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Synthesis of New 18-Substituted Analogues of Calcitriol Using a Photochemical Remote Functionalization

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A novel convergent synthetic approach to new analogues of calcitriol modified at the C-18 position is reported. The key step in the synthesis is the 20-hydroxyl-directed photochemical iodination of the 18-methyl group in the presence of (diacetoxyiodo)benzene. Using this methodology, two new analogues of calcitriol were prepared: the first contains a hydroxylated alkyl side chain attached at C-18 with the natural side chain replaced by an isopropylidene group; the second is a conformationally locked analogue due to an extra oxacycle between the C-18 and C-20 positions.

Introduction

Calcitriol (1α,25-dihydroxyvitamin D_3, **1b**, Figure 1), the hormonally active form of vitamin D_3 (**1a**), participates in a wide range of metabolic functions.[1] Besides the regulation of calcium and phosphorus metabolism, this compound is involved in the promotion of cellular differentiation processes, the inhibition of proliferation of various tumor cell lines, and other functions related to the immune system. However, the therapeutic value of calcitriol is limited by the potent calcemic effects associated with it, and for this reason, the synthesis of analogues with a selective biological function is an important goal.[2] Calcitriol exerts its biological activity after interaction with a protein receptor (vitamin D receptor, VDR) or receptors (VDRs) in the nucleus cell or in the cellular membrane.[3]

The vitamin D structure has been extensively modified in order to explore structure−function relationships and to find the ideal analogue to give the desired properties.[4] Small modifications in the vitamin D structure and changes in the conformation adopted during the interaction with VDR can modify the biological activity dramatically,[4] and several analogues have been identified as promising drugs for the treatment of certain cancers and psoriasis.[1] Most of the modifications have been made in the flexible parts of the molecule, i.e., the side chain and the A ring, while other topological regions such as the triene system or the CD ring remain less explored due to the absence of efficient synthetic approaches.[2] In this paper, we report a novel convergent synthetic approach to new calcitriol derivatives modified in the CD ring region based in the intramolecular photochemical remote iodination of the 18-methyl group.

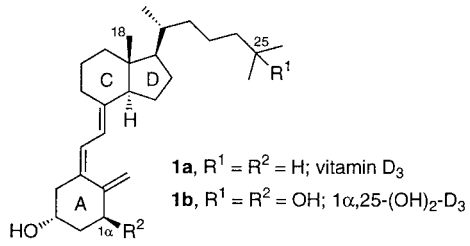

FIGURE 1. Vitamin D_3 and calcitriol [1α,25-$(OH)_2$-D_3].

It has recently been discovered that inversion of the stereochemistry at the C-20 position gives rise to highly active and selective analogues.[5] This suggests that in the conformationally active form of calcitriol the 25-hydroxy side chain is situated in the upper-left side of the vitamin D structure.[6] Indeed, a recent X-ray diffraction study of the calcitriol−VDR complex confirmed this hypothesis.[7]

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[‡] Universidade de Santiago de Compostela.

(1) (a) *Vitamin D*; Feldman, D., Glorieux, F. H., Pike, J. W., Eds.; Academic Press: New York, 1997. (b) Calverley, M. J.; Jones, J. In *Antitumor Steroids*; Blickenstaff, R. T., Ed.; Academic Press: San Diego, 1992; Chapter 7, pp 193−270. (c) Norman, A. W.; Litwack, G. *Hormones*; Academic Press: San Diego, 1997.

(2) (a) Dai, H.; Posner, G. H. *Synthesis* **1994**, 1383−1398. (b) Zhu, G.-D.; Okamura, W. H. *Chem. Rev.* **1995**, *95*, 1877−1952. (c) Okamura, W. H.; Zhu, G.-D. In *Vitamin D*; Feldman, D., Glorieux, F. H., Pike, J. W., Eds.; Academic Press: New York, 1997; p 939−971.

(3) Freedman, L. P.; Lemon, B. D. In *Vitamin D*; Feldman, D., Glorieux, F. H., Pike, J. W., Eds.; Academic Press: San Diego, 1997; Chapter 9, p 127−148 and references therein.

(4) (a) Okamura, W. H.; Palenzuela, J. A.; Plumet, J.; Midland, M. M. *J. Cell Biochem.* **1992**, *49*, 10−18. (b) Bouillon, R.; Okamura, W. H.; Norman, A. W. *Endocr. Rev.* **1995**, *16*, 200−257.

(5) (a) Binderup, L.; Latini, S.; Binderup, E.; Bretting, C.; Calverley, M.; Hansen, K. *Biochem. Pharmacol.* **1991**, *42*, 1569−1575. (b) Dilworth, F. J.; Calverley, M. J.; Makin, H. L.; Jones, G. *Biochem. Pharmacol.* **1994**, *47*, 987−993. (c) Liu, Y.-Y.; Collins, E. D.; Norman, A. W.; Peleg, S. *J. Biol. Chem.* **1997**, *272*, 3336−3345. (d) Yang, W.; Freedman, L. P. *J. Biol. Chem.* **1999**, *274*, 16838−16845.

(6) (a) Yamamoto, K.; Ooizumi, H.; Umesono, K.; Verstuyf, A.; Bouillon, R.; DeLuca, H. F.; Shinki, T.; Suda, T.; Yamada, S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1041−1046. (b) Yamamoto, K.; Masuno, H.; Choi, M.; Nakashima, K.; Taga, T.; Ooizumi, H.; Umesono, K.; Sicinska, W.; VanHooke, J.; DeLuca, H. F.; Yamada, S. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 1467−1472. (c) Yamada, S.; Yamamoto, K.; Masuno, H.; Choi, M. *Steroids* **2001**, *66*, 177−187.

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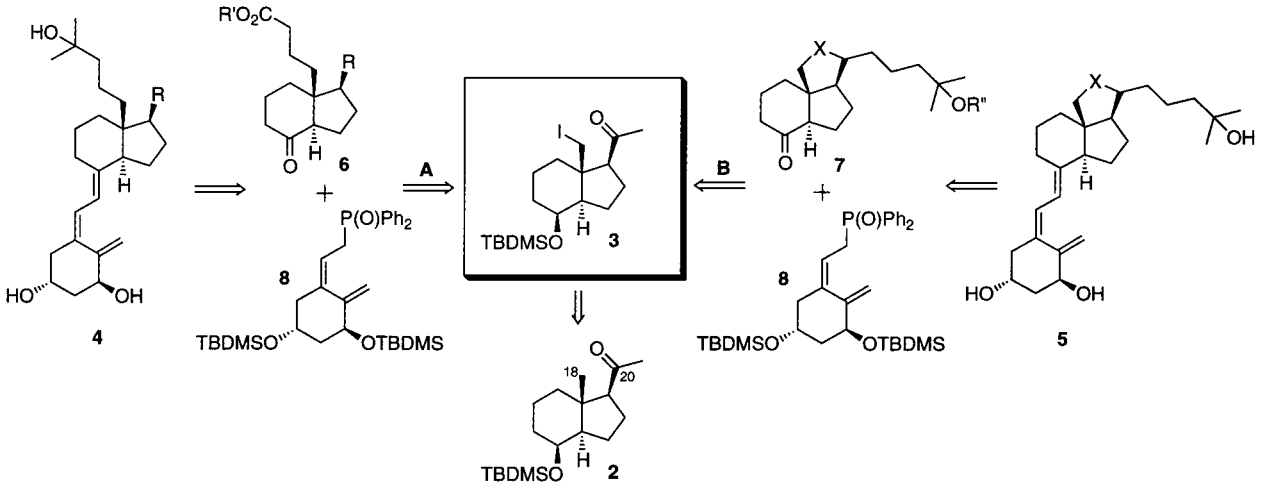
SCHEME 1. Retrosynthetic Analysis

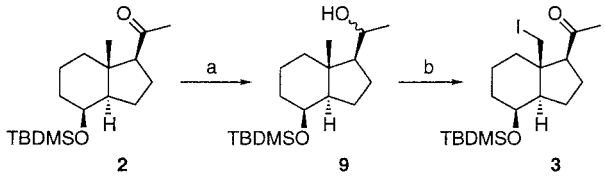


For these reasons, the synthesis of analogues in which the 25-hydroxy group has this orientation and also analogues that have a conformationally restricted[8] side chain are now of great interest. In the work described here, we devised a promising family of calcitriol analogues (**4**, Scheme 1) in which a hydroxylated alkyl side chain, similar to the calcitriol one, is placed at the C-18 position. By exploiting the C-18 functionalization, we also envisioned the synthesis of calcitriol analogues (such as **5**) with restricted mobility in the side chain by constructing a new cycle between the C-18 and C-20 or C-21 positions.

Results and Discussion

The C-18 position in the vitamin D structure has been previously functionalized by the introduction of a hydroxyl group through a radical reaction with $Pb(OAc)_4$ under thermal or photochemical conditions using an alkoxy radical inductor placed in the C-8 position.[9] Herein, we studied the introduction of an iodine atom by reaction with (diacetoxyiodo)benzene (DIB) and iodine under photochemical conditions using a hydroxyl group at C-20 as the radical inductor. The use of DIB in photochemical remote functionalization reactions was first reported by Suárez some years ago in steroids.[10] Irradiation of alkylic alcohols with visible light in the presence of DIB and iodine can induce, under adequate reaction conditions, the remote iodination of nonactivated carbons. In this reaction, a hydroxyl group reacts with DIB in the presence of iodine to produce an alkoxy radical, presumably via a hypoiodite intermediate, which is able to abstract close hydrogen atoms intramolecularly from suitable positioned nonactivated carbons.

SCHEME 2. Synthesis of Iodo Ketone 3[a]



[a] Key: (a) $NaBH_4$, MeOH, 0 °C [**9a**/**9b** (20*S*/20*R*) = 3:7], 99%; (b) DIB, I_2, cyclohexane, *hν*, then Jones' reagent, acetone, 0 °C, 84%.

The incorporation of an iodine atom offers several synthetic advantages in terms of further transformations such as nucleophilic substitutions, halogen−metal exchange reactions, as well as radical or transition-metal-promoted reactions. To explore this possibility, we chose the known C-20 methyl ketone **2**[11] (Scheme 1), which contains the CD rings of the vitamin D structure. The ketone reduction should afford the necessary alkylic alcohol for posterior photolysis under Suárez conditions for iodination. Analogues of types **4** and **5** should be available from iodo ketone **3**.

The first step in our synthetic venture was therefore the preparation of iodo ketone **3** (Scheme 2). Reduction of methyl ketone **2** with $NaBH_4$ afforded a mixture of alcohols **9** (20*R*/20*S* = 7:3).[12] Irradiation of **9** with visible light under Suárez conditions [DIB (1.1 equiv) and I_2 (1.0 equiv) in cyclohexane] gave an unstable iodo alcohol that was immediately oxidized with Jones' reagent to give the iodo ketone **3** (84%, 2 steps).

With iodo ketone **3** in hand, we explored its synthetic utility for C-18 substituted calcitriol analogues. For analogues of type **4** (Scheme 1, route A), we tried the introduction of a hydroxylated side chain at C-18. The halogen−metal exchange reaction with *t*-BuLi at low

(7) (a) Rochel, N.; Wurtz, J. M.; Mitschler, A.; Klaholz, B.; Moras, D. *Mol. Cell* **2000**, *5*, 173−179. (b) Tocchini-Valentini, G.; Rochel, N.; Wurtz, J. M.; Mitschler, A.; Moras, D. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 5491−5496.

(8) For recent examples, see: (a) Martínez-Pérez, J. A.; Sarandeses, L.; Granja, J.; Palenzuela, J. A.; Mouriño, A. *Tetrahedron Lett.* **1998**, *39*, 4725−4728. (b) Rey, M. A.; Martínez-Pérez, J. A.; Fernández-Gacio, A.; Halkes, K.; Fall, Y.; Granja, J.; Mouriño, A. *J. Org. Chem.* **1999**, *64*, 3196−3206. (c) Fernández-Gacio, A.; Vitale, C.; Mouriño, A. *J. Org. Chem.* **2000**, *65*, 6978−6983.

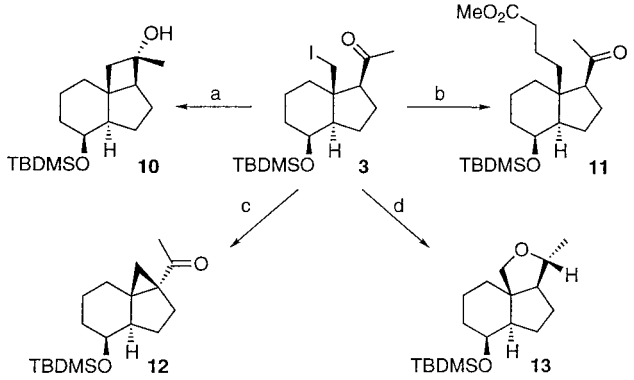
(9) (a) Vallés, M. J.; Castedo, L.; Mouriño, A. *Tetrahedron Lett.* **1992**, *33*, 1503−1506. (b) Maynard, D. F.; Norman, A. W.; Okamura, W. H. *J. Org. Chem.* **1992**, *57*, 3214−3217. (c) Nilsson, K.; Vallés, M. J.; Castedo, L.; Mouriño, A.; Halkes, S. J.; van de Velde, J. P. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1855−1858. (d) Grue-Sorensen, G.; Hansen, C. H. *Bioorg. Med. Chem.* **1998**, *6*, 2029−2039.

(10) (a) Concepción, J. I.; Francisco, C. G.; Hernández, R.; Salazar, J. A.; Suárez, E. *Tetrahedron Lett.* **1984**, *25*, 1953−1956. (b) de Armas, P.; Concepción, J. I.; Francisco, C. G.; Hernández, R.; Salazar, J. A.; Suárez, E. *J. Chem. Soc., Perkin Trans. 1* **1989**, 405−411.

(11) Fernández, B.; Martínez Pérez, J. A.; Granja, J. R.; Castedo, L.; Mouriño, A. *J. Org. Chem.* **1992**, *57*, 3173−3178.

(12) (a) Kirk, D. N.; Mudd, A. *J. Chem. Soc. C* **1969**, 968−974. (b) Fall, Y. *Tetrahedron Lett.* **1997**, *38*, 4909−4912.

SCHEME 3. Reactivity of Iodo Ketone 3[a]

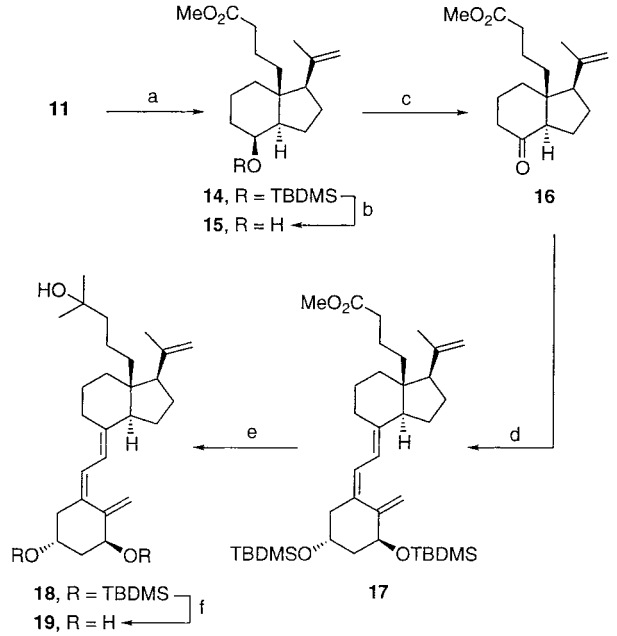


[a] Key: (a) *t*-BuLi, THF, −78 °C, 75%; (b) methyl acrylate, Zn, CuI, EtOH/H_2O (7:3), sonication, 40%; (c) KO-*t*-Bu, THF, Δ, 91%; (d) $NaBH_4$, MeOH, then AgOAc, acetone, Δ, 75%.

temperatures followed by addition of electrophiles (such as aldehydes or primary halides) failed; instead, the cyclobutanol **10** (Scheme 3) was obtained.[13] The nucleophilic substitution reaction of organocuprates with iodo ketone **3** resulted in the recovery of the starting material. At that time, we tried the zinc−copper sonochemical induced conjugate addition reaction of iodides to α,β-unsaturated systems, developed by Luche[14] and later used in our group for the synthesis of 25-hydroxyvitamin D derivatives.[15] The sonication of iodo ketone **3** and methyl acrylate with Zn and CuI in aqueous ethanol (70% v/v) gave the desired 1,4-conjugate addition product, the ketoester **11**, in moderate yield (40%, Scheme 3).[16]

Additionally, we tested the formation of a cycle between the position C-18 and C-20 or C-21, with a view in the synthesis of calcitriol analogues with a conformationally restricted side chain. Attempts of intramolecular cyclization of the kinetic enolate from **3** did not give any reaction product. Alternately, when the iodo ketone **3** was treated with KO-*t*-Bu under reflux, the cyclopropanol **12** was obtained stereoselectively and in good yield (91%).[17] These results prompted us to explore the formation of an oxygen bridge between the C-20 and C-18. Stereoselective reduction of **3** with $NaBH_4$ and treatment of the resulting alcohol with silver acetate afforded the ether

SCHEME 4. Synthesis of Calcitriol Analogue 19[a]



[a] Key: (a) Ph_3PCH_3Br, *n*-BuLi, THF, 0 °C, 80%; (b) *n*-Bu_4NF, THF, Δ, 87%; (c) PDC, CH_2Cl_2, 88%; (d) **8**, *n*-BuLi, THF, −78 °C, 65%; (e) MeLi, THF, −78 °C, 86%; (f) *n*-Bu_4NF, THF, rt, 99%.

13 in 75% yield. The stereochemistry of this ether was assigned by comparison with the ^1H NMR chemical shifts of analogous steroidal compounds.[10b,18] The high stereoselectivity observed in the reduction step (20*R*/20*S* ≈ 20:1) can be explained by the presence of the iodine atom at C-18, blocking the *re*-face of the carbonyl group.[19]

At this point, we selected compounds **11** and **13** for the synthesis of analogues of calcitriol modified at C-18. In the case of ketoester **11**, we planned the synthesis of analogues of type **4** (Scheme 1, route A). The ester group could be transformed to a hydroxyalkyl side chain analogous to the natural in calcitriol and the methyl ketone converted to a isopropylene group, a suitable precursor for the natural side chain[20] that could also reduce the flexibility of the hydroxylated side chain at C-18.[9d] The vitamin D triene system could be achieved following the Lythgoe approach.[21]

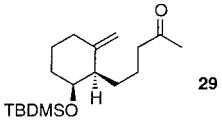
Wittig reaction of ketoester **11** with the ylide of methylene triphenylphosphonium bromide afforded regioselectively the ester **14** (Scheme 4) in good yield. Removal of the silyl group at C-8 with *n*-Bu_4NF (**14** → **15**) and oxidation of the resulting alcohol **15** with PDC led to the desired C-8 ketone **16** (76%, two steps). Wittig−Horner

(13) Suginome, H.; Nakayama, Y. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1843−1848.

(14) (a) Petrier, C.; Dupuy, C.; Luche, J. L. *Tetrahedron Lett.* **1986**, *27*, 3149−3152. (d) Dupuy, C.; Petrier, C.; Sarandeses, L. A.; Luche, J. L. *Synth. Commun.* **1991**, *21*, 643−651. (e) Sarandeses, L. A.; Mouriño, A.; Luche, J. L. *J. Chem. Soc., Chem. Commun.* **1992**, 798−799.

(15) (a) Castedo, L.; Mascareñas, J. L.; Mouriño, A.; Sarandeses, L. A. *Tetrahedron Lett.* **1988**, *29*, 1203−1206. (b) Mascareñas, J. L.; Sarandeses, L. A.; Castedo, L.; Mouriño, A. *Tetrahedron* **1991**, *47*, 3485−3498. (c) Mascareñas, J. L.; Pérez Sestelo, J.; Castedo, L.; Mouriño, A. *Tetrahedron Lett.* **1991**, *32*, 2813−2816. (d) Pérez Sestelo, J.; Mascareñas, J. L.; Castedo, L.; Mouriño, A. *J. Org. Chem.* **1993**, *58*, 118−123. (e) Pérez Sestelo, J.; Mascareñas, J. L.; Castedo, L.; Mouriño, A. *Tetrahedron Lett.* **1994**, *35*, 275−278.

(16) The major side product (40%) corresponds to the β-scission compound **29**; see the Experimental Section and ref 13.



29

(17) Kirk, D. N.; Rajagopalan, M. S. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1064−1068.

(18) Choay, P.; Monneret, C.; Khuong-Huu, Q. *Bull. Soc. Chim. Fr.* **1973**, 1456−1459.

(19) For stereochemical studies in the addition of Grignard reagents to 20-keto steroids, see: (a) Chaudhuri, N. K.; Williams, J. G.; Nickolson, R.; Gut, M. *J. Org. Chem.* **1969**, *34*, 3759−3766. (b) Makino, T.; Shibata, K.; Rohrer, D. C.; Osawa, Y. *J. Org. Chem.* **1978**, *43*, 276−280.

(20) The calcitriol side chain has already been prepared from the isopropylene moiety at C-17; see: (a) Kwon, Y. C.; Midland, M. M. *J. Am. Chem. Soc.* **1983**, *105*, 3725−3727. (b) Sas, B.; De Clercq, P.; Vandewalle, M. *Synlett* **1997**, 1167−1170.

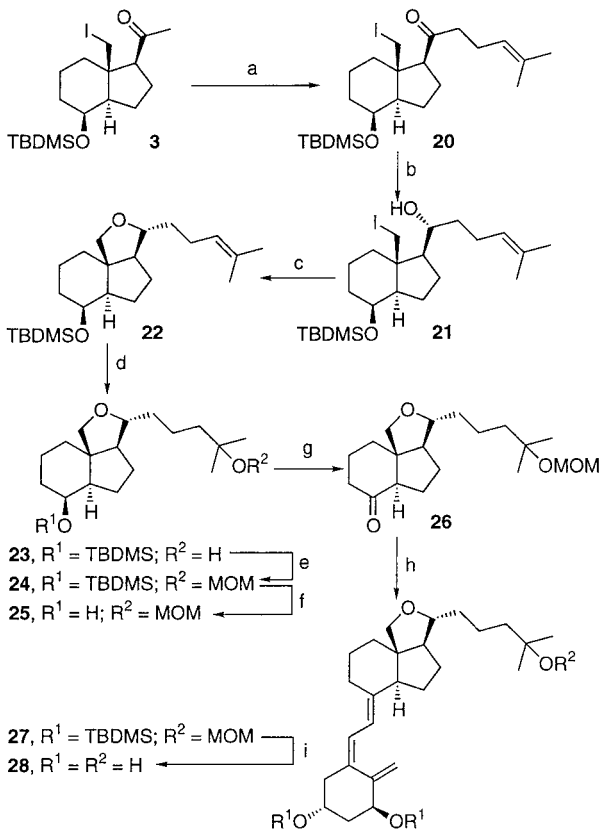
(21) (a) Lythgoe, B.; Moran, T. A.; Namburidy, M. E. N.; Ruston, S.; Tideswell, J.; Wright, P. W. *Tetrahedron Lett.* **1975**, 3863−3866. (b) Lythgoe, B. *Chem. Soc. Rev.* **1980**, 449−475. (c) Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Batcho, A. D.; Sereno, J. F.; Uskokovic, M. R. *J. Org. Chem.* **1986**, *51*, 3098−3108.

reaction of ketone **16** with the anion derived from phosphine oxide **8**,[22] generated by treatment with *n*-BuLi at low temperature, gave the silyl-protected vitamin D analogue **17** in 65% yield. Addition of methyllithium followed by treatment with *n*-Bu_4NF gave the desired calcitriol analogue **19** in 85% overall yield. In this way, the synthesis of the first analogue of calcitriol with a hydroxylated alkyl side chain, analogous to the natural chain, attached at C-18 was achieved. Moreover, the addition of other organometallics to the ester group in the vitamin **17** would give a variety of 18-substituted analogues.

Following with the use of the compounds obtained from iodo ketone **3** in Scheme 3, we pursued the synthesis of conformationally restricted side chain analogues of calcitriol type **5** (Scheme 1, route B). With the experience gained in the preparation of ether **13**, we planned the synthesis of calcitriol analogue with an ether bridge between the C-18 and C-20 positions.[23] The retrosynthetical analysis was based in the Lythgoe approach for the construction of the vitamin D triene system and intramolecular Williamson reaction of a iodo alcohol furnished with the calcitriol side chain.

Regioselective alkylation of iodo ketone **3** with LDA and 3,3-dimethylallyl bromide gave **20** in 89% yield, which contains a precursor of the 25-hydroxycalcitriol side chain. Stereoselective reduction of ketone **20** with $NaBH_4$ yielded iodo alcohol **21** as the only product detected by ^1H NMR spectroscopy.[24] As in the reduction of iodo ketone **3**, the presence of the iodine atom at the C-18 position seems to induce the high stereoselectivity. Iodo alcohol **21** was converted to ether **22** by an intramolecular Williamson reaction using silver acetate (80% yield). An oxymercuration−demercuration protocol allowed the introduction of the C-25 hydroxyl group (**23**), which was protected as the MOM ether (**24**, 76%, two steps). Removal of the silyl group at C-8 (**24** → **25**) followed by oxidation of the resulting alcohol **25** with PDC gave ketone **26** (85%, two steps).[25] A Wittig−Horner reaction between ketone **26** and the anion derived from phosphine oxide **8** afforded the protected vitamin D analogue **27** in 78% yield. Treatment of **27** with *n*-Bu_4NF and AG 50W-X4 led to the desired calcitriol analogue **28** in nine steps and 27% overall yield (Scheme 5).

SCHEME 5. Synthesis of 28[a]



[a] Key: (a) LDA, THF/HMPA, −78 °C, then 3,3-dimethylallyl bromide, THF, −78 °C to rt, 89%. (b) $NaBH_4$, MeOH, 0 °C, 99%; (c) AgOAc, acetone, Δ, 80%; (d) $Hg(OAc)_2$, THF/H_2O, then $NaBH_4$, NaOH, H_2O, 84%; (e) MOMCl, *i*-Pr_2NEt, DMAP, CH_2Cl_2, 91%; (f) *n*-Bu_4NF, THF, Δ, 99%; (g) PDC, CH_2Cl_2, 85%; (h) **8**, *n*-BuLi, THF, −78 °C, 78%; (i) *n*-Bu_4NF, THF, rt, then AG 50W-X4, MeOH, rt, 75%.

In summary, a novel synthetic strategy for the functionalization of the C-18 position, based on the introduction of an iodine atom into the bicyclic moiety of the vitamin D structure by means of a photochemical remote functionalization using DIB, was developed. This new methodology allowed the efficient synthesis of two new calcitriol derivatives from iodo ketone **3**: analogue **19**, the first containing a hydroxylated alkyl side chain at C-18, and analogue **28**, with restricted mobility in the side chain. The synthesis of other new C-18 analogues of calcitriol from cyclobutanol **12** and cyclopropanol **14** as well as analogues derived from ester **13** are now underway.

Experimental Section

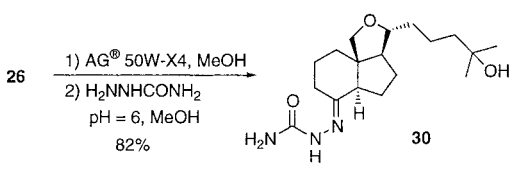
General Materials and Methods. Unless otherwise stated, all reactions were conducted in flame-dried glassware under a positive pressure of argon. Reaction temperatures refer to external bath temperatures. All dry solvents were distilled under argon immediately prior to use. Tetrahydrofuran (THF) was distilled from the sodium ketyl of benzophenone. Dichloromethane (CH_2Cl_2) was distilled from P_2O_5. Cyclohexane

(22) Mouriño, A.; Torneiro, M.; Vitale, C.; Fernández, S.; Pérez Sestelo, J.; Anné, S.; Gregorio, C. *Tetrahedron Lett.* **1997**, *38*, 4713−4716.

(23) Analogues of calcitriol with oxygen atoms in the side chain have shown interesting biological properties; see: (a) 20-oxa analogues: Kubodera, N.; Miyamoto, K.; Ochi, K.; Matsunaga, I. *Chem. Pharm. Bull.* **1986**, *34*, 2286−2289. (b) 22-Oxa analogues: Kubodera, N.; Watanabe, H.; Kawanishi, T.; Matsumoto, M. *Chem. Pharm. Bull.* **1992**, *40*, 1494−1499. (c) 23-Oxa analogues: Kubodera, N.; Miyamoto, K.; Akiyama, M.; Matsumoto, M.; Mori, T. *Chem. Pharm. Bull.* **1991**, *39*, 3221−3224. (d) 24-Oxa analogues: Allewaert, K.; Sarandeses, L. A.; Mouriño, A.; Convents, R.; Tan, B.-K.; Zhao, J.; Bouillon, R. *Steroids* **1995**, *60*, 484−490.

(24) The stereochemistry of this alcohol was assigned as (20*R*) on the basis of literature precedents; see ref 19a and: (a) Mijares, A.; Cargill, D. I.; Glasel, J. A.; Lieberman, S. *J. Org. Chem.* **1967**, *32*, 810−812. (b) Piatak, D. M.; Wicha, J. *Chem. Rev.* **1978**, *78*, 199−241.

(25) At this step, the stereochemistry at C-20 was definitively confirmed from the X-ray structure of the semicarbazone **30** prepared from ketone **26**. For experimental details see the Supporting Information.



and *i*-Pr_2NH were distilled from CaH_2. Absolute MeOH and EtOH were distilled from Mg turnings. Methyl acrylate and HMPA were distilled under vacuum prior use. Zinc was purified as described in the literature.[26] Copper iodide was purified by recrystallization from saturated potassium iodide solution.[27] Jones' reagent was prepared by slow addition of concentrated H_2SO_4 (10.4 mL) to a cold solution of CrO_3 (12.1 g) in water (17 mL) and dissolving the resulting red precipitate by the addition of water (34 mL).[28] Organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated using a rotary evaporator at aspirator pressure (20−30 mmHg). For reactions where a component was added by cannula, the total volume of solvent is given. The compound was usually dissolved in 80% of the given volume, and the flask was then rinsed with the remaining 20% of fresh solvent. Thin-layer chromatography was effected on silica gel 60 F_{254} (layer thickness 0.2 mm), and components were located by observation under UV light and/or by treating the plates with a phosphomolybdic acid or *p*-anisaldehyde reagent followed by heating. Flash column chromatography was performed on silica gel 60 (230−400 mesh) by Still's method.[29] ^{1}H NMR spectra were recorded on a 200 MHz spectrometer, and ^{13}C NMR spectra were recorded at 50 MHz.

(8*β*,20*ξ*)-8-[(*tert*-Butyldimethylsilyl)oxy]des-*A*,*B*-pregnan-20-ol (9).[12,30] To a cooled solution of **2**[11] (1580 mg, 5.09 mmol) in MeOH (50 mL) at −20 °C was added $NaBH_4$ (570 mg, 15.07 mmol) in portions. After 30 min of stirring, HCl 5% (30 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was washed with a saturated solution of $NaHCO_3$ (70 mL), dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (10% EtOAc/hexanes) affording, after concentration and high vacuum-drying, 1145 mg of **9b** (72%) as a colorless oil and 430 mg of its epimer **9a** (27%) as a white solid. **(20*R*)-9 (9b):** R_f 0.3 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 0.00 (s, 3 H), 0.01 (s, 3 H), 0.89 (s, 9 H), 1.00 (s, 3 H), 1.12 (d, J = 6.1 Hz, 3 H), 3.74 (br s, 1 H), 4.01 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ −5.2, −4.8, 14.4, 17.5, 18.0, 23.2, 23.3, 24.7, 25.8 (3), 34.4, 40.9, 42.0, 52.6, 59.1, 69.1, 70.2. **(20*S*)-9 (9a):** R_f 0.2 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 0.01 (s, 3 H), 0.02 (s, 3 H), 0.88 (s, 9 H), 0.91 (s, 3 H), 1.20 (d, J = 6.2 Hz, 3 H), 3.69 (dd, J = 8.4, 6.2 Hz, 1 H), 4.01 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ −5.2, −4.8, 14.4, 17.4, 18.0, 23.0, 23.3, 25.0, 25.8 (3), 34.3, 39.7, 41.4, 52.9, 59.0, 69.2, 70.2.

(8*β*)-8-[(*tert*-Butyldimethylsilyl)oxy]des-*A*,*B*-18-iodopregnan-20-one (3). A degassed solution of **9** (600 mg, 1.92 mmol), DIB (680 mg, 2.11 mmol), and iodine (487 mg, 1.92 mmol) in dry cyclohexane (250 mL) was irradiated with visible light (300 W) for 15 h. The solution was washed with saturated aqueous $Na_2S_2O_3$ (70 mL), and the organic phase was dried (Na_2SO_4), filtered, and concentrated in vacuo. To the crude iodo alcohol dissolved in acetone (150 mL) and cooled to 0 °C was added Jones' reagent (1.40 mL, 1.9 M). The mixture was stirred for 2 h, and *i*-PrOH (12 mL) was added, neutralized by addition of saturated aqueous $NaHCO_3$ (30 mL), and filtered. The filtrate was concentrated in vacuo, the residue was extracted with Et_2O (3 × 70 mL), and the organic phase was washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (3% EtOAc/hexanes) to afford, after concentration and high vacuum-drying, 702 mg of **3** (84%) as a pale yellow oil: R_f 0.45 (10% EtOAc/hexanes); IR (neat) 2951, 1706 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.01 (s, 3 H), 0.03 (s, 3 H), 0.87 (s, 9 H), 2.28 (s, 3 H), 3.18 and 4.45 (2 d, AB system, J = 11.0 Hz, 2 H), 4.06 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ −5.5, −4.9, 11.7, 17.1, 17.9, 22.1, 23.1, 25.7 (3), 33.7, 33.9, 40.5, 46.5, 53.4, 63.1, 69.0, 208.8; MS (EI) *m*/*z* 437 (M^+ + 1, 2), 379 (M^+ − C_4H_9, 39), 309 (M^+ − I, 7), 133 (100); HRMS (EI) calcd for $C_{14}H_{24}IO_2Si$ 379.0590 (M^+ − C_4H_9), found 379.0589.

(8*β*)-(20*S*)-8-[(*tert*-Butyldimethylsilyl)oxy]des-*A*,*B*-18,20-cyclopregnan-20-ol (10). To a cooled solution of **3** (97 mg, 0.22 mmol) in THF (10 mL) at −78 °C was slowly added a solution of *t*-BuLi in hexanes (0.16 mL, 1.7 M, 0.25 mmol) during 10 min. The resulting solution was stirred for 15 min, and an electrophile (RI or RCHO, 0.56 mmol) was added. The mixture was warmed to room temperature and the reaction quenched by addition of few drops of MeOH. The resulting mixture was concentrated to small volume, and Et_2O (20 mL) and a saturated solution of $NaHCO_3$ (10 mL) were added. The organic phase was washed with a saturated solution of NaCl (10 mL), dried, filtered, and concentrated in vacuo. The crude was purified by flash chromatography (5% EtOAc/hexanes) to afford, after concentration and high vacuum-drying, 51 mg of **10** (75%) as a colorless oil: R_f = 0.35 (10% EtOAc/hexanes); IR (neat) 3400 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.01 (s, 3 H), 0.03 (s, 3 H), 0.88 (s, 9 H), 1.36 (s, 3 H), 1.71 and 2.36 (2 d, AB system, J = 13.5 Hz, 2 H), 4.13 (dd, J = 4.8, 2.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ −5.0, −4.9, 17.7, 18.0, 24.1, 25.9 (3), 27.2, 30.5, 34.5, 36.5, 39.3, 43.1, 50.9, 52.6, 68.8, 69.3; MS (FAB) *m*/*z* 310 (M^+, 1), 309 (M^+ − 1, 5), 295 (M^+ − CH_3, 1), 293 (M^+ − H_2O, 12), 217 (100); HRMS (EI) calcd for $C_{18}H_{34}O_2Si$ 310.2328 (M^+), found 310.2335.

(8*β*)-8-[(*tert*-Butyldimethylsilyl)oxy]des-*A*,*B*-18-[2-(methoxycarbonyl)ethyl]pregnan-20-one (11). A mixture of Zn (59 mg, 0.90 mmol) and CuI (58 mg, 0.30 mmol) in aqueous EtOH (3 mL, 70%) was sonicated for 5 min, and to the resulting black mixture was succesively added a solution of **3** (120 mg, 0.27 mmol) and methyl acrylate (0.5 mL, 5.8 mmol) in EtOH (0.8 mL). After 3 h, more Zn (29 mg, 0.44 mmol) and CuI (28 mg, 0.15 mmol) were added, and the sonication was continued for 1 h. The mixture was diluted with EtOAc (8 mL) and filtered through a short pad of Celite, washing the solids with EtOAc (3 × 10 mL). The organic phase was washed with saturated NH_4Cl (30 mL) and NaCl (30 mL), dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (12% EtOAc/hexanes) to afford, after concentration and high vacuum-drying, 44 mg of **11** as a colorless oil (40%), 34 mg of (1′*R*,2′*S*)-5-[2′-[(*tert*-butyldimethylsilyl)oxy]-6′-methylenecyclohexyl]-2-pentanone (**29**, 40%), and 11 mg of ketone **2** (12%). **11**: R_f 0.35 (30% EtOAc/hexanes); IR (neat) 2931, 1741, 1704 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.00 (s, 3 H), 0.02 (s, 3 H), 0.87 (s, 9 H), 2.20 (s, 3 H), 3.64 (s, 3 H), 4.05 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ −5.3, −4.8, 17.6, 18.0, 20.0, 22.3, 22.7, 25.8 (3), 25.9, 32.4, 34.3, 34.7, 35.9, 47.9, 51.3, 54.9, 63.7, 69.2, 174.0, 210.2; MS (EI) *m*/*z* 397 (M^+ + 1, 9), 339 (M^+ − C_4H_9, 100); HRMS (EI) calcd for $C_{22}H_{40}O_4Si$ 396.2696 (M^+), found 396.2689. **29**: R_f 0.65 (30% EtOAc/hexanes); IR (neat) 3070, 2936, 1719, 1092 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.04 (s, 6 H), 0.88 (s, 9 H), 2.13 (s, 3 H), 3.75 (m, 1 H), 4.64 (br s, 1 H), 4.73 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ −4.9, −4.6, 18.1, 21.9, 24.2, 24.7, 25.8 (3), 29.7, 31.0, 31.2, 44.0, 50.8, 73.1, 109.3, 149.3, 209.2; MS (EI) *m*/*z* 311 (M^+ + 1, 6), 293 (25), 253 (M^+ − C_4H_9, 22), 161 (100); HRMS (EI) calcd for $C_{18}H_{34}O_2Si$ 310.2328 (M^+), found 310.2331.

(8*β*)-(17*S*)-8-[(*tert*-Butyldimethylsilyl)oxy]des-*A*,*B*-17,18-cyclo-17α-pregnan-20-one (12). A mixture of **3** (48 mg, 0.11 mmol) and KO-*t*-Bu (26 mg, 0.23 mmol) in THF (10 mL) was refluxed for 3.5 h. The solvent was evaporated in vacuo, and Et_2O (20 mL) was added. The organic layer was washed succesively with saturated solutions of $NaHCO_3$ (10 mL) and NaCl (10 mL), dried, filtered and concentrated in vacuo. The crude was purified by flash chromatography (5% EtOAc/hexanes) to afford 31 mg of **12** (91%) as a colorless oil: R_f = 0.55 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 0.00 (s, 3 H), 0.04 (s, 3 H), 0.89 (s, 9 H), 1.25 (br s, 2 H), 2.14 (s, 3 H), 4.06 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ −5.1, −4.7, 18.0, 20.3,

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21.2, 21.9, 25.8 (3), 28.4, 28.7, 30.5, 34.3, 41.0, 42.5, 47.6, 68.8, 208.7; MS (EI) *m*/*z* 308 (M^+, 7), 195 ($M^+ - C_6H_{15}OSi$, 5), 118 (100); HRMS (EI) calcd for $C_{18}H_{32}O_2Si$ 308.2172 (M^+), found 308.2176.

(8*β*)-(20*R*)-8-[(*tert*-Butyldimethylsilyl)oxy]des-*A*,*B*-18,20-epoxypregnane (13). To a cooled solution of **3** (234 mg, 0.54 mmol) in MeOH (10 mL) at 0 °C was added $NaBH_4$ (80 mg, 2.11 mmol) in portions. After 30 min of stirring, water (30 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic phase was washed with a saturated solution of $NaHCO_3$ (15 mL), dried, filtered, and concentrated in vacuo to afford 234 mg of an unstable iodo alcohol (99%, 20*R*/20*S* ≈ 20:1) as a colorless oil. This crude compound was dissolved in acetone (19 mL), and AgOAc (267 mg, 1.60 mmol) was added. The resulting mixture was refluxed for 10 h with protection from the light, cooled, and filtered through Celite, washing the solids with acetone (3 × 15 mL). The filtrate was concentrated, and the residue was purified by flash chromatography (10% EtOAc/hexanes) to give 124 mg of **13** (75%) as a yellowish oil: R_f = 0.55 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 0.01 (s, 3 H), 0.02 (s, 3 H), 0.89 (s, 9 H), 1.24 (d, J = 6.2 Hz, 3 H), 3.58 (dd, J = 9.8, 2.0 Hz, 1 H), 3.60 (dq, J = 6.2, 3.9 Hz, 1 H), 3.78 (d, J = 9.8 Hz, 1 H), 4.08 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ −5.1, −4.9, 18.0, 18.7, 22.1, 25.2, 25.8 (3), 30.6, 34.4, 36.5, 51.4, 54.3, 55.9, 68.6, 72.6, 83.3; HRMS (EI) calcd for $C_{18}H_{34}O_2Si$ 310.2328 (M^+), found 310.2329.

(8*β*)-8-[(*tert*-Butyldimethylsilyl)oxy]des-*A*,*B*-18-[2-(methoxycarbonyl)ethyl]-20-methyl-20-pregnene (14). To a suspension of methyltriphenylphosphonium bromide (65 mg, 0.18 mmol) in THF (20 mL) at 0 °C was added a solution of *n*-BuLi in hexanes (0.11 mL, 1.64 M, 0.18 mmol), and the resulting yellow mixture was warmed and stirred for 15 min at room temperature. Then, a solution of ketone **11** (32 mg, 0.08 mmol) in THF (9 mL) was slowly added by cannula. After being stirred for 20 h, a saturated solution of NH_4Cl (20 mL) was added, and the mixture was extracted with EtOAc (4 × 8 mL). The combined organic phase was dried, filtered, concentrated in vacuo, and purified by flash chromatography (8% EtOAc/hexanes) to give 57 mg of **14** (80%) as a colorless oil: R_f 0.6 (20% EtOAc/hexanes); IR (neat) 1742, 1252, 1026 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.01 (s, 3 H), 0.02 (s, 3 H), 0.89 (s, 9 H), 1.82 (s, 3 H), 3.65 (s, 3 H), 4.03 (m, 1H), 4.78 (br s, 1 H), 4.83 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ −5.2, −4.8, 17.8, 18.0, 19.9, 22.5, 24.5, 25.1, 25.8 (3), 26.1, 34.6, 35.3, 36.1, 45.8, 51.3, 54.4, 57.7, 69.6, 110.3, 146.4, 174.4; MS (EI) *m*/*z* 394 (M^+, 23), 379 ($M^+ - CH_3$, 47), 337 ($M^+ - C_4H_9$, 100); HRMS (EI) calcd for $C_{23}H_{42}O_3Si$ 394.2903 (M^+), found 394.2891.

(8*β*)-Des-*A*,*B*-18-[2-(methoxycarbonyl)ethyl]-20-methylpregn-20-en-8-ol (15). To a solution of **14** (40 mg, 0.10 mmol) in THF (12 mL) was added a solution of *n*-Bu_4NF in THF (0.31 mL, 1 M, 0.31 mmol), and the resulting mixture was heated to reflux during for 22 h. The reaction mixture was cooled to room temperature, poured into a separatory funnel with EtOAc (30 mL), washed succesively with HCl (3%, 12 mL), saturated solutions of $NaHCO_3$ (20 mL), and NaCl (20 mL), dried, filtered, and concentrated in vacuo. The crude was purified by flash chromatography (35% EtOAc/hexanes) to afford 24 mg of **15** (87%) as a colorless oil: R_f 0.15 (20% EtOAc/hexanes); IR (neat) 3450, 3000, 2925, 1757, 1290 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.83 (s, 3 H), 3.65 (s, 3 H), 4.12 (m, 1 H), 4.80 (br s, 1 H), 4.84 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 17.7, 20.0, 22.0, 24.5, 25.1, 26.3, 33.9, 35.1, 36.0, 45.5, 51.3, 54.0, 57.5, 69.4, 110.5, 146.1, 174.4; MS (EI) *m*/*z* 280 (M^+, 18), 262 ($M^+ - H_2O$, 42), 119 (100); HRMS (EI) calcd for $C_{17}H_{28}O_3$ 280.2038 (M^+), found 280.2037.

Des-*A*,*B*-18-[2-(methoxycarbonyl)ethyl]-20-methylpregn-20-en-8-one (16). A mixture of **15** (16 mg, 0.06 mmol) and PDC (64 mg, 0.17 mmol) in CH_2Cl_2 (5 mL) was stirred for 6 h. Et_2O (10 mL) was added, and the resulting mixture was stirred for 15 min and filtered through Celite, washing the solids with Et_2O (5 × 10 mL). The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography (18% EtOAc/hexanes), affording, after concentration and high vacuum-drying, 14 mg of **16** (88%) as a colorless oil: R_f 0.2 (20% EtOAc/hexanes); IR (neat) 1716, 1079 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.86 (s, 3 H), 3.64 (s, 3 H), 4.88 (br s, 2 H); ^{13}C NMR ($CDCl_3$) δ 18.5, 18.8, 23.9, 24.65, 24.70, 26.4, 34.5, 34.6, 41.0, 51.4, 52.3, 57.4, 63.1, 111.9, 144.8, 173.8, 211.5; MS (EI) *m*/*z* 278 (M^+, 17), 260 ($M^+ - H_2O$, 18), 177 (100); HRMS (EI) calcd for $C_{17}H_{26}O_3$ 278.1882 (M^+), found 278.1893.

(5*Z*,7*E*)-(1*S*,3*R*)-1,3-Di[(*tert*-butyldimethylsilyl)oxy]-18-[2-(methoxycarbonyl)ethyl]-20-methyl-9,10-secopregna-5,7,10(19),20-tetraene (17). To a cooled solution of the phosphine oxide **8** (69 mg, 0.12 mmol) in THF (3 mL) at −78 °C was added dropwise a solution of *n*-BuLi in hexanes (0.075 mL, 1.47 M, 0.11 mmol). The red solution was warmed to 0 °C, stirred for 20 min, and cooled again to −78 °C. Then a solution of **16** (14 mg, 0.05 mmol) in THF (3 mL) was added by cannula. The mixture was warmed to −50 °C and quenched by addition of a few drops of MeOH. The resulting mixture was concentrated to small volume, and Et_2O (8 mL) and a saturated solution of NH_4Cl (10 mL) were added. The organic phase was washed with a saturated solution of NaCl (10 mL), dried, filtered, and concentrated with protection from the light. The residue was purified by flash chromatography (30% EtOAc/hexanes) to afford, after concentration and high vacuum-drying, 21 mg of **17** (65%) as a colorless oil: R_f 0.75 (50% EtOAc/hexanes); ^{1}H NMR (CD_2Cl_2) δ 0.14 (s, 6 H), 0.21 (s, 3 H), 0.22 (s, 3 H), 1.02 (s, 9 H), 1.08 (s, 9 H), 1.78 (s, 3 H), 3.39 (s, 3 H), 4.28 (m, 1 H), 4.56 (m, 1 H), 4.88 (s, 1 H), 4.91 (s, 1 H), 5.20 (br s, 1 H), 5.43 (br s, 1 H), 6.37 and 6.53 (2 d, AB system, J = 11.2 Hz, 2 H); ^{13}C NMR (CD_2Cl_2) δ −4.7 (2), −4.4 (2), 19.6, 22.0, 23.9, 25.0, 25.1, 25.7, 26.0 (6), 26.1, 29.1, 30.2, 30.4, 35.0, 35.9, 45.4, 46.5, 48.7, 50.8, 57.8, 57.9, 68.0, 72.4, 119.3, 123.7, 128.3, 135.8, 140.9, 145.9, 149.0, 173.2; MS (FAB) *m*/*z* 642 (M^+, 8), 525 ($M^+ - C_6H_{17}Si$, 100); HRMS (EI) calcd for $C_{38}H_{66}O_4Si_2$ 642.4500 (M^+), found 642.4491.

(5*Z*,7*E*)-(1*S*,3*R*)-1,3-Di[(*tert*-butyldimethylsilyl)oxy]-18-(3-hydroxy-3-methylbutyl)-20-methyl-9,10-secopregna-5,7,10(19),20-tetraene (18). To a cooled solution of **17** (19 mg, 0.03 mmol) in THF (3 mL) at −78 °C was slowly added a solution of MeLi in hexanes (0.18 mL, 1.22 M, 0.22 mmol) during 10 min. The mixture was warmed to −10 °C, stirred for 5 h, and quenched with a few drops of MeOH. The resulting mixture was concentrated to small volume, and the residue was dissolved in CH_2Cl_2 (8 mL), washed with saturated NH_4Cl (10 mL), dried, filtered, and concentrated in vacuo. The crude was purified by flash chromatography (20% EtOAc/hexanes) to afford, after concentration and high vacuum-drying, 16 mg of **18** (86%) as a colorless oil: R_f 0.7 (50% EtOAc/hexanes); IR (neat) 3447, 1642 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.12 (s, 3 H), 0.13 (s, 3 H), 0.21 (s, 3 H), 0.23 (s, 3 H), 1.02 (s, 9 H), 1.09 (s, 9 H), 1.10 (s, 6 H), 1.82 (s, 3 H), 4.29 (m, 1 H), 4.55 (m, 1 H), 4.90 (br s, 1 H), 4.94 (br s, 1 H), 5.23 (d, J = 2.9 Hz, 1 H), 5.43 (d, J = 2.9 Hz, 1 H), 6.43 and 6.57 (2 d, AB system, J = 11.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ −4.6 (4), 18.3, 18.4, 18.5, 22.1, 24.0, 24.9, 25.1, 26.0 (6), 26.2 (2), 26.5, 28.9, 29.2, 29.9, 36.1, 45.38, 45.42, 46.6, 49.2, 57.88, 57.93, 67.9, 72.5, 110.8, 111.7, 119.2, 123.8, 128.3, 135.7, 146.3; MS (FAB) *m*/*z* 643 (M^+, 3), 511 ($M^+ - C_6H_{15}OSi$, 7), 288 (100); HRMS (EI) calcd for $C_{39}H_{70}O_3Si_2$ 642.4864 (M^+), found 642.4872.

(5*Z*,7*E*)-(1*S*,3*R*)-18-(3-Hydroxy-3-methylbutyl)-20-methyl-9,10-secopregna-5,7,10(19),20-tetraene-1,3-diol (19). To a solution of **18** (15 mg, 0.02 mmol) in THF (5 mL), with protection from light, was added *n*-$Bu_4NF{\cdot}3H_2O$ (30 mg, 0.09 mmol). The solution was stirred for 20 h and poured into a separatory funnel with EtOAc (8 mL), and the organic layer was washed with a saturated solution of NH_4Cl (10 mL), dried, filtered, and concentrated in vacuo. The crude was purified by flash chromatography (20% MeOH/EtOAc) to afford 13 mg of **19** (99%) as a white solid: R_f 0.2 (EtOAc); ^{1}H NMR (CD_3OD) δ 1.13 (s, 3 H), 1.15 (s, 3 H), 1.88 (s, 3 H), 4.17 (m, 1 H), 4.40 (m, 1 H), 4.83 (s, 1 H), 4.89 (s, 1 H), 4.95 (br s, 1 H), 5.34 (br s, 1 H), 6.14 and 6.37 (2 d, AB system, J = 11.2 Hz, 2 H); ^{13}C NMR (CD_3OD) δ 15.5, 20.4, 23.8, 24.7, 26.0, 26.2, 26.9, 28.3,

29.4, 30.6, 31.0, 34.1, 38.1, 44.7, 47.0, 47.2, 59.9, 68.4, 72.5, 112.1, 113.2, 120.7, 125.8, 137.0, 143.4, 148.4, 150.8; MS (EI) *m*/*z* 414 (M^+, 5), 396 ($M^+ - H_2O$, 10), 69 (100); HRMS (EI) calcd for $C_{27}H_{42}O_3$ 414.3134 (M^+), found 414.3131.

(8*β*)-8-[(*tert*-Butyldimethylsilyl)oxy]des-*A*,*B*-18-iodo-21-norcholest-24-en-20-one (20). To a solution of LDA, prepared by addition of *i*-Pr_2NH (0.07 mL, 0.55 mmol) to a solution of *n*-BuLi in hexanes (0.33 mL, 1.61 M, 0.53 mmol) at −78 °C and dilution with THF (5 mL),[31] was slowly added a solution of **3** (190 mg, 0.43 mmol) in THF (5 mL) by cannula. After 45 min, HMPA (0.24 mL, 1.37 mmol) and 3,3-dimethylallyl bromide (0.16 mL, 1.37 mmol) were succesively added. The solution was warmed to room temperature for 4 h, the solvents were evaporated in vacuo, and the resulting residue was dissolved in Et_2O (15 mL). The organic phase was succesively washed with water (15 mL) and brine (15 mL), dried, filtered, and concentrated in vacuo. The crude was purified by flash chromatography (7% EtOAc/hexanes) to afford, after concentration and high vacuum-drying, 193 mg of **20** (89%) as a colorless oil: R_f 0.55 (10% EtOAc/hexanes); IR (neat) 3068, 2930, 1705, 1254, 1022 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.01 (s, 3 H), 0.03 (s, 3 H), 0.87 (s, 9 H), 1.62 (s, 3 H), 1.68 (s, 3 H), 3.15 and 4.46 (2 d, AB system, J = 10.7 Hz, 2 H), 4.07 (br s, 1 H), 5.12 (t, J = 7.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ −5.2, −4.8, 11.6, 17.1, 17.7, 17.9, 22.3, 22.9, 23.3, 25.66, 25.72 (3), 33.8, 40.7, 46.3, 46.7, 53.5, 61.9, 69.1, 123.1, 132.4, 210.1; MS (FAB) *m*/*z* 503 ($M^+ - 1$, 5), 447 ($M^+ - C_4H_9$, 6), 377 ($M^+ - I$, 29); HRMS (EI) calcd for $C_{23}H_{41}O_2SiI$ 504.1921 (M^+), found 504.1929.

(8*β*)-(20*R*)-8-[(*tert*-Butyldimethylsilyl)oxy]des-*A*,*B*-18-iodo-21-norcholest-24-en-20-ol (21). To a cooled solution of **20** (94 mg, 0.19 mmol) in MeOH (10 mL) at 0 °C was added $NaBH_4$ (25 mg, 0.66 mmol) in portions. After 30 min of stirring, water (30 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic phase was washed with a saturated solution of $NaHCO_3$ (15 mL), dried, filtered, and concentrated in vacuo to afford 94 mg of **21** (99%) as a colorless oil: R_f 0.3 (5% EtOAc/hexanes); ^1H NMR ($CDCl_3$) δ 0.01 (s, 3 H), 0.04 (s, 3 H), 0.89 (s, 9 H), 1.64 (s, 3 H), 1.70 (s, 3 H), 3.11 and 4.61 (2 d, AB system, J = 11.0 Hz, 2 H), 3.90 (m, 1 H), 4.04 (br s, 1 H), 5.12 (t, J = 7,3 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ −5.2, −4.8, 12.7, 16.7, 17.7, 17.9, 23.0, 23.9, 24.3, 25.8 (3), 29.7, 33.9, 35.3, 41.2, 44.7, 52.8, 57.4, 69.2, 71.0, 124.4, 131.8; MS (EI) *m*/*z* 505 ($M^+ - 1$, 4), 488 ($M^+ - H_2O$, 7), 379 ($M^+ - I$, 29), 229 (100); HRMS (EI) calcd for $C_{23}H_{43}IO_2Si$ 506.2077 (M^+), found 506.2064.

(8*β*)-(20*R*)-8-[(*tert*-Butyldimethylsilyl)oxy]des-*A*,*B*-18,20-epoxy-21-norcholest-24-ene (22). A mixture of **21** (230 mg, 0.45 mmol) and AgOAc (227 mg, 1.36 mmol) in acetone (19 mL) was refluxed during 5 h with protection from light. The resulting mixture was filtered through Celite, washing the solids with acetone (3 × 15 mL), the filtrate was concentrated, and the residue was purified by flash chromatography (10% EtOAc/hexanes) to give 136 mg of **22** (80%) as a yellowish oil: R_f 0.65 (10% EtOAc/hexanes); IR (neat) 2930, 1253, 1021 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.01 (s, 3 H), 0.02 (s, 3 H), 0.89 (s, 9 H), 1.61 (s, 3 H), 1.69 (d, J = 1.1 Hz, 3 H), 3.44 (dt, J = 6.6, 3.7 Hz, 1 H), 3.57 (dd, J = 9.8, 2.0 Hz, 1 H), 3.79 (d, J = 9.8 Hz, 1 H), 4.08 (br s, 1 H), 5.13 (br t, J = 7.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ −5.1, −4.8, 17.7, 18.0, 18.7, 25.0, 25.2, 25.7, 25.8 (3), 30.8, 34.4, 36.4, 36.8, 51.4, 53.9, 54.4, 68.6, 72.3, 87.3, 124.2, 131.5; MS (EI) *m*/*z* 378 (M^+, 12), 321 ($M^+ - C_4H_9$, 46), 75 (100); HRMS (EI) calcd for $C_{23}H_{42}O_2Si$ 378.2954 (M^+), found 378.2957.

(8*β*)-(20*R*)-8-[(*tert*-Butyldimethylsilyl)oxy]des-*A*,*B*-18,20-epoxy-21-norcholestan-25-ol (23). A mixture of **22** (130 mg, 0.34 mmol) and $Hg(OAc)_2$ (120 mg, 0.37 mmol) in THF/H_2O (20 mL, 1:1) was stirred for 7 days. Then, NaOH (8 mL, 3 M) and a solution of $NaBH_4$ in 3 M NaOH (3.4 mL, 0.5 M, 1.7 mmol) were succesively added. After the mixture was stirred for 15 min, saturated NaCl (15 mL) was added, and the mixture was extracted with Et_2O (3 × 15 mL). The combined organic phase was dried, filtered, and concentrated in vacuo to afford a yellow residue that was flash chromatographed (20% EtOAc/hexanes) to give, after concentration and high vacuum-drying, 113 mg of **23** (84%) as a colorless oil: R_f 0.6 (50% EtOAc/hexanes); IR (neat) 3490, 1254, 1021 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.01 (s, 3 H), 0.02 (s, 3 H), 0.88 (s, 9 H), 1.21 (s, 6 H), 3.45 (m, 1 H), 3.58 (dd, J = 9.8, 2.0 Hz, 1 H), 3.79 (d, J = 9.8 Hz, 1 H), 4.08 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ −5.1, −4.9, 18.0, 18.7, 21.4, 25.2, 25.8 (3), 29.0, 29.3, 30.8, 34.4, 36.4, 37.1, 43.9, 51.4, 53.9, 54.5, 68.6, 71.0, 72.3, 87.6; MS (EI) *m*/*z* 396 (M^+, 10), 381 ($M^+ - CH_3$, 19), 378 ($M^+ - H_2O$, 19), 295 (100); HRMS (EI) calcd for $C_{23}H_{44}O_3Si$ 396.3059 (M^+), found 396.3047.

(8*β*)-(20*R*)-8-[(*tert*-Butyldimethylsilyl)oxy]des-*A*,*B*-18,20-epoxy-25-[(methoxymethyl)oxy]-21-norcholestane (24). To a cooled solution of **23** (42 mg, 0.11 mmol) and DMAP (5 mg, 0.04 mmol) in CH_2Cl_2 (5 mL) at 0 °C were succesively added *i*-Pr_2NEt (0.08 mL, 0.44 mmol) and MOMCl (0.04 mL, 0.50 mmol). After the mixture was stirred at room temperature for 30 h, water (5 mL) was added, and the organic phase was washed with HCl (3%, 15 mL) and saturated $NaHCO_3$ (15 mL), dried, filtered, and concentrated in vacuo. The residue was flash chromatographed (20% EtOAc/hexanes) to give 44 mg of **24** (91%) as a colorless oil: R_f 0.75 (50% EtOAc/hexanes); ^1H NMR ($CDCl_3$) δ 0.01 (s, 3 H), 0.02 (s, 3 H), 0.88 (s, 9 H), 1.21 (s, 6 H), 3.36 (s, 3 H), 3.43 (m, 1 H), 3.57 (dd, J = 9.8, 2.0, 1 H), 3.79 (d, J = 9.8 Hz, 1 H), 4.07 (br s, 1 H), 4.70 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ −5.1 (2), 18.0, 18.7, 21.1, 25.2, 25.8 (2), 26.1, 26.3, 30.8, 34.4, 36.4, 37.2, 42.0, 51.4, 53.9, 54.4, 55.1, 68.6, 72.3, 87.7, 91.0; MS (EI) *m*/*z* 439 ($M^+ - 1$, 6), 425 ($M^+ - CH_3$, 10), 321 (100); HRMS (EI) calcd for $C_{25}H_{48}O_4Si$ 440.3322, found 440.3308.

(8*β*)-(20*R*)-Des-*A*,*B*-18,20-epoxy-25-[(methoxymethyl)oxy]-21-norcholestan-8-ol (25). Following the same experimental procedure as for **15**, reaction of **24** (40 mg, 0.07 mmol) with *n*-$Bu_4NF{\cdot}3H_2O$ (100 mg, 0.30 mmol) afforded, after purification by flash chromatography (25% EtOAc/hexanes), 33 mg of **25** (99%) as a colorless oil: R_f 0.3 (50% EtOAc/hexanes); ^1H NMR ($CDCl_3$) δ 1.21 (s, 6 H), 3.36 (s, 3 H), 3.45 (m, 1 H), 3.56 (dd, J = 9.8, 2.0 Hz, 1 H), 3.83 (d, J = 9.8 Hz, 1 H), 4.17 (br s, 1 H), 4.70 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 18.6, 21.0, 24.8, 26.1, 26.3, 30.8, 33.9, 36.3, 37.0, 42.0, 51.0, 53.7, 54.3, 55.1, 68.1, 71.9, 76.3, 87.7, 91.0; MS (EI) *m*/*z* 311 ($M^+ - CH_3$, 1), 265 ($M^+ - C_2H_5O_2$, 16), 181 (100); HRMS (EI) calcd for $C_{19}H_{34}O_4$ 326.2457 (M^+), found 326.2462.

(20*R*)-Des-*A*,*B*-18,20-epoxy-25-[(methoxymethyl)oxy]-21-norcholestan-8-one (26). Following the same experimental procedure as for **16**, alcohol **25** (33 mg, 0.10 mmol) was oxidized with PDC (115 mg, 0.31 mmol) to give 28 mg of ketone **26** (85%) as a colorless oil: R_f 0.4 (50% EtOAc/hexanes); IR (neat) 1707, 1040 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 1.17 (s, 6 H), 2.60 (m, 1 H), 3.19 (dd, J = 9.8, 2.0 Hz, 1 H), 3.51 (d, J = 9.8 Hz, 1 H), 3.30 (s, 3 H), 3.57 (m, 1 H), 4.64 (s, 2 H); ^{13}C NMR (CD_2Cl_2) δ 21.1, 22.8, 25.7, 26.36, 26.39, 31.7, 35.8, 36.2, 41.1, 42.2, 54.1, 55.1, 60.6, 60.8, 71.3, 76.2, 88.8, 91.3, 210.4; MS (EI) *m*/*z* 323 ($M^+ - 1$, 12), 309 ($M^+ - CH_3$, 6), 263 ($M^+ - C_2H_5O_2$, 53), 83 (100); HRMS (EI) calcd for $C_{19}H_{32}O_4$ 324.2301 (M^+), found 324.2308.

(5*Z*,7*E*)-(1*S*,3*R*,20*R*)-1,3-Di[(*tert*-butyldimethylsilyl)oxy]-18,20-epoxy-25-[(methoxymethyl)oxy]-21-nor-9,10-secocholesta-5,7,10(19)-triene (27). Following the same experimental procedure as for **17**, reaction of ketone **26** (17 mg, 0.05 mmol) with the anion formed from phosphine oxide **8** (78 mg, 0.13 mmol) generated by addition of *n*-BuLi in hexanes (0.06 mL, 2.17 M, 0.13 mmol) afforded, after purification by flash chromatography (35% EtOAc/hexanes), 28 mg of **27** (78%) as a colorless oil: R_f 0.7 (50% EtOAc/hexanes); ^1H NMR (CD_2Cl_2) δ 0.05 (s, 6 H), 0.07 (s, 6 H), 0.86 (s, 9 H), 0.89 (s, 9 H), 1.17 (s, 6 H), 3.20 (dd, J = 9.8, 2.0 Hz, 1 H), 3.42 (d,

(31) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188−196.

J = 9.8 Hz, 1 H), 3.30 (s, 3 H), 3.55 (m, 1 H), 4.20 (m, 1 H), 4.39 (m, 1 H), 4.64 (s, 2 H), 4.85 (d, J = 2.4 Hz, 1 H), 5.21 (d, J = 2.4 Hz, 1 H), 6.07 and 6.18 (2 d, AB system, J = 11.2 Hz, 2 H); ^{13}C NMR (CD_2Cl_2) δ −5.0, −4.9, −4.72, −4.68, 21.1, 25.4, 25.9 (3), 26.0 (3), 26.37, 26.42, 28.8, 28.9, 32.3, 36.1, 37.7, 42.2, 44.3, 46.1, 54.1, 55.1, 55.4, 55.5, 57.9, 67.5, 67.9, 70.8, 71.8, 76.3, 89.2, 91.3, 115.7, 117.2, 121.8, 123.1, 143.4, 153.9; MS (EI) m/z 688 (M^+, 28), 627 ($M^+ - C_2H_5O_2$, 6), 556 ($M^+ - C_6H_{15}OSi$, 85), 248 (100); HRMS (EI) calcd for $C_{40}H_{72}O_5Si_2$ 688.4918 (M^+), found 688.4921.

(5*Z*,7*E*)-(1*S*,3*R*,20*R*)-18,20-Epoxy-21-nor-9,10-secocholesta-5,7,10(19)-trien-1,3,25-triol (28). To a solution of **27** (22 mg, 0.03 mmol) in THF (5 mL) protected from the light was added *n*-$Bu_4NF{\cdot}3H_2O$ (40 mg, 0.13 mmol). The solution was stirred for 22 h and poured into a separatory funnel with EtOAc (10 mL), and the organic layer was washed with a saturated solution of NH_4Cl (10 mL), dried, filtered, and concentrated in vacuo. The residue was dissolved in deoxygenated MeOH (5 mL), and resin AG 50W-X4 (150 mg) was added. The mixture was stirred for 22 h and filtered, the solids were washed with MeOH (4 × 5 mL) and concentrated in vacuo. The residue was purified by flash chromatography (3% MeOH/EtOAc) to afford, after concentration and high vacuum-drying, 10 mg of **28** (75%) as a colorless oil: R_f 0.2 (EtOAc); ^{1}H NMR (CD_2Cl_2) δ 1.16 (s, 6 H), 3.22 (dd, J = 9.3, 1.5 Hz, 1 H), 3.42 (d, J = 9.3 Hz, 1 H), 3.56 (m, 1 H), 4.16 (m, 1 H), 4.37 (m, 1 H), 4.95 (br s, 1 H), 5.30 (br s, 1 H), 6.08 and 6.28 (2 d, AB system, J = 11.2 Hz, 2 H); ^{13}C NMR (CD_2Cl_2) δ 21.4, 25.4, 26.1, 29.0, 29.3, 29.5, 32.3, 35.9, 37.7, 43.4, 44.2, 45.6, 53.8, 55.5, 57.9, 67.1, 70.9 (2), 71.9, 89.2, 111.7, 116.5, 124.4, 134.7, 142.7, 148.5; MS (FAB) m/z 417 ($M^+ + 1$, 8), 416 (M^+, 4), 307 (100). HRMS (EI) calcd for $C_{26}H_{40}O_4$ 416.2927 (M^+), found 416.2921.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all new compounds. Experimental procedure for the preparation of **30** and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

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