Studies on Vitamin D (Calciferol) and Its Analogues. 21. Solvolytic Ring Expansions of Vitamin D_3. Formation of 1,4-Dihydroxy-*A*-homo-19-nor-9,10-secocholesta-5,7-diene[1]

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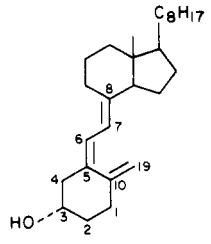
Buffered acetolysis (70 °C, 2 h) of the *trans*-benzoyloxy tosylate **3f** afforded a 2:1 mixture of *A*-homoacetoxy benzoates **7a** and **7b**, which upon saponification afforded the *A*-homo-19-nor analogue of 1α-hydroxyvitamin D_3, **7c**. Similar acetolysis of the *cis*-benzoyloxy tosylate **4f** afforded a 2.8:1 mixture of **8a** and **9b**, which upon chromatographic separation and then saponification afforded the *cis*-diols **8c** and **9c**, respectively. The benzoyloxy tosylates **3f** and **4f** were prepared in three steps from vitamin D_3. Based on spectral data and mechanistic consideration, the structural and stereochemical assignments for **7–9** are discussed. The three diols **7c–9c** failed to exhibit any biological activity in terms of intestinal calcium absorption (ICA) and bone calcium mobilization (BCM) in the chick. Interestingly, the analogue **8c** selectively inhibited the BCM activity of natural vitamin D_3 and, in addition, it enhanced the normal ICA effect of the active hormone, 1α,25-dihydroxyvitamin D_3 (**12b**).

Introduction

Studies in various laboratories directed toward probing the stereostructural requirements necessary for optimal, minimal, or other novel vitamin D like biological activity have led to the preparation of A-ring analogues of vitamin D_3 (**1**)[2] involving direct modification of its triene moiety.



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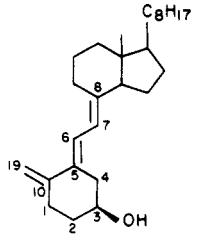

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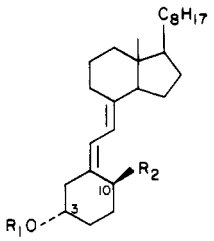

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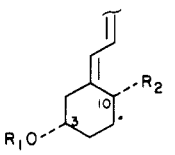

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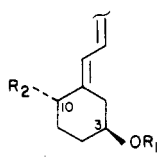

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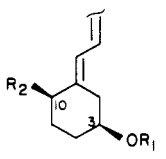

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	R_1	R_2
a	H	CH_3
b	H	CH_2OH
c	H	CH_2Cl
d	H	CH_2I
e	C_6H_5CO	CH_2OH
f	C_6H_5CO	$CH_2OSO_2C_6H_4$-p-CH_3

Whereas direct reduction of the $\Delta^{10(19)}$ double bond[3] of **1** leads to the biologically inactive **3a** and **4a** (in vivo in the chick: ICA, intestinal calcium absorption; BCM, bone calcium mobilization),[4,5] successive Δ^5 isomerization and $\Delta^{10(19)}$ reduction via intermediate **2** give **5a** and **6a**, which exhibit both ICA and BCM activity.[4] Replacement of one of the C-19 methyl hydrogens of **5a** and **6a** by a hydroxyl group, as in **5b** and **6b**, completely suppresses biological activity.[4a] Interestingly, although neither **3b** nor **4b** exhibit ICA or BCM activity, when administered simultaneously with vitamin D_3, **3b**, but not **4b–6b**, is able to suppress the normal activity of D_3 (**1**) (i.e., an antagonist effect is observed).[4a] The halides **3c** and **3d**, synthesized via hydrozirconation–halogenation of **1**,[6] when administered simultaneously with **1** in vivo cause **1** to elicit greater than its normal ICA and BCM activity (i.e., a synergistic effect is observed).[7] In view of the observations of novel antagonistic[8] and synergistic[7] properties of these 19-substituted-10,19-dihydrovitamins, we were encouraged to pursue studies directed toward additional structural and stereochemical modifications in this series. Noting that 19-substituents in these steroids are homoallylic, we envisaged the possibility that these derivatives, in spite of the presence of the sensitive diene function, might be encouraged to undergo solvolytic ring expansion to the first

(1) (a) For paper 20, see: Mouriño, A.; Lewicka-Piekut, S.; Norman, A. W.; Okamura, W. H. *J. Org. Chem.* **1980**, *45*, 4015.

(2) For general reviews on the subject of vitamin D, see: (a) Norman, A. W. "Vitamin D, the Calcium Homeostatic Steroid Hormone"; Academic Press: New York, 1979; (b) De Luca, H. F.; Paaren, H. E.; Schnoes, H. K. *Top. Curr. Chem.* **1979**, *83*, 1–65; (c) Georghiou, P. E. *Chem. Soc. Rev.* **1977**, *6*, 83; (d) Fieser, L. F.; Fieser, M. "Steroids"; Reinhold: New York, 1959; Chapter 4.

(3) (a) Okamura, W. H.; Hammond, M. L.; Rego, A.; Norman, A. W.; Wing, R. M. *J. Org. Chem.* **1977**, *42*, 2284. (b) Mouriño, A.; Okamura, W. H. *Ibid.* **1978**, *43*, 1653. (c) Messing, A. W.; Ross, F. P.; Norman, A. W.; Okamura, W. H. *Tetrahedron Lett.* **1978**, 3635. See also the references cited.

(4) (a) Hammond, M. L.; Mouriño, A.; Blair, P.; Wecksler, W.; Johnson, R. L.; Norman, A. W.; Okamura, W. H. "Vitamin D: Biochemical, Chemical and Clinical Aspects Related to Calcium Metabolism"; (Norman, A. W., Schaefer, K., Coburn, J. W., DeLuca, H. F., Fraser, D., Grigoleit, H. G., Herrath, D. V., Eds; W. de Gruyter Publ.: Berlin, 1977; pp 1–4. (b) Norman, A. W.; Johnson, R. L.; Osborn, T. W.; Procsal, D. A.; Carey, S. C.; Hammond, M. L.; Mitra, M. N.; Pirio, M. R.; Rego, A.; Wing, R. M.; Okamura, W. H. *Clin. Endocrinol.* **1976**, *5*, 121s.

(5) For the method of assay, see: Hibberd, K.; Norman, A. W. *Biochem. Pharmacol.* **1969**, *18*, 2347.

(6) Messing, A. W.; Ross, F. P.; Miura, M.; Norman, A. W.; Okamura, W. H. "Vitamin D, Basic Research and Its Clinical Application"; Norman, A. W.,, Schaefer, K., Herrath, D. v., Grigoleit, H.-G., DeLuca, H. F., Mawer, E. B., Suda, T, Eds.; W. de Gruyter Publ.; Berlin, 1979; pp 51–54.

(7) Okamura, W. H.; Miura, M.; Norman, A. W., unpublished observations.

(8) For a detailed discussion of the first antivitamin D factor, the method of biological assay, and leading references, see: Norman, A. W.; Johnson, R. L.; Okamura, W. H. *J. Biol. Chem.* **1979**, *254*, 11 450.

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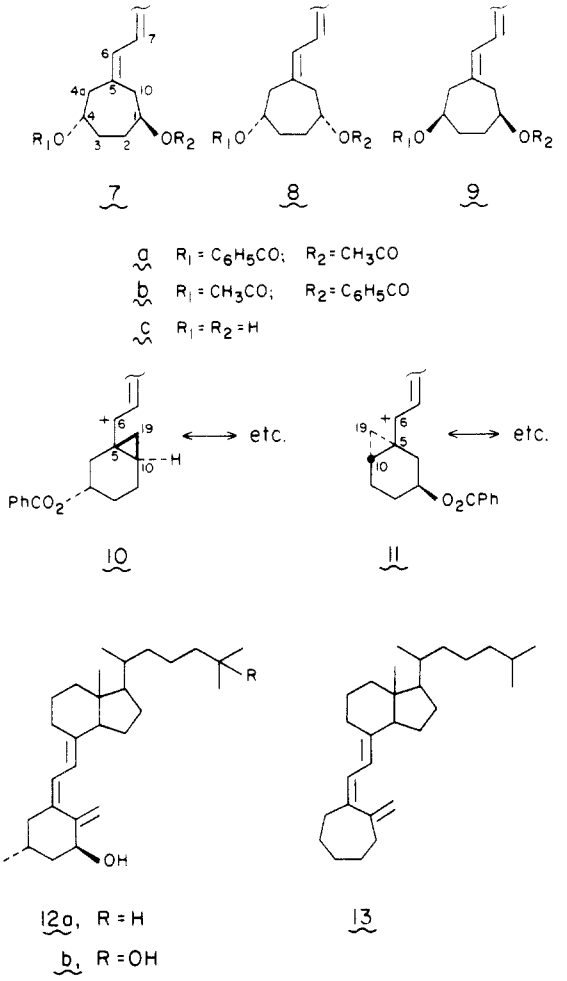
functionalized *A*-homovitamin D analogues.[9] This paper describes our success in this venture.

Results and Discussion

The benzoate of vitamin D_3 (1) was hydroborated (9-BBN) and then oxidized (H_2O_2, aqueous NaOH) to afford a mixture of 19-hydroxy diastereomers **3e** and **4e**, which were separated by chromatography.[3a,b] The alcohols were converted in a standard way to the corresponding tosylates **3f** and **4f**. Acetolysis[10] of **3f** (K_2CO_3, Ac_2O, HOAc; 70 °C, 2 h, N_2) afforded after workup a 2:1 mixture of **7a** and **7b**,



which could be separated and then saponified (or more conveniently saponified without separation) to a single crystalline diol **7c** (mp 80–81 °C). Similar acetolysis[10] of **4f** afforded a 2.8:1 mixture of **8a** and **9b**. After chromatographic separation, **8a** and **9b** afforded the crystalline diols **8c** (mp 112–114 °C) and **9c** (mp 63–65 °C), respectively. The four acetoxy benzoates **7a**, **7b**, **8a**, and **9b** (oils) proved stable when subjected to the acetolysis conditions.

The formation of **7a** (major) and **7b** (minor) from *trans*-benzoyloxy tosylate **3f** is readily rationalized by analogy with related solvolysis reactions of other homoallylic sulfonates.[10] The delocalized cation **10** is presumably involved, which is trapped by stereospecific endo-face nucleophilic attack by acetate at C_{10} to afford **7a**. Stereomutation of **10** by 180° rotation about the 5,6 single bond leads to a new cation **11**, which, by analogous endo-face acetate attack at C_{10}, presumably accounts for the minor product **7b**. A similar process can be envisaged for the production of **8a** (major) and **9b** (minor) from **4f**. Thus, the stereostructures **7–9** are assigned in part on the basis of their method of synthesis including the attendant stereomechanistic arguments. Moreover, their spectral characteristics (Supplemetary Material) are in complete accord with the structural assignments.

The question of the C_1 and C_4 configurations deserved further attention, however, even though the stereochemical course of homoallylic isomerizations appears reasonably predictable.[10] The diols **7c–9c** were subjected to a ^1H NMR lanthanide induced shift (LIS) study[11] using tris-(2,2,6,6-tetramethyl-3,5-heptanedianoto)europium [Eu-(thd)$_3$]. Titration of a $CDCl_3$ solution of each of the diols with Eu(thd)$_3$ revealed the following downfield shifts (Hz) of the C_{18}-methyl resonance when the titration curves were extrapolated to the molar equivalency point (1:1 diol to LIS reagent): **9c**, 19.8 Hz; **7c**, 11.0 Hz; **8c**, 8.6 Hz. Since the diene is *s-trans* and planar, the seven-membered ring and the C/D fragment can be construed to be approximately coplanar. The *cis*-diol **9c**, with both of its hydroxyls oriented on the same face of this approximate plane as the C_{18}-methyl, should exhibit the largest shift; the *cis*-diol **8c**, with both hydroxyyls oriented on the face opposite that of the C_{18}-methyl, should exhibit the smallest shift; the *trans*-diol **7c**, with one of the two hydroxyls oriented on the same face as this methyl, should produce an intermediate shift value. This is the predicted order and, in fact, this corresponds exactly to the stereochemistries assigned to the three diols on the basis of mechanistic considerations alone. In the 3200–3600-cm^{-1} region of the infrared, the diols **8c** and **9c** are similar in that they are characterized by a weak, broad band centered near 3400 cm^{-1} (polymeric intermolecular hydrogen bonded hydroxyl).[12] By contrast, the intensity of this same absorption is strong for the diol **7c**. These observations are in accordance with the notion that competing intramolecular hydrogen bonding for the assigned cis isomers **8c** and **9c** attenuates the normally intense 3400-cm^{-1} band and therefore that the hydroxyls in **7c** must be trans. The ^1H NMR–LIS and infrared data are summarized in the Supplementary Material.

Finally, we briefly comment on the in vivo biological evaluation[5] of the diols **7c–9c**. It is known that 1α-hydroxyvitamin D_3 (**12a**) is a highly potent synthetic analogue and metabolic precursor of the natural steroid hormone 1α,25-dihydroxyvitamin D_3 (**12b**).[2a,b] Because of superficial resemblance of the *trans*-diol **7c** to **12a**, particularly in regard to the topology of the diol fragment, foresight suggested that this *A*-homo analogue might mimic or inhibit the biological properties of **12**. Because **9c** possesses the proper orientation (pseudo-1α)[13] of the C_1-OH, it too was considered a possible candidate for eliciting a biological effect. However, both **7c** and **9c** failed to exhibit any in vivo ICA or BCM activity in the chick even at high dose levels.[14] These analogues also failed to

(9) The only previously reported *A*-homovitamin D steroid is **13**. See: Sine, S. M.; Conklin, T. E.; Okamura, W. H. *J. Org. Chem.* **1974**, *39*, 3797.
(10) Tadanier, J. *J. Org. Chem.* **1966**, *31*, 3204.
(11) For earlier applications of LIS reagents in the vitamin D field, see: (a) Wing, R. M.; Okamura, W. H.; Rego, A.; Pirio, M. R.; Norman, A. W. *J. Am. Chem. Soc.* **1975**, *97*, 4980; (b) LaMar, G. N.; Budd, D. L. *Ibid.* **1974**, *96*, 7317; (c) ref 3a.
(12) Nakanishi, K.; Solomon, P. H. "Infrared Absorption Spectroscopy", 2nd ed.; Holden-Day, Inc.: San Francisco, 1977; p 25.
(13) The unusual importance for biological activity of a hydroxyl topologically equivalent to the 1α-OH in **12** has been discussed. For leading references, see: Okamura, W. H.; Norman, A. W.; Wing, R. M. *Proc. Nat. Acad. Sci. U.S.A.* **1974**, *71*, 4194.
(14) By use of the assay method described in ref 5, no ICA or BCM activity could be detected at dose levels up to at least 310 nmol ($\sim^1/_8$ mg) of analogue per bird and for time periods ranging from 13 to 45 h before bioassay.

inhibit (antagonist activity) or enhance (synergistic activity) the normal activity of the natural metabolites **1**, 25-hydroxyvitamin D_3, and **12b**. Quite remarkably, while diol **8c** also failed to elicit ICA or BCM,[14] it inhibited the BCM effect of D_3 and, in addition, enhanced the normal ICA effect of the natural hormone **12b**. The details of the biological assays will be presented elsehere. Attempts are currently underway to prepare analogues possessing an intact exocyclic methylene group as in **13**. The hydrocarbon **13**, the only previously reported[9] *A*-homovitamin D analogue, prepared during the course of model studies lacked the critical hydroxyl group at C_1.

Experimental Section

General Procedures. Ultraviolet (UV) and infrared (IR) spectra, nuclear magnetic resonance spectra, mass spectra, and other analytical data are summarized in the Supplementary Materials; melting points (mp, uncorrected) were obtained with a Thomas-Hoover capillary apparatus. Lbpe refers to 30–60 °C low-boiling petroleum ether. The air-sensitive dienes were normally stored in the cold under nitrogen. The acetolysis buffer solution[10] was prepared by refluxing a mixture of potassium carbonate (3.45 g, 25 mmol), acetic anhydride (5 mL), and glacial acetic acid (250 mL) for 16 h. The mixture was stored at room temperature. Semi-preparative high-pressure liquid chromatography (high-pressure LC) was carried out on a Waters 6000A solvent delivery system equipped with a U6K injector and a dual detector system (UV at 2537 Å and a refractive index detector). A Whatman M9 10/50 partisil (10 μ, 9.4 mm (i.d.) × 50 cm) column was used. Preparative high-pressure LC was carried out on a Waters Prep-500 system equipped with an RI detector (standard Prep-pak silica cartridges). Reagent-grade isopropyl alcohol, ethyl acetate, and Skellysolve B (distilled from CaH_2) were used as solvents. Solvents and solvent combinations for the Waters 6000 A system were normally vacuum filtered through a 0.45-μm Millipore filter immediately before use. Medium-pressure liquid chromatography (medium-pressure LC) was carried out on an apparatus designed by Meyers and co-workers[15] and flash chromatography was performed according to Still's procedure.[16] The absorbant in both cases was silica gel 60 (40–600 μm) from E. Merck. For thin-layer chromatography (TLC), silica gel G (EM Reagents, type 60) was used to prepare analytical plates (0.25 mm).

(3*S*,10*S*)- (3e) and (3*S*,10*R*,5*Z*,7*E*)-3-(Benzoyloxy)-19-hydroxy-9,10-secocholesta-5,7-diene (4e). Vitamin D_3 benzoate[17] was subjected to hydroboration–oxidation with 9-borabicyclo[3.3.1]nonane–H_2O_2/NaOH; the procedure and results (yields, **3e**/**4e** product ratio) were essentially the same as those described previously for vitamin D_2 benzoate.[3b] Ms. Michi Miura, Mr. E. David Murray, and Mr. Edward Digiamarino are acknowledged for providing large-scale mixtures of **3e** and **4e**. The (3*S*,10*S*)- and (3*S*,10*R*)-3-(benzoyloxy)-19-alcohols, **3e** and **4e**, respectively, were separated by Waters 500 preparative high-pressure LC (16:1 Skellysolve B/isopropyl alcohol). The more polar (10*S*) alcohol fraction was chromatographed again by preparative high-pressure LC (16:1 Skellysolve B/isopropyl alcohol) followed by medium-pressure LC (3:2, diethyl ether/lbpe). The less polar (10*R*) alcohol fraction was similarly purified. The homogeneous ester alcohols exhibited the following data. (10*S*)-**3e**: R_f 0.51 (TLC, 3:2 ether/lbpe); white amorphous foam; mp 52–54 °C. (10*R*)-**4e**: R_f 0.54 (TLC, 3:2 ether/lbpe); white amorphous foam; mp 53–55 °C.

(3*S*,10*S*,5*Z*,7*E*)-3-(Benzoyloxy)-19-(tosyloxy)-9,10-secocholesta-5,7-diene, 3f. The diene **3e** (870.3 mg, 1.72 mmol), *p*-toluenesulfonyl chloride (1.309 g, 6.87 mmol, recrystallized), and pyridine (7.5 mL, freshly distilled) were stirred at room temperature for 7 h under a nitrogen atmosphere. Ice water (80 mL) was added to the ice-cooled mixture, the resulting precipitate was rinsed thoroughly with water, and then the precipitate was taken up in ether (100 mL). After the solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure, the tosylate **3f** (1.03 g, 91%) was obtained as a white amorphous foam pure by TLC [R_f 0.37 (1:3.3 diethyl ether/lbpe)] and ^{1}H NMR; mp 53–55 °C.

(1*S*,4*S*,5*E*,7*E*)-1-Acetoxy-4-(benzoyloxy)- and (1*S*,4*S*,5*Z*,7*E*)-1-(Benzoyloxy)-4-acetoxy-*A*-homo-19-nor-9,10-secocholesta-5,7-diene, 7a and 7b. The (10*S*)-tosylate **3f** (176.2 mg, 0.266 mmol) in acetolysis buffer solution (5.2 mL) was heated at 70 °C for 2 h under a nitrogen atmosphere. The cooled reaction mixture was taken up in diethyl ether (30 mL) and washed with water (3 × 30 mL) and brine (1 × 30 mL). Ethereal fractions were combined, washed with saturated aqueous sodium bicarbonate and then brine, dried ($MgSO_4$), and filtered. Removal of solvent under reduced pressure afforded a yellow oil (111.2 mg, 76%). The diastereomeric ratio of products **7a** and **7b** was determined by ^{1}H NMR (C_{18}-methyl peak heights) as 2.01:1.00, respectively. The mixture was separated by medium-pressure LC (1:4.6 ether/lbpe). Minor isomer **7b**: R_f 0.50 (1:3 ether/lbpe); colorless and viscous oil; pure by ^{1}H NMR and TLC. Major isomer **7a**: R_f 0.45 (1:3 ether/lbpe); colorless and viscous oil; pure by ^{1}H NMR and TLC.

In separate experiments, subjection of the individual isomers **7a** and **7b** to the acetolysis conditions (70 °C, 2 h, buffer solution) revealed that they were unchanged. Also, saponification of pure **7a** or pure **7b** afforded the same diol **7c**. It is therefore not practical to separate **7a** from **7b** for obtaining **7c** (see next section).

(1*S*,4*S*,7*E*)-1,4-Dihydroxy-*A*-homo-19-nor-9,10-secocholesta-5,7-diene, 7c. The benzoyloxy tosylate **3f** (435.4 mg, 0.659 mmol) in acetolysis buffer solution (13 mL) was heated at 70 °C for 2 h under a nitrogen atmosphere. The mixture was cooled, diluted with ether (50 mL), and then washed thoroughly with water. The ether phase was washed successively with brine, saturated aqueous sodium bicarbonate, and brine. The ether extract was dried ($MgSO_4$), filtered, and then concentrated under reduced pressure. The yellow oily residue in 5% KOH in methanol (42 mL) was heated at 70 °C for 2 h. The mixture was brought to room temperature, diluted with water, and worked up in the usual way with ether, water, aqueous sodium bicarbonate, and brine. Drying ($MgSO_4$) and concentrating afforded an oil, which was chromatographed by Still's procedure (ether). Solvent was removed under reduced pressure, affording crude crystalline diol (214.2 mg, 80.8%). Recrystallization from pentane afforded **7c** (205.3 mg, 77.4%) pure by TLC [R_f 0.33 (ether)], ^{1}H NMR, and ^{13}C NMR; mp 80–81 °C.

(3*S*,10*R*,5*Z*,7*E*)-3-(Benzoyloxy)-19-(tosyloxy)-9,10-secocholesta-5,7-diene, 4f. The (10*R*)-3-benzoyloxy 19-alcohol **4e** (455.4 mg, 0.898 mmol), *p*-toluenesulfonyl chloride (0.684 g, 3.59 mmol), and freshly distilled pyridine were stirred at room temperature for 6 h under a nitrogen atmosphere. Standard workup as above afforded the tosylate **4f** as a colorless solid (555.5 mg, 93%): pure by ^{1}H NMR and TLC; R_f 0.42 (1:3 ether/lbpe); mp 48–50 °C.

(1*R*,4*S*,5*E*,7*E*)-1-Acetoxy-4-(benzoyloxy)- (8a) and (1*S*,4*R*,5*Z*,7*E*)-1-(Benzoyloxy)-4-acetoxy-*A*-homo-19-nor-9,10-secocholesta-5,7-diene (9b). The (10*R*)-3-benzoyloxy 19-tosylate **4f** (473.5 mg, 0.717 mmol) in acetolysis buffer solution (14 mL) was heated at 70 °C for 2 h under a nitrogen atmosphere. The reaction was worked up with ether, water, aqueous sodium bicarbonate, and brine in the usual manner. The organic extracts were combined, dried over magnesium sulfate, filtered, and then concentrated under reduced pressure. The oily mixture of diastereomers (304.3 mg, 78%) consisted of a ratio of 1:2.77 of **9b** and **8a** (determined by ^{1}H NMR C_{18}-methyl peak height ratio). The diatereomeric mixture was chromatographed (medium-pressure LC, 4.6:1 lbpe/ether) to afford the pure isomers. Minor isomer **9b**: colorless oil; pure by TLC (R_f 0.66, 1:3 ether/lbpe) and ^{1}H NMR. Major isomer **8a**: colorless oil; pure by TLC (R_f 0.58, 1:3 ether/lbpe) and ^{1}H NMR. The individual isomers **8a** and **9b** proved stable to the acetolysis reaction conditions (70 °C, 2 h, buffer solution).

(1*S*,4*R*,7*E*)-1,4-Dihydroxy-*A*-homo-19-nor-9,10-secocholesta-5,7-diene, 9c. The 1-(benzoyloxy)-4-acetoxy diene **9b** (52.6 mg, 0.095 mmol) in 5% KOH/methanol (6 mL) was heated at 70 °C for 2 h under a nitrogen atmosphere. The mixture was

(15) Meyers, A. I.; Slade, J.; Smith, R. K.; Mihelich, E. D.; Hershenson, F. M.; Liang, C. D. *J. Org. Chem.* **1979**, *44*, 2247.
(16) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(17) Bharucha, K. R.; Martin, F. M. *Chem. Abstr.* **1965**, *62*, P9213e.

brought to room temperature and diluted with ether. Conventional ether–water workup afforded the crude oil, which was purified by high-pressure LC (ethyl acetate). The solvent was removed under reduced pressure to yield 300 mg (87%) of a light yellow solid, which was recrystallized (pentane) to afford (1*S*,4*R*)-diol **9c**: tan crystals, mp 63–65 °C; pure by TLC (R_f 0.37, ether), ^{1}H and ^{13}C NMR.

(1*R*,4*S*,7*E*)-1,4-Dihydroxy-*A*-homo-19-nor-9,10-secocholesta-5,7-diene, 8c. The 1-acetoxy-4-benzoyloxy isomer **8a** (90.2 mg, 0.165 mmol) in 5% KOH–methanol (11 mL) was heated at 70 °C for 2 h under a nitrogen atomosphere. The usual water–ether workup afforded an orange oil (61.1 mg), which was chromatographed (high-pressure LC, ethyl acetate). The resulting white crystals were recrystalized in pentane to afford the pure (1*R*,4*S*)-diol **8c**: mp 112–114 °C; pure by TLC (R_f 0.32, ether), ^{1}H and ^{13}C NMR; 54.4 mg (82%).

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Registry No. 1 benzoate, 2174-12-1; **3e**, 75896-12-7; **3f**, 75896-13-8; **4e**, 75947-25-0; **4f**, 75946-86-0; **7a**, 75896-14-9; **7b**, 75896-15-0; **7c**, 75896-16-1; **8a**, 75896-17-2; **8c**, 75946-87-1; **9b**, 75896-18-3; **9c**, 75946-88-2.

Supplementary Material Available: Spectral and analytical data for **3e,f**, **4e,f**, **7a–c**, **8a,c**, and **9b,c** (10 pages). Ordering information is given on any current masthead page.

Aldehydes from Nitriles. Formation of *N*-Alkylnitrilium Ions and Their Reduction to *N*-Alkylaldimines by Organosilicon Hydrides

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A two-step procedure for the partial reduction of nitriles to aldehydes under mild reaction conditions is presented. This approach involves the N-alkylation of nitriles in dichloromethane solution and reductive capture of the resulting nitrilium ions to *N*-alkylaldimines with an organosilicon hydride such as triethylsilane or tri-*n*-hexylsilane. Mild hydrolysis of the aldimines produces aldehydes in generally good-to-excellent yield. Use of both triethyloxonium tetrafluoroborate and isopropyl chloride–iron(III) chloride reagents to effect alkylation is reported. Selective reduction of the nitrile function in polyfunctional substrates is possible with this technique. Over reduction to amines does not occur. Close control of reducing agent and reaction temperatures is not required. Attempts to effect reduction of nitrile–boron trifluoride complexes with triethylsilane were unsuccessful, even at elevated temperatures.

Organic nitriles are often available as starting materials, thus synthetic routes leading directly from them to less readily available aldehydes are frequently quite useful. Such transformations generally take the form of partial reduction of the nitrile to an aldimine followed by hydrolysis of the aldimine to the aldehyde (eq 1).[1,2] One of

$$RC{\equiv}N \rightarrow RCH{=}NR' \rightarrow RCH{=}O \qquad (1)$$

the oldest variations of this potentially attractive synthetic route is the Stephen reaction.[3] It is usually limited to reactions involving aromatic nitriles and is sometimes undependable.[4] Other methods employ various metal hydrides as reducing agents such as lithium trialkoxyaluminohydrides,[5] sodium dialkylaluminohydrides,[6,7] and diisobutylaluminum hydride.[8] These reagents, while generally useful, are strong reducing agents which must be used wiith caution to prevent over reduction or reduction of other functional groups present.

We have studied an alternative general approach for the conversion of the nitrile functionality to the formyl group in which the nitrile function is selectively "activated" prior to reduction. Nitriles may be alkylated to form electron-deficient *N*-alkylnitrilium ions which are much more susceptible to nucleophilic attack at carbon than are their parent nitriles.[9,10] For example, although nitriles themselves resist reduction by sodium borohydride, this reagent completely reduces the derived *N*-alkylnitrilium ions to the corresponding secondary amines in high yields.[11,12]

Our choice of a mild reducing agent for nitrilium ions was triethylsilane. Organosilicon hydrides are able to effect the reduction of a wide variety of carbocations by selective transfer of hydride from silicon to electron-deficient carbon.[13] Under the proper conditions, organosilicon hydrides are such mild reducing agents that neutral species are not reduced by them and even unusually stable car-

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