morimoto, S.; Onishi, T.; Imanaka, S.; Yukawa, H.; Kozuka, T.; Kitano, Y.; Yoshikawa, K.; Kumahara, Y. *Calcif. Tissue Int.* **1986**, *38*, 119; (e) Ostrem, V. K.; Lau, W. F.; Lee, S. H.; Perlman, K.; Prahl, J.; Schnoes, H. K.; DeLuca, H. F.; Ikekawa, N. *J. Biol. Chem.* **1987**, *262*, 14164; (f) Suda, T. *Proc. Soc. Exp. Biol. Med.* **1989**, *191*, 215.
4. (a) Paaren, H. E.; Mellon, W. S.; Schnoes, H. K.; DeLuca, H. F. *Bioorg. Chem.* **1985**, *13*, 62; (b) Shiuey, S. -J.; Partridge, J. J.; Uskoković, M. R. *J. Org. Chem.* **1988**, *53*, 1040; (c) Zhou, J. -Y.; Norman, A. W.; Lubbert, M.; Collins, E. D.; Uskoković, M. R.; Koeffler, H. P. *Blood* **1989**, *74*, 82; (d) Okano, T.; Tsugawa, N.; Masuda, S.; Takeuchi, A.; Kobayashi, T.; Nishii, Y. *Biochem. Biophys. Res. Commun.* **1989**, *163*, 1444; (e) Zhou, J. -Y.; Norman, A. W.; Akashi, M.; Chen, D-L.; Uskoković, M. R.; Aurrecoechea, J. M.; Dauben, W. G.; Okamura, W. H.; Koeffler, H. P. *Blood* **1991**, *78*, 75; (f) Posner, G. H.; Nelson, T. D.; Guyton, K. Z.; Kensler, T. W. *J. Med. Chem.* **1992**, *35*, 3280; and references cited therein.
5. (a) Morisaki, M.; Koizumi, N.; Ikekawa, N. *J. Chem. Soc. Perkin Trans. I* **1975**, 1421; (b) Murayama, E.; Miyamoto, K.; Kubodera, N.; Mori, T.; Matsunaga, I. *Chem. Pharm. Bull.* **1986**, *34*, 4410; (c) Calverley, M. J. *Tetrahedron* **1987**, *43*, 4609; (d) Ostrem, V. K.; Tanaka, Y.; Prahl, J.; DeLuca, H. F. *Proc. Natl.*

Acad. Sci. U.S.A. **1987**, *84*, 2610; (e) Figadere, B.; Norman, A. W.; Henry, H. L.; Koeffler, H. P.; Zhou, J. -Y.; Okamura, W. H. *J. Med. Chem.* **1991**, *34*, 2452; (f) Uskoković, M. R.; Baggiolini, E.; Shiuey, S. -J.; Iacobelli, J.; Hennessy, B.; Kiegiel, J.; Daniewski, A. R.; Pizzolato, G.; Courtney, L. F.; Horst, R. L. *Vitamin D: Gene Regulation, Structure-Function Analysis and Clinical Application*; Norman, A. W.; Bouillon, R.; Thomasset, M., Eds.; Walter de Gruyter: Berlin, 1991, pp. 139-145; (g) Bretting, C.; Calverley, M. J.; Binderup, L. *Vitamin D: Gene Regulation, Structure-Function Analysis and Clinical Application*; Norman, A. W.; Bouillon, R.; Thomasset, M., Eds.; Walter de Gruyter: Berlin, 1991, pp. 159-160; (h) Calverley, M. J.; Binderup, E.; Binderup, L. *Vitamin D: Gene Regulation, Structure-Function Analysis and Clinical Application*; Norman, A. W.; Bouillon, R.; Thomasset, M., Eds.; Walter de Gruyter: Berlin, 1991, pp. 163-164; (i) Colston, K. W.; Mackay, A. G.; Chander, S.; Binderup, L.; Coombes, R. C. *Vitamin D: Gene Regulation, Structure-Function Analysis and Clinical Application*; Norman, A. W.; Bouillon, R.; Thomasset, M., Eds.; Walter de Gruyter: Berlin, 1991, pp. 465-466; (j) Kubodera, N.; Watanabe, H.; Kawanishi, T.; Matsumoto, M. *Chem. Pharm. Bull.* **1992**, *40*, 1494.

6. (a) Perlman, K. L.; Sicinski, R. R.; Schnoes, H. K.; DeLuca, H. F. *Tetrahedron Lett.* **1990**, *31*, 1823; (b) Perlman, K. L.; Swenson, R. E.; Paaren, H. E.; Schnoes, H. K.; DeLuca, H. F. *Tetrahedron Lett.* **1991**, *32*, 7663.
7. For examples of nitrogen-containing side chain analogs, see: (a) DeLuca, H. F.; Paaren, H. E.; Schnoes, H. K. *Topics in Current Chemistry*; Springer-Verlag: Berlin, 1979, pp. 1-65; (b) Matoba, K.; Kondo, K.; Yamazaki, T. *Chem. Pharm. Bull.* **1982**, *30*, 4593; (c) Kubodera, N.; Miyamoto, K., Akiyama, M.; Matsumoto, M.; Mori, T. *Chem. Pharm. Bull.* **1991**, *39*, 3221.
8. Kost, A. N.; Grandberg, I. I. *Zhur. Obschei Khim.* **1956**, *26*, 1717.
9. Inhoffen, H. H.; Quinkert, G.; Shütz, S.; Kampe, D.; Domagk, G. F. *Chem. Ber.* **1957**, *90*, 664.
10. Unchanged Grundmann's ketones **4** were also isolated (40-50%).
11. HPLC conditions: Zorbax-Sil (DuPont) 6.4 mm x 25 cm column, hexane/2-propanol solvent systems, monitoring at 240 nm.
12. Spectral data for selected compounds: ^{1}H NMR (500 MHz, $CDCl_3$), UV (EtOH), MS (EI, 70 eV, rel. int.).
5a: ^{1}H NMR δ 0.657 (3H, s, 18-H_3), 0.868 and 0.872 (3H and 3H, each d, J = 6.6 Hz, 26- and 27-H_3), 0.938 (3H, d, J = 6.0 Hz, 21-H_3), 2.19 (1H, dd, J = 11.8, 7.1 Hz, 14α-H), 2.37 (at least 4H, m), 2.93 (1H, m, 9β-H); UV λ_{max} 211.0 nm (ε 19600), 233.5 (4300); MS m/z 358 (M^+, 100), 343 (15), 315 (31), 245 (9), 98 (20).
5b: ^{1}H NMR δ 0.860 and 0.864 (3H and 3H, each d, J = 6.7 Hz, 26- and 27-H_3), 0.887 (3H, d, J = 6.2 Hz, 21-H_3), 1.010 (3H, s, 18-H_3), ca. 2.3 (at least 6H, m); UV λ_{max} 211.0 nm (ε 19000), 235.0 (4500); MS m/z 358 (M^+, 33), 343 (38), 315 (30), 290 (37), 273 (25), 245 (16), 98 (100).
6: ^{1}H NMR δ 0.864 (6H, br d, J = 6 Hz, 26- and 27-H_3), ca. 0.88 (3H, 21-H_3), 0.966 (3H, s, 18-H_3), ca. 2.3 (at least 6H, m), 2.98 (1H, ~dd, J ≈ 10 and 7 Hz, 14β-H); UV λ_{max} 211.5 nm (ε 15300), 236.5 (3000); MS m/z 358 (M^+, 47), 343 (42), 315 (35), 290 (42), 273 (24), 245 (14), 98 (100).
7a: ^{1}H NMR δ 0.663 (3H, s, 18-H_3), 0.869 and 0.874 (3H and 3H, each d, J = 6.6 Hz, 26- and 27-H_3), 0.938 (3H, d, J = 6.1 Hz, 21-H_3), 2.20 (1H, dd, J = 11.8, 7.1 Hz, 14α-H), 2.39 (1H, dd, J = 13.8, 6.8 Hz, 4β-H), 2.47 (1H, dd, J = 13.8, 7.4 Hz, 10α-H), 2.67 (1H, dd, J =13.8, 3.7 Hz, 4α-H), 2.77 (1H, dd, J = 13.8, 4.0 Hz, 10β-H), 2.96 (1H, m, 9β-H), 4.23 (1H, m, 1β-H), 4.33 (1H, m, 3α-H); UV λ_{max} 209.0 nm, 232.5 (sh), A209/A232 = 5.2; MS m/z 390 (M^+, 100), 373 (56), 354 (13), 331 (50), 304 (30), 277 (16), 112 (99); exact mass calcd for $C_{24}H_{42}N_2O_2$ 390.3246, found 390.3244.
7c: ^{1}H NMR δ 0.665 (3H, s, 18-H_3), 0.956 (3H, d, J = 5.9 Hz, 21-H_3), 1.220 (6H, s, 26- and 27-H_3), 2.20 (1H, dd, J = 11.8, 7.2 Hz, 14α-H), 2.39 (1H, dd, J = 13.8, 6.7 Hz, 4β-H), 2.46 (1H, dd, J = 13.5, 7.4 Hz, 10α-H), 2.67 (1H, dd, J = 13.8, 3.7 Hz, 4α-H), 2.77 (1H, dd, J = 13.5, 4.0 Hz, 10β-H), 2.96 (1H, m, 9β-H), 4.23 (1H, m, 1β-H), 4.33 (1H, m, 3α-H); UV λ_{max} 210.5 nm (ε 18800), 235.0 (sh, ε 4300); MS m/z 406 (M^+, 17), 388 (31), 370 (58), 320 (50), 112 (100); exact mass calcd for

$C_{24}H_{42}N_2O_3$ 406.3195, found 406.3202.

8a: ^1H NMR δ 0.663 (3H, s, 18-H_3), 0.873 (6H, br d, J = 6.9 Hz, 26- and 27-H_3), 0.939 (3H, d, J = 5.6 Hz, 21-H_3), 2.20 (1H, dd, J = 11.7, 7.2 Hz, 14α-H), 2.39 (1H, dd, J = 13.6, 6.9 Hz, 4α-H), 2.50 (1H, dd, J = 13.8, 7.4 Hz, 10β-H), 2.68 (1H, dd, J = 13.6, 4.1 Hz, 4β-H), 2.74 (1H, dd, J = 13.8, 4.2 Hz, 10α-H), 2.95 (1H, m, 9β-H), 4.22 (1H, m, 1α-H), 4.33 (1H, m, 3β-H); UV λ_{max} 208.0 nm, 233.0 (sh), A208/A233 = 6.0; MS m/z 390 (M^+, 100), 373 (73), 354 (34), 331 (55), 304 (46), 277 (19), 112 (99); exact mass calcd for $C_{24}H_{42}N_2O_2$ 390.3246, found 390.3256.

8c: ^1H NMR δ 0.663 (3H, s, 18-H_3), 0.957 (3H, d, J = 5.9 Hz, 21-H_3), 1.220 (6H, s, 26- and 27-H_3), 2.20 (1H, dd, J = 11.7, 7.3 Hz, 14α-H), 2.39 (1H, dd, J = 13.7, 7.1 Hz, 4α-H), 2.50 (1H, dd, J = 14.0, 7.2 Hz, 10β-H), 2.68 (1H, dd J = 13.7, 3.8 Hz, 4β-H), 2.74 (1H, dd, J = 14.0, 3.8 Hz, 10α-H), 2.95 (1H, m, 9β-H), 4.22 (1H, m, 1α-H), 4.33 (1H, m, 3β-H); UV λ_{max} 210.5 nm (ε 19800), 235.0 (sh, ε 4400); MS m/z 406 (M^+, 31), 388 (25), 370 (70), 320 (41), 112 (100); exact mass calcd for $C_{24}H_{42}N_2O_3$ 406.3195, found 406.3198.

13. Elguero, J.; Jacquier, R.; Marzin, C. *Bull. Soc. Chim. Fr.* **1968**, 713.
14. Literature data[15] indicate that during the reaction of six-membered cyclic ketones with hydroxylamine one can expect the formation of a product having the oxime hydroxy group anti to the α-carbon bearing the bulkier equatorial substituent. In the case of the 8-ketocompound **4a** with the rigid trans-hydrindane system the equatorial substituent at C-9 (hydrogen) is much smaller than the 15-methylene group being formally the equatorial substituent at C-14.
15. Snatzke, G.; Frelek, J.; Szczepek, W. J. *Tetrahedron: Asymmetry* **1990**, *1*, 649; and references cited therein.
16. Analogous strong deshielding of equatorial hydrogens at α-syn carbons has been observed in the case of 6-membered ketoximes.[15] Molecular models of **5a** indicate that the equatorial 9β-hydrogen lies in the plane of the C_8=N_7 bond. Considerable deshielding of protons similarly situated with respect to the C=N bond in compounds of the general formula R_1R_2C=NZ (oximes,[17] hydrazones[18] and azines[13]) has been reported.
17. Karabatsos, G. J.; Taller, R. A. *Tetrahedron* **1968**, *24*, 3347.
18. Karabatsos, G. J.; Osborne, C. E. *Tetrahedron* **1968**, *24*, 3361.
19. The carbon numbers of the steroidal azines are expressed according to the vitamin D_3 numbering in this paper; the same concerns the α/β abbreviation system.
20. Molecular mechanics (MM+) calculations reveal that both ring conformers of 7E-azine **5b** resulting from C/D ring inversion have similar steric energies whereas for 7Z-isomer **6** its conformer with an axial 14β-hydrogen is destabilized by steric repulsion between 15α-H and N_6. Analysis of these results leads to the conclusion that the signal of equatorial 14β-H is shifted to a lower field in the predominating conformer of **6** whereas in the two equally populated conformers of **5b** an averaged resonance of equatorial and axial protons at C-9 is observed near δ 2.3 ppm.
21. Kitaev, Yu. P.; Nivorozhkin, L. E.; Plegontov, S. A.; Raevskii, O. A.; Titova, S. Z. *Dokl. Akad. Nauk SSSR, Ser. Khim.* **1968**, *178*, 1328.
22. The hydroxy ketone **4c** was prepared in 43% yield by RuO_4 oxidation of **4a**; for experimental procedure, see: (a) Kiegiel, J.; Wovkulich, P. M.; Uskoković, M. R. *Tetrahedron Lett.* **1991**, *32*, 6057; (b) Sicinski, R. R.; DeLuca, H. F. *BioMed. Chem. Lett.* **1995**, *5*, 159.
23. Mawhinney, T. P.; Madson, M. A. *J. Org. Chem.* **1982**, *47*, 3336.
24. (a) Stensiö, K. -E.; Wachtmeister, C. A. *Acta Chem. Scand.* **1964**, *18*, 1013; (b) Stensiö, K. -E. *Acta Chem. Scand.* **1971**, *25*, 1125.
25. The abundance of trans-1,3,5-cyclohexanetriol in the commercial material amounted only to 10-11% of the isomer mixture.
26. Perlman, K.; Kutner, A.; Prahl, J.; Smith, C.; Inaba, M.; Schnoes, H. K.; DeLuca, H. F. *Biochemistry* **1990**, *29*, 190.

(*Received in USA* 30 *December* 1994; *accepted* 14 *March* 1995)