Ultrasonically Induced Conjugate Addition of Iodides to Electron-Deficient Olefins and Its Application to the Synthesis of Side-Chain Analogs of the Hormone 1α,25-Dihydroxyvitamin D_3[1]

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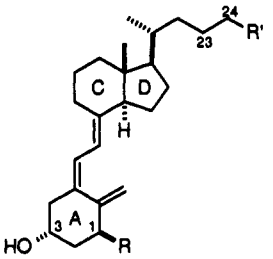
Received July 13, 1992

A versatile method for the rapid construction of fragments related to the upper part of vitamin D_3 from the Lythgoe–Inhoffen diol is described. The key feature of the strategy is a new zinc–copper-induced conjugate addition of iodo triflate **10a** to electron-deficient olefins under sonochemical aqueous conditions. These fragments are rapidly and efficiently transformed via the dienyne convergent approach to several derivatives of the hormone 1α,25-$(OH)_2$-D_3 modified at C-25.

Introduction

Vitamin D_3 (**1a**) is a prohormone classically associated with homeostasis of calcium and phosphorus through the regulation of intestinal calcium absorption and bone calcium mobilization.[2] It is now well-established that these biological effects of vitamin D_3 occur as a consequence of its sequential metabolism to 25-hydroxyvitamin D_3 (**1b**) in the liver and to the hormone 1α,25-dihydroxyvitamin D_3 (**1c**) in the kidney. Like other steroid hormones, the mode of action of **1c** on target cells is mediated by specific receptors.[2,3]



1a R = H, R' = $CHMe_2$
1b R = H, R' = $C(OH)Me_2$
1c R = OH, R' = $C(OH)Me_2$
14 R = OH, R' = $C(OH)(CD_3)_2$
15 R = OH, R' = C(OH)(cyclopropyl)$_2$
16 R = OH, R' = C(OH)(*t*-butyl)$_2$
17 R = OH, R' = $C(OH)Ph_2$
18 R = OH, R' = SO_2Me

Investigations carried out during the last decade have shown that 1α,25-dihydroxyvitamin D_3 is involved in the regulation of the function of a broader range of cells than those of bone and intestine.[4] It has been found that the hormone induces the terminal differentiation and supresses the proliferation of human myeloid leukemic cells,[5] epidermal keratinocytes,[6] and several types of cancer cell[7] and alters the immune response of lymphocytes.[8] These findings have enormously stimulated research aimed at evaluating the clinical possibilities of the hormone and its derivatives in the treatment of cancer, psoriasis, and immune disorders.[5-9] The cellular mechanisms by which these effects are brought about are not yet fully understood, but is believed that both classical nuclear receptor-mediated regulation of gene transcription and nongenomic pathways may be involved.[10]

A key issue with regard to the spectrum of biological effects of 1α,25-$(OH)_2$-D_3 (**1c**) is whether it is possible to design analogs which are capable of inducing selective or differential biological responses, e.g., promotion of cell differentiation without stimulation of calcium activity.[11] A growing amount of research is being directed to this end, and the results reported so far indicate that side-chain modifications are especially effective for modulating the selectivity and activity of the hormone.[10,12] It is

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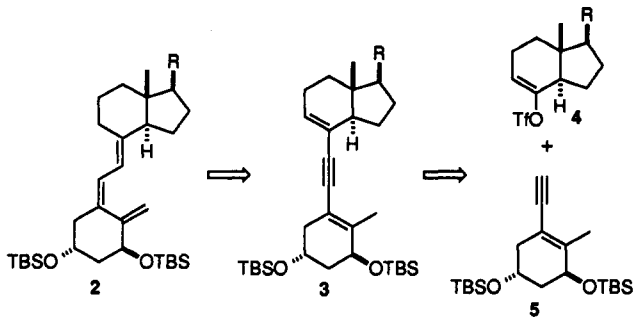
Scheme I



therefore of interest to develop flexible methods allowing the synthesis of a wide variety of side-chain analogs that could be screened for clinical application and/or used as biochemical tools for investigating the molecular mechanisms underlying the biological actions.

We have recently reported a short, flexible route to 25,26,27-trisnor-24-(methoxycarbonyl)vitamin D_3. The key steps were a sonochemical-induced conjugate addition of iodide **6b** to methyl acrylate and a Wittig–Horner coupling between the keto ester **7** and a known vitamin D ring-A phosphine oxide synthon.[13] Here, we report the application of the sonochemical methodology in conjunction with the dienyne approach to the vitamin D triene[14] for the preparation of the more important 1α-hydroxylated derivatives. Our efforts have led to the development of a versatile route for the synthesis of the hormone **1c** and several analogs modified at C-25 of potential biomedical interest (14–18). The key feature of the strategy is a new zinc–copper-induced conjugate addition of the iodo triflate **10a** to methyl acrylate and other α,β-unsaturated compounds under sonochemical aqueous conditions.

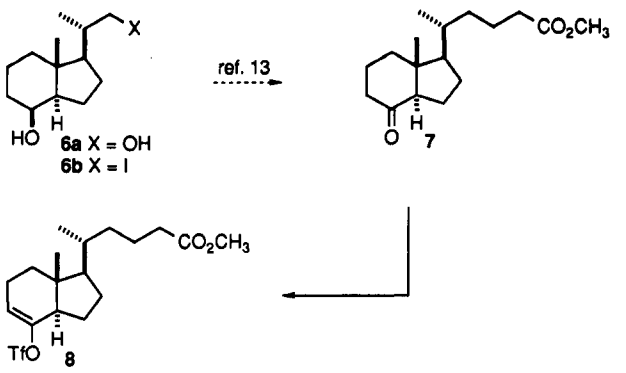
Results and Discussion

The synthetic plan for the preparation of the 1α-hydroxy derivatives shown above is based on our recently improved convergent dienyne strategy (Scheme I).[14] The availability of ring-A enyne **5**[15] makes this route especially convenient.

Synthesis of Ester 13. Although the required triflate **8** can be prepared from the known keto ester **7**,[13] the best conditions found to carry out this transformation [slow addition of **7** to a cold (−90 °C) solution of LDA (1.1 equiv) in THF and subsequent quenching with excess *N*-phenyltriflimide] gave **8** in only 51% yield (Scheme II).

We then envisaged the possibility of forming the vinyl triflate before the introduction of the side chain so as to avoid problems arising from the presence of acidic hydrogens in the latter. It was reasoned that the mild conditions used for sonochemical conjugate addition or alkyl halides to electron-deficient olefins might permit the construction of the side chain in the presence of the vinyl triflate.[13,18] Iodide **6b**, previously synthesized from

Scheme II



the Inhoffen–Lythgoe diol **6a** by a two-step procedure,[14c] was better prepared in 95% yield by reaction of **6a** with Ph_3P and I_2 at 0 °C following Samuelson's procedure.[16] Iodo alcohol **6b** was efficiently oxidized with PDC to iodo ketone **9** (Scheme III), and the kinetic enolate prepared by treatment of this ketone with LDA at low temperature was trapped with *N*-phenyltriflimide to give triflate **10a** (86% for two steps). Interestingly, sonication of a mixture of **10a**, Zn, CuI, and methyl acrylate in 7:3 EtOH/H_2O at room temperature afforded ester **8** in a satisfactory 65% yield.[13,17] Most of the remaining material separated was identified as the protonated product **10b**. Although the mechanism of the reaction is still not clear, studies by Luche and co-workers indicate that the reaction follows most probably a radical pathway, the key step being a sonochemically promoted single-electron transfer from the metal to the C–X bond.[18] The compatibility of the sonochemical reaction with the vinyl triflate, which would not be left intact by most current organometallic methods for C–C bond formation, expands the scope and usefulness of this procedure and further illustrates the high potential of ultrasound in synthesis.[19]

Palladium-catalyzed coupling between vinyl triflate **8** and enyne **5** furnished dienyne **11** in 86% yield. Partial hydrogenation of the dienyne in the presence of Lindlar catalyst poisoned with quinoline, with careful monitoring of the reaction to avoid overreduction of the triple bond, afforded **12** in 95% yield. The previtamin **12** was refluxed in isooctane for 4 h to bring about equilibration to the vitamin **13**.[20]

Synthesis of C-25 Dialkylated Derivatives of the Hormone 1c. With ester **13** at hand, the preparation of **1c**, its labeled counterpart **14**, and C-25 dialkylated derivatives was straightforward. As shown in Table I the hormone **1c** as well as the hexadeuteriated derivative **14** were efficiently obtained by treatment of ester **13** with the corresponding Grignard reagent and subsequent removal of the silyl groups with TBAF. The number of steps and overall yield of the synthesis of **1c** (eight steps from the

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Scheme III

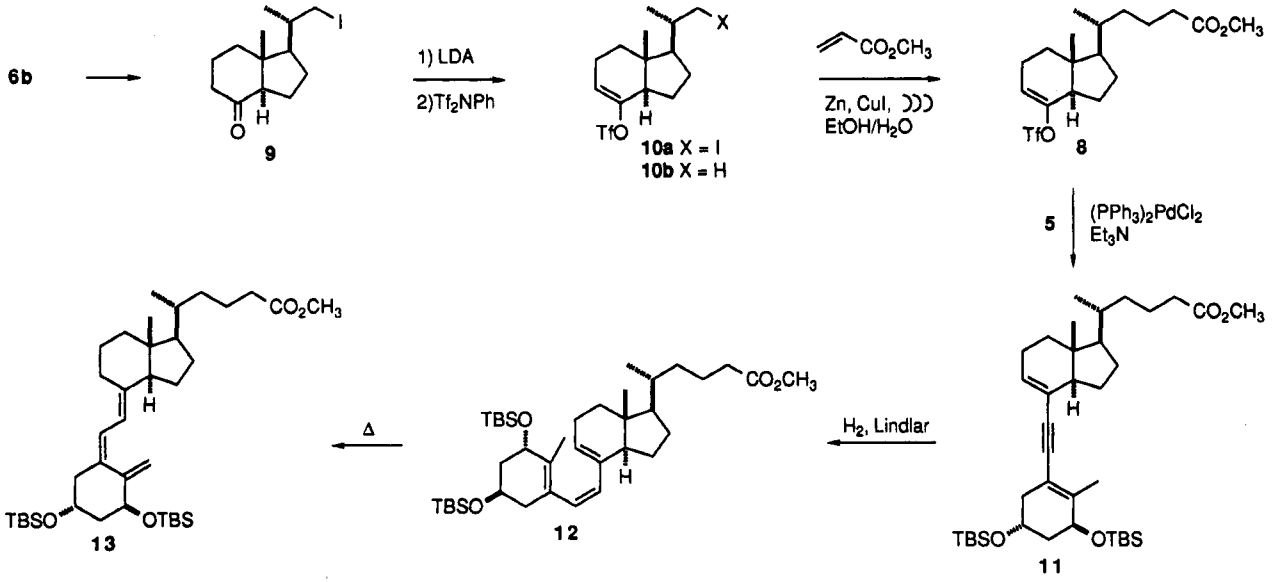


Table I. Dialkylation of Ester 13

entry	organomet reagent[a]	product[b]	% yield[c]
1	$IMgCH_3$	1c	73
2	$IMgCD_3$	14	72
3	cyclopropyllithium	15	65
4	*tert*-butyllithium	16	68
5	phenyllithium	17	71

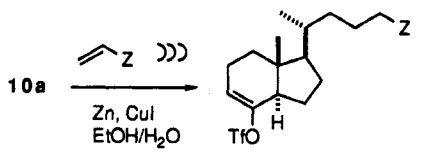
[a] 2.2 equiv. [b] These are the products obtained after removal of the silyl groups with TBAF. [c] Overall yield for two steps.

Inhofen–Lythgoe diol, 41% overall yield) compare favorably with previously reported approaches.[14c,21]

The remarkably low calcemic and potent antiproliferative properties exhibited by several 26,27-dialkylated derivatives of the hormone[10,22] prompted us to use ester **13** to prepare derivatives of this kind. The methods previously described for the synthesis of these 26,27-dialkylated derivatives generally involve long linear approaches.[22] Analogs **15**, **16**, and **17**, in which the 26,27-CH_3 groups of the hormone are replaced by cyclopropyl, *tert*-butyl, and phenyl groups, respectively, were readily synthesized by reaction of **13** with the corresponding lithium carbanions and subsequent desilylation (Table I). The biological activity of these compounds is now being tested, and the results will be reported elsewhere. We hope that the data obtained will confirm the therapeutical possibilities of this kind of compounds and will contribute to understanding the relation between the spatial environment of the 25-OH group and biological activity.

Sonochemical Addition of Iodo Triflate 10a to other Olefins. With the purpose of applying our approach to the synthesis of a wider range of side-chain analogs of the hormone and to assess the scope and potential of the sonochemical reaction described above, the addition of iodide **10a** to other types of olefins was studied. The results are summarized in Table II. Reaction of **10a** with methyl vinyl ketone, acrylonitrile, and acrylamide gave the adducts in synthetically useful yields. Reaction with olefins having sulfone or sulfoxide as electron-withdrawing groups was also satisfactory. The efficiency of the addition to the vinyl sulfoxide is particularly noteworthy since other carbon nucleophiles are usually unreactive toward this unsaturated functionality.[23]

Table II. Sonochemical Conjugate Additions



Z[a]	adduct	time (min)	yield[b] (%)
CO_2CH_3	8	45	65
$COCH_3$	19	35	73
CN	20	40	65
$CONH_2$	21	75	35
SO_2CH_3	22	15	72
SOPh	23	70	45

[a] 5–20 equiv in excess of the olefin are used. [b] Isolated yield.

Synthesis of Sulfonyl Derivative 18. It has been reported that introduction of heteroatoms into the side chain of hormone **1c** can afford biologically interesting analogs.[12b,24] However, few derivatives with heteroatoms in place of carbon atoms at C-25 have hitherto been synthesized.[25] Having shown that the above sonochemical reaction of the key iodo triflate **10a** allows rapid and practical construction of side chains with heteroatoms at that position, we validated the dienyne route to the corresponding vitamin D analogs by using it to prepare

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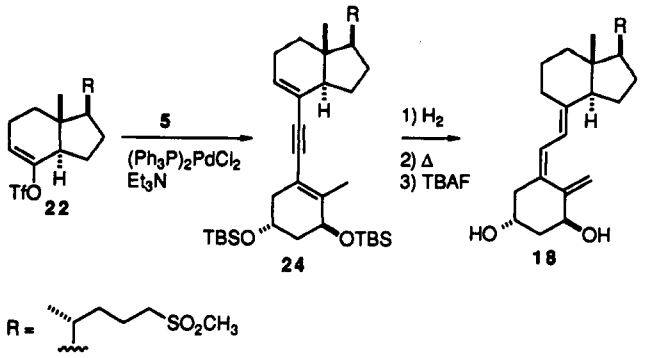
Scheme IV



sulfone **18**. It is expected that the presence of the polar sulfone group will alter the transport and binding properties of the compound and that this may affect its biological behavior.

Palladium-catalyzed coupling of triflate **22** with enyne **5** gave dienyne **24** in a moderate 65% yield (Scheme IV). Partial hydrogenation, thermal isomerization, and removal of the silyl groups afforded the hormone analog **18** (78% yield for three steps). The application of our approach to the synthesis of other analogs of the hormone and the biological evaluation (antiproliferative and calcemic activity as well as receptor affinities) of all these compounds will be reported elsewhere.

Conclusion

A short, versatile approach to side-chain derivatives of the hormone $1\alpha,25\text{-}(OH)_2\text{-}D_3$ modified at C-25 has been described. The key feature of the strategy is the ultrasonically-induced conjugate addition of iodo trilfate **10a** to electron-deficient olefins under aqueous conditions. The mildness and simplicity of this method and the fact that, unlike current methods for carbon–carbon bond formation it is compatible with the vinyl triflate group, illustrates the potential of sonochemical procedures in organic synthesis.

In contrast to lengthy linear approaches previously reported, the route described here is especially efficient for preparation of C-25 dialkylated and C-25 heterosubstituted derivatives of hormone **1c**. It is our expectation that the information obtained from assays of the biological activity and binding properties of such analogs will contribute to our understanding of the mode of action of the hormone and will make feasible the design of new, more effective analogs.

Experimental Section

General. All dry solvents were freshly distilled under argon from the appropriate drying agent before use. Et_2O, benzene, toluene, and THF were distilled from sodium/benzophenone. CH_2Cl_2 was distilled from P_2O_5, and hexanes from LAH. Absolute MeOH was distilled from Mg turnings. Py was distilled from KOH. *i*-Pr_2NH, Et_3N, and isooctane were distilled and then redistilled from CaH_2. DMF was distilled from P_2O_5 under vacuum and stored under type 4A molecular sieves. All reactions were conducted in dry solvents under argon atmosphere unless otherwise stated. Kugelrohr distillation boiling points refer to the external air bath temperature (at). Boiling points and melting points (open capillary tubes) are uncorrected. CuI was purified by the method of Kauffman[26] and Zn as recommended in the book by Fieser and Fieser.[27] Flash chromatography was performed by Still's method.[28] TLC was performed on silica gel plates, and components were located by observation under UV light and/or by treating the plates with a phosphomolybdic acid reagent followed by heating. Sonications were carried out in a Bandelin 120–240 W 35-kHz cleaning bath (Ultrasonic). Dryings were carried out with anhydrous Na_2SO_4. Concentrations were carried out in a rotary evaporator.

Full spectral and analytical data and the ^1H NMR and ^{13}C NMR spectra are given in the supplementary material. Essential ^1H NMR and ^{13}C NMR data (including carbon types determined from DEPT experiments) are also presented in the Experimental Section. Satisfactory combustion analysis and/or high-resolution mass spectra were obtained for all new compounds.

Des-*A,B*-22-iodo-23,24-dinorcholan-8β-ol (6b). Ph_3P (6.5 g, 27.76 mmol) and imidazole (4.8 g, 70.7 mmol) were added to a solution of Inhoffen–Lythgoe diol **6a**[29] (5 g, 23.6 mmol) in THF (100 mL). The suspension was cooled to −20 °C, and I_2 (6.28 g, 24.76 mmol) was added. After being stirred for 15 min, the reaction mixture was warmed to rt, further stirred for 1.5 h, cooled to 0 °C, and poured into saturated aqueous $NaHCO_3$ (50 mL). The mixture was extracted with Et_2O (2 × 60 mL), and the extract was washed with saturated aqueous $Na_2S_2O_3$ and H_2O, dried, and filtered. Concentration afforded a residue which was purified by flash chromatography (8% EtOAc/hexanes) to give 7.32 g of **6b** (96%).[14c] The white solid was crystallized from EtOAc/hexanes (mp 51 °C): ^{13}C NMR δ 69.1 (C-8), 55.9, 52.3, 41.8 (C), 40.0 (CH_2), 36.3, 33.5 (CH_2), 26.4 (CH_2), 22.3 (CH_2), 21.1 (CH_2), 20.6, 17.3 (CH_2), 14.3. Anal. Calcd for $C_{13}H_{23}OI$: C, 48.46; H, 7.19. Found: C, 48.58; H, 7.36.

Des-*A,B*-22-iodo-23,24-dinorcholan-8-one (9). PDC (8.66 g, 24 mmol) was added to a solution of the alcohol **6b** (3.99 g, 12 mmol) in CH_2Cl_2 (50 mL). The mixture was stirred for 6 h at rt. Et_2O (60 mL) was added, and the resulting suspension was stirred for 15 min and filtered through a short pad of Celite and silica gel. The filtrate was washed with brine (35 mL), dried, filtered, and concentrated. The residue was purified by flash chromatography (10% EtOAc/hexanes) to give iodo ketone **9** (3.57 g, 90%). The white solid was crystallized from Et_2O/hexanes (mp 65 °C): ^1H NMR δ 3.31 (1 H, dd, $J \sim 9.7$, 2.5 Hz, H-22), 3.19 (1 H, dd, $J \sim 9.7$, 4.8 Hz, H-22), 1.06 (3 H, d, $J \sim 5.8$ Hz, C_{21}-CH_3), 0.68 (3 H, s, C_{18}-CH_3); ^{13}C NMR δ 211.1 (CO), 61.3, 55.6, 49.3 (C), 40.6 (CH_2), 38.4 (CH_2), 36.1, 26.6 (CH_2), 23.7 (CH_2), 20.6, 20.3 (CH_2), 18.7 (CH_2), 13.0. Anal. Calcd for $C_{13}H_{21}OI$: C, 48.76; H, 6.61. Found: C, 48.68; H, 6.47.

Procedure for the Preparation of Vinyl Triflates: Des-*A,B*-22-iodo-23,24-dinorchol-8-enyl Trifluoromethanesulfonate (10a). Lithium diisopropylamide (LDA) was prepared by addition of *i*-Pr_2NH (0.54 mL, 3.9 mmol) to a cooled (−78 °C) solution of *n*-BuLi in hexanes (1.43 mL, 2.50 M, 3.5 mmol). After the mixture was stirred for 10 min, a white precipitate appeared. The mixture was diluted with THF (4 mL), stirred at 0 °C for 30 min, and cooled to −78 °C. A solution of ketone **9** (1 g, 3.12 mmol) in THF (14 mL) was slowly added (35 min), followed by a solution of *N*-phenyltriflimide (1.225 g, 3.43 mmol) in THF (4 mL). The mixture was stirred for 2 h at −78 °C. After being warmed to 0 °C, the reaction was quenched by addition of a few drops of MeOH and water. Concentration gave a crude product which was diluted with EtOAc/hexanes (30 mL, 1:3), washed with brine (20 mL), dried, filtered, and concentrated. The resulting viscous residue was purified by flash chromatography (2% EtOAc/hexanes) affording 1.29 g of iodo triflate **10a** (92%, colorless oil): ^1H NMR δ 5.59 (1 H, dd, $J \sim 6.9$, 3.5 Hz, H-9), 3.32 (1 H, dd, $J \sim 9.7$, 2.6 Hz, H-22), 3.18 (1 H, dd, $J \sim 9.7$, 5.1 Hz, H-22), 2.52 (1 H, m, H-14), 2.30 (2 H, m, two H-11), 1.06 (3 H, d, $J \sim 5.8$ Hz, C_{21}-CH_3), 0.8 (3 H, s, C_{18}-CH_3); ^{13}C NMR δ 149.4

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(C-8), 121.0 (CF_3), 116.0 (C-9), 53.4, 49.7, 45.0 (C), 36.7, 34.4 (CH_2), 27.4 (CH_2), 23.6 (CH_2), 21.2 (CH_2), 20.6, 19.8 (CH_2), 11.9. Anal. Calcd for $C_{14}H_{20}O_3F_3SI$: C, 37.18; H, 4.46. Found: C, 37.43; H, 4.36.

Procedure for Sonochemical Conjugate Additions: Methyl Des-*A,B*-8-[(trifluoromethanesulfonyl)oxy]chol-8-ene-24-carboxylate (8). A suspension of CuI (201 mg, 1.06 mmol) and Zn (161 mg, 2.5 mmol) in EtOH/H_2O (6 mL, 7:3, previously deoxygenated under reduced pressure) was sonicated for 5 min. The olefin, in this case methyl acrylate (637 μL, 7.8 mmol, freshly distilled under vacuum), and a solution of iodide **10a** (160 mg, 0.35 mmol) in EtOH/H_2O (1 mL, 7:3) were successively added, and the resulting mixture was sonicated for 40 min. Dilution with Et_2O (15 mL) and filtration through a short pad of celite (washed repeatedly with Et_2O) gave a solution that was washed with brine. The aqueous phase was extracted with Et_2O (30 mL), and the combined organic extracts were dried, filtered, and concentrated. Flash chromatography of the residue (6% EtOAc/hexanes) afforded 96 mg of methyl ester **8** (65%, colorless oil) and 23 mg of the protonated product **10b** (16%). Data for **8**: ^1H NMR δ 5.57 (1 H, dd, $J \sim 6.9$, 3.5 Hz, H-9), 3.67 (3 H, s, OCH_3), 2.45 (1 H, m, H-14), 2.28 (4 H, m, two H-11 and two H-24), 0.95 (3 H, d, $J \sim 6.4$ Hz, C_{21}-CH_3), 0.76 (3 H, s, C_{18}-CH_3); ^{13}C NMR δ 173.7 (CO_2), 149.7 (C-8), 121.0 (CF_3), 115.8 (C-9), 55.9, 53.8, 49.9, 44.9 (C), 35.4, 34.9 (CH_2), 34.6 (CH_2), 33.4 (CH_2), 27.9 (CH_2), 23.4 (CH_2), 21.1 (CH_2), 18.1, 10.8. Anal. Calcd for $C_{18}H_{27}O_5F_3S$: C, 52.42; H, 6.60. Found: C, 52.69; H, 6.27.

Des-*A,B*-25-oxo-27-norcholest-8-enyl trifluoromethanesulfonate (19): ^1H NMR δ 5.56 (1 H, dd, $J \sim 6.9$, 3.5 Hz, H-9), 2.40 (1 H, m, H-14), 2.30 (2 H, m, H-11), 2.14 (3 H, s, C_{26}-CH_3), 2.00 (2 H, m, H-24), 0.95 (3 H, d, $J \sim 6.4$ Hz, C_{21}-CH_3), 0.75 (3 H, s, C_{18}-CH_3); ^{13}C NMR δ 209.1 (CO), 149.9 (C-8), 121.1 (CF_3), 116.0 (C-9), 54.0, 50.1, 45.2 (C), 44.0 (CH_2), 37.8, 35.2 (CH_2), 34.8 (CH_2), 29.8, 28.2 (CH_2), 23.7 (CH_2), 21.4 (CH_2), 20.2 (CH_2), 18.4, 11.2. Anal. Calcd for $C_{18}H_{27}O_4F_3S$: C, 54.53; H, 6.86. Found: C, 54.87; H, 6.83.

Des-*A,B*-8-[(trifluoromethanesulfonyl)oxy]-chol-8-ene-24-carbonitrile (20): ^1H NMR δ 5.58 (1 H, dd, $J \sim 6.9$, 3.5 Hz, H-9), 2.47 (1 H, m, H-14), 2.29–2.33 (4 H, m, two H-11 and two H-24), 0.96 (3 H, d, $J \sim 6.5$ Hz, 3 H, C_{21}-CH_3), 0.77 (3 H, s, C_{18}-CH_3); ^{13}C NMR δ 149.7 (C-8), 120.0 (CF_3), 119.7 (CN), 116.1 (C-9), 53.9, 50.0, 45.1, 35.3, 34.7 (CH_2), 34.7 (CH_2), 28.1 (CH_2), 23.6 (CH_2), 22.0 (CH_2), 21.3 (CH_2), 18.2, 17.2 (CH_2), 11.1. Anal. Calcd for $C_{17}H_{24}O_3F_3SN$: C, 53.81; H, 6.37; N, 3.69. Found: C, 53.47; H, 6.20; N, 3.51.

Des-*A,B*-8-[(trilfuoromethanesulfonyl)oxy]chol-8-ene-24-carboxamide (21): ^1H NMR δ 5.70 (br s, NH_2), 5.58 (1 H, dd, $J \sim 6.9$, 3.5 Hz, H-9), 2.50 (1 H, m, H-14), 2.29 (2 H, m, H-11), 2.18 (2 H, m, H-24), 0.96 (3 H, d, $J \sim 12.3$ Hz, C_{21}-CH_3), 0.76 (3 H, s, C_{18}-CH_3); ^{13}C NMR δ 175.6 ($CONH_2$), 149.9 (C-8), 124.2 (CF_3), 116.1 (C-9), 54.0, 50.1, 45.2, 36.1, 35.7, 35.2, 34.8, 28.2, 23.8, 21.9, 21.6, 18.5, 11.2.

Des-*A,B*-24-(methanesulfonyl)chol-8-enyl trifluoromethanesulfonate (22): ^1H NMR δ 5.58 (1 H, dd, $J \sim 6.9$, 3.5 Hz, H-9), 2.98 (2 H, m, H-24), 2.90 (3 H, s, SO_2CH_3), 2.46 (1 H, m, H-14), 2.30 (2 H, m, H-11), 0.98 (3 H, d, $J \sim 6.5$ Hz, C_{21}-CH_3), 0.76 (3 H, s, C_{18}-CH_3); ^{13}C NMR δ 149.6 (C-8), 121.1 (CF_3), 116.1 (C-9), 55.0 (CH_2), 53.8, 50.0, 45.2 (C), 40.5, 35.6, 34.7 (CH_2), 34.4 (CH_2), 28.2 (CH_2), 23.7 (CH_2), 21.3 (CH_2), 19.0 (CH_2), 18.3, 11.2. Anal. Calcd for $C_{17}H_{27}O_5F_3S_2$: C, 47.21 H, 6.29. Found: C, 47.02; H, 6.13.

Des-*A,B*-24-(phenylsulfinyl)chol-8-enyl trifluoromethanesulfonate (23): ^1H NMR δ 7.62 (2 H, m, *o*-H-Ph), 7.52 (3 H, m, *m*-2H-Ph and *p*-H-Ph), 5.57 (1 H, dd, $J \sim 6.9$, 3.5 Hz, H-9), 2.76 (2 H, m, H-24), 2.45 (1 H, m, H-14), 2.30 (2 H, *m*, H-11), 0.93 (3 H, d, $J \sim 6.5$ Hz, C_{21}-CH_3), 0.75 (3 H, s, C_{18}-CH_3); ^{13}C NMR δ 149.8 (C-8), 144.3 (PhSO), 131.0 (PhSO), 129.3 (PhSO), 124.0 (PhSO), 121.1 (CF_3), 116.1 (C-9), 57.8, 54.0, 50.1, 45.2, 35.8, 34.8, 29.6, 28.2, 23.8, 21.4, 19.1, 18.9, 18.4, 11.3.

Procedure for Palladium-Catalyzed Coupling between Vinyl Triflates and Enynes: 1α-[(*tert*-Butyldimethylsilyl)oxy]-6,7-didehydro-24-(methoxycarbonyl)-25,26,27-trisnorprevitamin D_3 *tert*-Butyldimethylsilyl Ether (11). A mixture of enyne **5** (507 mg, 1.33 mmol), triflate **8** (500 mg, 1.213 mmol), Et_3N (0.67 mL, 4.85 mmol), and $(Ph_3P)_2PdCl_2$ (16 mg, 0.024 mmol, 2%) in DMF (21 mL) was heated at 75 °C for 1 h. The mixture was cooled to room temperature, diluted with EtOAc/hexanes (50 mL, 1:3), and washed with brine (70 mL). Drying, filtration, and concentration gave a dark yellow residue which was purified by flash chromatography (2–4% Et_2O/hexanes) to afford 675 mg of dienyne **11** (86%, viscous liquid decomposing rapidly even at −10 °C but stable in hexanes in the refrigerator): ^1H NMR δ 5.97 (1 H, m, $J \sim 3.5$ Hz, H-9), 4.20 (1 H, m, H-1), 4.13 (1 H, m, H-3), 3.68 (3 H, s, OCH_3), 1.90 (3 H, s, C_{19}-CH_3), 0.96 (3 H, d, $J \sim 6.5$ Hz, C_{21}-CH_3), 0.89 (18 H, s, two *t*-BuSi), 0.70 (3 H, s, C_{18}-CH_3), 0.10 (6 H, s, $Si(CH_3)_2$), 0.07 (6 H, s, $Si(CH_3)_2$); ^{13}C NMR δ 174.0 (CO_2), 140.2 (C), 133.4 (C-9), 122.6 (C), 115.5 (C), 92.4 (C), 88.1 (C), 69.9 (CH), 64.1 (CH), 54.4, 51.2, 50.0, 41.7 (C), 41.2 (CH_2), 39.7 (CH_2), 35.8, 35.2 (CH_2), 34.3 (CH_2), 27.8 (CH_2), 25.7 (CH_3), 25.7 (CH_3), 25.6 (CH_2), 25.0 (CH_2), 24.0 (CH_2), 21.4, 19.0, 18.5, 17.9, 17.8, 10.9, −4.5 (CH_3), −4.8 (CH_3), −4.9 (CH_3), −5.0 (CH_3).

Procedure for Hydrogenation with Lindlar Catalyst: 1α-[(*tert*-Butyldimethylsilyl)oxy]-24-(methoxycarbonyl)-25,26,27-trisnorprevitamin D_3 *tert*-Butyldimethylsilyl Ether (12). A solution of quinoline in hexanes (0.2 mL of a solution of 50 μL of quinoline in 10 mL of hexanes) was added to a solution of dienyne **11** (305 mg, 0.475 mmol) in hexanes (12 mL). Lindlar catalyst (50 mg, previously high vacuum dried at 60 °C for 4 h) was added and the resulting solution was exposed to hydrogen gas at balloon pressure. After the solution was stirred for 8 h, TLC (2% EtOAc/hexanes) indicated that all the starting material had been converted to a product with a slightly higher R_f (monitoring by TLC is recommended in order to avoid overhydrogenation). After filtration and concentration, the residue was purified by flash chromatography (1–3% Et_2O/hexanes) to give 295 mg of protected previtamin D **12** (97%, colorless oil). This compound slowly equilibrates to the corresponding vitamin D at rt. In the ^1H NMR spectrum a small amount of the corresponding vitamin D form can be appreciated: ^1H NMR δ 5.87 and 5.72 (2 H, AB pattern, d, $J \sim 12$ Hz, H-6 and H-7), 5.52 (1 H, br s, $J \sim 3.5$ Hz, H-9), 4.15 (2 H, m, H-1 and H-3), 3.66 (3 H, s, OCH_3), 0.94 (3 H, d, $J \sim 6.5$ Hz, C_{21}-CH_3), 0.88 (9 H, s, *t*-BuSi), 0.86 (9 H, s, *t*-BuSi), 0.68 (3 H, s, C_{18}-CH_3), 0.08 (6 H, s, $Si(CH_3)_2$), 0.03 (6 H, s, $Si(CH_3)_2$); ^{13}C NMR δ 174.7 (CO_2), 136.9 (C), 131.2 (C), 130.5 (C), 130.4 (CH), 129.2 (CH), 125.7 (C-19), 71.9 (CH), 65.6 (CH), 54.6, 51.8, 51.4, 42.7, 42.5, 39.7, 36.8, 36.5, 36.0, 35.0, 28.8, 26.3, 26.2, 25.5, 24.1, 22.2, 19.0, 18.6, 18.5, 17.9, 11.6, −4.0, −4.3, −4.4, −4.5.

Procedure for the Isomerization of Previtamins D to Vitamins D: 1α-[(*tert*-Butyldimethylsilyl)oxy]-24-(methoxycarbonyl)-25,26,27-trisnorvitamin D_3 *tert*-Butyldimethylsilyl Ether (13). Previtamin D **12** (295 mg, 0.458 mmol) was dissolved in isooctane (15 mL, distilled from Na) and refluxed in the dark for 5 h. Concentration gave a residue which was purified by flash chromatography (2–4% Et_2O/hexanes) to afford 290 mg of **13** (96%). A small amount of the previtamin D form in equilibrium is observed in the ^1H NMR spectrum: ^1H NMR δ 6.24 and 6.02 (2 H, AB pattern, d, $J \sim 11.2$ Hz, H-6 and H-7), 5.18 (1 H, m, $J \sim 3.5$ Hz, H-19*E*), 4.87 (1 H, m, $J \sim 3.5$ Hz, H-19*Z*), 4.37 (1 H, m, H-1), 4.18 (1 H, m, H-3), 3.67 (3 H, s, OCH_3), 0.93 (3 H, d, $J \sim 6.2$ Hz, C_{21}-CH_3), 0.88 (18 H, s, two *t*-BuSi), 0.53 (3 H, s, C_{18}-CH_3), 0.07 (12 H, s, two $Si(CH_3)_2$; ^{13}C NMR δ 173.1 (CO_2), 148.4 (C), 141.0 (C), 135.0 (C), 123.2 (CH), 118.0 (CH), 111.2 (C-19), 72.1 (CH), 67.5 (CH), 56.3, 51.3, 46.0, 45.7, 44.8, 40.6, 35.8, 35.3, 34.4, 31.5, 28.8, 27.6, 25.8, 25.7, 23.4, 22.6, 22.1, 21.5, 18.7, 18.1, 18.0, 14.0, 11.9, −4.8, −4.8, −4.9, −5.2. Anal. Calcd for $C_{38}H_{66}O_4Si_2$: C, 70.75; H, 10.62. Found: C, 70.42; H, 10.43.

1α,25-Dihydroxyvitamin D_3 (1c). A solution of $IMgCH_3$ (0.33 mL, 1 M, 0.33 mmol) in Et_2O was slowly added to a cooled (−78 °C) solution of **13** (71 mg, 0.11 mmol) in THF (5 mL). The reaction mixture was warmed to rt and stirred for 10 h. The mixture was cooled to 0 °C, quenched with MeOH (several drops), poured into saturated aqueous NH_4Cl (15 mL), and extracted with Et_2O (50 mL). The organic extract was washed with brine (20 mL), dried, filtered, and concentrated. Filtration through a flash chromatography column (40% Et_2O/hexanes) gave a residue (62 mg) that was dissolved in THF (7 mL) and stirred at rt in the dark with TBAF (0.4 mL, 1 M in THF, 0.4 mmol) for 24 h. Concentration gave a solid residue that was diluted with EtOAc (15 mL), washed with brine (10 mL), dried, filtered, and

concentrated. Flash chromatography of the residue (60% EtOAc/hexanes) gave the hormone **1c** (85 mg, 73% over the two steps) that was identical (NMR, TLC) to an authentic sample.[14c]

26,27-Hexadeuterio-1α,25-dihydroxyvitamin D_3 (14).[20] See the procedure described for the preparation of **1c**: ^1H NMR (CD_2Cl_2) δ 6.33 and 5.98 (2 H, AB pattern, d, $J \sim 12.4$ Hz, H-6 and H-7), 5.26 (1 H, m, H-19*E*), 4.93 (1 H, br s, H-19*Z*), 4.34 (1 H, m, H-1), 4.13 (1 H, m, H-3), 0.90 (3 H, d, $J \sim 6.2$ Hz, C_{21}-CH_3), 0.51 (3 H, s, C_{18}-CH_3); ^{13}C NMR 148.7 (C), 143.5 (C), 133.9 (C), 125.1 (CH), 117.6 (CH), 111.8 (C-19), 71.2 (CH), 70.8, 67.2 (CH), 57.1, 56.8, 46.3, 45.8, 44.8, 43.5, 40.9, 36.9, 36.5, 29.4, 28.0, 24.0, 22.6, 21.2, 19.0, 12.1.

26,27-Dinor-25,25-dicyclopropyl-1α,25-dihydroxyvitamin D_3 (15). Cyclopropyl bromide (40 μL, 0.51 mmol) was slowly added to a cooled (−20 °C) solution of *t*-BuLi in Et_2O (0.602 mL, 1.7 M, 1.02 mmol). The resulting mixture was warmed to rt (a white solid appeared) and diluted with Et_2O (2.4 mL). This solution (1 mL) was slowly added to a cooled (−78 °C) solution of **13** (50 mg, 0.077 mmol) in Et_2O (3 mL). The reaction mixture was allowed to come to −40 °C (4 h) and quenched with a few drops of water. The resulting solution was diluted with Et_2O, washed with brine (25 mL), dried, filtered, and concentrated. The concentrate was filtered through a flash chromatography column (2% Et_2O/hexanes), affording a product (46 mg) which was dissolved in THF (7 mL) and stirred in the dark at rt with TBAF (0.36 mL, 1 M in THF, 0.36 mmol) for 24 h. Concentration gave a residue which was diluted with EtOAc (20 mL). The solution was washed with brine (10 mL), dried, filtered, concentrated, and flash chromatographed (60% EtOAc/hexanes) to give 23 mg of the desired compound **15** (65% over the two steps, white solid, mp 59 °C): ^1H NMR (CD_2Cl_2) δ 6.44 and 5.99 (2 H, AB pattern, d, $J \sim 11$ Hz, H-6 and H-7), 5.27 (1 H, brd, $J \sim 3.5$ Hz, H-19*E*), 4.95 (1 H, brd, $J \sim 3.5$ Hz, H-19*Z*), 4.35 (1 H, m, H-1), 4.15 (1 H, m, H-3), 0.92 (3 H, d, $J \sim 6.2$ Hz, C_{21}-CH_3), 0.81 (2 H, m, H-26 and H-27), 0.53 (3 H, s, C_{18}-CH_3), 0.34 (8 H, m, 4-cyclopropylic CH_2); ^{13}C NMR (CD_2Cl_2) δ 148.6 (c), 143.5 (c), 133.9 (C), 125.1 (CH), 117.6 (CH), 111.8 (C-19), 71.2 (CH), 71.0 (CH), 67.2, 57.2, 56.8, 45.8 (C-25), 43.5 (CH_2), 43.4 (CH_2), 41.0 (CH_2), 37.1 (CH_2), 36.6, 29.4 (CH_2), 28.0 (CH_2), 24.0 (CH_2), 22.6 (CH_2), 20.8 (CH_2), 19.0 (CH), 12.1, 0.8 (CH_2), −0.5 (CH_2).

26,27-Dinor-25,25-di-*tert*-butyl-1α,25-dihydroxyvitamin D_3 (16). A solution of *t*-BuLi in Et_2O (0.123 mL, 1.7 M, 0.21 mmol) was added to a cooled (−78 °C) solution of **13** (45 mg, 0.97 mmol) in Et_2O (5 mL). During the addition the reaction mixture changed from colorless to brown. The mixture was allowed to come to rt, and after stirring for 1.5 h was cooled to 0 °C, quenched by addition of a few drops of water, diluted with Et_2O (50 mL), washed with brine (20 mL), dried, filtered, and concentrated. The resulting white solid was dissolved in THF (8 mL). The solution was stirred in the dark at rt with TBAF (0.56 mL, 1 M in THF, 0.56 mmol) for 16 h. Concentration gave a residue which was diluted with EtOAc (20 mL), washed with brine (10 mL), dried, filtered, concentrated, and flash chromatographed (60% EtOAc/hexanes) to give 19 mg of **16** (68% over the two steps, colorless viscous oil): ^1H NMR δ 6.38, and 6.01 (2 H, AB pattern, d, $J \sim 11$ Hz, H-6 and H-7), 5.33 (1 H, m, H-19*E*), 5.00 (1 H, m, H19*Z*), 4.43 (1 H, m, H-1), 4.23 (1 H, m, H-3), 1.00 (18 H, s, two *t*-Bu), 0.93 (3 H, d, $J \sim 6.2$ Hz, C_{21}-CH_3), 0.54 (3 H, s, C_{18}-CH_3); ^{13}C NMR δ 148.7 (C), 143.4 (C), 134.0 (C), 125.0 (CH), 117.6 (CH), 111.8 (C-19), 80.0 (C-25), 71.1 (CH), 67.1 (CH), 60.6, 56.9, 56.8, 46.3 (CH_2), 45.8, 43.4 (CH_2), 42.8, 40.9 (CH_2), 37.0 (CH_2), 36.5, 34.2 (CH_2), 29.4 (CH_2), 28.8, 28.0 (CH_2), 24.0 (CH_2), 23.3 (CH_2), 22.7 (CH_2), 19.2, 12.1.

26,27-Dinor-25,25-diphenyl-1α,25-dihydroxyvitamin D_3 (17). Bromobenzene (53.3 μL, 0.51 mmol) was slowly added to a cooled (−70 °C) solution of *t*-BuLi in Et_2O (659 μL, 1.49 M). The reaction mixture was warmed to rt and diluted with Et_2O (1.3 mL), and the solution (1 mL) was added to a cooled (−78 °C) solution of **13** (70 mg, 0.11 mmol) in Et_2O (4 mL). The reaction mixture was stirred for 30 min, quenched with several drops of water, diluted with EtOAc/hexanes (20 mL 1:3), washed with saturated aqueous NH_4Cl (15 mL) and brine (25 mL), dried, filtered, and concentrated. The residue was filtered through a flash chromatography column (4% Et_2O/hexanes). The product (80 mg) was dissolved in THF (7 mL) and stirred in the dark at rt with TBAF (0.67 mL, 1.1 M in THF, 0.85 mmol) for 20 h. Concentration gave a residue which was diluted with EtOAc (20 mL), washed with brine (10 mL), dried, filtered, concentrated, and flash chromatographed (60% EtOAc/hexanes) to give 43 mg of **17** (71% over the two steps, mp 128 °C); ^1H NMR (CD_2Cl_2) δ 7.40 (4 H, d, $J \sim 8$ Hz, *o*-4H-Ph), 7.31 (4 H, t, $J \sim 7$ Hz, *m*-4H-Ph), 7.18 (2 H, t, $J \sim 7$ Hz, *p*-H-Ph), 6.34 and 5.99 (2 H, AB pattern, $J \sim 11.5$ Hz, H-6 and H-7), 5.28 (1 H, br s, H-19*E*), 4.94 (1 H, br s, H-19*Z*), 4.35 (1 H, m, H-1), 4.15 (1 H, m, H-3), 0.83 (3 H, d, $J \sim 6.5$ Hz, C_{21}-CH_3), 0.50 (3 H, s, C_{18}-CH_3); ^{13}C NMR (CD_2Cl_2) δ 148.6 (C), 148.0 (C), 143.4 (C), 133.9 (C), 128.5 (CH), 127.1 (CH), 126.4 (CH), 125.0 (CH), 117.6 (CH), 111.8 (C-19), 78.5 (C), 71.2 (CH), 67.2 (CH), 57.1, 56.7, 46.2, 45.7 (CH_2), 43.4 (CH_2), 42.7 (CH_2), 40.9 (CH_2), 36.6 (CH_2), 36.4, 29.4 (CH_2), 28.0 (CH_2), 24.0 (CH_2), 22.6 (CH_2), 20.7 (CH_2), 18.9, 12.1.

1α-[(*tert*-Butyldimethylsilyl)oxy]-6,7-didehydro-24-(methanesulfonyl)-25,26,27-trisnorprevitamin D_3 *tert*-Butyldimethylsilyl Ether (24). This compound was prepared from triflate **22** and enyne **5** following the same procedure used for the preparation of **11**: ^1H NMR δ 5.97 (1 H, m, H-9), 4.19 (1 H, m, 1H, H-1), 4.10 (1 H, m, H-3), 2.95 (2 H, m, H-24), 2.91 (3 H, s, SO_2CH_3), 0.99 (3 H, d, $J \sim 6.5$ Hz, C_{21}-CH_3), 0.89 (9 H, s, *t*-BuSi), 0.88 (9 H, s, *t*-BuSi), 0.71 (3 H, s, C_{18}-CH_3), 0.10 (6 H, s, $Si(CH_3)_2$), 0.07 (6 H, s, $Si(CH_3)_2$); ^{13}C NMR δ 140.5 (C), 133.2 (CH), 122.5 (C), 115.5 (C), 92.3 (C), 82.3 (C), 70.0 (CH), 64.2 (CH), 55.3, 54.3, 50.1, 41.9, 41.2, 40.5, 39.8, 35.8, 34.6, 27.9, 25.8 (CH_3), 25.7 (CH_3), 25.0, 24.1, 19.1, 19.1, 18.4, 18.0, 18.0, 11.0, −4.4 (CH_3), −4.7 (CH_3), −4.8 (CH_3), −4.9 (CH_3).

24-(Methanesulfonyl)-1α,25-dihydroxy-25,26,27-trisnorvitamin D_3 (18). Partial hydrogenation and thermal isomerization were carried out following the same procedures used for the preparation of **13** from **11**. Desilylation was carried out as above. Compound **18** (colorless oil) was obtained in a 73% yield over the three steps. ^1H NMR δ 6.34 and 5.98 (2 H, AB pattern, $J \sim 11.2$ Hz, H-7 and H-6), 5.29 (1 H, br s, H-19*E*), 4.94 (1 H, br s, H-19*Z*), 4.35 (1 H, m, H-1), 4.15 (1 H, m, H-3), 2.88–2.97 (2 H, m, H-24), 2.84 (3 H, s, SO_2CH_3), 0.94 (3 H, d, $J \sim 6.4$ Hz, C_{21}-CH_3), 0.53 (3 H, s, C_{18}-CH_3); ^{13}C NMR δ 148.6 (C), 143.2 (C), 134.1 (C), 125.0 (CH), 117.0 (CH), 111.8 (CH19), 71.2 (CH), 67.2 (CH), 56.7, 56.6, 55.7, 53.5, 46.3, 45.8, 43.4, 40.9, 36.2, 35.0, 29.4, 28.0, 23.9, 22.6, 19.7, 18.8, 12.1.

Acknowledgment. Support for this research under Grant PB90-0759 from the DGICYT (M.E.C., Spain) is gratefully acknowledged. J.P.S. thanks the Xunta de Galicia for a fellowship. We also thank Duphar for the generous gift of vitamin D_2 used for the preparation of Lythgoe–Inhoffen diol (**6a**).

Supplementary Material Available: Spectral and analytical data (^1H NMR, ^{13}C NMR, IR, UV, MS, HRMS, and other analytical data) and ^1H and ^{13}C NMR spectra (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.