$(CH_2)_3OCH_2(CH_2OCH_2)_2(CH_2)_2NH_2$, 4246-51-9; $H_2N(CH_2)_3N(Me)(CH_2)_3NH_2$, 105-83-9; $H_2NCH_2C_6H_4$-*p*-CH_2NH_2, 539-48-0; $BrCH_2C_6H_4$-*p*-CH_2NH_2, 623-24-5; 4-(2-hydroxyethyl)-9-methylene-1,7-dioxa-4-azacyclodecane, 140605-27-2.

Supplementary Material Available: ^1H NMR spectra for *N,N'*-ditrityl-4,8-dithia-1,11-undecanediamine, 1-(5-hexenyl)-1,2-bis(3-cyanoethoxy)ethane, 1,10-diamino-5-(5-hexenyl)-4,7-dioxadecane, 4-(2-hydroxyethyl)-9-methylene-1,7-dioxa-4-azacyclodecane, and 18, ^{13}C NMR spectrum for 18, experimental details for the X-ray data, a comparison of the conformations of the 18-membered rings of 1, 2, and [2.2.2], and 10 tables of X-ray data for 1 and 2 (22 pages). Ordering information is given on any current masthead page.

Synthesis of Hydrindan Derivatives Related to Vitamin D[1]

Benito Fernández, José A. Martínez Pérez, Juan R. Granja, Luis Castedo, and Antonio Mouriño*

Departamento de Química Orgánica, Facultad de Química y Sección de Alcaloides del CSIC, Universidad de Santiago de Compostela, 15706 Santiago de Compostela, Spain

Received December 12, 1991

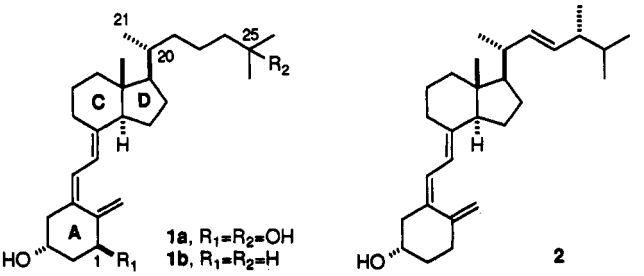
Two independent routes to the CD fragment of vitamin D metabolites and analogues are described. The *trans*-hydrindanol **4** was synthesized from enedione **5**. The key step in this synthesis was the hydroxyl-directed hydrogenation of hydrindenols of type **15** in the presence of Wilkinson's catalyst. The *trans*-hydrindanone **6** was efficiently prepared by degradation of the Lythgoe–Inhoffen diol (**3**). Both **4** and **6** are suitable precursors for the preparation of new potentially useful analogues of 1α,25-dihydroxyvitamin D_3 that are funtionalized at C_{20}, C_{21}, or ring D.

Introduction

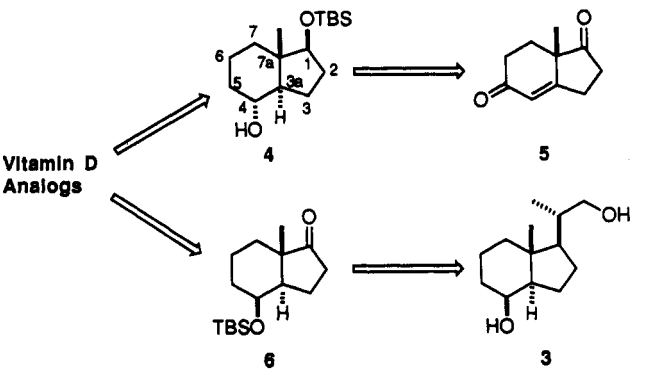
1α,25-Dihydroxyvitamin D_3 [**1a**, 1α,25-$(OH)_2$-D_3, calcitriol] (Chart I), the hormonally active form of vitamin D_3 (**1b**), in addition to controlling intestinal calcium absorption and bone calcium mobilization,[2] is also involved in cell differentiation and proliferation processes.[3] The fact that this hormone cannot be used for the treatment of certain cancers due to its potent calcemic effects[4] has led to interest in the synthesis of structurally modified analogues of 1α,25-$(OH)_2$-D_3 with potent effects on cell differentiation and proliferation without causing hypercalcemia.[5] To date, a number of side-chain-modified analogues of 1α,25-$(OH)_2$-D_3 have been subjected to preliminary clinical studies with promising results.[6]

Among the various routes now available for the synthesis of vitamin D metabolites and analogues, those based on the convergent coupling of the upper fragment (bicycle CD and side chain) to the bottom fragment (ring A) are particularly attractive.[7] In these syntheses the CD and side-chain fragments are usually prepared from the Lythgoe–Inhoffen diol (**3**), which is obtained by degradation

Chart I



Scheme I



(1) A short account of this work was partially been presented at the 7th workshop on vitamin D: *Vitamin D. Molecular, Cellular and Clinical Endocrinology*; Norman, A. W., Schaefer, K., Grigoleit, H. G., Herrath, D. V., Eds.; Walter de Gruyter: Berlin, New York, 1988; p 34. This work was taken in part from the PhD thesis of B. Fernandez.

(2) (a) Norman, A. W. *Vitamin D, The Calcium Homeostatic Steroid Hormone*; Academic Press: New York, 1979. (b) DeLuca, H. F.; Paaren, H. E.; Schnoes, H. K. *Top. Curr Chem.* **1979**, *83*, 1. (c) Dickson, I. *Nature* **1987**, *325*, 18. (d) Jones, G. *Steroids* **1987**, *49*, 1. (e) DeLuca, H. F.; Burmester, J.; Darwish, H.; Krisinger, J. *Comprehensive Medicinal Chemistry*; Pergamon Press: New York, 1990; Vol. 3, p 1129.

(3) (a) Provvedini, D. M.; Tsoukas, C. D.; Deftos, L. J.; Manolagas, S. C. *Science (Washington, D.C.)* **1983**, *121*, 1181. (b) Tsoukas, C. D.; Provvedini, D. M.; Manolagas, S. C. *Ibid.* **1984**, *224*, 1438. (c) For review, see: Ostrem, V. K.; DeLuca, H. F. *Steroids* **1987**, *49*, 73.

(4) Koeffler, H. P.; Hirji, K.; Itri, L. *Cancer Treat. Rep.* **1985**, *69*, 1399.

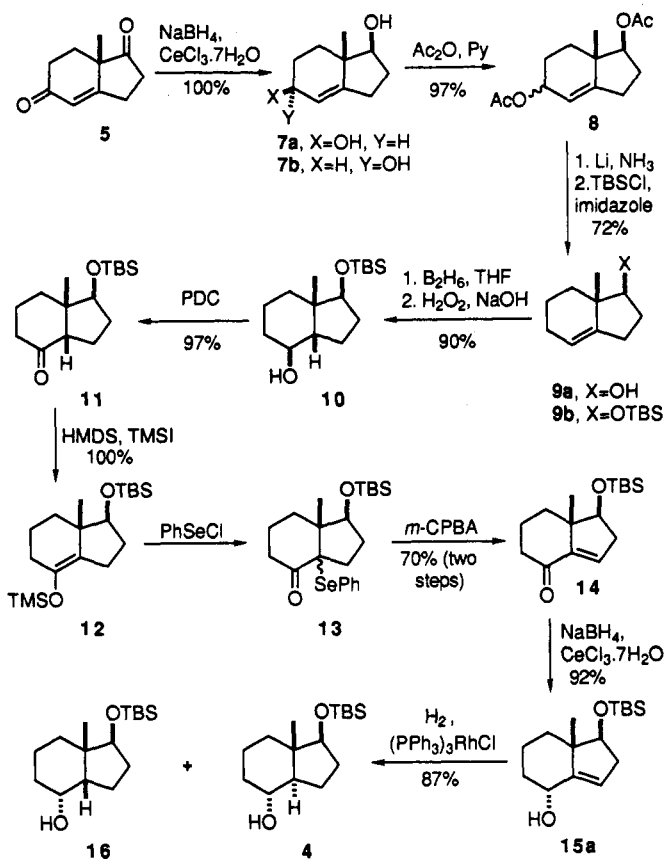
(5) Figadère, B.; Norman, A. W.; Henry, H. L.; Koeffler, H. P.; Zhou, J.-Y.; Okamura, W. H. *J. Med. Chem.* **1991**, *34*, 2452 and references cited therein.

(6) (a) Wovkulich, P. M.; Batcho, A. D.; Baggiolini, E. G.; Boris, A.; Truitt, G.; Uskokovic, M. R. *Vitamin D, Chemical, Biochemical and Clinical Update*; Norman, A. W.; Schaefer, K.; Grigoleit, H. G.; Herrath, D. V. Eds.; Walter de Gruyter: Berlin, 1985; p 755. (b) Abe, J.; Morikawa, M.; Miyamoto, K.; Kaiho, S.; Fukushima, M.; Miyaura, C.; Abe, E.; Suda, T.; Nishii, Y. *FEBS Lett.* **1987**, *226*, 58. (c) Calverley, M. J. *Tetrahedron* **1987**, *43*, 4609. (d) Zhou, J. Y.; Norman, A. W.; Collins, E.; Lubbert, M.; Uskokovic, M. R.; Koeffler, H. P. *Blood* **1989**, *74*, 82. (e) Binderup, E. *Drugs Future* **1990**, *15*, 15.

(7) (a) Okamura, W. H. *Acc. Chem. Res.* **1983**, *16*, 81. (b) Pardo, R.; Santelli, M. *Bull. Soc. Chim. Fr.* **1985**, 98. (c) Vitamin D Active Compounds. Quinkert, G., Ed. *Synform* **1985**, **1986**, **1987**, *3*, *4*, *5*. (d) Castedo, L.; Mouriño, A.; Sarandeses, L. A. *Tetrahedron Lett.* **1986**, *27*, 1523. (e) Castedo, L.; Mascareñas, J. L.; Mouriño, A.; Sarandeses L. A. *Tetrahedron Lett.* **1988**, *29*, 1203.

0022-3263/92/1957-3173$03.00/0

Scheme II



of vitamin D_2 (2). However, this prevents functionalization of other positions such as C_{20}, C_{21}, or ring D. As suitable precursors of new potentially useful vitamin D analogues functionalized at theses positions, we have synthesized the *trans*-hydrindanol **4**[8] and the enedione **5**[9] and the *trans*-hydrindanone **6** by degradation of the Lythgoe–Inhoffen diol (3) (Scheme I).

Total Synthesis of Hydrindanol 4 (Scheme II). The commercially available enedione **5** was reduced under Luche's conditions[10] to a mixture of alcohols **7a** and **7b** in quantitative yield. These alcohols, which can be separated by column chromatography (**7a**, 93%; **7b**, 7%), were treated with acetic anhydride under standard conditions to give the mixture of diacetates **8** in 97% yield. The acetates **8** were treated with lithium in ammonia–diethyl ether to give the alcohol **9a** (72%) and **7a,b** (21%). Protection of the alcohol **9a** with *tert*-butyldimethylsilyl chloride afforded **9b** (100%).[11] The next stage of the planned synthesis required conversion of **9b** to the corresponding *trans*-hydrindanol **4**. Unfortunately, hydroboration–oxidation of **9b** under the usual conditions [(1) B_2H_6 or 9-BBN; (2) H_2O_2, NaOH] afforded the *cis*-hydrindanol **10** as the major product (90% yield). Hydroboration of this type of compounds therefore appears to take place, like hydrogenation,[12] from the more exposed β-face. In view of this result, we decided to attempt hydroxyl-directed hydrogenation of hydrindenols of type **15**, which are similar to those successfully hydrogenated in this way by Okamura and co-workers[13] for the introduction of the *trans*-hydrindane nucleus.

Table I. Hydrogenation of 15

15a, R_1=TBS, R_2=H
15b, R_1=TBS, R_2=Ac
15c, R_1=TBS, R_2=MOM
15d, R_1=*t*-BuPh$_2$Si, R_2=H

starting compd	catalyst	solvent	cis:trans ratio	yield (%)
15a	Crabtree	CH_2Cl_2	100:0	92
15a	Wilkinson	PhH	25:75	87
15b	Crabtree	CH_2Cl_2	100:0	78
15b	Wilkinson	PhH	0:0	**15b**
15c	Crabtree	CH_2Cl_2	0:0	**15c**
15c	Wilkinson	PhH	0:0	**15c**
15d	Crabtree	CH_2Cl_2	100:0	87
15d	Wilkinson	PhH	35:65	85

Oxidation of alcohol **10** with pyridinium dichromate[14] and subsequent treatment of the ketone **11** with trimethylsilyl iodide (LiI, TMSCl, CH_2Cl_2) in hexamethyldisilazane (HMDS)[13,15] afforded the silyl enol ether **12** (97%, two steps). Treatment of **12** with phenylselenyl chloride in diethyl ether gave a 1:2.5 mixture of the α- and β-seleno derivatives **13**, which after purification by column chromatography were oxidized with *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane to give the enone **14** in 70% yield (two steps).[16] Reduction of the latter under Luche's conditions[10] afforded the desired allyl alcohol **15a** (92%).

We first attempted hydrogenation of hexahydrindanol **15a** to obtain the *trans*-hydrindane system using Crabtree's iridium catalyst ([Ir(Cod)Py(PCy$_3$)]PF$_6$).[17] The sole product, however, was the *cis*-hydrindanol **16** (97% yield). The cis-fusion was easily inferred from the ^{1}H NMR spectrum, which showed a singlet at δ 1.04 typical of the 7a-methyl group of the *cis*-hydrindan system, and from the recovery of ketone **11** by oxidation of the alcohol **16** (PDC, CH_2Cl_2, 98%). In view of this unexpected result we tried Wilkinson's catalyst[18] instead of Crabtree's. Hydrogenation of **15a** in the presence of 25 mol % of this catalyst

(8) For other syntheses of trans-fused hydrindans related to **4** starting from **5**, see: (a) Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 2945. (b) Wovkulich, P. M.; Barcelos, F.; Batcho, A. D.; Sereno, J. F.; Baggiolini, E. G.; Hennnessy, B. M.; Uskokovic, M. R. *Tetrahedron* **1984**, *40*, 2283. (c) Baggiolini, E. G.; Jacobelli, J. A.; Hennessy, B. M.; Batcho, A. D.; Sereno, J. F.; Uskokovic, M. R. *J. Org. Chem.* **1986**, *51*, 3098. (d) Daniewski, A. R.; Kiegiel, J. *J. Org. Chem.* **1988**, *53*, 5534. Daniewski, A. R.; Kiegiel, J. *Synth. Commun.* **1988**, *18*, 115. For other syntheses of trans-fused CD ring system in optically pure form, see: (e) Micheli, R. A.; Hajos, Z. G.; Cohen, N.; Parrish, D. R.; Portland, L. A.; Sciamana, W.; Scott, M. A.; Wehrli, P. A. *J. Org. Chem.* **1975**, *40*, 675. (f) Lythgoe, B.; Roberts, D. A.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2608. (g) Grieco, P. A.; Takigawa, T.; Moore, D. R. *J. Am. Chem. Soc.* **1979**, *101*, 4380. (h) Desmaele, D.; Ficini, J.; Guingant, A.; Touzin, A. M. *Tetrahedron Lett.* **1983**, *24*, 3083. (i) Haynes, R. K.; Vonwiller, S. C.; Hambley, T. W. *J. Org. Chem.* **1989**, *54*, 5162. (j) Yamada, H.; Shimizu, K.; Nisar, M.; Takahashi, T.; Tsuji, *J. Tetrahedron Lett.* **1990**, *31*, 2407.

(9) Enedione **5** (Aldrich) can be easily synthesized from 2-methyl-1,3-cyclopentadione: Hajos, Z. G.; Parrish, D. R. *Org. Synth.* **1984**, *63*, 26. See also ref 8e.

(10) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

(11) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(12) Fieser, L. F., Fieser, M., Eds. *Steroids*; Reinhold: New York, **1959**; p 212.

(13) (a) Hoeger, C. A.; Okamura, W. H. *J. Am. Chem. Soc.* **1985**, *107*, 268. (b) Hoeger, C. A.; Johnston, A. D.; Okamura, W. H. *J. Am. Chem. Soc.* **1987**, *109*, 4690. See also ref 8b.

(14) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

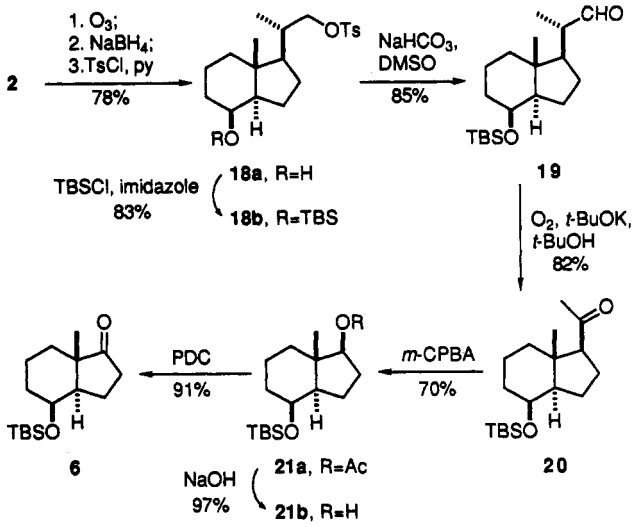
(15) Miller, R. D.; McKean, D. R. *Synthesis* **1979**, 730.

(16) (a) For a review of organoselenium reagents, see: Reich, H. J. *Acc. Chem. Res.* **1979**, *12*, 22. (b) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137. (c) Reich, H. J.; Wollowitz, S.; Trend, J. E.; Chow, F.; Wendelborn, D. F. *J. Org. Chem.* **1978**, *43*, 1697.

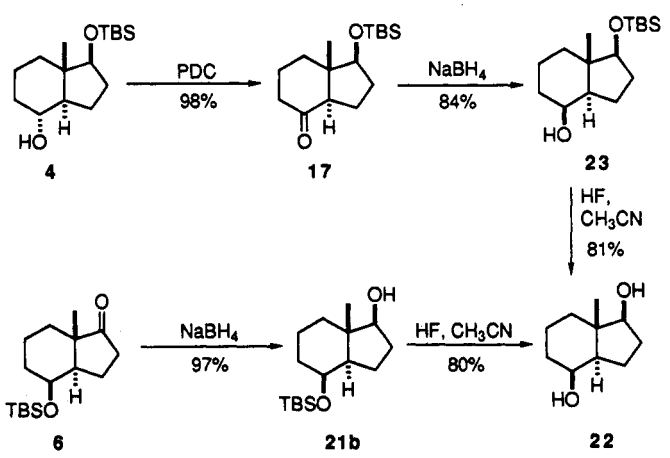
(17) Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655.

(18) Birch, A. J.; Williamson, D. H. *Org. React.* **1974**, *24*, 74.

Scheme III



Scheme IV



afforded a 3:1 mixture of the desired *trans*-hydrindanol **4** (65% isolated yield) and the cis isomer **16**, which were separated by flash chromatography. The structure of **4** was confirmed by oxidation to the trans-fused ketone **17** (PDC, CH_2Cl_2, 98%), whose ^1H NMR spectrum showed a singlet corresponding to the 7a-methyl group at δ 0.70 (as against δ 1.04 for the cis compound **11**). Encouraged by the stereoselectivity of this hydrogenation, we extended our study to the directing effect of various protecting groups, with the results listed in Table I.[19] We concluded (a) that only hydrogenation in the presence of Wilkinson's catalyst with the unprotected C_4 hydroxyl as directing group gives the desired *trans*-hydrindanol and (b) that the protecting group of the C_1 hydroxyl group must determine the degree of molecular convexity and therefore the ease with which the catalyst can coordinate to the C_4 alcohol from the α-face.[20]

Partial Synthesis of Hydrindanone 6 (Scheme III). The starting material for the partial synthesis of **6** was the tosylate **18a**, which can easily be prepared in 78% yield from vitamin D_2 (**2**) (O_3, MeOH-Py; $NaBH_4$/*p*-TsCl, Py).[21] Protection of **18a** (TBSCl, imidazole, DMF/CH_2Cl_2)[11] gave the known tosylate **18b** in 83% yield.[22] In an attempt to obtain the aldehyde **19** we used standard Kornblum conditions (10 equiv of $NaHCO_3$, DMSO),[23] but under these conditions epimerization occurred at C_{20}.[24] With 1 equiv of dry $NaHCO_3$, the aldehyde **19** was obtained in 85% yield without detection of its 20*R* epimer by ^1H NMR (which clearly distinguishes the aldehyde hydrogens of the two epimers). The aldehyde **19** was transformed into **20** in good yield (82%) via an α-hydroperoxy aldehyde by bubbling oxygen through a *tert*-butyl alcohol solution of the aldehyde in the presence of potassium *tert*-butoxide.[25]

Compound **6** was prepared in a three-step sequence by Baeyer–Villiger oxidation of **20** (*m*-CPBA, CH_2Cl_2, rt),[26] hydrolysis of the resulting acetate **21a** to the alcohol **21b** (NaOH, MeOH–H_2O, rt), and oxidation of **21b** to ketone **6** (PDC, CH_2Cl_2) [61% yield from **20**, 35% overall yield from the Lythgoe–Inhoffen diol (**3**)]. An attempt to obtain ketone **6** directly from compound **20** under Siddall conditions (O_2, *t*-BuOH–THF, 0–5 °C)[27] afforded only 35–55% yields.

Correlation between Alcohol 4 and Ketone 6. To further prove the structures of compounds **4** and **6** we proceeded to convert both into the diol **22** (Scheme IV). Oxidation of **4** with pyridinium dichromate in dichloromethane provided the ketone **17** (98%), which was reduced with sodium borohydride in methanol to give the β-alcohol **23** (84%) together with the α-alcohol **4** (15%). Compound **23** was then deprotected (HF, acetonitrile)[28] to afford the diol **22** in 81% yield. Sodium borohydride reduction of **6** provided the alcohol **21b** (97%), and deprotection (HF, acetonitrile) afforded an 80% yield of a product with a ^1H NMR and ^{13}C spectra identical to those of the diol obtained from **4**.

Experimental Section

General. All dry solvents were distilled under argon. Et_2O, THF, and benzene were distilled from sodium/benzophenone. CH_2Cl_2 and DMF were distilled from P_2O_5 and DMF was stored under type 4-Å molecular sieves. Pyridine was distilled from KOH and dioxane from sodium. DMSO was purified by standing overnight with chromatographic grade alumina and distillation from CaH_2 at low pressure and was stored under type 4-Å molecular sieves. *m*-CPBA was crystallized from CH_2Cl_2.[29] All reactions were conducted under Ar unless otherwise stated. Boiling points and melting points (open capillary tubes) are uncorrected. Kugelrohr oven temperatures (ot) refer to the external air bath temperature. ^1H NMR and ^{13}C spectra were recorded at 250 and 62.83 MHz using $CDCl_3$ as solvent. Mass spectra were measured using electron impact at 70 eV. Catalytic hydrogenations were carried out with a PARR 3915 hydrogenator. Flash chromatography was performed by Still's method.[30] TLC was

(19) The bulky *tert*-butyldiphenylsilyl protecting group was introduced with the idea of preventing complexation of the catalyst with the oxygen at C_1. Compound **15d** was obtained as above starting from **9a**.

(20) Attempts to obtain **17** by treatment **13** with *n*-Bu_3SnH, Et_3B, toluene, −20 °C, *n*-Bu_3SnH, AIBN, benzene, 60 °C, or *n*-Bu_3SnH, *n*-Bu_3SnSn*n*-Bu_3, $h\nu$, benzene, 0 °C led to a 6:1 mixture of the ketones **11** and **17** as determined by ^1H NMR. For the preparation of *trans*-hydrindan system using *n*-Bu_3SnH, see: Satoh, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1991**, *56*, 2278.

(21) (a) Leyes, G. A.; Okamura, W. H. *J. Am. Chem. Soc.* **1982**, *104*, 6099. (b) Sardina, F. J.; Mouriño, A.; Castedo, L. *J. Org. Chem.* **1986**, *51*, 1264.

(22) This compound was previously prepared from vitamin D_2 by an alternative route (27%, eight steps): Castedo, L.; Mascareñas, J. L.; Mouriño, A. *J. Org. Chem.* **1986**, *51*, 1269.

(23) Kornblum, N.; Jones, W. J.; Anderson, G. J. *J. Am. Chem. Soc.* **1959**, *81*, 4113.

(24) For a better understanding, steroidal numbering was used in this case. While this work was in progress, an alternative procedure for the preparation of aldehyde **19** was reported (35%, seven steps): Dauben, W. G.; Ollmann, R. R.; Funhoff, A. S.; Neidlein, R. *Tetrahedron Lett.* **1989**, *30*, 677.

(25) Sucrow, W. *Chem. Ber.* **1967**, *100*, 259.

(26) Alternative Baeyer–Villiger reagents (Oxone, magnesium monoperphthalate in MeOH/H_2O, and magnesium monoperphthalate in phase-transfer $Bu_4N^+Br^-$, CH_2Cl_2/H_2O) gave lower yields.

(27) Siddall, J. B.; Baddeley, G. V.; Edwards, J. A. *Chem. Ind.* (*London*) **1966**, 25.

(28) Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, 3981.

(29) Traylor, T. G.; Mikształ, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 2770.

perfomed on plates of silica gel (2 × 5 cm, 0.2-mm thickness). Components were located by observation of the plates under UV light and/or by treating the plates with a phosphomolybdic acid reagent followed by heating. Concentrations were carried out in a rotary evaporator. Dryings were carried out with anhydrous Na_2SO_4.

[1*S*-(1α,5α,7aα- and 1α,5β,7aα)]-2,3,5,6,7,7a-Hexahydro-1,5-dihydroxy-7a-methyl-1*H*-indene (7a and 7b). Enedione 5[9] (15 g, 91.5 mmol) and $CeCl_3·7H_2O$ (34 g, 91.2 mmol) were dissolved in absolute EtOH (100 mL). The solution was cooled to 0 °C, and $NaBH_4$ (7 g, 183 mmol) was slowly added. The mixture was stirred for 10 min at rt and quenched by dropwise addition of H_2O. The resulting mixture was continuously extracted with Et_2O for 24 h, and the extract was dried, filtered, and concentrated to give a mixture of **7a** and **7b** (15 g, 100%). A 5-g portion of this mixture was flash chromatographed (3 × 25 cm, 30% EtOAc/hexanes) to give 4.64 g of **7a** (93%) and 0.3 g of **7b** (7%). **7a** (R_f 0.36, 60% EtOAc/hexanes): IR ($CHCl_3$) 3400 cm^{-1}; ^1H NMR δ 5.37 (1 H, m, H-4), 4.26 (1 H, m, H-5), 3.62 (1 H, dd, J = 10 and 7.8 Hz, H-1), 1.02 (3 H, s, Me-7a); MS m/z 168 (M^+, 1), 150 ($M^+ - H_2O$, 36), 135 (28), 109 (100). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.37; H, 9.60. Found: C, 71.19; H, 9.69. **7b** (R_f 0.25, 60% EtOAc/hexanes): ^1H NMR δ 5.49 (1 H, m, H-4), 4.15 (1 H, m, H-5), 3.62 (1 H, dd, J = 10 and 7.8 Hz, H-1), 0.92 (3 H, s, Me-7a).

[1*S*-(1α,5α,7aα- and 1α,5β,7aα)]-2,3,5,6,7,7a-Hexahydro-1,5-bis(acetyloxy)-7a-methyl-1*H*-indene (8). A solution of the epimeric mixture of **7** (14 g, 83.3 mmol) in dry pyridine (40 mL) and acetic anhydride (10.5 mL, 110 mmol) was stirred at rt for 48 h. Water was added (100 mL), and the mixture was extracted with Et_2O (3 × 75 mL). The combined organic phases were successively washed with 10% HCl until no pyridine was present (2 × 20 mL) and then with aqueous saturated $NaHCO_3$ (2 × 20 mL) and water (20 mL). Drying, filtration, and concentration in vacuo afforded 21.5 g of a yellow tar which was distilled bulb-to-bulb to give 20.4 g of **8** (97%, ot 120–130 °C/0.5 mm Hg; R_f 0.85, 40% EtOAc/hexanes): IR (film) 1740 cm^{-1}; ^1H NMR δ 5.36 (1 H, m, H-4), 5.25 (1 H, m, H-5), 4.63 (1 H, dd, J = 10 and 6.7 Hz, H-1), 2.06 and 2.07 (3 H, 2 s, MeCO), 1.08 and 1.04 (3 H, 2 s, Me-7a). Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.63; H, 8.01. Found: c, 66.78; H, 8.21.

[1*S*-(1α,7aα)]-2,3,5,6,7,7a-Hexahydro-7a-methyl-1*H*-inden-1-ol (9a). NH_3 (400 mL) was collected in a flame-dried three-necked round-bottomed flask, fitted with NH_3 and N_2 inlets and previously cooled to −78 °C. Lithium was added in portions (5.25 g, 750 mmol), and the mixture was stirred for 20 min. A solution of **8** (11 g, 43.65 mmol) in Et_2O (100 mL) was slowly added with a syringe. The dry ice–acetone bath was removed after 2 h. The reaction mixture was stirred for 1.5 h and quenched by slow addition of solid NH_4Cl until the blue color disappeared. Water was added (100 mL), and NH_3 was removed by stirring under a stream of N_2. The mixture was concentrated, and the residue was extracted with EtOAc (200 mL). This organic phase was washed with water (2 × 30 mL), dried, filtered, and concentrated to give a yellowish oil which was flash chromatographed (3 × 60 cm, 20–40% EtOAc/hexanes) to afford **9a** (4.8 g, 72%; mp 95–7 °C; R_f 0.66, 30% EtOAc/hexanes) and **7** (1.55 g, 21%; R_f 0.18, 30% EtOAc/hexanes): IR (KBr) 3300 cm^{-1}; ^1H NMR δ 5.36 (1 H, d, J = 2.8 Hz, H-4), 3.64 (1 H, dd, J = 9.8 and 7.7 Hz, H-1), 2.46 and 2.13 (2 H, m, CH_2-5), 0.95 (3 H, s, Me-7a); ^{13}C NMR δ 144.2, 119.4, 82.2, 42.8, 34.4, 29.3, 25.7, 25.0, 18.6, 16.6; MS m/z 152 ($M^+ - H_2O$, 40), 137 (16), 134 (25), 108 (49), 93 (100); high-resolution MS calcd for $C_{10}H_{16}O$ ($C_{10}H_{18}O_2 - H_2O$) 152.1201, found 152.1230. Anal. Calcd for $C_{10}H_{18}O_2$: C, 78.88; H, 10.61. Found: C, 78.66; H, 10.50.

[1*S*-(1α,7aα)]-2,3,5,6,7,7a-Hexahydro-1-[(*tert*-butyldimethylsilyl)oxy]-7a-methyl-1*H*-indene (9b). A solution of **9a** (2.3 g, 15.13 mmol), imidazole (2.04 g, 30 mmol), and TBSCl (3.3 g, 22 mmol) in dry CH_2Cl_2 (20 mL) and dry DMF (50 mL) was stirred at rt for 24 h. Ice was added in portions, and the mixture was extracted with Et_2O (4 × 100 mL). The organic layers were dried, filtered, and concentrated to give 4 g of **9b** as a colorless oil (100%; R_f 0.63, hexanes): IR (film) 1110 cm^{-1}; ^1H NMR δ 5.33 (1 H, m, H-4), 3.55 (1 H, dd, J = 9.7 and 8.0 Hz, H-1), 0.91 (3 H, s, Me-7a), 0.89 (9 H, s, t-Bu), 0.025 and 0.022 (6 H, 2 s, Me_2Si); ^{13}C NMR δ 144.7, 118.9, 82.0, 43.3, 34.9, 29.8, 26.0, 25.8, 25.2, 18.8, 18.0, 17.1, −4.52, −4.87.

[1*S*-(1α,3aα,4α,7aα)]-Octahydro-1-[(*tert*-butyldimethylsilyl)oxy]-7a-methyl-1*H*-inden-4-ol (10). A solution of diborane in dry THF (45 mL, 45 mmol) was added dropwise to an ice–water-cooled solution of **9b** (4 g, 15 mmol) in dry THF (50 mL). The mixture was stirred at rt for 6 h. The solution was cooled to 0 °C and successively treated dropwise with solutions of NaOH (10%, 20 mL) and H_2O_2 (30%, 50 mL). This mixture was heated to 60 °C for 1 h. THF was removed in vacuo, and H_2O (30 mL) was added. The mixture was extracted with EtOAc (3 × 40 mL). The combined organic phases were dried, filtered, and concentrated to give 4.1 g of a viscous liquid which was flash chromatographed (3 × 40 cm, hexanes–20% Et_2O/hexanes) to afford 3.9 g of **10** (90%; mp 79–81 °C; R_f 0.37, 30% Et_2O/hexanes): IR (KBr) 3300, 1100 cm^{-1}; ^1H NMR δ 3.92 (1 H, t, J = 7.4 Hz, H-1), 3.32 (1 H, m, H-4), 0.91 (3 H, s, Me-7a), 0.87 (9 H, s, t-BuSi), 0.004 (6 H, s, Me_2Si); ^{13}C NMR δ 75.3, 72.2, 51.9, 45.8, 33.9, 32.0, 30.5, 25.7, 23.9, 22.4, 19.4, 17.9, −4.5, −5.1; MS m/z 227 ($M^+ - t$-Bu, 9), 209 ($M^+ - H_2O$, t-Bu, 93), 135 (29), 93 (35), 75 (100); high-resolution MS calcd for $C_{12}H_{23}O_2Si$ ($C_{16}H_{32}O_2Si - t$-Bu) 227.1467, found 227.1461. Anal. Calcd for $C_{16}H_{32}O_2Si$: C, 67.53; H, 11.30. Found: C, 67.12; H, 11.30.

[1*S*-(1α,3aα,7aα)]-Octahydro-1-[(*tert*-butyldimethylsilyl)oxy]-7a-methyl-4*H*-inden-4-one (11). PDC (10 g, 27 mmol) was added to an ice–water-cooled solution of alcohol **10** (3.8 g, 13.4 mmol) in dry CH_2Cl_2 (150 mL). The mixture was stirred at rt for 10 h, filtered through Celite, and concentrated. The residue was dissolved with EtOAc (100 mL), and the solution was washed with saturated $NaHCO_3$ (2 × 50 mL). The organic phase was dried, filtered, and concentrated to give 4 g of a brownish viscous oil, which was flash chromatographed (3 × 35 cm, 5% Et_2O/hexanes) to afford a colorless liquid. Bulb-to-bulb distillation gave 3.7 g of **11** (97%, ot 120 °C/0.4 mmHg; R_f 0.64, 20% Et_2O/hexanes): IR (film) 1710 cm^{-1}; ^1H NMR δ 3.73 (1 H, t, J = 6.0 Hz, H-1), 1.04 (3 H, s, Me-7a), 0.89 (9 H, s, t-BuSi), 0.031 (6 H, s, Me_2Si); ^{13}C NMR δ 213.6, 56.6, 50.3, 39.3, 31.8, 31.0, 25.7, 21.9, 21.7, 21.0, 19.2, 17.9, −4.6, −5.1; MS m/z 267 (M^+ − Me, 2), 225 ($M^+ - t$-Bu, 100), 149 (8.5), 133 (38), 91 (13), 75 (99); high-resolution MS calcd for $C_{12}H_{21}O_2Si$ ($C_{16}H_{30}O_2Si - t$-Bu) 225.1311, found 225.1314. Anal. Calcd for $C_{16}H_{30}O_2Si$: C, 68.01; H, 10.72. Found: C, 67.62; H, 10.76.

[1*S*-(1α,7aα)]-2,3,5,6,7,7a-Hexahydro-1-[(*tert*-butyldimethylsilyl)oxy]-7a-methyl-4-[(trimethylsilyl)oxy]-1*H*-indene (12). Dry LiI (2 g, 14.85 mmol) and TMSCl (1.42 g, 13.1 mmol, freshly distilled from CaH_2 under N_2) were successively added to a cooled solution (−5 °C) of **11** (3.7 g, 13.1 mmol) and HMDS (2.09 mL, 16.9 mmol, freshly distilled from CaH_2 under N_2) in dry CH_2Cl_2 (80 mL). The mixture was stirred at −5 °C for 3 h and then transferred to a separatory funnel containing ice. The organic phase was washed with an aqueous saturated solution of $NaHCO_3$ (2 × 30 mL), dried, filtered, and concentrated. The resulting yellowish liquid (**12**, 4.6 g, 100%) was used in the next experiment without further purification: ^1H NMR δ 3.48 (1 H, m, H-1), 0.88 (12 H, s, (t-BuSi and Me-7a), 0.15 (15 H, 2 s, Me_2Si and Me_3Si); MS m/z 281 (M^+ − 45, 4), 257 (10), 239 (18), 197 (33), 165 (61), 137 (28), 95 (29), 75 (100).

[1*S*-(1α,7aα)]-1,2,5,6,7,7a-Hexahydro-1-[(*tert*-butyldimethylsilyl)oxy]-7a-methyl-4-[(trimethylsilyl)oxy]-4*H*-inden-4-one (14). A solution of PhSeCl (2.6 g, 13.8 mmol) in dry Et_2O (30 mL) was slowly added via syringe to dry ice–acetone-cooled solution of **12** (4.6 g, 13.1 mmol) in dry Et_2O (40 mL). After 45 min of stirring, an aqueous saturated solution of $NaHCO_3$ (30 mL) was added. The organic layer was washed with saturated $NaHCO_3$ (2 × 15 mL), dried, filtered, and concentrated to give 5.3 g of a yellowish solid which was flash chromatographed (3 × 40 cm, hexanes) to afford 5.1 g of phenylselenyl ketones **13**: ^1H NMR δ 7.47–7.24 (5 H, m, Ph), 3.80 (1 H, t, J = 8.6 Hz, H-1), 1.19 and 0.87 (3 H, 2s, Me-7a), 0.89 (9 H, s, t-Bu), 0.01 (6 H, Me_2Si). The mixture was dissolved in dry CH_2Cl_2 (200 mL), and the solution was cooled to −78 °C. Pure m-CPBA (4.5 g, 26 mmol) was added, and the reaction mixture was stirred at this temperature for 30 min. A few drops of a saturated solution of $NaHCO_3$ were added, and the mixture was washed with a satu-

(30) Stille, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* 1978, *43*, 2923.

rated solution of $NaHCO_3$ (2 × 30 mL) and water (30 mL). The organic phase was dried, filtered, and concentrated to give a yellowish liquid which was flash chromatographed (3 × 30 cm, 5% Et_2O/hexanes) to afford 2.6 g of **14** (70%): IR (film) 1690 cm^{-1}; UV (EtOH) λ_{max} 252.3 nm (ϵ = 11 000); ^1H NMR δ 6.4 (1 H, m, H-3), 4.08 (1 H, m, H-1), 0.97 (3 H, s, Me-7a), 0.87 (9 H, s, *t*-Bu), 0.03 (6 H, s, Me_2Si). Anal. Calcd for $C_{16}H_{28}O_2Si$: C, 68.49; H, 10.00. Found: C, 68.06; H, 10.24.

[1*S*-(1α,4β,7aα)]-2,4,5,6,7,7a-Hexahydro-1-[(*tert*-butyldimethylsilyl)oxy]-7a-methyl-1*H*-inden-4-ol (15a). $NaBH_4$ (1.2 g, 31.5 mmol) was added to an ice–water-cooled solution of **14** (2.8 g, 10 mmol) and $CeCl_3 \cdot 7H_2O$ (2 g, 5.4 mmol) in MeOH (50 mL). After 15 min of stirring, the reaction was quenched by addition of drops of water. The mixture was concentrated and the residue dissolved in EtOAc (100 mL). The organic phase was washed with H_2O (3 × 50 mL), dried, filtered, and concentrated to give a residue which was flash chromatographed (2 × 30 cm, 10% EtOAc/hexanes). Bulb-to-bulb distillation afforded 2.6 g of **15a** (92%; ot 120–130 °C/1 mmHg, colorless liquid): ^1H NMR δ 5.35 (1 H, m, H-3), 4.17 (1 H, m, H-4), 3.99 (1 H, t, J = 8.0 Hz, H-1), 0.94 (3 H, s, Me-7a), 0.89 (9 H, s, *t*-Bu), 0.04 (6 H, s, Me_2Si); MS *m/z* 267 (M^+ – Me, 2), 264 ($M^+ - H_2O$, 10), 225 (M^+ – *t*-Bu, 33), 149 (15), 133 (36), 75 (100); high-resolution MS calcd for $C_{12}H_{21}O_2Si$ ($C_{16}H_{30}O_2Si$ – *t*-Bu) 225.1311, found 225.1298. Anal. Calcd for $C_{16}H_{30}O_2Si$: C, 68.01; H, 10.72. Found: C, 67.89; H, 10.48.

[1*S*-(1α,3aα,4β,7aα)]-Octahydro-1-[(*tert*-butyldimethylsilyl)oxy]-7a-methyl-1*H*-inden-4-ol (16). Hydrogenation of 15a in the Presence of Crabtree's Catalyst. Crabtree's catalyst, $[Ir(Cod)Py(PCy_3)]PF_6$ (30 mg, 0.04 mmol), was added to a degassed and cooled (–78 °C) solution of **15a** (50 mg, 0.2 mmol) in dry CH_2Cl_2 (25 mL). The mixture was degassed, and H_2 was introduced at a pressure of 40 psi. After 30 h of stirring, the mixture was concentrated and the residue was flash chromatographed (2 × 15 cm, 10% EtOAc/hexanes) to afford 46 mg of **16** (92%; R_f 0.6, 30% EtOAC/hexanes): ^1H NMR δ 3.88 (1 H, m, H-4), 3.66 (1 H, dd, J = 5.5 and 1.0 Hz, H-1), 0.98 (3 H, s, Me-7a), 0.88 (9 H, s, *t*-Bu), 0.02 and 0.01 (6 H, 2 s, Me_2Si); ^{13}C NMR δ 82.0, 69.6, 47.6, 47.5, 32.1, 30.7, 29.5, 25.7, 21.3, 20.4, 19.4, 18.0, –4.7, –5.0; MS *m/z* 284 (M^+, 0.9), 227 (M^+ – *t*-Bu, 18), 209 ($M^+ - H_2O$, *t*-Bu, 100), 151 (16), 133 (31), 107 (22), 93 (34), 75 (67). Anal. Calcd for $C_{16}H_{32}O_2Si$: C, 67.53; H, 11.36. Found: C, 67.22; H, 11.48.

[1*S*-(1α,3aα,4β,7aα)]-Octahydro-1-[(*tert*-butyldimethylsilyl)oxy]-7a-methyl-1*H*-inden-4-ol (4). Hydrogenation of 15a in the Presence of Wilkinson's Catalyst. A degassed solution of Wilkinson's catalyst (200 mg, 0.22 mmol) in dry benzene (50 mL) was hydrogenated (40 psi) with stirring for 1 h, and then a solution of the alcohol **15a** (250 mg, 0.89 mmol) in dry benzene (50 mL) was added. The mixture was hydrogenated at the same pressure for 24 h with stirring. After concentration, the residue was flash chromatographed (2 × 20 cm, 10% EtOAc/hexanes) to give 162 mg of **4** as a colorless solid (65%; mp 72–3 °C; R_f 0.5, 30% EtOAc/hexanes) and 55 mg of **16** (22%): ^1H NMR δ 3.60 (2 H, m, H-1 and H-4), 0.87 (9 H, s, *t*-Bu), 0.70 (3 H, s, Me-7a), 0.004 (6 H, s, Me_2Si); ^{13}C NMR δ 81.6, 71.2, 51.6, 45.3, 36.3, 36.1, 30.4, 25.7, 22.7, 21.5, 18.0, 11.1, –4.6, –4.9; MS *m/z* 284 (M^+, 0.5), 227 (M^+ – *t*-Bu, 65), 209 ($M^+ - H_2O$, *t*-Bu, 23), 151 (39), 135 (43), 93 (28), 75 (100). Anal. Calcd for $C_{16}H_{32}O_2Si$: C, 67.53; H, 11.36. Found: C, 67.59; H, 11.34.

[1*R*-(1α(*S),3aβ,4α,7aα)]-Octahydro-4-[(*tert*-butyldimethylsilyl)oxy]-β,7a-dimethyl-1*H*-indene-1-ethanol *p*-Toluenesulfonate (18b).** Imidazole (0.17 g, 2.5 mmol) and TBSCl (200 mg, 1.32 mmol) were successively added to a solution of **18a**[8f,21] (300 mg, 0.82 mmol) in dry CH_2Cl_2 (3 mL) and DMF (8 mL). The solution was stirred at rt for 24 h and at 55 °C for 30 h and then quenched by the addition of ice. The mixture was extracted with Et_2O (3 × 20 mL) and washed with an aqueous solution of HCl (10%, 20 mL) and brine (20 mL). The combined organic phases were dried, filtered, and concentrated to give a residue which was flash chromatographed (hexanes) to afford 334 mg of **18b** (85%; R_f 0.7, 8% EtOAc/hexanes; mp 50 °C (lit.[22] mp 50 °C), white solid: ^1H NMR δ 7.79 (2 H, d, J = 8.35 Hz, Ar), 7.35 (2 H, d, J = 8.4 Hz, Ar), 3.98 (1 H, m, H-4), 3.95 (1 H, dd, J = 9.2 and 3.1 Hz, H-α), 3.8 (1 H, dd, J = 9.2 and 6.3 Hz, H-α), 2.46 (3 H, s, MeAr), 0.95 (3 H, d, J = 6.7 Hz, Me-β), 0.88 (9 H, s, *t*-BuSi), 0.87 (3 H, s, Me-7a), 0.005 (6 H, s, Me_2Si).

[1*R*-(1α(*S),3aβ,4α,7aα)]-Octahydro-4-[(*tert*-butyldimethylsilyl)oxy]-β,7a-dimethyl-1*H*-indene-1-acetaldehyde (19).** A solution of tosylate **18b** (150 mg, 0.31 mmol) and dry $NaHCO_3$ (26 mg, 0.31 mmol) in dry DMSO (5 mL, previously heated at 150 °C for 5 min and allowed to reach rt under argon) was heated at 120 °C for 2 h. The mixture was cooled to rt, and solutions of brine (10 mL) and Et_2O (10 mL) were successively added. The organic phase was washed with H_2O (2 × 10 mL). The combined aqueous phases were extracted with Et_2O (2 × 10 mL). The combined organic phases were dried, filtered, and concentrated. The residue was flash chromatographed (1 × 16 cm, 1% EtOAc/hexanes) to afford 85 mg of aldehyde **19**[24] (85%; R_f 0.48, 15% EtOAc/hexanes): IR (film) 1710 cm^{-1}; ^1H NMR δ 9.58 (1 H, d, J = 3.2 Hz, H-α), 4.04 (1 H, m, H-4), 2.36 (1 H, m, H-β), 1.08 (3 H, d, J = 7.0 Hz, Me-β), 0.95 (3 H, s, Me-7a), 0.88 (9 H, s, *t*-BuSi), 0.01 (6 H, 2 s, Me_2Si); ^{13}C NMR δ 205.2, 69.1, 52.4, 51.7, 49.1, 42.6, 40.4, 34.3, 30.3, 26.2, 25.8, 23.3, 17.5, 14.0, 13.3, –4.9, –5.2.

[1*S*-(1α,3aβ,4α,7aα)]-Octahydro-1-acetyl-4-[(*tert*-butyldimethylsilyl)oxy]-7a-methyl-1*H*-indene (20). O_2 was bubbled through a solution of KO-*t*-Bu (1.8 g, 16 mmol) in dry *t*-BuOH (35 mL, freshly distilled from CaH_2), at rt, for 10 min, and then a solution of aldehyde **19** (1.06 g, 3.27 mmol) in *t*-BuOH (20 mL) was added. O_2 was bubbled through the suspension for 10 min followed by N_2 for 15 min. Water (25 mL) was added, and the mixture was extracted with Et_2O (3 × 50 mL). The combined organic phases were dried, filtered, and concentrated. The residue was flash chromatographed (2.5 × 19 cm, 1–2% EtOAc/hexanes) to afford 818 mg of **20** (82%; R_f 0.41, 15% EtOAc/hexanes; mp 34–5 °C, white solid); IR (film) 1700 cm^{-1}; ^1H NMR δ 4.04 (1 H, m, H-4), 2.47 (1 H, t, J = 8.7 Hz, H-1), 2.09 (3 H, s, MeCO), 0.87 (9 H, s, *t*-BuSi), 0.85 (3 H, s, Me-7a), 0.01 and 0.005 (6 H, s, Me_2Si); ^{13}C NMR δ 209.5, 69.0, 64.5, 53.2, 43.7, 39.8, 34.2, 30.8, 25.7, 23.2, 21.8, 17.6, 15.4, –4.9, –5.3; MS *m/z* 267 (M^+ – 43, 5), 253 (M^+ – *t*-Bu, 69), 225 (19), 179 (10), 161 (17), 145 (25), 119 (46), 75 (100); high-resolution MS calcd for $C_{14}H_{25}O_2Si$ ($C_{18}H_{34}O_2Si$ – *t*-Bu) 253.1624, found 253.1642.

[1*S*-(1α,3aβ,4α,7aα)]-Octahydro-1-(acetyloxy)-4-[(*tert*-butyldimethylsilyl)oxy]-7a-methyl-1*H*-indene (21a). Pure *m*-CPBA (130 mg, 0.75 mmol) was added to an ice-cooled solution of ketone **20** (110 mg, 0.36 mmol) in dry CH_2Cl_2 (3 mL). The mixture was stirred at rt for 7 days [additional amounts of *m*-CPBA were successively added (60 mg, 24 h; 50 mg, 78 h; 30 mg, 98 h; 55 mg, 120 h)]. An aqueous saturated solution of $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL) were added, and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were dried, filtered, and concentrated to afford, after flash chromatography (1.5 × 16 cm, 1% EtOAc/hexanes), 81 mg of **21a** (70%, white solid; mp 47–9 °C): ^1H NMR δ 4.54 (1 H, dd, J = 9.0 and 7.7 Hz, H-1), 4.01 (1 H, m, H-4), 2.03 (3 H, s, $MeCO_2$), 1.01 (3 H, s, Me-7a), 0.89 (9 H, s, *t*-BuSi), 0.017 and 0.003 (6 H, 2 s, Me_2Si); ^{13}C NMR δ 171.3, 82.9, 69.1, 47.8, 25.8, 22.2, 21.1, 18.0, 17.1, 13.7, –4.9, –5.2; MS *m/z* 326 (M^+, 17), 283 (M^+ – Ac, 12), 281 (M^+ – 45, 38), 269 (M^+ – *t*-Bu, 25), 135 (100), 105 (44), 91 (37), 75 (45). Anal. Calcd for $C_{18}H_{34}O_3Si$: C, 66.21; H, 10.49. Found: C, 66.07; H, 10.77.

[1*S*-(1α,3aβ,4α,7aα)]-Octahydro-4-[(*tert*-butyldimethylsilyl)oxy]-7a-methyl-1*H*-inden-1-ol (21b). A solution of acetate **21a** (70 mg, 0.22 mmol) in MeOH (2 mL) and H_2O (0.1 mL) was cooled in an ice–water bath and treated with NaOH (200 mg, 5 mmol). The resulting mixture was stirred at rt overnight and then washed with an aqueous saturated solution of NH_4Cl and extracted with Et_2O (4 × 15 mL). The combined organic phases were dried, filtered, and concentrated to give a white solid which was flash chromatographed (1 × 15 cm, 5% EtOAc/hexanes) to afford 56 mg of **21b** (92%; R_f 0.27, 15% EtOAc/hexanes; mp 69–71 °C, white solid): ^1H NMR δ 4.01 (1 H, m, H-4), 3.57 (1 H, t, J = 8.3 Hz, H-1), 2.04 (1 H, m, H-3a), 0.97 (3 H, s, Me-7a), 0.90 (9 H, s, *t*-BuSi), 0.023 and 0.007 (6 H, 2 s, Me_2Si); ^{13}C NMR δ 82.2, 69.2, 48.1, 42.1, 37.4, 34.4, 29.9, 25.8, 22.3, 18.0, 17.2, 12.5, –4.9, –5.2; MS *m/z* 284 (M^+, 7), 227 (M^+ – *t*-Bu, 53), 209 (M^+ – *t*-Bu – H_2O, 100), 191 (10), 133 (24), 107 (27), 93 (33), 75 (45); high-resolution MS calcd for $C_{16}H_{32}O_2Si$ 284.2171, found 284.2147.

[3a*R*-(3aβ,4α,7aα)]-Octahydro-4-[(*tert*-butyldimethylsilyl)oxy]-7a-methyl-1*H*-inden-1-one (6). PDC (85 mg, 0.23

mmol) was added to a solution of alcohol **21b** (42 mg, 0.15 mmol) in dry CH_2Cl_2 (8 mL). The resulting suspension was stirred at rt overnight and then filtered through a Celite path. The solution was concentrated to give a residue which was flash chromatographed (1 × 14 cm, 3% EtOAc/hexanes) to afford 38 mg of ketone **6** (91%) which shows ^1H NMR and ^{13}C NMR identical to those of the compound obtained above.

Preparation of [1*S*-(1α,3aβ,4α,7aα)]-Octahydro-1,4-dihydroxy-7a-methyl-1*H*-indene (22) from 4 through 17 and 23. [1*S*-(1α,3aβ,7aα)]-Octahydro-1-[(*tert*-butyldimethylsilyl)oxy]-7a-methyl-4*H*-inden-4-one (17). PDC (140 mg, 0.53 mmol) was added to an ice–water-cooled solution of alcohol **4** (100 mg, 0.35 mmol) in dry CH_2Cl_2 (20 mL). The resulting suspension was stirred at rt for 4 h, filtered through Celite, and concentrated to give a residue which was dissolved with EtOAc (100 mL). This solution was washed with an aqueous saturated solution of $NaCHO_3$ (2 × 50 mL), dried, filtered, and concentrated to give a brown viscous liquid which was flash chromatographed (5% Et_2O/hexanes) to afford 98 mg of **17** (98%; R_f 0.55, 15% EtOAc/hexanes; colorless liquid): IR (film) 1710 cm^{-1}; ^1H NMR δ 3.84 (1 H, t, J = 8.5 Hz, H-3a), 0.88 (9 H, s, *t*-BuSi), 0.67 (3 H, s, Me-7a), 0.04 and 0.03 (6 H, 2 s, Me_2Si). Anal. Calcd for $C_{16}H_{30}O_2Si$: C, 68.01; H, 10.72. Found: C, 67.86; H, 10.53.

[1*S*-(1α,3aβ,4α,7aα)]-Octahydro-1-[(*tert*-butyldimethylsilyl)oxy]-7a-methyl-1*H*-inden-4-ol (23). (23). $NaBH_4$ (30 mg, 0.79 mmol) was added to an ice–water-cooled solution of **17** (109 mg, 0.39 mmol, prepared from **4** as above) in absolute EtOH (4 mL). The resulting mixture was stirred for 1 h at rt, and then H_2O (5 mL) was added. The mixture was concentrated to a small volume, and the residue was extracted with Et_2O (2 × 5 mL). The combined organic phases were dried, filtered, and concentrated to give a residue which was flash chromatographed (1 × 15 cm, 5% EtOAc/hexanes) to afford 94 mg of **23** (84%; R_f 0.7, 30% EtOAc/hexanes; colorless oil) and 18 mg of **4** (15%; R_f 0.6, 30% EtOAc/hexanes; white solid): ^1H NMR δ 4.03 (1 H, m H-4), 3.52 (1 H, t, J = 7.8 Hz, H-1), 0.95 (3 H, m, Me-7a), 0.88 (9H, s, *t*-Bu), 0.01 (3 H, s, Me_2Si); ^{13}C NMR δ 81.8, 69.3, 47.3, 42.2, 37.5, 33.8, 29.9, 25.8, 21.8, 18.0, 17.1, 12.6, −4.6, −5.0.

[1*S*-(1α,3aβ,4α,7aα)]-Octahydro-1,4-dihydroxy-7a-methyl-1*H*-indene (22). An aqueous solution of HF (48%, 17 drops) was added to a solution of **23** (91 mg, 0.32 mmol) in CH_3CN (5 mL). The resulting solution was stirred overnight at rt. After concentration, an aqueous saturated solution of $NaHCO_3$ (15 mL) was added and the mixture was extracted with Et_2O (4 × 10 mL). The combined organic phases were dried, filtered, and concentrated. The residue was flash chromatographed (1 × 10 cm, 20% EtOAc/hexanes) to give 44 mg of **22** (81%: R_f 0.15, 30% EtOAc/hexanes; white solid; mp 135–7 °C): ^1H NMR δ 4.08 (1 H, m, H-4), 3.61 (1 H, t, J = 8.5 Hz, H-1), 1.00 (3 H, s, Me-7a); ^{13}C NMR δ 81.9, 69.0, 47.6, 41.9, 37.1, 33.7, 29.6, 21.7, 17.0, 12.2.

Alternative Route for Preparation of 22 from 6 through 21b. $NaBH_4$ (20 mg, 0.53 mmol) was added to an ice–water-cooled solution of **6** (43 mg, 0.15 mmol) in absolute EtOH (3 mL). The resulting mixture was stirred for 1 h at rt, and then H_2O (5 mL) was added. The mixture was concentrated to a small volume. The residue was extracted with Et_2O (2 × 5 mL), and the combined organic phases were dried, filtered, and concentrated to give 42 mg of **21b** (97%; R_f 0.3, 15% EtOAc/hexanes; white solid), which shows ^1H NMR and ^{13}C NMR identical to those of the compound obtained above. An aqueous solution of HF (48%, five drops) was added to a solution of **21b** (34 mg, 0.12 mmol) in CH_3CN (2 mL). The solution was stirred for 20 h. After concentration, an aqueous saturated solution of $NaHCO_3$ (10 mL) was added and the mixture was extracted with Et_2O (4 × 10 mL). The combined organic phases were dried, filtered, and concentrated, and the resulting residue was flash chromatographed (1 × 10 cm, 20% EtOAc/hexanes) to give 16 mg of **22** (80%; R_f 0.15, 30% EtOAc/hexanes; white solid, mp 134–6 °C). The ^1H NMR and ^{13}C NMR spectra were identical to those of the compound obtained from **23** as above.

Acknowledgment. We thank the Spanish Ministry of Education and Science for financial support (DGICYT Project no. PB87-0478). We also thank Duphar for the generous gift of vitamin D_2 used for the preparation of Lythgoe–Inhoffen diol (**3**). We thank J. Sestelo for the preparation of aldehyde **19** via the modified Kornblum's method, G. Tojo for the high-resolution MS, and Prof. J. M. Aizpurua (Universidad del Pais Vasco) for some elemental analyses.

Supplementary Material Available: ^1H NMR spectra of **4, 6, 7a, 7b, 8, 9a, 9b, 10–14, 15a, 16, 17, 18b, 19, 20, 21a, 21b, 22,** and **23** and ^{13}C NMR spectra of **4, 6, 9a, 9b, 10, 11, 16, 19, 20, 21a, 21b, 22,** and **23** (35 pages). Ordering information is given on any current masthead page.

Transmetalation Reactions of Alkenylalanes: Copper-Catalyzed Conjugate Addition to Enones

Peter Wipf,* Jacqueline H. Smitrovich, and Choong-Woon Moon

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Received January 22, 1992

An improved synthetic strategy for the in situ preparation of vinyl cuprates from alkynes is presented and used for the stereospecific synthesis of di-, tri-, and tetrasubstituted olefins. Hydroalumination or Cp_2ZrCl_2-catalyzed carboalumination of alkynes, followed by in situ transmetalation to bis-alkynyl-copper complex $[(C_4H_9C{\equiv}C)_2CuCN]Li_2$ and addition of enones, led to the isolation of 1,4-addition products in high yields. Stoichiometric or catalytic amounts of copper complex gave similar results. However, in the presence of less than 10 mol % of Cu(I) complex, side products were formed and a significant drop in the yield of the desired conjugate addition product was observed. An ate-transfer mechanism is postulated for the rapid exchange of vinyl ligands from Al(III) to Cu(I) at low temperatures.

Introduction

The development of the chemistry of organocuprates has resulted in many important applications in organic synthesis, such as conjugate additions to α,β-unsaturated carbonyl compounds,[1] nucleophilic displacements on halides,[2] sulfonates,[3] and allylic acetates,[4,5] epoxide ring openings,[6] and additions to acetylenes.[7] However, the vast

(1) House, H. O.; Respess, W. L.; Whitesides, G. M. *J. Org. Chem.* **1966**, *31*, 3128.

(2) (a) Corey, E. J.; Posner, G. H. *J. Am. Chem. Soc.* **1967**, *89*, 3911. (b) Marfat, A.; McGuirk, P. R.; Helquist, P. *J. Org. Chem.* **1979**, *44*, 3888. (c) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841.

(3) Johnson, C. R.; Dutra, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 7783.

(4) Anderson, R. J.; Henrick, C. A.; Siddall, J. B.; Zurfluh, R. *J. Am. Chem. Soc.* **1972**, *94*, 5379.

0022-3263/92/1957-3178$03.00/0