Organopalladium Approaches to Prostaglandins. 3.[1] Synthesis of Bicyclic and Tricyclic 7-Oxaprostaglandin Endoperoxide Analogues via Oxypalladation of Norbornadiene

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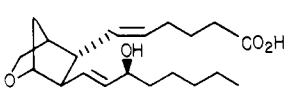
Oxypalladation of norbornadiene provides an organopalladium intermediate **12** readily carbonylated and subsequently elaborated into the first bicyclic and tricyclic 7-oxaprostaglandin endoperoxide analogues **18** and **24** in 22% and 24% overall yields, respectively.

Prostaglandins in which a methylene unit has been replaced by an oxygen have received considerable attention. A number of 7-oxa analogues of the primary prostaglandins have been synthesized and they exhibit substantial biological activity.[2-6] More recently attention has turned to prostaglandin endoperoxide analogues in which either the 9,11-endoperoxide linkage contains only one oxygen atom,[7-13] such as compound **1**, or the C-10 position has



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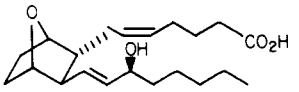

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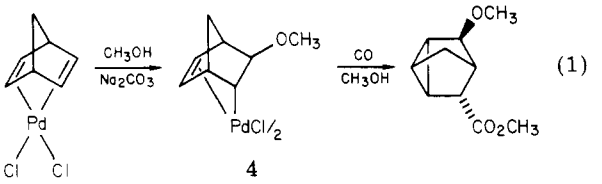
been substituted by oxygen[14-19] as in compound **2**. Once again significant biological activity has been shown by a number of these compounds. At this time, we report the first syntheses of bicyclic and tricyclic 7-oxaprostaglandin endoperoxide analogues using a novel oxypalladation approach.

Results and Discussion

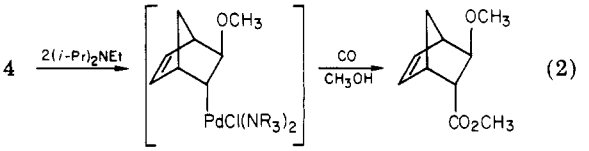
The methoxypalladation of norbornadiene[20,21] and subsequent carbonylation[22] of the resulting organopalladium intermediate are known reactions (eq 1). This reaction



(1)

3 **4**

sequence looked promising as a useful route to 7-oxaprostaglandin endoperoxide analogues. Working with readily available **4** as a model system, we briefly examined several methods which might allow us to rapidly introduce the allylic alcohol side chain common to prostaglandins. To our surprise, we discovered that carbonylation of **4** *in the presence of diisopropylethylamine* afforded bicyclic ester **5** in 87% yield (eq 2). Presumably, the organic



(2)

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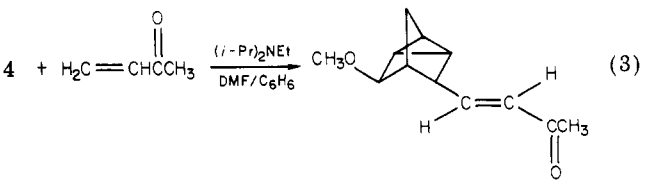
amine displaces the intramolecularly coordinated carbon–carbon double bond present in **4** and thereby prevents subsequent formation of the tricyclic skeleton.

We have also examined the Heck olefination of compound **4**. Under conditions similar to those employed by Holton[23] in his synthesis of $PGF_{2\alpha}$, the reaction of **4** and methyl vinyl ketone afforded the nortricyclic enone **6** in 53% yield (eq 3). An olefin moiety was also readily in-



(3)

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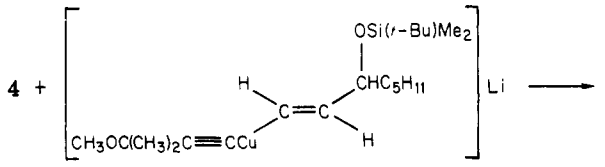
troduced upon reaction of **4** and mixed cuprate **7**, although the yield was only 28% and the product proved to be a mixture of isomers as judged by ^{13}C NMR spectroscopy (eq 4). Unfortunately, attempts to directly introduce an

(1) For "Organopalladium Approaches to Prostaglandins. 2." see: Larock, R. C.; Burkhart, J. P.; Oertle, K. *Tetrahedron Lett.* **1982**, *23*, 1071.
(2) Fried, J.; Santhankrishnan, T.; Himizu, J.; Lin, C.-H.; Ford, S. *Nature (London)* **1969**, *223*, 208.
(3) Fried, J.; Mehra, M.; Kao, W.; Lin, C.-H. *Tetrahedron Lett.* **1970**, 2695.
(4) Fried, J.; Mehra, M.; Kao, W. *J. Am. Chem. Soc.* **1971**, *93*, 5544.
(5) Fried, J.; Lin, C.; Mehra, M.; Kao, W.; Delven, P. *Ann. N.Y. Acad. Sci.* **1971**, *180*, 38.
(6) McDonald-Gibson, R. G.; Flack, J. D.; Ramwell, P. W. *Biochem. J.* **1973**, *132*, 117.
(7) Bundy, G. L. *Tetrahedron Lett.* **1975**, 1957.
(8) Bundy, G. L.; Peterson, D. *Tetrahedron Lett.* **1978**, 41.
(9) Ohno, K.; Naruto, M.; Naruse, M.; Takeuchi, H. *Tetrahedron Lett.* **1979**, 251.
(10) Bertele, V.; Di Minno, G.; De Gaetano, G. *Thromboxane Res.* **1980**, *18*, 543.
(11) Bonne, C.; Martin, B.; Regnault, F. *Thromboxane Res.* **1980**, *20*, 701.
(12) Sakai, K.; Inoue, K.; Amemiya, S.; Morita, A.; Kojima, K. *Chem. Pharm. Bull.* **1980**, *28*, 1814.
(13) Bundy, G. L. U.S. Patent 4 275 213, 1981; *Chem. Abstr.* **1981**, *95*, 203415y.
(14) Eggelte, T. A.; De Koning, H.; Huisman, H. O. *J. Chem. Soc., Perkin Trans. 1* **1978**, 980.
(15) Suzuki, T.; Tomino, A.; Matsude, Y.; Unno, K.; Kametani, T. *Heterocycles* **1980**, *14*, 1735.
(16) Sprague, P.; Heikes, J.; Harris, D.; Greenberg, R. *Adv. Prostaglandin Thromboxane Res.* **1980**, *6*, 493.
(17) Sprague, P. U.S. Patent 4 228 180, **1980**; *Chem. Abstr.* **1981**, *94*, 83679t.
(18) Kametani, T.; Suzuki, T.; Tomino, A.; Kamada, S.; Unno, K. *Heterocycles* **1981**, *16*, 905.
(19) Harris, D.; Phillips, M.; Michel, I.; Goldenburg, H.; Heikes, J.; Sprague, P.; Antonacio, M. *Prostaglandins* **1981**, *22*, 295.
(20) Stille, J. K.; Morgan, R. A. *J. Am. Chem. Soc.* **1966**, *88*, 5135.
(21) Green, M.; Hancock, R. I. *J. Chem. Soc. A* **1967**, 2054.
(22) Hines, L. F.; Stille, J. K. *J. Am. Chem. Soc.* **1972**, *94*, 485.
(23) Holton, R. *J. Am. Chem. Soc.* **1977**, *99*, 8083.

0022-3263/84/1949-2144$01.50/0



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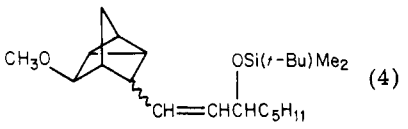
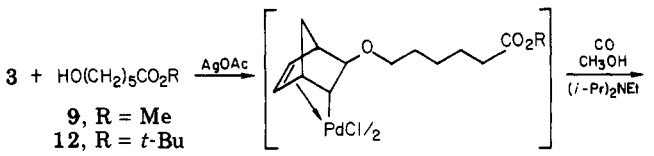


8 (4)

acetylene moiety by reacting **4** with 3-((tetrahydropyranyl)oxy)-1-lithio-1-octyne and triphenylphosphine at −78 °C to room temperature, as previously employed by us in the synthesis of other prostaglandin endoperoxide analogues,[1,24] failed completely.

With several potential approaches to the desired prostaglandin skeleton now established, we turned our attention to the oxypalladation step. Unfortunately, all attempts to oxypalladate **3** by using methyl 6-hydroxyhexanoate (**9**) in the presence of sodium carbonate or sodium bicarbonate and several different solvents failed to produce any of the desired organopalladium intermediates. In situ carbonylation also afforded none of the expected ester. Reasoning that the low solubility of **3** in most organic solvents might be the source of our difficulties, we attempted to prepare a more soluble complex by reacting **3** with silver acetate (1 equiv) in the presence of **9** (1.02 equiv) for 1 h. All attempts to isolate the organopalladium product, after filtering through Celite to remove silver chloride, either by recrystallization or precipitation with hexanes, were unsuccessful. However, carbonylation of the crude product in methanol in the presence of an excess of diisopropylethylamine provided the diester **11** in 76% yield (eq 5). The stereochemistry of **11** is assigned in analogy



9, R = Me
12, R = *t*-Bu

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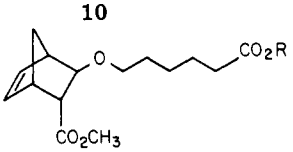
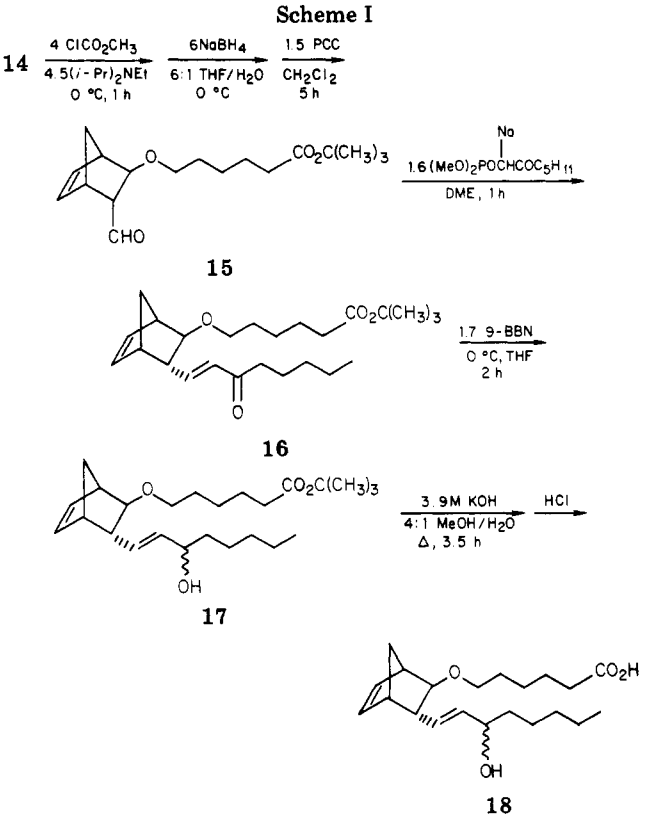


11, R = Me
13, R = *t*-Bu (5)

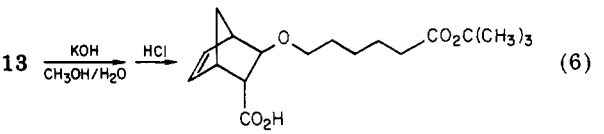
to the known stereochemistry of methoxypalladation[20,21] and subsequent carbonylation[22] of **3**. The fact that carbonylation in the absence of amine (see latter) provides the nortricyclic skeleton is also only consistent with an endo palladium intermediate.

The successful synthesis of diester **11** leaves only the introduction of the unsaturated alcohol chain to complete the synthesis of the desired 7-oxa PGH_2 analogue. From the previously described work on the methoxy model system **4**, the most attractive approach appeared to be one involving carbonylation, reduction to an aldehyde, Wittig olefination, and enone reduction. This approach required that we be able to readily differentiate the two ester groups in our diester. This was best accomplished by employing

Scheme I



tert-butyl 6-hydroxyhexanoate (**12**) in the oxypalladation step. The desired diester **13** was obtained after carbonylation in methanol in 68% yield. Selective reduction of the methyl ester with either diisobutylaluminum hydride or sodium bis(2-methoxyethoxy)aluminum hydride (Vitride) failed, but we were able to selectively saponify the methyl ester by heating **13** with 3.1 equiv of KOH in aqueous methanol for 30 min at 60 °C (eq 6). Compound



14 (6)

14 was formed in 71% yield alongside about 10% of the corresponding diacid and 16% of the starting diester.

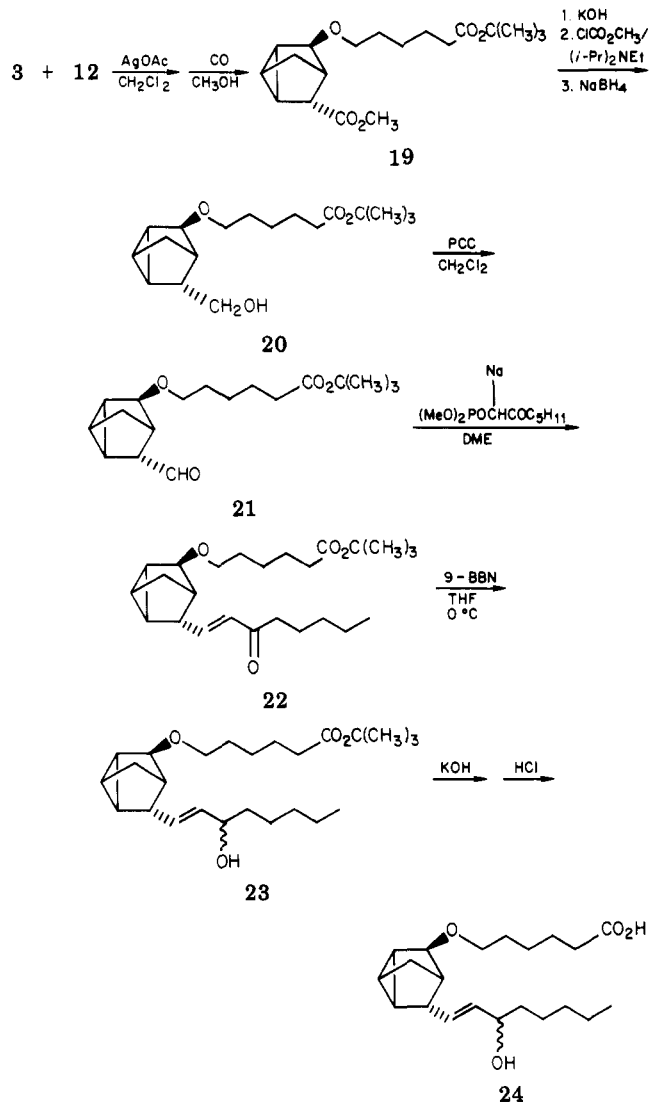
The reaction sequence used to complete the prostaglandin skeleton is outlined in Scheme I. Reduction to the aldehyde **15** was affected by using a three-step sequence developed by Corey[25] in 76% overall yield. Olefination with dimethyl (1-sodio-2-oxoheptyl)phosphonate in dimethoxyethane (DME) gave enone **16** in 76% yield. Reduction to the allylic alcohol using 9-borabicyclo-[3.3.1]nonane (9-BBN) provided allylic alcohol **17** in quantitative yield. Finally, saponification of the *tert*-butyl ester by refluxing with 10 equiv of KOH in aqueous methanol for 3.5 h and subsequent acidification afforded the desired bicyclic 7-oxaprostaglandin analogue **18** in 82% yield. The overall yield of **18** is approximately 22% with no effort having been made to optimize any of the individual reaction steps.

Using an almost identical sequence of reactions, one can also easily prepare a tricyclic analogue of compound **18** (Scheme II). If carbonylation of the initial organo-

(24) Larock, R. C.; Leach, D. R.; Bjorge, S. M. *Tetrahedron Lett.* **1982**, *23*, 715.

(25) Corey, E. J.; Narasaka, K.; Shibasaki, M. *J. Am. Chem. Soc.* **1976**, *98*, 6417.

Scheme II



palladium intermediate, presumed to be **10**, is carried out *in the absence of diisopropylethylamine*, the tricyclic ester **19** is obtained in 68% isolated yield. The stereochemistry of **19** is again based on the known stereochemistry of methoxypalladation–carbonylation of **3**.[22] Selective saponification and reduction as described above afforded the corresponding hydroxy ester **20** in 64% yield. Pyridinium chlorochromate (PCC) oxidation (73% yield), Wittig olefination (99% yield), 9-BBN reduction (100% yield), and saponification (77% yield) as described above resulted in a 24% overall yield of tricyclic 7-oxaprostaglandin endoperoxide analogue **24**, with no effort having been made to optimize any of the steps.

Thus, the simple process of oxypalladation–carbonylation and subsequent elaboration provides a totally new approach to prostaglandin endoperoxide analogues and affords the novel new bicyclic and tricyclic 7-oxaprostanoids **18** and **24** in high overall yields. Biological testing of these two compounds is presently underway and the results will be reported elsewhere.

Experimental Section

Equipment. The infrared spectra were recorded on a Beckman IR-4250 infrared spectrophotometer and the ^{1}H NMR spectra on a Varian Associates EM-360 or a HA-100 NMR spectrometer. Carbon-13 NMR spectra were recorded on a JEOL FX-90Q NMR spectrometer. The mass spectra were obtained on an AEI MS-902 high-resolution mass spectrometer, while the GC–mass spectra were recorded on a Finnegan 4023 GC-MS data system. GLC analyses were performed by using a Varian 3700 gas chromatograph with an attached Varian CDS-111 chromatography data system. Thin-layer chromatography was performed on Merck 60F-254 silica gel plates from MCB Manufacturing Chemists, Inc. Silica gel for column chromatography was purchased from Davison Chemical (60–200 mesh) and MCB Manufacturing Chemists, Inc. (230–400 mesh).

Reagents. All chemicals were used directly as obtained commercially unless otherwise noted. Tetrahydrofuran (THF) and dimethoxyethane (DME) were distilled from calcium hydride and lithium aluminum hydride, respectively. Commercial chloroform was purified by washing repeatedly with water, drying over magnesium sulfate, and distilling from 4-Å molecular sieves. 1-Buten-3-one was distilled immediately prior to use and *n*-butyllithium and *tert*-butyllithium were obtained from Alfa and titrated before use with 2,5-dimethoxybenzyl alcohol.[26] Copper(I) iodide was obtained from Alfa and purified by a literature procedure.[27] (*E*)-3-((*tert*-Butyldimethylsilyl)oxy)-1-iodo-1-octene,[28] norbornadiene–palladium dichloride (**3**),[28] methyl 6-hydroxyhexanoate (**9**),[30] and compound **4**[20] were prepared by using literature procedures.

Synthesis of 5. Compound **4** (185 mg, 0.698 mmol) and 0.70 g (5.4 mmol) of diisopropylethylamine were dissolved in 8 mL of CH_3OH and cooled to −78 °C. The flask was flushed with carbon monoxide and allowed to slowly warm to room temperature overnight. The reaction mixture was diluted with ether, filtered to remove palladium metal, washed with water and saturated ammonium chloride, and dried over sodium sulfate. After removal of the solvent, the product was distilled via Kugelrohr [bp 110 °C (0.2 torr)] to afford 110 mg (87%) of **5**: ^{1}H NMR ($CDCl_3$) δ 1.4–1.9 (3 H, m), 2.68 (1 H, t, J = 2.5 Hz), 2.96 (1 H, br s), 3.10 (1 H, br s), 3.42 (3 H, s, OCH_3), 3.69 (3 H, s, CO_2CH_3), 6.13 (2 H, m, CH=CH); IR ($CHCl_3$) 1740 (C=O), 1630 (C=C) cm^{-1}; MS, m/z (relative intensity) 182 (1), 151 (3), 117 (63), 85 (63), 66 (100).

Synthesis of 6. Compound **4** (132.5 mg, 0.50 mmol), 0.18 g (2.6 mmol) of methyl vinyl ketone, and 0.52 g (4.0 mmol) of diisopropylethylamine were stirred at room temperature in 7 mL of *N*,*N*-dimethylformamide and 3 mL of benzene for 36 h. The reaction mixture was diluted with ether, filtered, washed with water and saturated ammonium chloride, and dried over sodium sulfate. After removal of the solvent, the product was distilled via Kugelrohr [bp 140 °C (0.02 torr)] to provide 51 mg (53%) of **6**: ^{1}H NMR ($CDCl_3$) δ 1.0–2.5 (8 H, m), 2.27 (3 H, s, $COCH_3$), 3.23 (3 H, s, OCH_3), 6.03 (1 H, d, J = 16 Hz, C=CHCO), 6.72 (1 H, d, J = 16 Hz, CH=CCO); IR ($CHCl_3$) 1670 (C=O), 1620 (C=C), 1105 (C—O) cm^{-1}; MS, m/z (relative intensity) 192 (9), 177 (12), 160 (12), 149 (58), 117 (100), 91 (66).

Synthesis of 8. Compound **4** (264 mg, 1.00 mmol) and 529 mg (2.02 mmol) of triphenylphosphine were stirred in 8 mL of THF for 30 min at room temperature and then cooled to −78 °C. To this was added a −78 °C solution of 1.05 mmol of mixed cuprate **7** in 3 mL of THF. This mixture was stirred for 1 h at −78 °C and then quenched by the addition of 1 mL of methanol. The reaction mixture was diluted with hexanes and washed repeatedly with saturated ammonium chloride buffer (pH 8) until the washes were colorless. The organic layer was then dried over sodium sulfate and concentrated. Chromatography on silica gel afforded 100 mg (28%) of **8**: R_f 0.29, benzene:ethyl acetate (9:1); ^{1}H NMR ($CDCl_3$) δ 0.15 (6 H, s, $SiCH_3$), 1.0 [12 H, overlapping t and s, CH_3 and $SiC(CH_3)_3$], 1.2–1.7 (12 H, m), 1.8–2.1 (3 H, m), 2.4 (1 H, br s), 3.35 (3 H, s, OCH_3), 3.7 (1 H, br s, CHOMe), 4.2 (1 H, br m, CHOSi), 5.5–5.7 (2 H, m, vinyl); ^{13}C NMR ($CDCl_3$) δ 134.05, 132.53, 131.88, 130.86, 130.48, 83.62, 82.97, 73.00, 63.30, 56.42, 46.29, 46.02, 38.71, 37.30, 37.03, 36.59, 35.18, 31.72, 31.12, 30.80, 28.52, 27.92, 26.19, 25.59, 25.05, 22.40, 17.90, 17.04, 13.90, 13.52, 12.60, −4.80.

Synthesis of 11. Norbornadiene–palladium dichloride (**3**) (269 mg, 1.00 mmol), 167 mg (1.00 mmol) of silver acetate, and 149

(26) Winkle, M. R.; Lansinger, J. M.; Ronald, R. C. *J. Chem. Soc., Chem. Commun.* **1980**, 87.
(27) Kauffman, G. B.; Teter, L. A. *Inorg. Synth.* **1963**, *7*, 9.
(28) Corey, E. J.; Beames, D. *J. Am. Chem. Soc.* **1972**, *94*, 7210.
(29) Drew, D.; Doyle, J. R. *Inorg. Synth.* **1972**, *13*, 52.
(30) Young, D. M.; Hostettler, F. British Patent 877 180, 1962; *Chem. Abstr.* **1962**, *57*, 6091.

mg (1.02 mmol) of methyl 6-hydroxyhexanoate (9) were stirred for 1 h in 10 mL of ethanol-free chloroform. The reaction mixture was then filtered through Celite and concentrated in vacuo. Diisopropylethylamine (0.74 g, 5.7 mmol) was added after which 10 mL of methanol was added. The flask was flushed with nitrogen and then cooled to −78 °C, flushed with carbon monoxide, and allowed to slowly warm to room temperature. After diluting with ether, the reaction mixture was filtered, washed with water and brine, and dried over magnesium sulfate. Flash chromatography provided 220 mg (76%) of 11: R_f 0.30, hexanes:ethyl acetate (4:1); ^{1}H NMR ($CDCl_3$) δ 1.1–1.9 (8 H, m), 2.28 (2 H, t, J = 6 Hz, CH_2CO), 2.6 (1 H, t, J = 3 Hz), 2.9 (1 H, br), 3.05 (1 H, br), 3.47 (2 H, t, J = 6 Hz, CH_2O), 3.70 (7 H, s overlapping peaks, OCH_3, CHO), 6.05 (2 H, m, vinyl); IR (neat) 1740 (C=O), 1630 (C=C) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 173.83, 137.28, 134.29, 82.78, 69.13, 52.35, 51.18, 47.41, 46.50, 43.70, 33.75, 29.26, 25.56, 24.52; MS, m/z (relative intensity) 264 (0.1), 231 (5), 199 (23), 129 (83), 97 (39), 66 (100).

Synthesis of *tert*-Butyl 6-Hydroxyhexanoate (12). 6-Hexanolactone (3.65 g, 32.0 mmol) and 3.93 g (35.0 mmol) of potassium *tert*-butoxide were refluxed for 2.5 h in 100 mL of *tert*-butyl alcohol. After diluting with ether and benzene, the reaction mixture was washed with water and brine, dried over magnesium sulfate, and concentrated on a rotary evaporator. Distillation afforded 4.10 g (68%) of *tert*-butyl 6-hydroxyhexanoate: bp 84–86 °C (0.4 torr); ^{1}H NMR ($CDCl_3$) δ 1.45 (15 H, overlapping peaks), 2.2 (2 H, t, J = 7 Hz, CH_2CO), 3.03 (1 H, s, OH), 3.53 (2 H, t, J = 6 Hz, CH_2O); IR (neat) 3400 (OH), 1740 (C=O), 1400 [$C(CH_3)_3$], 1375 [$C(CH_3)_3$], 1160 (ester C—O) cm^{-1}; MS, m/z 132.07840; calcd for $C_6H_{12}O_3$ ($M^+ - C_4H_8$), 132.07865.

Synthesis of 13 and 19. Norbornadiene–palladium dichloride (3) (270 mg, 1.00 mmol), 207 mg (1.10 mmol) of *tert*-butyl 6-hydroxyhexanoate (12), and 183 mg (1.10 mmol) of silver acetate were stirred for 1 h in 10 mL of methylene chloride and then filtered through Celite. After removal of the methylene chloride, 0.64 g (5.0 mmol) of diisopropylethylamine was added and the mixture was dissolved in 10 mL of methanol under nitrogen. After stirring for 10 min the mixture was cooled to −78 °C, flushed with carbon monoxide, and allowed to warm to room temperature overnight. The mixture was then diluted with ether, washed with water and saturated ammonium chloride, and dried over magnesium sulfate. Purification by flash chromatography provided 230 mg (68%) of 13: R_f 0.30, hexanes:ethyl acetate (6:1); ^{1}H NMR ($CDCl_3$) δ 1.4 [9 H, s, $C(CH_3)_3$], 1.4–1.9 (8 H, m), 2.18 (2 H, t, J = 6 Hz, CH_2CO), 2.6 (1 H, t, J = 3 Hz), 2.9 (1 H, br), 3.1 (1 H, br), 3.47 (2 H, t, J = 6 Hz, CH_2O), 3.63 (4 H, overlapping peaks, OCH_3, CHO), 6.05 (2 H, m, vinyl); IR (neat) 1735 (C=O), 1635 (C=C), 730 (C=C) cm^{-1}; MS, m/z (relative intensity) 282 (1), 217 (31), 185 (22), 151 (42), 115 (65), 66 (100).

Compound 19 was prepared similarly in 68% yield except that diisopropylethylamine was excluded: R_f 0.28, hexanes:ethyl acetate (5:1); ^{1}H NMR ($CDCl_3$) δ 1.1–1.9 (11 H, m), 1.4 [9 H, s, $C(CH_3)_3$], 1.9–2.3 (3 H, m), 2.4 (1 H, t, J = 1 Hz), 3.3 (2 H, t, J = 6 Hz, OCH_2), 3.63 (3 H, s, OCH_3), 3.7 (1 H, s, CHO); IR (neat) 1730 (C=O) cm^{-1}.

Synthesis of 14. Compound 13 (1.04 g, 3.07 mmol) and 0.54 g (9.6 mmol) of KOH were heated for 30 min at 60 °C in 30 mL of a 5:1 mixture of methanol and water. After diluting with ether, the reaction mixture was acidified with dilute HCl, washed with water and brine, and dried over magnesium sulfate. Purification by chromatography afforded 170 mg (16%) of recovered 13 and 0.60 g (71%) of 14: R_f 0.35, hexanes:ethyl acetate:acetic acid (160:80:1); ^{1}H NMR ($CDCl_3$) δ 1.3–1.9 (8 H, m), 1.4 [9 H, s, $C(CH_3)_3$], 2.2 (2 H, t, J = 6 Hz, CH_2CO), 2.7 (1 H, t, J = 3 Hz), 2.8 (1 H, br), 3.0 (1 H, br), 3.45 (2 H, CH_2O), 3.6 (1 H, br, CHO), 5.9–6.2 (2 H, m, vinyl), 10.7 (1 H, s, CO_2H); IR (neat) 1740 (ester C=O), 1715 (acid C=O), 1635 (C=C) cm^{-1}.

Synthesis of 15. Compound 14 (0.36 g, 1.11 mmol), 0.42 g (4.4 mmol) of methyl chloroformate, and 0.65 g (5.0 mmol) of diisopropylethylamine were stirred in 18 mL of THF for 1 h at 0 °C. After removal of the THF, the crude product was dissolved in 32 mL of 6:1 THF–H_2O at 0 °C, after which 0.25 g (6.6 mmol) of sodium borohydride was added. This was stirred for an additional hour. The reaction mixture was then diluted with ether, acidified with dilute HCl, washed with brine, and dried over magnesium sulfate. Oxidation of the crude alcohol (0.42 g, 1.36 mmol) with 0.44 g (2.04 mmol) of pyridinium chlorochromate using Corey's procedure[31] was accomplished by stirring in 5 mL of methylene chloride for 2 h. The mixture was then diluted with 25 mL of ether and decanted into a short Florisil column. The black residue from the flask was washed twice with 10 mL of ether and this was added to the column. Elution of the column with 500 mL of ether afforded 318 mg (76%) of 15: ^{1}H NMR ($CDCl_3$) δ 1.0–1.8 (8 H, m), 1.43 [9 H, s, $C(CH_3)_3$], 2.17 (2 H, t, J = 6 Hz, CH_2CO), 2.6 (1 H, m), 2.9 (1 H, br), 3.0 (1 H, br), 3.3–3.5 (2 H, m, CH_2O), 3.57 (1 H, br s, CHO), 5.8–6.2 (2 H, m, vinyl), 9.39 (1 H, d, J = 2 Hz, CHO); IR (neat) 2710 (CHO), 1740 (ester C=O), 1715 (aldehyde C=O) cm^{-1}.

Synthesis of 20. Compound 19 (492 mg, 1.45 mmol) and 0.41 g (7.3 mmol) of KOH were refluxed for 30 min in 20 mL of 5:1 methanol–H_2O. After diluting with ether, the mixture was acidified with dilute HCl, washed with brine, and dried over magnesium sulfate. The crude acid thus obtained was treated with 0.55 g (5.8 mmol) of methyl chloroformate and 0.75 g (5.8 mmol) of diisopropylethylamine in 20 mL of THF for 1 h at 0 °C. After removal of the THF, the crude product was dissolved in 28 mL of 6:1 THF–H_2O at 0 °C, after which 0.33 g (8.7 mmol) of sodium borohydride was added. This solution was stirred for an additional hour. The reaction mixture was then diluted with ether, acidified with dilute HCl, washed with brine, and dried over magnesium sulfate. Purification by flash chromatography afforded 266 mg (64%) of 20: R_f 0.32, hexanes:ethyl acetate (1:1); ^{1}H NMR ($CDCl_3$) δ 1.0–2.3 (15 H, br m), 1.43 [9 H, s, $C(CH_3)_3$], 3.2–3.7 (4 H, m, CH_2OH, CH_2O), 3.73 (1 H, s, CHO), 4.3 (1 H, br, OH); IR (neat) 3440 (OH), 1735 (C=O) cm^{-1}.

Synthesis of 21. Compound 20 (260 mg, 0.838 mmol) and 0.27 g (1.25 mmol) of pyridinium chlorochromate were stirred for 2 h in 5 mL of methylene chloride. The mixture was then diluted with 25 mL of ether and decanted onto a 6-in. Florisil column. The black residue was washed twice with 10 mL of ether and this was added to the column. This product was then eluted with ether, providing 189 mg (73%) of 21: ^{1}H NMR ($CDCl_3$) δ 1.1–1.7 (9 H, m), 1.45 [9 H, s, $C(CH_3)_3$], 1.9 (1 H, br s), 2.0–2.5 (5 H, m), 3.35 (2 H, t, J = 6 Hz, CH_2O), 3.64 (1 H, br s, CHO), 9.77 (1 H, d, J = 2 Hz, CHO); IR (neat) 1715 (C=O) cm^{-1}.

Synthesis of 16 and 22. The synthesis of 16 is representative. Sodium hydride (67%) (51.4 mg, 1.43 mmol) was washed several times with hexanes under nitrogen. After drying for approximately 5 min under a gentle stream of nitrogen, this was suspended in 15 mL of DME. Dimethyl (2-oxoheptyl)phosphonate (0.370 g, 1.67 mmol) in 3 mL of DME was added, and the reaction was stirred for 1 h. Compound 15 (275 mg, 0.892 mmol) in 3 mL of DME was then added via syringe. After stirring for 3 h, 0.5 mL of acetic acid was added after which the solvent was removed with a rotary evaporator. The produce was then extracted with 40 mL of hexanes and filtered through Celite. After concentration, chromatography of the residue afforded 265 mg (76%) of 16: R_f 0.33, hexanes:ethyl acetate (7:1); ^{1}H NMR ($CDCl_3$) δ 0.86 (3 H, t, J = 5 Hz, CH_3), 1.1–1.9 (13 H, m), 2.0–3.0 (8 H, m), 3.13 (1 H, br s), 3.33 (2 H, t, J = 5 Hz, CH_2O), 6.00 (1 H, d, J = 15.5 Hz, =CHCO), 6.03 (2 H, m, vinyl), 6.46 (1 H, dd, J = 8, J = 15.5 Hz, CH=CCO).

Compound 22: 99% yield; R_f 0.29, hexanes:ethyl acetate (7:1); ^{1}H NMR ($CDCl_3$) δ 0.87 (3 H, t, J = 5 Hz, CH_3), 1.0–2.6 (17 H, m), 1.4 [9H, s, $C(CH_3)_3$], 3.3 (2 H, t, J= 6 Hz, CH_2O), 3.6 (1 H, br s, CHO), 6.08 (1 H, d, J = 16 Hz, =CHCO), 6.78 (1 H, dd, J = 6 Hz, J = 16 Hz, CH=CCO).

Synthesis of 17 and 23. The synthesis of 17 is representative. Compound 16 (190 mg, 0.469 mmol) was dissolved in 6 mL of THF and cooled to 0 °C. A solution of 0.10 g (0.82 mmol) of 9-BBN in 2 mL of THF was added via syringe. After stirring for 2 h at 0 °C, 0.5 mL of methanol was added to destroy excess hydride. The boronic acid derivative was oxidized by addition of 0.27 mL of 3 N aqueous sodium hydroxide followed by addition of 0.22 mL of 30% hydrogen peroxide. This mixture was then stirred for 1 h after which it was diluted with ether, washed twice with brine and five times with water to remove 1,5-cyclooctanediol, and dried over magnesium sulfate. Purification by chromatography afforded 193 mg (100%) of 17: R_f 0.38, hexanes:ethyl acetate

(31) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

(3:1); ^{1}H NMR ($CDCl_3$) δ 0.9 (3 H, t, J = 6 Hz, CH_3), 1.1-2.5 (29 H, m), 2.6-2.9 (2 H, m), 3.1 (1 H, br s), 3.38 (2 H, t, J = 6 Hz, CH_2O), 4.0 (1 H, br, C*H*OH), 5.3-5.6 (2 H, m, *trans*-C*H*=C*H*C(OH)), 5.9-6.2 (2 H, m, *cis*-CH=CH); IR (neat) 3410 (OH), 1730 (C=O), 1140 (C-O) cm^{-1}.

Compound **23**: 100% yield; R_f 0.31, hexanes:ethyl acetate (3:1); ^{1}H NMR ($CDCl_3$) δ 0.87 (3 H, t, J = 5 Hz, CH_3), 1.0-2.4 (32 H, m), 3.32 (2 H, t, J = 6 Hz, CH_2O), 3.67 (1 H, br s, CHO), 4.0 (1 H, br, C*H*OH), 6.5-6.6 (2 H, m, *trans*-CH=CH); IR (neat) 3410 (OH), 1730 (C=O) cm^{-1}.

Synthesis of 18 and 24. The synthesis of **24** is representative. Compound **23** (158 mg, 0.389 mmol) and 0.22 g (3.9 mmol) of KOH were refluxed for 2.5 h in 10 mL of 4:1 methanol-H_2O. After cooling, the reaction mixture was diluted with ether, acidified with dilute HCl, washed with brine, and dried over magnesium sulfate. Flash chromatography afforded 105 mg (77%) of **24**: R_f 0.26, hexanes:ethyl acetate:acetic acid (30:15:1); ^{1}H NMR ($CDCl_3$) δ 0.87 (3 H, t, J = 5 Hz, CH_3), 1.1-2.5 (23 H, m), 3.33 (2 H, t, J = 6 Hz, CH_2O), 3.67 (1 H, br s, CHO), 4.1 (1 H, br, C*H*OH), 5.5 (2 H, m, CH=CH), 8.3 (2 H, br s, OH, CO_2H); IR (neat) 3400 br (OH), 1720 (C=O), 1160 (C-O) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 177.96, 133.51, 131.23, 131.10, 82.07, 73.08, 68.67, 46.17, 37.07, 33.95, 31.67, 30.89, 29.52, 25.69, 25.03, 24.45, 22.50, 20.68, 17.04, 13.92, 13.79, 12.62; MS, m/z 332.23676; calcd for $C_{21}H_{32}O$ ($M^+ - H_2O$); 332.23515.

Compound **18**: 82% yield; R_f 0.29, hexanes:ethyl acetate:acetic acid (30:15:1); ^{1}H NMR ($CDCl_3$) δ 0.85 (3 H, t, J = 5 Hz, CH_3), 1.0-2.0 (15 H, m), 2.1-2.4 (4 H, m), 2.5-2.9 (2 H, m), 3.0 (1 H, br s, CHO), 3.38 (2 H, t, J = 6 Hz, CH_2O), 3.8-4.1 [1 H, br, C*H*OH], 5.2-5.5 (2 H, m, *trans*-CH=CH), 5.9-6.2 (2 H, m, *cis*-CH=CH); IR (neat) 3420 br (OH), 1715 (C=O), 1090 (C-O) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 178.96, 137.86, 134.94, 134.03, 132.86, 86.23, 73.09, 69.00, 50.59, 47.67, 47.47, 46.95, 46.43, 46.24, 37.07, 33.95, 31.60, 29.46, 25.69, 25.04, 24.45, 22.57, 13.98; MS, m/z 332.23574; calcd for $C_{21}H_{32}O_3$ ($M^+ - H_2O$), 332.23515.

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Synthesis of 25-Hydroxyvitamin D_2 and Its 24-Epimer

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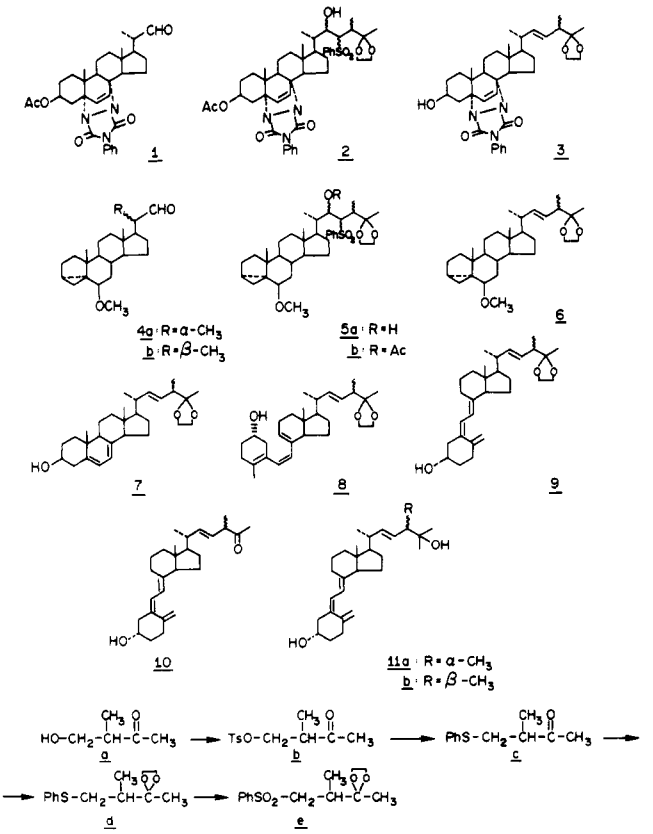
The synthesis of 25-hydroxyvitamin D_2 (25-hydroxyergocalciferol, **11a**) and its 24-epimer **11b** is described. The synthetic product **11a** proved to be identical in all respects with the natural metabolite of vitamin D_2.

Studies on the metabolism of vitamin D_2 (ergocalciferol) have shown that it undergoes both 25-hydroxylation and 1α-hydroxylation during its conversion to the active calcium mobilizing hormone.[1] This activation pathway is the same as that described for vitamin D_3.[2,3] The major circulating metabolite of vitamin D_2, 25-hydroxyergocalciferol (25-hydroxyvitamin D_2, 25-OH-D_2, **11a**), was first isolated in 1969 from the blood of hogs fed massive doses of vitamin D_2, and its structure was established by spectral correlations based on its mass spectrum, ^{1}H NMR characteristics, and ultraviolet absorption.[4] A synthesis of 25-OH-D_2, **11a**, has been achieved some year ago by chemists of the Upjohn Company,[5] using 6β-methoxy-3,5α-cyclocholesta-22,24-diene described by Salmond[6] and Hutchins[7] as starting material for side chain elaboration by selective epoxidation and C-24 alkylation, but other than a brief mention of it[6], that work has not been published to date.

In initiating our own work on the synthesis of 25-OH-D_2 we were guided by two principal objectives, namely, to obtain material for a thorough assessment of its biological activity and properties, and to devise a route that would be conveniently adaptable to the generation of highly radiolabeled material required for metabolite assays and further metabolism studies.

The latter objective, in particular, dictated a different synthetic approach from that used by the Upjohn chemists[5,6] in which complete side chain elaboration precedes generation of the 5,7-diene. In the case of the vitamin D_2 series, the usual allylic bromination/dehydrobromination sequence for introduction of the 7,8-double bond[8] suffers from fairly low yields presumably due to side reactions evolving the 22,23-double bond. More satisfactory for our

Chart I



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