Tetrahedron Vol 40, No. 12, pp. 2283 to 2296, 1984
Printed in Great Britain.

0040-4020/84 $3.00 + .00

STEREOSELECTIVE TOTAL SYNTHESIS OF 1α,25S,26-TRIHYDROXYCHOLECALCIFEROL

P. M. WOVKULICH, F. BARCELOS, A. D. BATCHO, J. F. SERENO, E. G. BAGGIOLINI, B. M. HENNESSY and M. R. USKOKOVIĆ
Chemical Research Department, Hoffmann-La Roche Inc., Nutley, NJ 07110, U.S.A.

(*Received in Japan* 14 *June* 1983)

Abstract—A total synthesis of 1α,25S,26-trihydroxycholecalciferol (**2**) has been accomplished via an efficient convergent approach. The remote chiral center at C-25 was introduced by a regiospecific and diastereoselective 1,3-dipolar cycloaddition of the C-23 nitrone **27** with methyl methacrylate. Subsequent transformation of the resulting isoxazolidine led to the key synthon **3**, which on coupling to the anion **4** and deprotection produced the metabolite **2**.

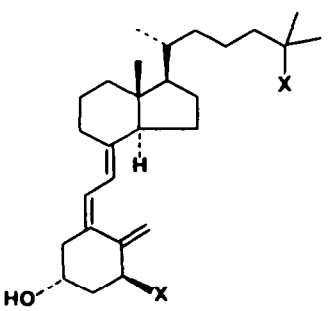
THE recognition of the important role that metabolites of vitamin D_3 play in the regulation of serum levels of calcium and phosphorous, calcium absorption in the intestine, and bone mineralization processes has stimulated a surge of research activity in the areas of their isolation, characterization, and synthesis as well as the synthesis of analogs.[1] Vitamin D_3 (**1a**) itself displays rather weak biological activity until it is hydroxylated *in vivo* to the 1α,25-dihydroxy metabolite **1b**. While the mode of action of 1α,25-dihydroxycholecalciferol (**1b**) is being elucidated, the influence of the other metabolites is still poorly understood. One recently isolated[2] and fully characterized[3] metabolite, 1α,25S,26-trihydroxycholecalciferol (**2**) is of particular interest since it appears to exert an inhibitory effect on the biosynthesis of 1α,25-dihydroxycholecalciferol (**1b**).

We based our synthesis of **2** on a convergent approach in which a CD ring synthon **3** would be coupled with the phosphinoxy anion **4** to give **5** which on removal of the protecting groups would yield **2** (Scheme 1). Such an approach has already been successful in the total synthesis of **1b**.[4] The major portion of the synthetic effort was therefore directed at the preparation of the CD ring synthon **3**.

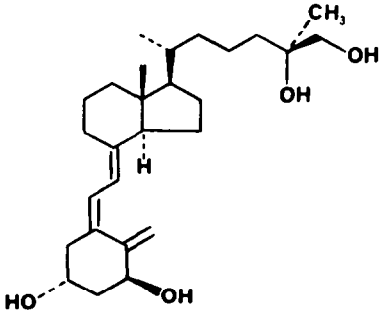
One of the objectives in the synthesis of **3** was to generate the isolated chiral functionality at the C-25 position without resorting to the use of additional chiral pieces. For this purpose, we wished to explore methods which would utilize the existing asymmetry in the bicyclic ring portion of the CD synthon. Specifically, the concept was to take advantage of the chirality at C-20 to influence the diastereoselectivity of a 1,3-dipolar cycloaddition of the C-23 nitrone **8** with methyl methacrylate. Synthon **6** would then be accessible from the resulting isoxazolidine **7**. The starting nitrone **8** would be obtained by a one carbon homologation of **9** which ultimately could be derived from the known acid **11**[5] via **10**.

Following the procedure outlined in ref. 4, the asymmetrically synthesized acid **11**[5] was converted by a five-step process to **12**, which was subjected directly to a Baeyer–Villiger oxidation[6] to produce **13a** (Scheme 3).[4] Removal of the t-Bu group with trimethylsilyliodide to alcohol **13b**, followed by oxidation to ketone **13c** with pyridinium chlorochromate, acetate saponification (**13d**) and Wittig reaction with ethylidene triphenylphosphorane gave the olefin **10**. The ene reaction[7] of **10** with paraformaldehyde in the presence of boron trifluoride etherate gave **14** which on hydrogenation produced the known diol **9**.[8,9] In this manner, we have created **9**, with five contiguous chiral centers, stereospecifically from **11** which contained only one of these chiral centers.

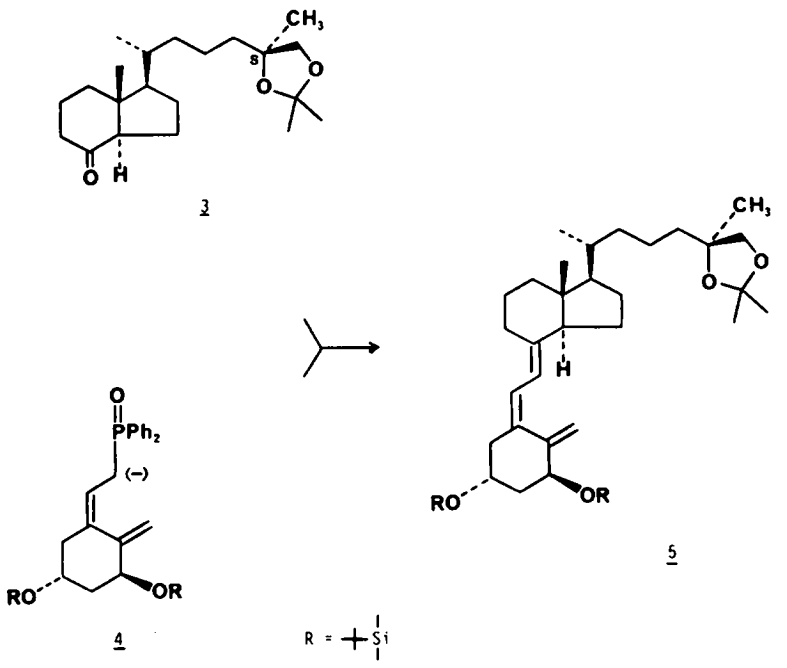
Monotosylation of **9**[9] and displacement with cyanide generated the nitrile **15**, which on reduction with diisobutylaluminum hydride gave aldehyde **16**



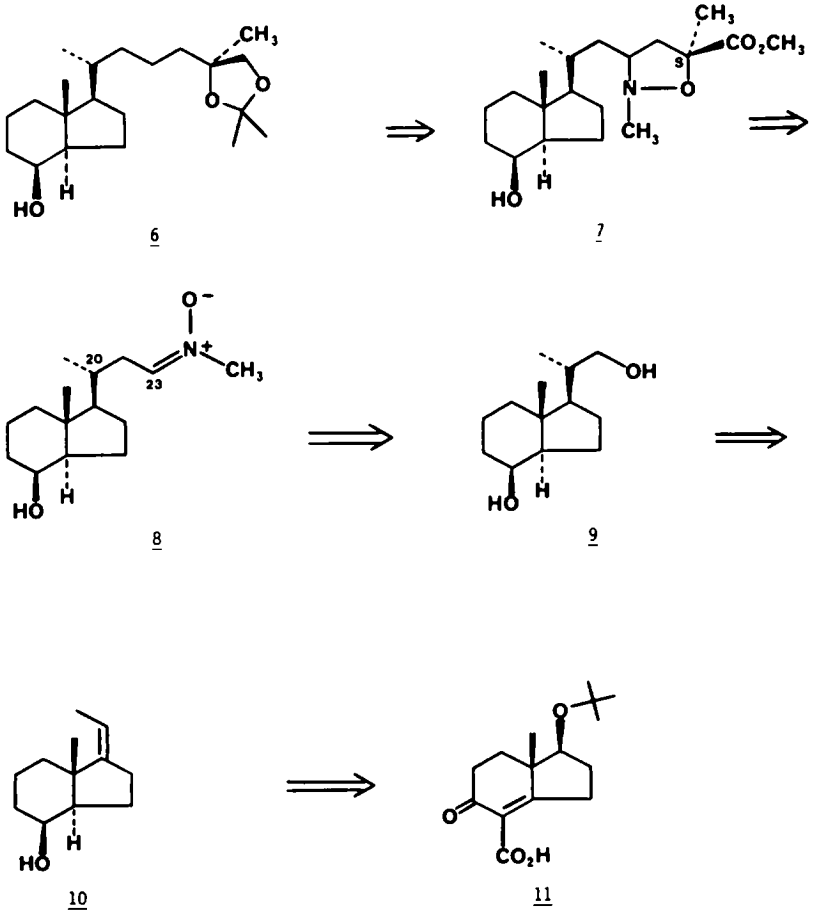
1a X = H
b X = OH



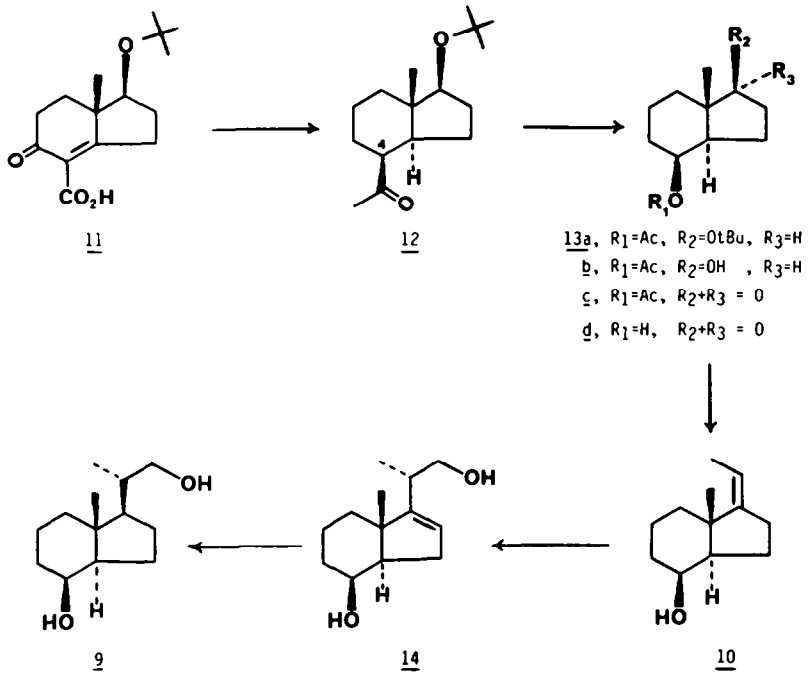
2



Scheme 1.



Scheme 2.



Scheme 3.

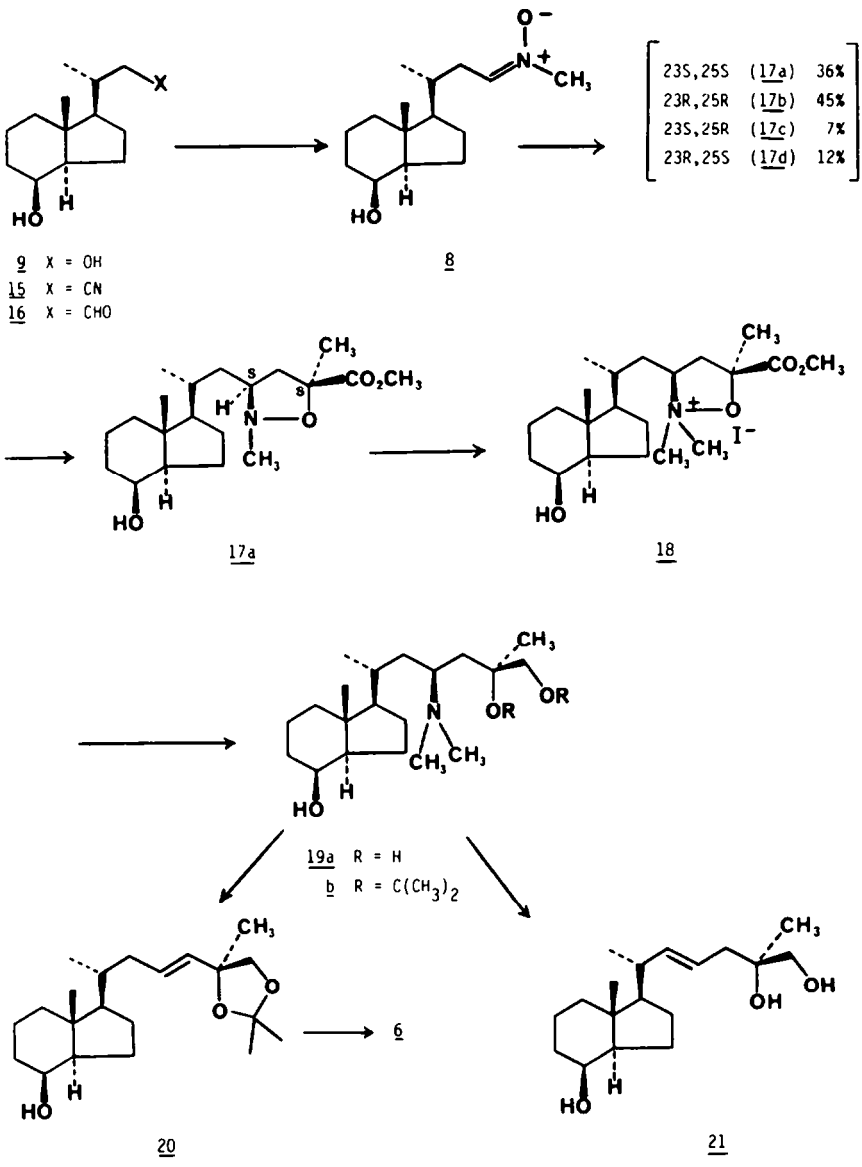
(Scheme 4). The nitrone **8** was obtained by exposure of **16** to methylhydroxylamine and was determined to have the Z-configuration by an X-ray analysis.

The key cycloaddition reaction with methyl methacrylate proceeded smoothly at room temperature. To our disappointment, this reaction though regiospecific[10] produced a 36:45:7:12 ratio of diastereomeric isoxazolidines in high yield. In spite of this low diastereoselectivity, the product outcome could be controlled by taking advantage of the thermal reversibility of this nitrone cycloaddition reaction.[11] After separating the desired *SS*-isomer **17a**, the other three components together (**17b–d**) were equilibrated at 140° in xylenes and an excess of methyl methacrylate back to a four component mixture (**17a–d**). By four repetitions of this separation-equilibration sequence, the *SS*-isomer **17a** was ultimately obtained in 71% total yield from **8**. The desired CD-side chain synthon **6** was then completed by N-methiodide formation (**18**), reduction of the N–O bond and the carbomethoxy group to amino-triol **19a**, acetonide formation (**19b**), regiospecific elimination of the amino function by Hofmann degradation to the Δ^{23}-olefin **20** (73%) and hydrogenation over a palladium-on-carbon catalyst.

In contrast when the dimethylamino-triol **19a** was subjected to the elimination sequence without first forming the acetonide, the Δ^{22}-double bond isomer was formed in 59% yield along with minor amounts of starting amino-triol and by-products. It is noteworthy that only 2% of the corresponding Δ^{23}-olefin was formed. To explain the difference in the regiospecificity of elimination between **19a** and **19b**, the conformations of the side chain need to be considered. An X-ray crystallographic analysis of the dimethylamino-acetonide **19b** shows the side chain in a staggered form with C-20 *anti* to the nitrogen, and C-22 *anti* to C-25. Then assuming a similar solution conformation for the N-methiodide, *anti*-elimination of a proton could only occur from C-24 and not from C-22, thus resulting in the *trans* Δ^{23}-double bond as observed. A different side chain conformation in the methiodide of alcohol **19a** can account for the change in product formation. If under the basic reaction conditions the free OH at C-25 is deprotonated, a conformational change of the side chain would result from the favorable intra-molecular interaction of the negative C-25 alkoxide and the positive nitrogen. In that form, neither proton at C-24 would be available for *anti*-elimination thus leaving as the only alternative removal of a C-22 proton, which would produce a Δ^{22}-double bond.

In an alternative conformation where C-25 and the nitrogen are *anti*, the C-22 proton which is *anti* to nitrogen would also be in close proximity to the alkoxide at C-25. Then, proceeding via a 6-membered transition state, intra-molecular proton transfer from C-22 to the C-25 oxygen with concomitant loss of nitrogen would lead to the *trans* Δ^{22}-double bond.[12]

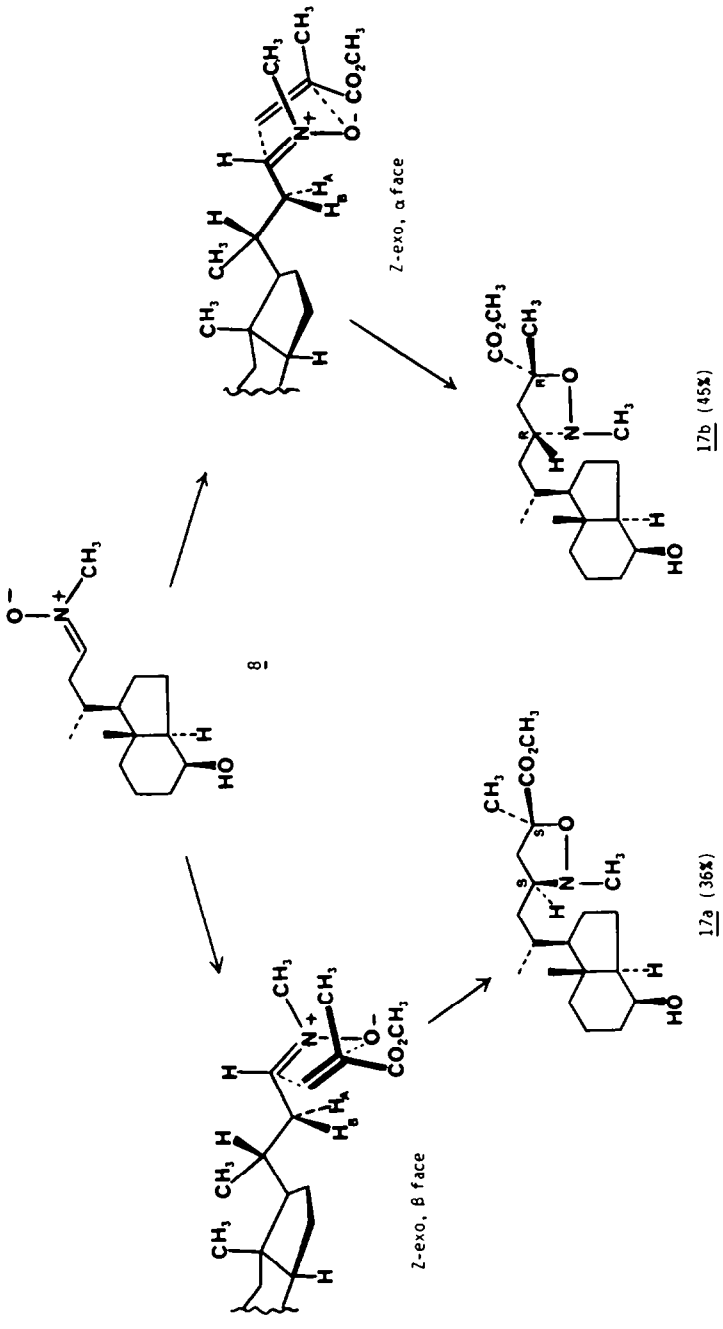
While the diastereoselectivity of the 1,3-dipolar cycloaddition was low, the mode of cycloaddition (i.e. *exo* vs *endo*) is significant. As illustrated in Scheme 5, where the *Z*-nitrone **8** is shown in the extended form, the two predominant diastereomers **17a** and **17b** arise from the *exo* transition state in which approach of the methacrylate from the same face as H_B (β face) produces **17a** and approach from the H_A (α) face gives **17b**. Consequently, the proportion of **17b** would be expected to decrease if approach from the H_A face were made less favorable. To test



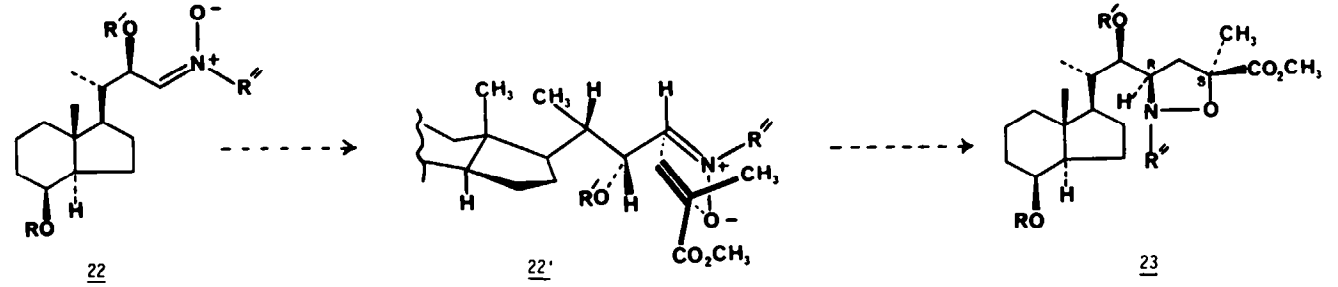
Scheme 4.

this hypothesis, a system where H_A is replaced by a removable "steric protecting" function (R_2O-) was considered. For example, a nitrone such as **22** might be expected to form preferentially the isoxazolidine **23** via the *Z-exo* transition state **22'** (Scheme 6). Its synthesis was undertaken next.

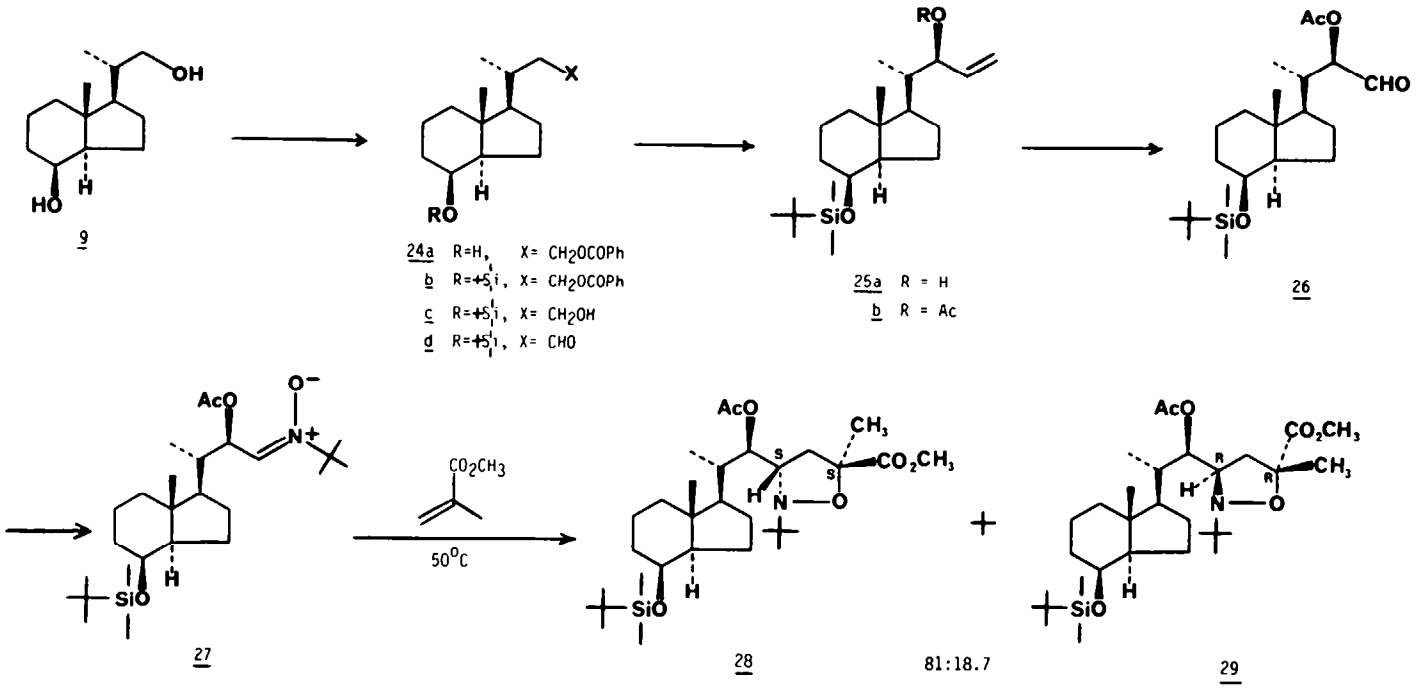
The diol **9**, on treatment with a slight excess of benzoyl chloride in pyridine gave the mono benzoate **24a** which was silylated (**24b**) and then debenzoylated to give the crystalline silyl ether **24c** (Scheme 7). Oxidation with pyridinium chlorochromate led to aldehyde **24d** which on exposure to vinyl magnesium bromide gave alcohol **25a** in 63% yield from **24c** as well as 12% of the epimeric alcohol. Acetylation of **25a** followed by ozonolysis in methanol at $-78°$ and dimethylsulfide workup gave the α-acetoxy aldehyde **26** which with t-butylhydroxylamine produced the desired nitrone **27**. Heating the nitrone **27** at 50° with methyl methacrylate for 42 hr gave an 81:18.7:0.3 mixture of isomers in 99% yield. An X-ray crystallographic analysis of the major isomer revealed it to be the SS adduct **28** and not the expected RS isomer **23** as portrayed in Scheme 6. The near identity of the proton NMR signals of the next most-predominant isomer, particularly of the isoxazolidine ring protons, suggested that the relative stereochemistry at C-23 and C-25 was the same as in **28** (i.e. *trans*) but of the opposite absolute configuration. The RR configuration of **29** was also confirmed by an X-ray crystallographic analysis. This result is especially intriguing since the mode of cycloaddition is > 99% from the *endo* transition state and not the *exo* mode as experienced with nitrone **8** (Scheme 8). From the work of Vasella,[13] one might expect a change in the rotational orientation of the nitrone when an alpha proton is replaced by oxygen but it was not apparent that the dramatic shift from *exo* to *endo* as observed here would occur. The benzyl analog of



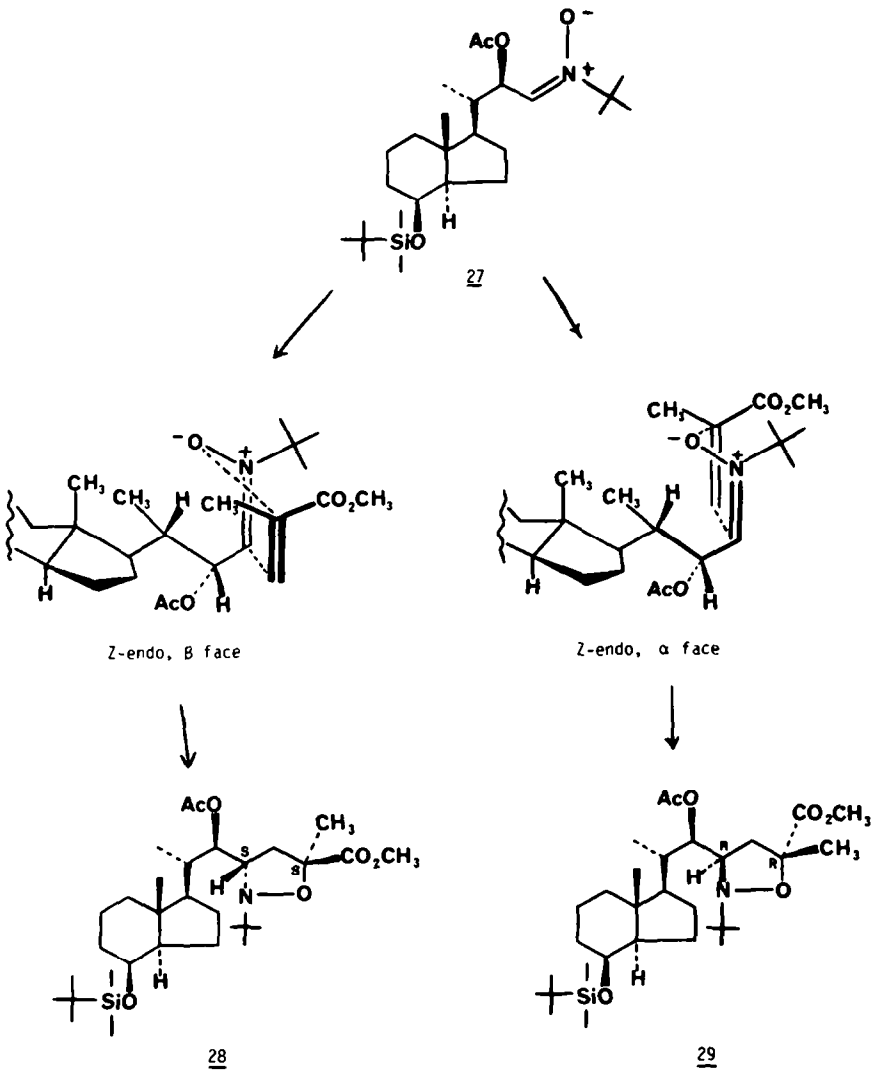
Scheme 5.



Scheme 6.



Scheme 7.



Scheme 8.

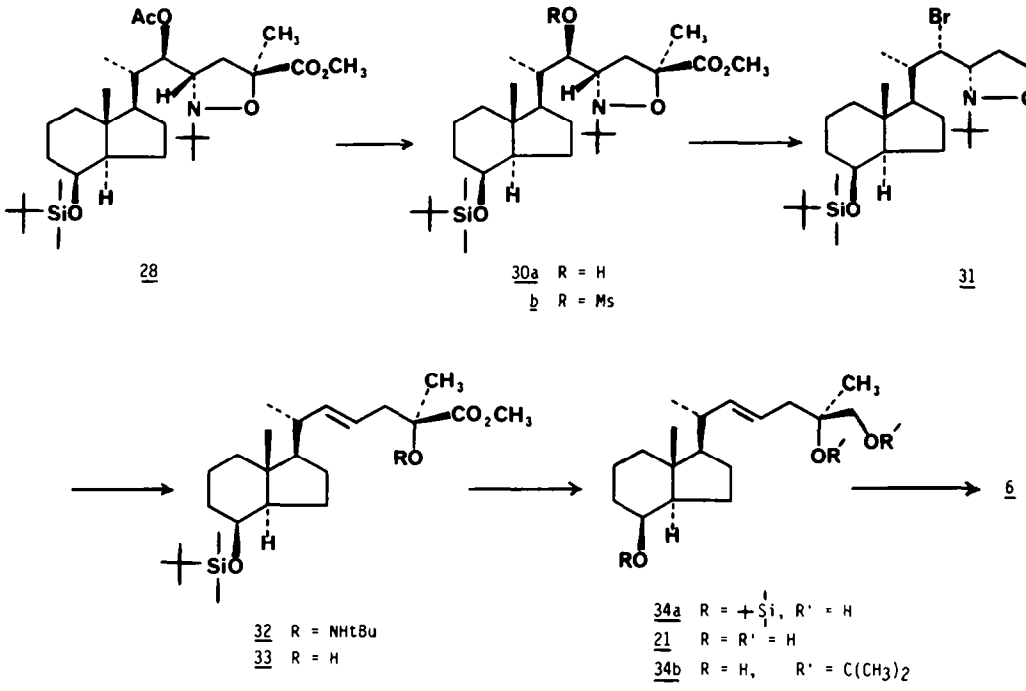
nitrone **27** produced an 82:1:7:10 mixture of isomers where the major adduct bears the same absolute configuration as **28**. The drop in the *endo/exo* ratio from >99% *endo* in the t-butyl case to 92:8 in the N-benzyl suggests that the steric bulk of the substituent on nitrogen may in part govern the *endo/exo* selectivity. While other factors, such as substituents on the carbon end of the nitrone undoubtedly make contributions as well, it appears that whatever the *endo/exo* ratio is, it will be increased when the bulk of the nitrogen substituent is increased.

Having fulfilled their role in controlling the C-25 stereochemistry, the oxygen and nitrogen groups now had to be excised. Treatment of **28** with sodium methoxide in methanol gave **30a** (Scheme 9). Mesylation of the free hydroxyl (**30b**) followed directly by displacement with bromide generated the bromoisoxazolidine **31**. Reductive elimination of **31** with zinc in acetic acid proceeded rapidly (15–20 min) to olefin **32** followed more slowly (5 hr) by N–O bond cleavage to **33**. Reduction of the carbomethoxy group (**34a**) and then desilylation with aqueous HF[14] gave triol **21** which, on treatment with 2,2-dimethoxypropane in the presence of acid, produced acetonide **34b** in high overall yield. Then the double bond of **34b** was hydrogenated to give the protected synthon **6**.

The last stage of the synthesis followed in exactly the same manner as the previously described protocol for the preparation of **1b**. Oxidation of **6** with 2,2′-bipyridinium chlorochromate[15] produced the ketone **3**. Then, reaction of **3** with the anion **4** at −78°C gave the coupled product **5** (Scheme 1) which on removal of the protecting groups generated 1α,25S,26-trihydroxycholecalciferol(**2**) identical in all respects with authentic material.[3]

EXPERIMENTAL

General methods. M.ps were obtained on a Thomas–Hoover m.p. apparatus and are uncorrected. IR



Scheme 9.

spectra were obtained on a Digilab Model FTS-15E spectrometer. The proton NMR spectra were obtained on a Varian XL200 (200 mHz) spectrometer as solns in $CDCl_3$ or when indicated in other solvents or at 100 mHz on a Varian XL100 spectrometer. Chemical shifts are reported in ppm downfield from internal TMS and apparent splittings are given in herz. Mass spectral data was obtained on a Varian MAT CH-5 mass spectrometer. Preparative liquid chromatography was carried out at medium pressure on home built LC systems employing 40–60 μ silica gel packed in commercially available empty glass or steel columns.

Preparation of [1S-(1β,3aα,4β,7aβ)] - 1 - [*octahydro* - 7a - *methyl* - 1 - [(1,1-*dimethylethyl*) - *oxy*] - 1*H* - *inden* - 4 - *yl*]*ethanone* (**12**)

[1*S* - (1β,3aα,7aβ)] - 1 - [(1,1 - dimethylethyl)oxy] - 7a - methyl - [2,3,3a,6,7,7a - hexahydro - 1H - inden - 6 - yl]ethanone[4] was hydrogenated at atmospheric pressure over 3% by weight of 10% Rh/C in EtOAc to give **12** in 82% yield after silica gel chromatography (hexanes–EtOAc 97.5:2.5) as a 94:6 mixture with its α-isomer as determined by analytical LC (3μ porasil, EtOAc–heptane, 3.5:96.5). The analytical sample was recrystallized from acetonitrile-water, m.p. 78°, $[\alpha]_D^{25} = +131.65°$ (*c* 0.3160, $CHCl_3$). (Found: C, 75.84; H. 10.98. Calc for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18%). IR ($CHCl_3$) 1703 cm^{-1}. NMR δ 0.64 (s, 3H), 1.14 (s, 9H), 2.16 (s, 3H), 2.69 (t, J = 4.5 Hz, 1H), 3.32 (t, J = 8.5 Hz, 1H).

Preparation of [1*S* - (1β,3aα,4β,7aβ)] - 1 - [(1,1 - *dimethylethyl*)*oxy*] - 7a - *methyl* - *octahydro* - 1H - *inden* - 4 - *ol acetate* (**13a**)

A soln of trifluoroperacetic acid, prepared by the dropwise addition of 3.37 ml of trifluoroacetic anhydride to a cooled (0°) slurry of 0.49 ml of 90% H_2O_2 and 15 ml of CH_2Cl_2 with stirring at 0° for 1 hr before use, was added dropwise to a cooled (0°) slurry of 4.04 g disodium hydrogen phosphate (oven dried and pulverized before use), 60 ml CH_2Cl_2 and 1.0 g (3.9 mmol) of **12**. The cooling bath was removed after 1 hr and the mixture stirred for 30 hr at room temp. The mixture then was poured onto 50 ml of ice water-Na_2SO_3 and extracted 2 × 30 ml of CH_2Cl_2. The combined CH_2Cl_2 layers were washed, 2 × 25 ml $NaHCO_3$ aq, 1 × 25 ml of brine and dried over Na_2SO_4. Filtration, concentration and chromatography on silica gel (hexanes–EtOAc, 97.5:2.5) gave 0.60 g (57%) of acetate **13a** as a solid. The analytical sample was recrystallized from methanol–water, m.p. 64–65°C. $[\alpha]_D^{25} = +20.69°$ (c 0.8454, $CHCl_3$). (Found: C, 71.40; H, 10.44. Calc for $C_{16}G_{28}O_3$: C, 71.60; H, 10.52%). IR (KBr) 1733 cm^{-1}. NMR (100 mHz) δ 0.91 (s, 3H), 1.12 (s, 9H), 2.04 (s, 3H), 3.36 (m, 1H), 5.12 (br s, 1H).

Preparation of [1*S*(1β,3aα,4β,7aβ)] - 7a - *methyl* - *octahydro*-1H - *indene* - 1,4 - *diol* 4 - *acetate* (**13b**)

To a solution of 2.8 g (10 mmol) of t-butyl ether **13a** in 20 ml of CCl_4 under argon was added dropwise 1.6 ml (11 mmol) of iodotrimethylsilane. After stirring 4 hr, another 1.0 ml (6.7 mmol) of iodotrimethylsilane was added and the mixture stirred 1 hr. Then 9 ml (7.7 mmol) of t-butylmethyl ether was added, the mixture was stirred for 45 min then cooled to 0°, and 16 ml of MeOH was added. The cooling bath was removed and the mixture stirred at room temp for 20 min after which time the volatiles were removed under reduced pressure. The residue was dissolved in 200 ml of EtOAc and washed 2 × 100 ml of 10% Na_2SO_3aq, 3 × 100 ml of 2N K_2CO_3aq, 1 × 100 ml of brine, then dried over Na_2SO_4. Filtration and evaporation followed by silica gel chromatography gave 1.77 g (80%) of **13b** as a solid, m.p. 69°, $[\alpha]_D^{25} = +29.26°$ (c, 0.9636, $CHCl_3$). (Found: C, 67.83; H, 9.33, Calc for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50%). IR ($CHCl_3$) 1727 cm^{-1} NMR δ 0.95 (s, 3H), 2.07 (s, 3H), 3.60 (dd, J = 7, 7.5 Hz, 1H), 5.13 (s, 1H).

Preparation of [3a*R* - (3aα,4β,7aβ)] - 7a - *methyl* - 4 - *acetyloxy* - *octahydro* - 1H - *inden* - 1 - *one* (**13c**)

To a slurry of 4.6 g (21 mmol) of pyridinium chlorochromate in 18 ml of dry (4Å molecular sieves) CH_2Cl_2 was

added 1.67 g (7.9 mmol) of **13b** in 12 ml of dry CH_2Cl_2. The mixture was stirred at room temp for 2 1/2 hr; then 100 ml of diethyl ether was added, the mixture was filtered through celite, and chromatographed on silica gel (hexanes–EtOAc, 75:25) to give 1.61 g (97%) of **13c** as a solid. The analytical sample was recrystallized in the cold from hexanes–diethyl ether, m.p. 25–26°, $[\alpha]_D^{25} = +85.85°$ (*c* 0.9703, $CHCl_3$). (Found: C, 68.62; H, 8.76. Calc for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63%). IR ($CHCl_3$) 1733 cm^{-1}. NMR (100 mHz) δ 1.08 (s, 3H), 2.08 (s, 3H), 5.29 (br s, 1H).

Preparation of [3aR - (3aα,4β,7aβ)] - 7a - *methyl* - 4 - *hydroxy* - *octahydro* - 1H - inden - 1 - one (**13d**)

To a soln of 1.55 g (7.4 mmol) of **13c** in 15 ml of MeOH under argon was added 3.5 ml of 25% NaOMe in MeOH. The mixture was stirred 2 1/2 hr then an additional 1.25 ml of 25% NaOMe in MeOH was added. After stirring for 1 hr, 12.5 g of AG 50W-X4 cationic ion exchange resin was added, the mixture filtered, and solvents removed under reduced pressure. The residue was dissolved in 50 ml of EtOAc, washed 2 × 25 ml of brine and dried over Na_2SO_4 to give, after filtration and evaporation, 1.079 g (87%) of **13d**. The analytical sample was recrystallized from hexanes-EtOAc, m.p. 84–85°, $[\alpha]_D^{25} = +10.86$ (*c* 0.8930, $CHCl_3$). (Found: C, 71.36; H, 9.70. Calc for $C_{13}H_{22}O_2$: C, 71.39; H, 9.59%). IR ($CHCl_3$) 1734 cm^{-1}. NMR δ 1.15 (s, 3H), 4.26 (s, 1H).

Preparation of [3aR - [(Z); 3aα,4β7aβ)] - 1 - *ethylidene* - *octahydro* - 7a - *methyl* - 1H - 4 - *indenol* (**10**)

To a slurry of 7.42 g (17.7 mmol) of ethyltriphenylphosphonium iodide, 35 ml of dry THF and 2.0 g (17.9 mmol) of t-BuOK under an atmosphere of argon was added 1.0 g (5.9 mmol) of **13d** in 5 ml of dry THF. After stirring for 3 hr at room temp, an additional 7.42 g (17.7 mmol) of ethyltriphenylphosphonium iodide and 2.0 g (17.9 mmol) of t-BuOK were added. The mixture was stirred for 60 hr at room temp; then poured into 500 ml of ice water and extracted 3 × 100 ml of EtOAc. The combined extracts were washed 3 × 100 ml of water, 1 × 100 ml of brine and dried over Na_2SO_4. Filtration, concentration *in vacuo* and chromatography on silica gel (hexanes–EtOAc, 2:1) produced 0.823 g (77%) of olefin **10** as an oil which contained *ca* 3% of the *E*-isomer by NMR. (Found: C, 79.65; H, 11.12. Calc for $C_{12}H_{20}O$: C, 79.94; H, 11.18%). Raman IR (NEAT) 1688 cm^{-1}. NMR (100 mHz) δ 1.14 (s, 3H), 1.65 (dm, J = 8 Hz, 3H), 4.14 (m, 1H), 5.06 (qt, J = 8, 2 Hz, 1H).

Preparation of [1R - [3aβ(S*),7β,7aα]] - β,3a - *dimethyl* - 4-*hydroxy* - (3a,4,5,6,7,7a) - *hexahydro* - 1H - *indene* - 1 - *ethanol* (**14**)

To a cooled (0°) slurry of 0.10 g (0.55 mmol) of **10**, 0.020 g (0.67 mmol) of paraformaldehyde and 15 ml of CH_2Cl_2 (4Å molecular sieves) under an atmosphere of argon was added 0.017 ml of 0.813M $BF_3 \cdot Et_2O$ in CH_2Cl_2. After stirring for 2 hr, 2 ml of 2N NaOH was added. The mixture was transferred to a separatory funnel, washed with water and then dried over Na_2SO_4. After filtration, evaporation of solvent and chromatography on silica gel (hexanes–EtOAc, 1:1) 0.082 g (70%) of **14** was obtained as a solid, m.p. 93–94°, $[\alpha]_D^{25} + 10.86°$ (*c* 0.8930, $CHCl_3$). (Found: C, 74.22; H, 10.64. Calc for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54%). NMR (100 mHz) δ 1.03 (d, J = 8 Hz, 3H), 1.08 (s, 3H), 3.58 (m, 2H), 4.20 (m, 1H), 5.45 (m, 1H).

Preparation of [1R - [1β(S*),3aα,4β,7aβ]] - *octahydro* - 4 - *hydroxy* - β,7a - *dimethyl* - 1H - *indene* - 1 - *ethanol* (**9**)

Diol-olefin **14** was hydrogenated at atmospheric pressure over a 5% Pd/C catalyst in EtOAc to give **9** in 77% yield after silica gel chromatography (hexanes–EtOAc, 1:1). The product was identical to authentic material[8,9] by 200 mHz NMR δ 0.96 (s, 3H), 1.03 (d, J = 8 Hz, 3H), 3.37 (dd, J = 8, 10 Hz, 1H), 3.64 (dd, J = 4, 10 Hz, 1H), 4.09 (br s, 1H), by mixed ^{13}C NMR and when mixed with authentic material gave no m.p. depression (mixed m.p. 113–114°). ^{13}C NMR (50 mHz, $CDCl_3$, δ from internal TMS) C: 41.9; CH: 38.3, 52.4, 53.0, 69.2; CH_2: 17.4, 22.6, 26.7, 33.6, 40.2, 67.8; CH_3: 13.6, 16.7.

Preparation of [1R - [1β(R*),3aα,4β,7aβ]] - *octahydro* - 4 - *hydroxy* - β,7a - *dimethyl* - 1H - *indene* - 1 - *propanenitrile* (**15**)

To a soln of 72.50 g (198 mmol) of crude [1*R* - [1β(*S**), 3aα,4β,7aβ]] - octahydro - 4 - hydroxy - β,7a - dimethyl - 1H - indene - 1 - ethanol - α - (4 - methylbenzenesulfonate)[9] (m.p. 97–98°, recrystallized from MeOH) in 250 ml of DMSO (dist. from CaH) was added 13.60 g (275 mmol) of sodium cyanide. After heating at 90° for 30 min, a clear soln developed. Heating was continued for a total of 3.5 hr. The mixture was poured into 2.0 L. of water, and was extracted with 4 × 1 L of ether. The ether phases were washed counter-currently with 1 L of saturated brine, dried (Na_2SO_4), filtered, and evaporated to give 43.2 g of crude product. Chromatography on silica gel using two 0.5 m × 47 mm columns in series, gave, on elution with CH_2Cl_2–hexane–EtOAc (86:7:7), 39.5 g (90%) of **15**. An analytical sample was obtained from ether–hexanes as white crystals, m.p. 95–96°. (Found: C, 75.86; H, 10.49; N, 6.46, Calc for $C_{14}H_{23}NO$: C, 75.97, H, 10.47; N, 6.33%). $[\alpha]_D^{25} + 46.7°$(*c* 0.699, $CHCl_3$), MS *m/e* 221, IR ($CHCl_3$): 2250, 3620 cm^{-1}; NMR (100 mHz) δ 0.97 (s, 3H), 1.05 (d, J = 8 Hz, 3H), 2.30 (m, 2H), 4.10 (br s, 1H).

Preparation of [1R - [1β(R*),3aα,4β,7aβ]] - *octahydro* - 4 - *hydroxy* - β,7a - *dimethyl* - 1H - *indene* - 1 - *propanealdehyde* (**16**)

To a magnetically stirred soln of 175 ml of 1M diisobutylaluminum hydride and 80 ml of CH_2Cl_2 cooled to −5° under an argon atmosphere was added dropwise (maintaining temp below 0°) over 15 min, a soln of 11.1 g (50 mmol) of **15** in 80 ml of CH_2Cl_2 (reverse addition results in formation of a thick gel which is difficult to stir). After 1 hr the solution was poured into a chilled (5–10°) suspension of 500 ml of ether (hydrolysis of the imine complex takes more than 48 hr without the ether) and 500 ml of 3N HCl maintaining an argon atmosphere. After 2 hr, the phases were separated and the lower aqueous layer was extracted with 2 × 500 ml of CH_2Cl_2. The organic layers were washed countercurrently with 200 ml of saturated brine, dried (Na_2SO_4), filtered, and evaporated at reduced pressure (bath 40°). The crude aldehyde is sensitive to air and decomposes in the presence of any unhydrolyzed aluminum complex, consequently it was preferable to purify and use the aldehyde in the next step the same day. The crude aldehyde was percolated through a 0.3 m × 35 mm column of silica gel, 40–60μ, the fractions, eluted with 3:1, hexanes–EtOAc and combined according to TLC, were collected under N_2 and evaporated under reduced pressure (bath 40°) to give 11.2 g (100%) of chromatographically pure **16** as an oil.

Preparation of [1R - [1β(R*,Z),3aα,4β,7aβ] - *octahydro* - 7a-*methyl* - 1 - [1 - *methyl* - 3 - (*methylimino*)*propyl*] - 1H - *inden* - 4 - *ol* N - *oxide* (**8**)

To a magnetically stirred soln of 11.2 g (50 mmol) of crude **16** in 200 ml of CH_2Cl_2 under an argon atmosphere was added 5.0 g (60 mmol) of N-methyl hydroxylamine hydrochloride followed by 25 ml of Et_3N. After 3 hr, the suspension was poured onto 200 ml of sat $NaHCO_3$aq. The phases were separated and the aqueous layer was extracted with 4 × 200 ml of CH_2Cl_2. The combined organic phases were dried (Na_2SO_4), filtered, and evaporated to give 11.75 g (93%) of **8** as a white solid. ^{13}C NMR (50 mHz, $CDCl_3$) of the crude nitrone before crystallization showed only one isomer: C, 41.98; CH: 139.8, 68.9, 56.6, 52.6, 52.4, 33.4; CH_2: 40.3, 33.6, 33.5, 27.3, 22.5, 17.4; CH_3: 33.4, 19.7, 13.5. An analytical sample was obtained as white crystals from EtOAc, m.p. 145–146°. (Found: C, 70.89; H, 10.88; N, 5.55.

Calc for $C_{15}H_{27}NO_2$: C, 71.10; H, 10.74; N, 5.53%). MS *m/e* 253; $[\alpha]_D^{25} + 41.5°$ (*c* 0.808, $CHCl_3$), IR ($CHCl_3$): 3620, 1607 cm^{-1}; NMR δ 0.95 (s, 3H), 0.97 (d, J = 6 Hz, 3H), 2.48 (m, 2H), 3.70 (s, 3H), 4.09 (br s, 1H), 6.69 (t, J = 6 Hz, 1H).

Reaction of N-*methylnitrone* **8** *with methyl methacrylate*

A soln of 5.62 g (22.2 mmol) of **8**, 200 ml of toluene, and 11.8 ml (11.1 g, 110 mmol) of methyl methacrylate was heated in an oil bath at 90° under an argon atmosphere for 2 hr. After evaporation of volatile components, the residue (8.75 g) was chromatographed on silica gel using 0.5 m × 47 mm and two 1.0 m × 25 mm glass columns in series. Elution with 60:40, CH_2Cl_2–CH_3CN on an automatic fraction collector (20 ml fractions) and combining fractions according to TLC (2 developments, same solvent system) gave 2.283 g (29% yield) of the least polar product **17a**. An analytical sample was obtained by LC purification. (Found: C, 67.90; H, 9.81; N, 3.71, Calc for $C_{20}H_{35}NO_4$: C, 67.95; H, 9.98; N, 3.96%). $[\alpha]_D^{25} + 145.9°$ (*c* 1.047, $CHCl_3$); IR ($CHCl_3$): 3620, 1730 cm^{-1}, MS *m/e* 353. NMR δ 0.94 (d, J = 6 Hz, 3H), 0.94 (s, 3H), 1.49 (s, 3H), 2.26 (dd, J = 7.5, 12 Hz, 1H), 2.49 (dd, J = 9, 12 Hz, 1H), 2.69 (s, 3H), 3.79 (s, 3H), 4.09 (br s, 1H).

The three more polar products (**17b–d**) were combined (5.274 g, 67% yield) and heated at 140° overnight in xylenes in the presence of excess methyl methacrylate to generate an equilibrium mixture of the four isoxazolidines (see table). Separation was carried out as above. After four such equilibrations, a 71% yield of the 23*S*,25*S* isomer **17a** was produced (with 16% of a mixture of the other three isomers still remaining).

Analytical samples of the other isomers (also amorphous) were obtained by repeated LC until they were pure by TLC and analytical LC analysis.

[3R - [3α,5α[3(2R*),1R*(1β,3aα,4β,7aβ)]]] - 3 - [2 - (octahydro - 4 - hydroxy - 7a - methyl - 1H - *inden* - 1 - yl)propyl]- 2,5 - dimethyl - 5 - isoxazolidinecarboxylic acid methyl ester (**17b**). (Found: C, 67.74; H, 9.90; N, 3.91. Calc for $C_{20}H_{35}NO_4$: C, 67.95; H, 9.98; N, 3.96%). $[\alpha]_D^{25} = -66.3°$ (*c* 0.938, $CHCl_3$); NMR δ 0.94 (s, 3H), 0.95 (d, J = 6 Hz, 3H), 1.49 (s, 3H), 2.34 (m, 1H), 2.62 (m, 2H), 2.71 (s, 3H), 3.79 (s, 3H), 4.09 (br s, 1H).

[3*S* - [3β,5α[3(2*R**),1*R**(1β,3aα,4β,7aβ)]]] - 3 - (2 - (octahydro - 4 - hydroxy - 7a - methyl - 1H - inden - 1 - yl)propyl - 2,5 - dimethyl - 5 - isoxazolidinecarboxylic acid methyl ester (**17c**). (Found: C, 67.54; H, 9.92; N, 3.80, Calc for $C_{20}H_{35}NO_4$: C, 67.95; H, 9.98; N, 3.96%). $[\alpha]_D^{25} = +67.6°$(*c* 0.948, $CHCl_3$); NMR δ 0.92 (d, J = 6 Hz, 3H), 0.94 (s, 3H), 1.53 (s, 3H), 2.71 (s, 3H), 2.87 (m, 3H), 3.77 (s, 3H), 4.08 (br s, 1H). Calc for $C_{20}H_{35}NO_4$: C, 67.95; H, 9.98; N, 3.96%).

[3*R* - [3α,5β[3(2*R**), 1*R**(1β,3aα,4β,7aβ)]]] - 3 - (2 - (octahydro - 4 - hydroxy - 7a - methyl - 1H - inden - 1 - yl)propyl - 2,5 - dimethyl - 5 - isoxazolidinecarboxylic acid methyl ester (**17d**), (Found: C, 67.92; H, 9.94; N, 3.84; Calc for $C_{20}H_{35}NO_4$: C, 67.95; H, 9.98; N, 3.96%). $[\alpha]_D^{25} + 10.3°$ (*c* 0.942, $CHCl_3$); NMR δ 0.93 (d, J = 6 Hz, 3H), 0.94 (s, 3H), 1.52 (s, 3H), 2.72 (s, 3H), 2.81 (m, 2H), 3.76 (s, 3H), 4.06 (br s, 1H).

Analysis by analytic LC on Zorbax silica gel 25 cm × 4.5 mm column using 1.4% isopropanol, 21% acetonitrile, 78% dichloromethane.

Effect of temperature on the cycloaddition reaction of **8** with methyl methacrylate

	Temperature		
Product (%)	22°[a]	90°[b]	140°[c]
17*a*	36	34	31
17*b*	45	38	22
17*c*	7	11	26
17*d*	12	16	20

[a]in CH_2Cl_2, [b]in toluene, [c]in xylenes.

Preparation of [1R - [1β(R*,S*,S*),3aα,4β,7aβ]] - 6 - (*octahydro* - 4 - *hydroxy* - 7a - *methyl* - 1H - *inden* - 1 - *yl*) - 4 - *dimethylamino* - 2 - *methylheptane* - 1,2 - *diol* (**19a**)

To a soln of 4.88 g (13.8 mmol) of **17a**, 40.0 ml of dry (3A molecular sieves) MeOH was added 4.30 ml (69 mmol) of freshly distilled MeI. This clear soln was stirred under a static argon atmosphere in the dark (wrapped with Al-foil) for 18 hr. Evaporation under reduced pressure gave 6.807 g of **18** as a white solid, which was suspended in 200 ml of dry THF, cooled to about 20° (ice/water bath), and 2.80 g (73.8 mmol) of LAH was added in portions over 0.5 hr. The suspension was stirred for 15 min at room temp, then at reflux for 2 hr. After cooling the suspension to about 15°, 4.0 ml of water was added followed cautiously by 2.80 ml of 10% NaOH. After stirring for 0.25 hr, the suspension was filtered. The residue was reslurried with 200 ml of CH_2Cl_2 and refiltered. The digestion was repeated four times. The combined filtrates were evaporated to give 4.88 g of crude product. Purification, using LC (EtOAc–Et_3N–water, 94:5:1, 25 × 1000 mm column, 40–60 μ silica gel) gave 4.09 g (86% yield) of **19a**. An analytical sample (amorphous) was obtained by LC purification (as above). (Found: C, 70.13; H, 11.54; N, 4.07; Calc for $C_{20}H_{39}O_3N$: C, 70.34; H, 11.51; N, 4.10%). $[\alpha]_D^{25} + 83.8°$(*c* 0.806, $CHCl_3$); MS *m/e* 341; IR ($CHCl_3$) 3625 cm^{-1}; NMR δ 0.91 (d, J = 6 Hz, 3H), 0.93 (s, 3H), 1.18 (s, 3H), 2.22 (s, 6H), 2.88 (apparent t, J = 11 Hz, 1H), 3.35 (dd, J = 11, 15 Hz, 2H), 4.09 (br s, 1H).

Preparation of [1R - [1β(R*,S*,S*),3aα,4β,7aβ]] - *octahydro* - 7a - *methyl* - 1 - [3 - (*dimethylamino*) - 1 - *methyl* - 4 - (2,2,4 - *trimethyl* - 1,3 - *dioxolan* - 4 - *yl*)*butyl*] - 1H - *inden* - 4 - *ol* (**19b**)

To a soln of 1.94 g (5.68 mmol) of **19a** in 8.0 ml of dry (3A molecular sieves) acetone and 4.50 ml (28.4 mmol) of 2,2-dimethoxypropane was added 1.35 g (6.24 mmol) of toluenesulfonic acid monohydrate. The soln was stirred for 25 hr at room temp under argon, and then evaporated to dryness. The residue was dissolved in ether and washed with 100 ml of 10% $NaHCO_3$aq. The aqueous phase was washed with 3 × 100 ml of ether. The combined organic phases were evaporated to give 2.20 g of **19b** which was used without purification in the next step. An analytical sample obtained by crystallization from pentane, had m.p. 88–89°. (Found: C, 72.38; H, 11.32; N, 3.94; Calc for $C_{23}H_{43}NO_3$: C, 72.39; H, 11.36; N, 3.67%). $[\alpha]_D^{25} + 59.3°$ (*c* 0.782, $CHCl_3$). MS *m/e* 381. IR ($CHCl_3$) 3525, 2785, 2770 cm^{-1}. NMR δ 0.91 (d, J = 6 Hz, 3H), 0.93 (s, 3H), 1.32 (s, 3H), 1.48 (s, 3H), 1.53 (s, 3H), 2.15 (s, 3H), 2.58 (m, 1H), 3.65 (d, J = 8 Hz, 1H), 4.07 (br s, 1H), 4.18 (d, J = 8 Hz, 1H).

Preparation of [1R - [1β(R*,S*,E),3aα,4β,7aβ]] - *octahydro*- 7a - *methyl* - 1 - [1 - *methyl* - 4 - (2,2,4 - *trimethyl* - 1,3 - *dioxolan* - 4 - *yl*) - 3 - *butenyl*] - 1H - *inden* - 4 - *ol* (**20**)

A soln of 2.20 g (5.68 mol) of crude **19b** in 40.0 ml of absolute ether and 35.0 ml of freshly distilled MeI was stirred under a static argon atmosphere in a foil wrapped flask for 19 hr at room temp. The soln was evaporated to give 2.97 g of solid methiodide, which was dissolved in 75.0 ml of dry t-BuOH (freshly distilled from Na). After addition of 3.50 g (31.2 mmol) of t-BuOK, the mixture was heated at reflux for 23 hr. After the soln had cooled to room temp, the solvent was removed on a rotary evaporator, and the residue was triturated with 3 × 25 ml of hexane to give 2.23 g of crude product. Purification by flash chromatography through 20 g of silica gel using hexane–EtOAc (9:1) gave 1.402 g (73.4% yield) of **20**. An analytical sample (amorphous) was obtained by chromatography on silica gel (hexane–EtOAc, 1:2). (Found: C, 74.65; H, 10.93. Calc for $C_{21}H_{30}O_3$: C, 74.95; H, 10.78%). $[\alpha]_D^{25} + 31.7°$ (*c* 0.915, $CHCl_3$); IR ($CHCl_3$) 3620 cm^{-1}; NMR δ 0.89 (d, J = 6 Hz, 3H), 0.93 (s, 3H), 1.37 (s, 3H), 1.40 (s, 3H), 1.44 (s, 3H), 3.82 (dd, J = 9, 19 Hz, 1H), 4.09 (br s, 1H), 5.53 (d, J = 16 Hz, 1H), 5.67 (dt, J = 7, 16 Hz, 1H).

Preparation of [1R - [1β(R*,E,S*),3aα,4β,7aβ]] - 6 - (*octahydro* - 4 - *hydroxy* - 7a - *methyl* - 1H - *inden* - 1 - *yl*) - 2 - *methyl* - 4 - *heptene* - 1,2 - *diol* (**21**) *from* **19a**

A soln of 480 mg (1.4 mmol) of **19a** in 10 ml of dry toluene and 10 ml of distilled MeI was heated at 60° under an argon atmosphere for 23 hr. The volatile components were removed under reduced pressure. To the residue (methiodide) was added 4.5 ml of absolute EtOH and 735 mg (13.1 mmol) of KOH (ground in a mortar). The suspension was heated under an argon atmosphere at reflux (90° bath) for 23 hr. The EtOH was removed on a rotary evaporator, and the residue was partitioned between 5 ml of water and 25 ml of ether. After two additional 25-ml ether extractions, the ether phases were dried (Na_2SO_4), filtered, and evaporated to give 372 mg of crude product. Chromatography on two 0.5 m × 25 mm glass columns is series gave, on elution with EtOAc, three fractions: the first fraction (R_f 0.39, TLC, EtOAc) amounted to 50 mg (12%) of the C-23, C-26 cyclic ether (C-23 is presumably the R configuration). NMR δ 0.88 (d, J = 6 Hz, 3H), 0.90 (s, 3H), 1.33 (s, 3H), 3.38 (d, J = 10 Hz, 1H), 3.71 (d, J = 10 Hz, 1H), 3.95 (m, 1H), 4.03 (br S, 1H); the second fraction (R_f 0.23) was 9 mg (2%) of *trans* Δ^{23} olefin (isomer of **21**); NMR δ 0.91 (d, J = 6 Hz, 3H), 0.95 (s, 3H), 1.29 (s, 3H), 3.47 (br s, 1H), 4.10 (br s, 1H), 5.48 (d, J = 16 Hz, 1H), 5.73 (dt, J = 8, 16 Hz, 1H); the third fraction (R_f 0.18) afforded 246 mg (59%) of *trans* Δ^{22} olefine **21**. An analytical sample, m.p. 87–88° (MeOH-H_2O, 1:1). (Found: C, 72.66; H, 10.63. Calc for $C_{18}H_{32}O_3$: C, 72.93; H, 10.88%). $[\alpha]_D^{25}$ + 28.2° (*c* 0.748, $CHCl_3$); MS *m/e* 296; NMR δ 0.95 (s, 3H), 1.00 (d, J = 7 Hz, 3H), 1.16 (s, 3H), 2.19 (m, 2H), 3.44 (m, 2H), 4.09 (br s, 1H), 5.38 (m, 2H). ^{13}C NMR (25.2 mHz, $CDCl_3$, δ from internal TMS) C: 42.1, 72.7; CH: 40.3, 52.7, 56.2, 69.2, 121.6, 141.5; CH_2: 17.4, 22.5, 27.9, 33.9, 40.5, 42.1, 69.2; CH_3: 13.7, 20.5, 23.3.

Further elution of the columns with EtOAc–Et_3N–MeOH (8:1:1) led to the recovery of 23 mg (5%) of starting **19a** (R_f 0.28, EtOAc–Et_3N–MeOH, 94:5:1).

Preparation of [1R - [1β(R*,S*),3aα,4β,7aβ]] - *octahydro* - 7a - *methyl* - 1 - [1 - *methyl* - 4 - (2,2,4 - *trimethyl* - 1,3 - *dioxolan* - 4 - *yl*)*butyl*] - 1H - *inden* - 4 - *ol* **6**

To a soln of 1.33 g (3.95 mmol) of **20** in 25.0 ml of absolute EtOH was added 54 mg (0.39 mmol) of K_2CO_3 and 200 mg of 5% Pd–C. This suspension was stirred under H_2 atmosphere until absorption ceased (4 hr). After removal of the catalyst by filtration, the filtrate and washes were evaporated to give 1.27 g of residue. Chromatography on 25 × 1000 mm column of silica gel using hexane–EtOAc (3:1) gave 1.16 g (87% yield) of **6**. An analytical sample (amorphous). (Found: C, 74.51; H, 11.29; Calc for $C_{21}H_{38}O_3$: C, 74.51; H, 11.31%). $[\alpha]_D^{25}$ + 33.3° (c, 0.941, $CHCl_3$). IR ($CHCl_3$) 3620 cm^{-1}. NMR δ 0.91 (d, J = 6 Hz, 3H), 0.93 (s, 3H), 1.27 (s, 3H), 1.40 (s, 3H), 1.42 (s, 3H), 3.65 (AB d, J = 19 Hz, 1H), 3.77 (AB d, J = 19 Hz, 1H), 4.09 (br s, 1H).

Preparation of [1R[1β[β,S*],3aα,4β,7aβ]] - *octahydro* - β, 7a - *dimethyl* - 4 - [[(1,1 - *dimethylethyl*)*dimethylsilyl*]*oxy*] - 1H - *indene* - 1 - *ethanol* (**24c**)

To a soln cooled to 0° of 16.1 g (75.0 mmol) of **9** in 40 ml of dry pyridine in a 250 ml round-bottomed flask under an atmosphere of argon was added 9 ml (77.5 mmol) of benzoyl chloride over 10 min. The cooling bath was removed and the mixture stirred for 1 hr, then 2.5 ml of water was added. After stirring for 30 min the pyridine was removed under reduced pressure. The residue was taken up in 300 ml of CH_2Cl_2 and washed 4 × 50 ml of 1N HCl, 2 × 50 ml of sat $NaHCO_3$aq and 1 × 50 ml of brine, then dried over Na_2SO_4. Filtration and evaporation of solvent under reduced pressure yielded 24.0 g of crude monobenzoate. To a soln of the crude **24a** dissolved in 150 ml of dry dimethylformamide and 100 ml of CH_2Cl_2 under an atmosphere of argon was added 13.1 g (193 mmol) of imidazole and 16.4 g (109 mmol) of t-butyldimethylsilyl chloride. The mixture was stirred at room temp for 2 hr, then 20 hr at 45° after which an additional 5.0 g (33 mmol) of t-butyldimethylsilyl chloride and 4.0 g (59 mmol) of imidazole was added. The temp was raised to 80° and the CH_2Cl_2 was distilled from the reaction vessel. After 3 hr at 80° the cooled mixture was poured into a separatory funnel containing 200 ml of water. This was extracted 3 × 220 ml of hexane. The combined extracts were washed 3 × 100 ml of brine, 2 × 100 ml of water and dried over Na_2SO_4. Filtration and evaporation of volatiles under reduced pressure gave 39 g of crude **24b**. The crude **24b** was dissolved in 200 ml of MeOH and 50 ml of benzene and 14.4 g of 85% KOH pellets were added. The mixture was stirred at room temp for 2.5 hr, then solvents were removed under reduced pressure. The residue was taken up in 100 ml of water and extracted 3 × 100 ml of CH_2Cl_2. The combined extracts were dried over Na_2SO_4, filtered and solvent removed *in vacuo*. The crude product was filtered through a pad of silica gel with EtOAc and then chromatographed on silica gel eluting with EtOAc–hexanes–CH_2Cl_2 (7.5:42.5:50) to yield 20.0 g (82.6%) of **24c**. The analytical sample was recrystallized from acetonitrile, m.p. 65–66°, $[\alpha]_D^{25}$ + 43.26° (*c* 1.0403, $CHCl_3$). (Found: C, 69.68; H, 11.88. Calc for $C_{19}H_{38}O_2Si$: C, 69.87; H, 11.73%). NMR δ 0.02 (s, 6H), 0.90 (s, 9H), 0.96 (s, 3H), 1.03 (d, J = 7.5 Hz, 3H), 3.37 (dd, J = 8, 11 Hz, 1H), 3.65 (dd, J = 2, 11 Hz, 1H), 4.02 (br s, 1H).

Preparation of [1R - [1β,[β,S*],3aα,4β,7aβ]] - *octahydro* - β,7a - *dimethyl* - 4 - [[(1,1 - *dimethylethyl*)*dimethylsilyl*]*oxy*]- 1H - *indene* - 1 - *acetaldehyde* (**24d**)

To a soln of 1.64 g (5 mmol) of **24c** in 17 ml of dry CH_2Cl_2 was added 2.43 g (11 mmol) pyridinium chlorochromate. The mixture was stirred under an argon atmosphere for 1 hr then filtered through florisil eluting with diethyl ether. Evaporation of solvent gave 1.56 g (96%) of **24d** which was of sufficient purity to be used directly in the next step. IR ($CHCl_3$) 2715, 1720 cm^{-1}. NMR δ 0.02 (s, 6H), 0.90 (s, 9H), 0.97 (s, 3H), 1.10 (d, J = 7 Hz, 3H), 4.05 (br s, 1H), 9.61 (d, J = 3 Hz, 1H).

Preparation of [1R - [1β,[αS*,βS*],3aα,4aβ,7aβ]] - *octahydro* - β,7a - *dimethyl* - 4 - [[(1,1 - *dimethylethyl*)*dimethylsilyl*]*oxy*] - α - *ethenyl* - 1H - *indene* - 1 - *ethanol* (**25a**)

To a stirring soln of 40 ml of dry CH_2Cl_2 and 60.7 ml (79 mmol) of a 1.3M tetrahydrofuran soln of vinylmagnesium bromide which had been cooled under an argon atmosphere with a dry ice-acetone bath was added over 35 min, 8.5 g (26 mmol) of **24d** dissolved in 53 ml of dry CH_2Cl_2. The mixture was stirred 1.5 hr, then the excess vinylmagnesium bromide was quenched by the addition of 16 ml of sat Na_2SO_4aq and the mixture allowed to slowly warm to room temp. After approximately 30 min at room temp, the mixture was filtered through celite washing the solid with CH_2Cl_2. The filtrate was dried over anhydrous sodium sulfate, filtered and solvent removed under reduced pressure. The crude product was chromatographed on silica gel eluting with EtOAc–CH_2Cl_2–hexanes (5:20:75) to give 5.88 g (63%) of **25a**. The analytical sample was recrystallized from acetonitrile, m.p. 73.5–74°, $[\alpha]_D^{25}$ = + 10.58° (*c* 1.0207, $CHCl_3$). (Found: C, 71.56; H, 11.69. Calc for $C_{21}H_{40}O_2Si$: C, 71.53; H, 11.43%). NMR δ 0.02 (s, 6H), 0.86 (d, J = 7 Hz, 3H), 0.90 (s, 9H), 0.94 (s, 3H), 4.02 (s, 1H), 4.27 (br s, 1H), 5.13 (d, J = 11 Hz, 1H), 5.21 (d, J = 18 Hz, 1H), 5.86 (ddd, J = 4, 11, 18 Hz, 1H), and 1.108 g (12%) of the minor isomer; NMR δ 0.02 (s, 6H), 0.89 (s, 9H), 0.91 (d, J = 8 Hz, 3H), 0.94 (s, 3H), 4.00 (br s, 1H), 4.20 (br s, 1H), 5.16 (d, J = 11 Hz, 1H), 5.22 (d, J = 18 Hz, 1H), 5.87 (ddd, J = 7, 11, 18 Hz, 1H).

Preparation of [1R - [1β[αS*,βS*],3aα,4β,7aβ]] - *octahydro* - β,7a - *dimethyl* - 4 - [[1,1 - *dimethylethyl*)*dimethylsilyl*]*oxy*] - α - *ethenyl* - 1*H* - *indene* - 1 - *ethanol acetate* (**25b**)

Allylic alcohol **25a** (4.4 g (12 mmol)), 29 ml (0.31 mol) Ac_2O, 25 ml of pyridine and 0.1 g of 4 - N,N - dimethylaminopyridine were stirred under argon for 1.5 hr then diluted with 500 ml of diethylether and washed 4 × 100 ml

of 1N HCl, 2 × 100 ml of sat $NaHCO_3$aq, then dried over Na_2SO_4. After filtration and removal of volatiles *in vacuo*, the residue was filtered through 50 g of silica gel eluting with hexanes then EtOAc to give 4.9 g (99%) of **25b**, m.p. 42–43° (as obtained from LC), $[\alpha]_D^{25} = +8.8°$ (*c* 1.0297, $CHCl_3$). (Found: C, 69.86; H, 10.75. Calc for $C_{23}H_{42}O_3Si$: C, 70.00; H, 10.73%). IR ($CHCl_3$) 1730 cm^{-1}. NMR δ 0.02 (s, 6H), 0.89 (s, 9H), 0.92 (s, 3H), 0.94 (d, J = 7.5 Hz, 3H), 2.09 (s, 3H), 3.99 (br s, 1H), 5.06 (dm, J = 17 Hz, 1H), 5.15 (dm, J = 10 Hz, 1H), 5.38 (m, 1H), 5.74 (ddd, J = 6, 10, 17 Hz, 1H).

Preparation of [1R - [1β[α,R*,βS*],3aα,4β,7aβ]] - α - (*acetyloxy*)*octahydro* - β,7a - *dimethyl* - 4 - [[(1,1 - *dimethylethyl*)*dimethylsilyl*]*oxy*] - 1H - *indene* - 1 - *propanol* (**26**)

Ozone was passed through a cooled (− 78°) soln of 4.82 g (17 mmol) of **25b**, 400 ml of MeOH (which had been stored over molecular sieves) and 200 ml of CH_2Cl_2 (which had been stored over molecular sieves) until the soln became pale blue (10 min) then N_2 was bubbled through the soln for 10–15 min to remove the excess O_3. Dimethylsulfide (2.73 ml, 37 mmol) was added, the mixture was stirred at − 10° for 1 hr, 0° 1 hr, room temp 1 hr and then volatiles removed under reduced pressure. The solid residue was chromatographed (hexanes–EtOAc, 93:7) to give 4.37 g (90%) of **26** as a solid, m.p. 67–68°, $[\alpha]_D^{25} = +0.57°$ (*c* 1.0618, $CHCl_3$). (Found: C, 66.82; H, 10.29. Calc for $C_{22}H_{40}O_4Si$: C, 66.62; H, 10.17%). IR ($CHCl_3$) 2715, 1737 cm^{-1}. NMR δ 0.02 (s, 6H), 0.90 (s, 9H), 0.94(d, J = 7.5 Hz, 3H), 0.98 (s, 3H), 2.20 (s, 3H), 4.00 (br s, 1H), 5.10 (br s, 1H), 9.49 (s, 1H).

Preparation of [1R[1β,[αR*,βS*],3aα,4β,7aβ]] - *octahydro* - 4 - [[(1,1 - *dimethylethyl*) - *dimethylsilyl*]*oxy*] - β,7a - *dimethyl* - α - [[(1,1 - *dimethylethyl*)*imino*]*methyl*] - 1H - *indene* - 1 - *ethanol acetate* (*ester*) N-oxide (**27**)

To a cooled (0°) slurry of 3.34 g (8.4 mmol) of **26**, 1.73 g (0.035 mol) of N-t-butylhydroxylamine hydrochloride and 97 ml of CH_2Cl_2 (dried over 4Å molecular sieves) under argon was added dropwise 2.0 ml (14.3 mmol) of Et_3N. The cooling bath was removed and the mixture stirred at room temp for 40 hr after which it was diluted with 500 ml of CH_2Cl_2 and washed 2 × 100 ml of sat $NaHCO_3$aq, then dried over Na_2SO_4. Filtration and removal of volatiles *in vacuo* gave a thick yellow oil which on silica gel chromatography (hexanes–EtOAc, 60:40) gave 3.751 g (95%) of **27** as a solid. The analytical sample was recrystallized from hexanes, m.p. 121–122°, $[\alpha]_D^{25} = +18.99°$ (*c* 1.0532, $CHCl_3$). (Found: C, 66.63; H, 10.37; N, 2.86. Calc for $C_{26}H_{49}NO_4Si$: C, 66.76; H, 10.56; N, 2.99%). IR ($CHCl_3$) 1738 cm^{-1}. NMR δ 0.02 (s, 6H), 0.88 (s, 9H), 0.96 (s, 3H), 0.97 (d, J = 8 Hz, 3H), 1.50 (s, 9H), 2.10 (s, 3H), 3.98 (br s, 1H), 5.83 (br d, J = 5 Hz, 1H), 6.77 (d, J = 5 Hz, 1H).

Following a similar procedure, the N-benzylnitrone was obtained as a solid (m.p. 46–51°) after chromatography, $[\alpha]_D^{25} = +10.27°$ (*c* 0.9640, $CHCl_3$). (Found: C, 69.22; H, 9.46; N, 2.79. Calc for $C_{29}H_{47}NO_4Si$: C, 69.42; H, 9.44; N, 2.79%). IR ($CHCl_3$) 1737 cm^{-1}. NMR δ 0.02 (s, 6H), 0.89 (s, 9H), 0.91 (d, J = 8 Hz, 3H), 0.96 (s, 3H), 2.08 (s, 3H), 4.00 (br s, 1H), 4.89 (s, 2H), 5.85 (br d, J = 5 Hz, 1H), 6.63 (d, J = 5 Hz, 1H), 7.39 (s, 5H).

Preparation of [1R[1β[1S*,2R*[3S*(3α,5β)],3aα,4β,7aβ]] - 3 - [1 - (*acetyloxy*) - 2 - [*octahydro* - 4 - [[(1,1 - *dimethylethyl*) *dimethylsilyl*]*oxy*] - 7a - *methyl* - 1H - *inden* - 1 - *yl*] - 2 - *methylethyl*] - 2 - (1,1 - *dimethylethyl*) - 5 - *methyl* - 5 - *isoxazolidinecarboxylic acid methyl ester* **28**

A mixture of 3.313 g (7.1 mmol) of **27** and 37 ml of methyl methacrylate was heated under argon at 50° for 42 hr. Then the excess methacrylate was removed under reduced pressure. An analytical LC analysis (ether–heptane, 10:90) of the crude product showed an 81:0.3:18.7 mixture of three components. Since the middle component was never isolated, we can only speculate that it is indeed a diastereomer of the other two. The crude product was chromatographed on silica gel (ether–hexanes, 20:80) to give 3.26 g (81%) of the *SS* isomer **28**. The analytical sample was crystallized from MeOH (m.p. 119–120°), $[\alpha]_D^{25} = +61.01°$ (*c* 1.0228, $CHCl_3$). (Found: C, 65.33; H, 10.14; N, 2.24: Calc for $C_{31}H_{57}NO_6Si$: C, 65.57; H, 10.12; N, 2.47%). IR ($CHCl_3$) 1733 cm^{-1}; NMR δ 0.02 (s, 6H), 0.86 (d, J = 8 Hz, 3H), 0.89 (s, 9H), 0.92 (s, 3H), 1.05 (s, 9H), 1.54 (s, 3H), 1.96 (d, J = 14 Hz, 1H), 2.10 (s, 3H), 2.79 (dd, J = 8.5, 14 Hz, 1H), 3.44 (dd, J = 8.5, 9 Hz, 1H), 3.75 (s, 3H), 3.98 (br s, 1H), 5.05 (d, J = 9 Hz, 1H), (homonuclear decoupling at δ 3.44 indicates the coupling to 2.79 and 5.05); and 0.722 g (18%) of **29**, the analytical sample of which was recrystallized from MeOH, m.p. 109.5–110.5°, $[\alpha]_D^{25} = -1.04°$ (*c* 0.9645, $CHCl_3$). (Found: C, 65.46; H, 10.33; N, 2.40; Calc for $C_{31}H_{57}NO_6Si$: C, 65.57; H, 10.12; N, 2.47%). IR ($CHCl_3$) 1730 cm^{-1}; NMR δ 0.02 (s, 6H), 0.90 (s, 9H), 0.92 (d, J = 6 Hz, 3H), 0.96 (s, 3H), 1.02 (s, 9H), 2.04 (d, J = 14 Hz, 1H), 2.08 (s, 3H), 2.85 (dd, J = 9.5, 14 Hz, 1H), 3.47 (t, J = 9.5 Hz, 1H), 3.76 (s, 3H), 3.99 (br s, 1H), 5.11 (d, J = 9.5 Hz, 1H).

In similar fashion, when the N-benzylnitrone was stirred with excess methyl methacrylate at room temp for 15 hr, a mixture of four products in an 82:1:7:10 ratio (by analytical LC) was obtained. The major isomer, [1*R* - [1β[1*S**,2*R**[3*S**(3α,5β)],3aα,4β,7aβ]]] - 3 - [- 1 - (acetyloxy) - 2 - [octahydro - 4 - [[(1,1 - dimethylethyl)dimethylsilyl] oxy] - 7a - methyl - 1H - inden - 1 - yl] - 2 - methylethyl]- 5 - methyl - 2 - (phenylmethyl) - 5 - isoxazolidinecarboxylic acid methyl ester was obtained as a solid, m.p. 49–52° from chromatography on silica gel (hexanes–diethylether, 70:30) in 72% yield; $[\alpha]_D^{25} = +60.03°$ (*c* 0.9595, $CHCl_3$). (Found: C, 67.87; H, 9.30; N, 2.35. Calc for $C_{34}H_{55}NO_6Si$: C, 67.85; H, 9.21; N, 2.33%). IR ($CHCl_3$) 1733 cm^{-1}. NMR δ 0.02 (s, 6H), 0.33 (d, J = 6 Hz, 3H), 0.91 (s, 3H), 0.92 (s, 9H), 1.57 (s, 3H), 2.05 (s, 3H), 3.08 (dd, J = 8, 11 Hz, 1H), 3.30 (t, J = 8 Hz, 1H), 3.62 (d, J = 12 Hz, 1H), 3.80 (s, 3H), 3.98 (br s, 1H), 4.18 (d, J = 12 Hz, 1H), 5.01 (d, J = 8 Hz, 1H), 7.32 (s, 5H). The assignment of the 23S, 25S configuration is by direct analogy to our initial work done in the corresponding steroid series in which the stereochemistry of the major isomer was established by X-ray. The rather dramatic upfield shift of the C-21 Me group of the major isomer is especially diagnostic. Tentative assignment of the other three isomers was carried out by obtaining the NMR spectra on a mixture (components 1% and 7% by LC) of two isomers and a purified sample of the (10% by LC) remaining isomer. Since the 1% isomer does not show a strongly shifted C-21 methyl group the 23 configuration is assigned as R, and since the isoxazolidine ring proton at δ 2.73 is a dd of 4.5 and 13 Hz coupling the relative isoxazolidine ring stereochemistry was assigned as *cis*. The 1% isomer is *cis* 23*R*,25*S*. The 7% isomer on the other hand does have the strongly shifted C-21 Me group (δ 0.54) and is assigned the 23*S* configuration. The isoxazolidine ring proton at δ 2.85 is a dd (J = 3, 14 Hz) suggesting that like the 1% isomer, the isoxazolidine is *cis*, hence a 23*S*,25*R* configuration assignment for the 7% isomer. The 10% isomer does not have an abnormally shifted C-21 Me group and is assigned as 23*R*, while the similarity of the isoxazolidine ring proton at δ 3.00 (dd, J = 8, 13 Hz) to the major benzyl diastereomer would suggest a *trans* isoxazolidine ring and thus the 23*R*,25*R* configuration.

Preparation of [1R - [1β - [1S*,2R*[3S*(3α,5β)],3aα,4β, 7aβ]] - 3 - [1 - *hydroxy* - 2 - [*octahydro* - 4 - [[(1,1 - *dimethylethyl*)*dimethylsilyl*]*oxy*] - 7a - *methyl* - 1H - *inden* - 1 - *yl*] - 2 - *methylethyl*] - 2 - (1,1 - *dimethylethyl*) - 5 - *methyl* - 5 - *isoxazolidinecarboxylic acid methyl ester* (**30a**)

To a mixture of 3.292 g (5.8 mmol) of **28**, 40 ml of dry 4Å molecular sieves) MeOH and 8 ml of dry ($Ø_2CO$, Na) THF under argon was added dropwise with stirring 7.98 ml of 4.4M NaOMe in MeOH. The mixture was stirred 28 1/2 hr then cooled to 0° and treated with 35 ml of 1N HCl. The mixture

was taken up in 1500 ml of $CHCl_3$ and washed 2 × 250 ml of sat $NaHCO_3$aq, 1 × 250 ml of brine and dried over Na_2SO_4. The mixture was filtered, concentrated *in vacuo*, and chromatographed on silica gel (hexanes–EtOAc, 80:20) to give 2.488 g (82%) of **30a**. The analytical sample was recrystallized from hexanes, m.p. 130.1–130.8°, $[\alpha]_D^{25} = +36.20°$ (*c* 1.0084, $CHCl_3$). (Found: C, 66.01; H, 10.30; N, 2.61. Calc for $C_{29}H_{55}NO_5Si$: C, 66.24; H, 10.54; N, 2.66%). IR ($CHCl_3$) 1735 cm^{-1}. NMR δ 0.01, 0.02 (s, 6H), 0.90 (s, 9H), 0.91 (d, J = 6 Hz, 3H), 0.94 (s, 3H), 1.53 (s, 3H), 2.56 (dd, J = 4.5, 13 Hz, 1H), 2.79 (dd, J = 8.5, 13 Hz, 1H), 3.29 (br dd, J = 4.5, 8.5 Hz, 1H), 3.67 (br s, 1H), 3.76 (s, 3H), 4.00 (br s, 1H).

Preparation of [1R - [1β - [1S*,2R*[3S*(3α,5β)],3aα,4β, 7aβ]] - 3 - [1 - (*methanesulfonyloxy*) - 2 - [*octahydro* - 4 - [[(1,1 - *dimethylethyl*)*dimethylsilyl*]*oxy*] - 7a - *methyl* - 1H - *inden* - 1 - *yl*] - 2 - *methylethyl*] - 2 - (1,1 - *dimethylethyl*) - 5 - *methyl* - 5 - *isoxazolidinecarboxylic acid methyl ester* (**30b**)

To a soln of 0.945 g (1.8 mmol) of **30a**, 17 ml of dry pyridine (4Å molecular sieves) and 22 mg of 4-N,N - dimethylaminopyridine under argon and cooled to 0° was added in small portions 1.56 g (8.9 mmol) of methanesulfonic anhydride. The cooling bath was removed, the mixture stirred 30 min, cooled to 0°, 5 ml of water added, cooling bath removed. After stirring at room temp for 1 hr, 76 ml of 2N H_2SO_4 was added and the mixture then added to 378 ml of 2N H_2SO_4, extracted 4 × 250 ml of EtOAc. The combined EtOAc extracts were washed 3 × 150 ml of 1N H_2SO_4, 1 × 150 ml of sat $NaHCO_3$aq, 1 × 150 ml of water and dried over Na_2SO_4. Filtration and evaporation of solvent *in vacuo* gave 1.2 g of crude product which was used directly in the next step. An analytical sample was obtained from a similar run by chromatography on silica gel to give a solid with m.p. 160–162°, $[\alpha]_D^{25} = +42.02°$ (*c* 1.0542, $CHCl_3$). (Found: C, 59.59; H, 9.52; N, 2.13. Calc for $C_{30}H_{57}NO_7SSi$: C, 59.66; H, 9.51; N, 2.32%). IR ($CHCl_3$) 1733 cm^{-1}. NMR δ 0.01, 0.02 (s, 6H), 0.90 (s, 9H), 0.95 (s, 3H), 0.97 (d, J = 7 Hz, 3H), 1.55 (s, 3H), 2.43 (dd, J = 5, 13 Hz, 1H), 3.00 (dd, J = 8, 13 Hz, 1H), 3.25 (s, 3H), 3.42 (m, 1H), 3.77 (s, 3H), 4.85 (d, J = 4 Hz, 1H).

Preparation of [1R - [1β - [1S*,2S* - [3S* - (3α,5β)],3aα,4β, 7aβ]] - 3 - [1 - *bromo* - 2 - [*octa* - *hydro* - 4 - [[(1,1 - *dimethylethyl*)*dimethylsilyl*]*oxy*] - 7a - *methyl* - 1H - *inden* - 1 - *yl*] - 2 - *methylethyl*] - 2 - (1,1 - *dimethylethyl*) - 5 - *methyl* - 5 - *isoxazolidinecarboxylic acid methyl ester* (**31**)

The crude **30b** from the previous reaction was refluxed under argon with 47 ml of reagent grade acetone and 1.25 g (14 mmol) of anhy. LiBr for 3 hr. The acetone removed *in vacuo*, the residue taken up in 400 ml of $CHCl_3$ and washed 2 × 100 ml of water, and the combined water washes re-extracted with 2 × 100 ml of $CHCl_3$. The combined $CHCl_3$ extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexanes–diethyl ether, 95:5) to give 1.422 g (75% for the two steps) of **31**. The analytical sample was recrystallized from isopropanol, m.p. 105–106°, $[\alpha]_D^{25} = +43.04°$ (*c* 0.9666, $CHCl_3$), (Found: C, 59.18; H, 9.44; N, 2.17. Calc for $C_{29}H_{54}BrNO_4Si$: C, 59.16; H, 9.25; N, 2.38%). IR ($CHCl_3$) 1733 cm^{-1}. NMR δ 0.02 (s, 6H), 0.88 (s, 9H), 0.89 (d, J = 6 Hz, 3H), 0.95 (s, 3H), 1.04 (s, 9H), 1.52 (s, 3H), 2.20 (m, 1H), 2.78 (dd, J = 2, 14 Hz, 1H), 2.90 (dd, J = 8, 14 Hz, 1H), 3.56 (br t, J = 8 Hz, 1H), 3.78 (s, 3H), 4.02 (br s, 1H), 4.23 (d, J = 11 Hz, 1H).

Preparation of [1R - [1β - (R*,E,S*),3aα,4β,7aβ]] - 6 - (*octahydro* - 4 - [(1,1 - *dimethylethyl*) - *dimethylsilyl*]*oxy* - 7a - *methyl* - 1H - *inden* - 1 - *yl*) - 2 - *hydroxy* - 2 - *methyl* - 4 - *heptenecarboxylic acid methyl ester* (**33**)

To a soln of 0.604 g (1.03 mmol) of **31** in 18 ml of AcOH under argon was added in small portions 6 g of Zn dust. The mixture was stirred for 5.5 hr during which time two more portions of Zn dust were added. The mixture was filtered through Celite washing successively with AcOH, EtOAc and $CHCl_3$. The solvents were removed *in vacuo* and the residue taken up in 600 ml of EtOAc, washed 2 × 200 ml of sat $NaHCO_3$aq and dried over Na_2SO_4. After filtration, concentration *in vacuo* and chromatography on silica gel (hexanes–EtOAc, 94:6), olefin **33** was isolated in 87% yield. $[\alpha]_D^{25} = +40.22$ (*c* 1.0566, $CHCl_3$). (Found: C, 68.29; H, 10.40. Calc for $C_{25}H_{46}O_4Si$: C, 68.44; H, 10.57%). IR ($CHCl_3$) 1735 cm^{-1}. NMR δ 0.02 (s, 6H), 0.89 (s, 9H), 0.92 (s, 3H), 0.97 (d, J = 7 Hz, 3H), 1.42 (s, 3H), 2.25 (dd, J = 6, 14 Hz, 1H), 2.42 (dd, J = 5, 14 Hz, 1H), 3.03 (s, 1H, OH), 3.77 (s, 3H), 3.99 (br s, 1H), 5.28 (m, 2H). When the reaction was stopped for 20 min, the corresponding N-t-butylhydroxylamine olefin (**32**) was isolated. NMR (100 mHz) δ 0.01, 0.02 (s, 6H), 0.90 (s, 9H), 0.92 (d, J = 7 Hz, 3H), 1.09 (s, 12H), 2.35 (m, 2H), 3.71 (s, 3H), 3.99 (br s, 1H), 5.28 (d, J = 12.5 Hz, 1H), 5.31 (d, J = 12.5 Hz, 1H).

Preparation of [1R - [1β - (R*,E,S*),3aα,4β,7aβ]] - 6 - (*octahydro* - 4 - [(1,1 - *dimethylethyl*) - *dimethylsilyl*] - *oxy* - 7a - *methyl* - 1H - *inden* - 1 - *yl*) - 2 - *methyl* - 4 - *heptene* - 1,2 - *diol* (**34a**)

To a cooled (0°) suspension of 0.122 g of LAH and 3.2 ml of dry ($Ø_2CO$, Na) THF was added 0.336 g (0.77 mmol) of **33** and 4 ml of dry THF over 2 min. After 1 hr, 0.061 g of LAH added, mixture stirred for 20 min, then the cooling bath was removed. After an additional 2 1/2 hr, the mixture was recooled to 0°, 0.6 ml of EtOAc was added. After stirring for 10 min, 3.5 ml of sat NH_4Claq was added, cooling bath removed and the mixture stirred 25 min, and then filtered through Celite washing with $CHCl_3$ and EtOAc. The filtrates were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexanes–EtOAc, 6:4) to give **34a** in 89% yield, $[\alpha]_D^{25} = +48.57°$ (*c* 0.9388, $CHCl_3$). (Found: C, 69.84; H, 11.39. Calc for $C_{24}H_{46}O_3Si$: C, 70.19; H, 11.29%). NMR δ 0.03 (s, 6H), 0.93 (s, 9H), 0.98 (s, 3H), 1.04 (d, J = 7 Hz, 3H), 1.19 (s, 3H), 3.46 (br s, 2H), 4.02 (br s, 1H), 5.39 (m, 2H).

Preparation of diol **21** *from* **34a**

To a soln of 0.257 g (0.63 mmol) of the silyl ether, 3.6 ml of acetonitrile and 3.0 ml of THF under argon was added 2.8 ml of 48% aqueous HF. The cloudy mixture was stirred for 3 hr then poured into 200 ml of $CHCl_3$ and 20 ml of water. The aqueous phase was extracted 2 × 100 ml of $CHCl_3$ and the combined $CHCl_3$ layers washed 1 × 20 ml of sat $NaHCO_3$aq. The extract was dried over $NaSO_4$, filtered and concentrated *in vacuo*. The residue was chromatographed (EtOAc) on silica gel to give 0.176 g (95%) of **21**. This material was identical to the **21** prepared from **19a** by ^1H NMR, ^{13}C NMR and mixed m.p.

Preparation of [1R - [1β - (R*,S*,E) - 3aα,4β,7aβ]] - *octahydro* - 7a - *methyl* - 1 - [1 - *methyl* - 4 - [(2,2,4 - *trimethyl* - 1,3 - *dioxolan* - 4 - *yl*) - 4 - *butenyl*] - 1H - *inden* - 4 - *ol* (**34b**)

A soln of 0.254 g (0.857 mmol) of **21**, 10 ml of 2,2-dimethoxypropane and 16 mg of toluenesulfonic acid monohydrate was stirred under argon at room temp for 50 min, then 2.0 ml of MeOH was added. The mixture was stirred an additional 45 min, then 2.5 ml of sat $NaHCO_3$aq was added. The mixture was stirred for 1 hr then diluted with 150 ml of $CHCl_3$ and washed 1 × 10 ml of water. The aqueous phase was extracted 2 × 50 ml of $CHCl_3$ and the combined $CHCl_3$ layers dried over Na_2SO_4. The mixture was filtered, concentrated under reduced pressure and chromatographed on silica gel (hexanes–EtOAc, 25:75) to give 0.259 g (90%) of **34c** as an oil. (Found: C, 74.65; H, 10.93. Calc for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78%). $[\alpha]_D^{25} = +21.27°$ (*c* 0.6018, $CHCl_3$). NMR δ 0.95 (s, 3H), 1.00 (d, J = 7 Hz, 3H), 1.26 (s, 3H), 1.40 (s, 6H), 3.64 (d, J = 8 Hz, 1H), 3.81 (d, J = 8 Hz, 1H), 4.07 (br s, 1H), 5.31 (m, 2H).

Preparation of **6** *from* **34b**

The acetonide **34b** was hydrogenated at atmospheric pressure over 10% Pd/C in EtOAc. Filtration and removal of solvent *in vacuo* gave the saturated **6** quantitatively. This material was identical to **6** prepared from **20** by ^{1}H NMR and mixed ^{13}C NMR. ^{13}C NMR (50 mHz, δ from TMS) C: 108.8, 81.3, 41.5; CH: 69.3, 56.4, 52.4, 34.7; CH_2: 74.0, 40.4, 40.0, 35.8, 33.2, 26.7, 22.1, 20.4, 17.1; CH_3: 26.7 (2), 24.3, 18.2, 13.3.

Preparation of [1R - [1β(R*,S*),3aα,7aβ]] - *octahydro* - 7a - *methyl* - 1 - [1 - *methyl* - 4 - [(2,2,4 - *trimethyl* - 1,3 - *dioxolan* - 4 - *yl*)*butyl*] - 4H - *inden* - 4 - *one* (**3**)

To a suspension of 1.720 g (5.87 mmol) of 2,2'-bipyridinium chlorochromate and 0.860 g (10.48 mmol) of anhyd NaOAc in 10 ml of CH_2Cl_2 was added a soln 0.500 g (1.47 mmol) of **6** in 5 ml of CH_2Cl_2 and the mixture obtained stirred at room temp for 2 hr. Additional 0.800 g (2.73 mmol) of 2,2'-bipyridinium chlorochromate was then added and the stirring continued for an additional 2.5 hr. After this time, 1 ml of 2-propanol was introduced and 15 min later, the mixture diluted with water and extracted with ether. The combined organic phases were dried, evaporated and the residue purified by fast filtration through silica gel (eluent: hexane–EtOAc, 3:1) to give 0.446 g (90% yield) of pure **3**. $[\alpha]_D^{25} = +14.4°$ (*c* 0.5, EtOH). NMR (100 mHz) δ 0.64 (s, 3H), 0.96 (br d, J = 6 Hz), 1.27 (s, 3H), 1.39 (s, 6H), 3.68 (d of AB, J = 8.0 Hz, 1H), 3.80 (d of AB, J = 8.0 Hz, 1H); IR ($CHCl_3$) 1705, 1380, 1240, 1060 cm^{-1}; MS *m/e* (%) 321 (66), 261 (24), 115 (100), (Found: C, 75.21; H, 10.71. Calc for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78%).

Preparation of 1α,25S,26 - *trihydroxycholecalciferol* (**2**)

A soln of 1.430 g (2.45 mmol) of **4** in 30 ml of anhyd THF was treated dropwise and under argon at − 78° with 1.4 ml (2.38 mmol) of a 1.7 molar soln of n-BuLi in hexane. Five min after the addition was completed, a soln of 0.460 g (1.36 mmol) of **3** in 5 ml of anhyd THF was added dropwise and the resulting mixture stirred at − 78° for 2.5 hr. It was then treated (at − 78°) with 5 ml of a 1N $NaHCO_3$aq and potassium sodium tartrate, allowed to come to room temp and extracted with EtOAc. The combined organic extracts were dried, evaporated and the residue purified by chromatography on silica gel (using hexanes–EtOAc, 5:1 as eluent) to give 0.910 g of **5** as a thick oil. This was dissolved in 200 ml of MeOH, to which 45 g of a cation exchange resin (AG 50W-X4, 200–400 mesh from Bio-Rad Laboratory, prewashed with MeOH) was added and the mixture stirred at room temp under argon for 16 hr. After filtration, the MeOH soln was evaporated to dryness and the residue redissolved in 100 ml of EtOAc and washed 3 × with brine. The organic phases were combined, dried, evaporated and the residue purified by chromatography on silica gel (eluted with EtOAc) to give 0.486 g (86% yield) of pure metabolite. Crystallization from methyl formate gave white needles, m.p. 163–164°, $[\alpha]_D^{25} = +58.8°$ (*c* 0.5, MeOH); NMR (200 mHz, CD_3OD) δ 0.57 (s, 3H), 0.96 (d, J = 6.4, 3H), 1.12 (s, 3H), 4.87 (br s, 1H), 5.28 (br s, 1H), 6.08 (d of AB, J = 10.4, 1H), 6.34 (d of AB, J = 10.4, 1H); IR (KBr) 3400, 1050 cm^{-1}; MS *m/e* (%) M^+ 432 (6), 414 (8), 396 (6), 287 (8), 269 (10), 251 (10), 152 (36), 134 (100); UV max (EtOH) 265 nm (ϵ 17,080). (Found: C, 74.88; H, 9.95 Calc for $C_{27}H_{44}O_4$: C, 74.96; H, 10.25%).

Acknowledgements—We wish to express our gratitude to the members of the Physical Chemistry Department of Hoffman-La Roche Inc. for determinations of spectral and analytical data and to Dr. J. F. Blount and his staff for carrying out the X-ray analyses. We also thank Mr. A. Williams for technical assistance.

REFERENCES

[1a]A. W. Norman, *Vitamin D, Molecular Biology and Clinical Nutrition*. Marcel Dekker, New York (1980); [b]H. F. DeLuca, H. E. Paaren and H. K. Schnoes, *Ann. Rep. Med. Chem.* **15**, 288 (1980).

[2]T. A. Reinhardt, J. L. Napoli, D. C. Beitz, E. T. Littledike and R. L. Horst, *Biochem. Biophys. Res. Commun.* **99**, 302 (1981).

[3]J. J. Partridge, S.-J. Shiuey, N. K. Chadha, E. G. Baggiolini, B. M. Hennessy, M. R. Uskoković, J. L. Napoli, T. A. Reinhardt and R. L. Horst, *Helv. Chim. Acta* **64**, 2138 (1981).

[4]E. G. Baggiolini, J. A. Iacobelli, B. M. Hennessy and M. R. Uskoković, *J. Am. Chem. Soc.* **104**, 2945 (1982).

[5]R. A. Micheli, Z. G. Hajos, N. Cohen, D. R. Parrish, L. A. Portland, W. Sciamanna, M. Scott and P. A. Wehrli, *J. Org. Chem.* **40**, 675 (1975).

[6]W. D. Emmons and G. B. Lucas, *J. Am. Chem. Soc.* **77**, 2287 (1955).

[7]For precedent in the steroid series see: A. D. Batcho, D. E. Berger, S. G. Davoust, P. M. Wovkulich and M. R. Uskoković, *Helv. Chim. Acta* **64**, 1682 (1981).

[8]H. H. Inhoffen, G. Quinkert, S. Schütz, G. Friedrich and E. Tober, *Chem. Ber.* **91**, 781 (1958). For a recent synthesis of diol **9**, see: B. M. Trost, P. R. Bernstein and P. C. Funfschilling, *J. Am. Chem. Soc.* **102**, 4378 (1979).

[9]B. Lythgoe, D. A. Roberts and I. Waterhouse, *J. Chem. Soc.* Perkin Trans. I 2608 (1977).

[10]For precedent of regiochemistry in [3 + 2] cycloadditions see: R. Huisgen, H. Hauck, R. Grashey and H. Seidl, *Chem. Ber.* **101**, 2568 (1968); K. N. Houk, J. Sims, R. E. Duke, R. W. Strozier and J. K. George, *J. Am. Chem. Soc.* **95**, 7287 (1973) and refs therein.

[11]For examples of reversible nitrone-olefin cycloadditions see: C. W. Brown, K. Marsden, M. A. T. Rogers, C. M. B. Tylor and R. Wright, *Proc. Chem. Soc. London* 254 (1960); G. R. Delpierre and M. Lamchen, *J. Chem. Soc.* 4693 (1963); N. A. LeBel, *Trans. N. Y. Acad. Sci.* **27**, 858 (1965); R. Huisgen, H. Hauck, R. Grashey and H. Seidl, *Chem. Ber.* **101**, 2568 (1968); J. J. Tufariello and G. B. Mullen, *J. Am. Chem. Soc.* **100**, 3638 (1978).

[12]We thank Dr. B. A. Pawson for suggesting this possibility.

[13]B. Bernet and A. Vasella, *Helv. Chim. Acta* **62**, 2411 (1979) and references therein.

[14]R. F. Newton and R. F. Reynolds, *Tetrahedron Letters* 3981 (1979).

[15]F. S. Gusiec and F. A. Luzzio, *Synthesis* 691 (1980).