ca. 1 mL of H_2O was added and thoroughly mixed with the reaction mixture for ca. 1 min. The reaction products and percent conversion were determined by comparison with authentic materials and mass spectrometry. (b) The cinnamyl halide substitutions were analyzed by ^1H NMR of the recovered organic material. Cinnamyl chloride (76 mg, 0.5 mmol) was shaken with the KSCN–support (2.5 molar equiv of KSCN) in 5.0 mL of cyclohexane, or without solvent as stated, at the indicated temperature. The reaction products were isolated by filtration and ether washing of the solid reagents, followed by evaporation of the combined fractions. ^1H NMR ($CDCl_3$) δ 3.73 (d, J = 7.5 Hz, CH_2SCN), 4.27 (d, J = 5.6 Hz, CH_2NCS).

Ethyl 2-Methyl-2-thiocyanatopropanoate[22] **(1).** A preparative scale synthesis involved stirring ethyl 2-bromo-2-methylpropanoate (0.39 g, 2 mmol) with KSCN–silica (2.18 g, 5 mmol of KSCN) in 15 mL of cyclohexane at gentle reflux for 24 h. The warm mixture was filtered through $MgSO_4$ and charcoal and the solid reagent further washed with diethyl ether. Evaporation of the combined filtrates afforded 1: yield 91%; bp 213–215 °C; ^{13}C NMR ($CDCl_3$) δ 171.1 (s, CO), 110.7 (s, SCN), 62.8 (t, CH_2), 55.1 (s, $(CH_3)_2C$), 26.7 (q, $(CH_3)_2C$), 13.9 (q, CH_3CH_2); ^1H NMR ($CDCl_3$) δ 1.33 (t, 3 H), 1.77 (s, 6 H), 4.27 (q, 2 H); IR (neat) 2150 (s, SCN), 1720 (C=O) cm^{-1}.

Anal. Calcd for $C_7H_{11}NO_2S$: C, 48.53; H, 6.40; N, 8.09; S, 18.51. Found: C, 48.04; H, 6.38; N, 8.22; S, 18.59.

1-Thiocyanatoadamantane[23] **(2)** was prepared by stirring 1-bromoadamantane (1.08 g, 5 mmol) with KSCN–alumina (7.5 g, 12.5 mmol of KSCN) in 15 mL of cyclohexane at gentle reflux for 24 h. The complete reaction mixture was poured into a column slurry packed (hexane) with 16 g of KSCN–silica (3 mmol/g)[24] and then products were eluted with hexane, followed by hexane/ether (50/50) and finally ether. The hexane fraction contained isothiocyanate (20%) plus impurities, while **2** was isolated from the ether-containing fractions[25] as a white crystalline solid after removal of solvent under vacuum: yield 38%; mp 65–66 °C [lit.[23] mp 66–67 °C]; ^{13}C NMR ($CDCl_3$) δ 110.9 (s, SCN), 43.7 (t, CH_2), 35.5 (t, CH_2), 30.3 (d, CH); ^1H NMR ($CDCl_3$) δ 1.72 (6 H), 2.07 (6 H), 2.16 (3 H); IR (KBr) 2145 (s, SCN) cm^{-1}.

***tert*-Butyl Thiocyanate**[26] **(3).** Preparative scale synthesis using a column involved passing *tert*-butyl bromide (4.0 mL, 35 mmol) down a water-jacketed column (2-cm diameter, 30-cm long) slurry packed (hexane) from bottom upward with activated charcoal (1.5 g), KSCN–silica (28 g, 65 mmol of KSCN), and KSCN–alumina (40 g, 67 mmol of KSCN). Elution with hexane was sufficiently slow to allow reaction on the column for 2–3 h while at 50 °C. The eluant was collected in fractions and monitored by GLC (isothiocyanate eluted first). Finally, after isothiocyanate had been eluted, the column was brought to room temperature and a hexane/ether (40/60) mixture was used to elute the remaining thiocyanate. For isolation of the pure thiocyanate the solvent was removed from the suitable combination of collected fractions by fractional distillation (under vacuum with a N_2 bleed to reduce product decomposition) to give **3**; yield 35%; bp 40 °C (1.33 kPa) [lit.[26] bp 39–40 °C (1.33 kPa)]; ^{13}C NMR ($CDCl_3$) δ 111.7 (s, SCN), 51.9 (s, $C(CH_3)_3$), 30.9 (q, CH_3); IR (neat) 2130 (s, SCN) cm^{-1}.

***tert*-Amyl thiocyanate**[27] was prepared similarly: yield 33%; bp 59–60 °C (1.33 kPa) [lit.[27] bp 57–60 °C (1.33 kPa)]; ^{13}C NMR ($CDCl_3$) δ 111.8 (s, SCN), 56.3 (s, $C(CH_3)_2CH_2$), 35.5 (t, CH_2), 28.2 (q, $2CH_3$), 9.2 (q, CH_3CH_2); IR (neat) 2130 (s, SCN) cm^{-1}.

Acknowledgment. We are grateful to The Royal Society and The Japan Society for the Promotion of Science for a research fellowship (to D.G.C.) and Morita Kagaku Kogyo Co., Ltd. for the gift of some chemicals.

Registry No. 1, 106162-82-7; 2, 39825-84-8; 3, 37985-18-5; $(Me)_2CBrCO_2Et$, 600-00-0; KSCN, 333-20-0; $BrC(CH_3)_3$, 507-19-7; $(CH_3)_2C(Br)CH_2CH_3$, 507-36-8; $(CH_3)_2C(CH_2CH_3)SCN$, 84356-30-9; $PhCH_2Br$, 100-39-0; $PhCH_2Cl$, 100-44-7; $CH_3(CH_2)_3Br$, 109-65-9; $PhCH(Br)CH_3$, 585-71-7; CaF_2, 7789-75-5; $PhCH_2SCN$, 3012-37-1; $CH_3(CH_2)_3SCN$, 628-83-1; $PhCH(SCN)CH_3$, 106162-83-8; $PhCH(NCS)CH_3$, 4478-92-6; $PhCH{=}CHCH_2Cl$, 2687-12-9; $PhCH{=}CHCH_2SCN$, 74394-96-0; $PhCH{=}CHCH_2NCS$, 65788-85-4; $(CH_3)_3CNCS$, 590-42-1; $CH_3CH_2C(CH_3)_2NCS$, 597-97-7; silica, 7631-86-9; 1-bromoadamantane, 768-90-1; alumina, 1344-28-1; Florisil, 1343-88-0; montmorillonite k 10, 1318-93-0; 1-adamantyl isothiocyanate, 4411-26-1.

(22) The corresponding methyl ester has been prepared by using KSCN in aqueous MeOH, 10 h reflux, 75%; Gagnon, P. E.; Boivin, J. L.; Brown, G. M. *Can. J. Chem.* **1959**, *37*, 1597.

(23) Previously prepared from sodium 1-adamantyl sulfide and tosyl cyanide (71% yield) or cyanogen chloride (36% yield) (Stetter, H.; Krause, M.; Last, W. D. *Chem. Ber.* **1969**, *102*, 3357) and also be reduction of 1-adamantanesulfinyl cyanide with triphenylphosphine (87% yield) (Boerma-Markerink, A.; Jagt, J. C.; Meyer, H.; Wildeman, J.; van Leusen, A. M. *Synth. Commun.* **1975**, *5*, 147).

(24) This reagent showed selective adsorption of **2** over the isothiocyanate for reactions in cyclohexane (Table III).

(25) Unreacted bromide is finally eluted, thus the eluant should be collected in fractions to prevent contamination of the desired product.

(26) Previous synthesis: reaction of *tert*-butyl chloride in aqueous NH_4SCN with $ZnCl_2$ (yield; 78/22% mixture of SCN/NCS). Schmidt, E.; Striewsky, W.; Seefelder, M.; Hitzler, F. *Ann.* **1950**, *568*, 192.

(27) Previous synthesis: reaction of *tert*-amyl sulfide with cyanogen chloride in ether, 10 °C, 3 days, yield 30%: Luskin, L. S.; Gantert, G. E.; Craig, W. E. *J. Am. Chem. Soc.* **1956**, *78*, 4965.

Diastereoselective Synthesis of (24*R*,25*S*)-5β-Cholestane-3α,24,26-triol[1]

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Sterols with hydroxylated side chains are important intermediates in the course of our studies directed toward the biochemical transformation of cholesterol to the bile acids. It is essential in these studies that the compounds be diastereomerically pure. Tedious separation of diastereomers from an epimeric mixture led us to explore more convenient methods.

This paper describes a synthetic approach to regio- and stereoselective access to chiral side-chain-hydroxylated sterols. Of particular interest is the appealing conversion of lithocholic acid (**1**) to (24*R*,25*S*)-5β-cholestane-3α,24,26-triol (**11**), a threo trihydroxylated steroid with chiral centers at C-24 and C-25.

The 3α-hydroxy group of lithocholic acid (**1**) was protected as the tetrahydropyranyl ether and the latter reduced with lithium aluminum hydride to the C-24 primary alcohol **2**, which was oxidized with pyridinium chlorochromate to yield 3α-[(tetrahydropyranyl)oxy]-5β-cholan-24-al (**3**), according to a previously published procedure.[3] Wittig condensation of the aldehyde **3** with methyl (triphenylphosphoranylidene)acetate under reflux in benzene gave the (24*E*)-conjugated ester **4**. A small amount (2%) of the (24*Z*)-conjugated ester **4z** was isolated by preparative TLC and characterized. Reduction of the (24*E*)-conjugated ester **4** with diisobutylaluminum hydride afforded the (24*E*)-allylic alcohol **5** in moderate yield.

The Sharpless procedure[4] for asymmetric epoxidation of allylic alcohols uniformly affords the respective enantiomer with high selectivity. Reaction of the (24*E*)-allylic alcohol **5** with anhydrous *tert*-butyl hydroperoxide in the presence of titanium tetraisopropoxide and D-(−)-diethyl tartarate gave the epoxide **6**. The configurarations at C-24

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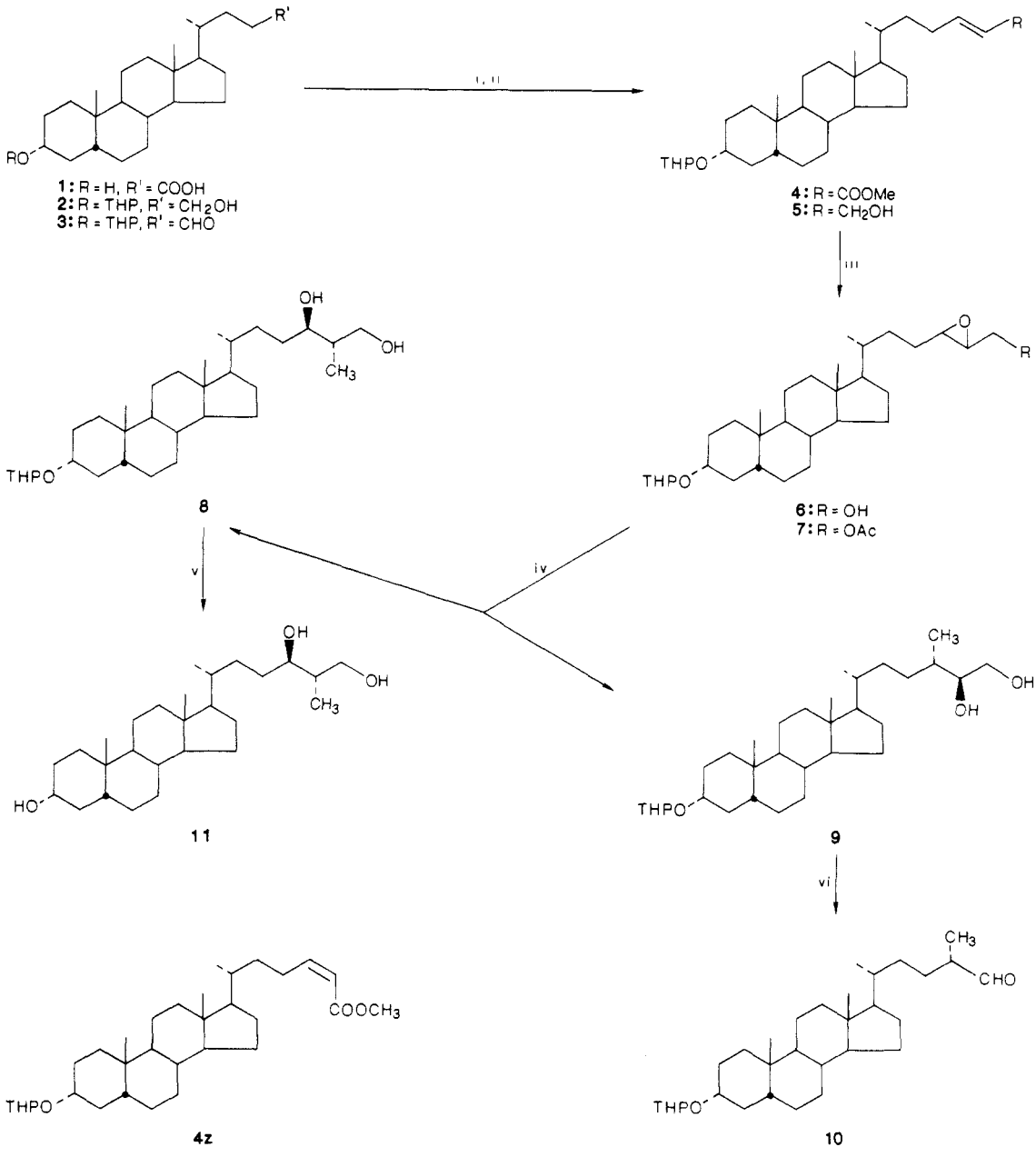
(3) Koizumi, N.; Ishiguro, M.; Yasuda, M.; Ikekan, N. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1401.

(4) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5084.

0022-3263/87/1952-0685$01.50/0

Scheme I[a]



[a] Key: (i) Ph_3P=CHCOOMe; (ii) Dibal; (iii) $Ti(OPr)_4$/(−)-DET/TBHP; (iv) Me_3CuLi_2; (v) TsOH; (vi) $NaIO_4$.

and C-25 of the epoxy alcohol **6** were tentatively assigned as 24*R*,25*R* according to the Sharpless projection. A greater than 95% diastereomer excess was determined by HPLC. This was confirmed by proton NMR using the chiral reagent tris[3-(heptafluorobutyryl)-*d*-camphorato]europium(III) on the epoxy acetate **7** (Scheme I).

Ring opening of the epoxy alcohol **6** with dilithium trimethyl cuprate[5,6] gave a 1:1 mixture of 1,2- and 1,3-diols as determined by HPLC. The 1,3-diol **8** was conveniently purified by treating the mixture of diols with sodium metaperiodate. This procedure transformed the 1,2-diol **9** to the less polar aldehyde **10**, which could easily be separated from the unreacted 1,3-diol **8** by preparative TLC. Hydrolysis of the pure 1,3-diol **8** gave the desired (24*R*,25*S*)-5β-cholestane-3α,24,26-triol (**11**), whose structure and stereochemistry was confirmed by X-ray crystallographic analysis[7] (Figure 1).

Experimental Section

Melting points were determined on a Kofler melting point apparatus and are uncorrected. For TLC, compounds were analyzed on 10 × 20 cm glass-backed silica gel plates with fluorescent indicator (Analtech 02521). They were usually developed with an ethyl acetate/hexane solvent system or as indicated with the respective compounds. The spots were visualized with UV (254 nm—if chromophoric), iodine, or a 10% ethanolic solution of phosphomolybdic acid (and heating to 200 °C). For preparative TLC the compounds were purified on 20 × 20 cm glass-backed 1000-μm-layer (Analtech 02013) or 2000-μm-layer (Analtech 02015) silica gel plates with fluorescent indicator. They were usually run with an ethyl acetate/hexane solvent system or as indicated in their respective Experimental Section. The appropriate bands were then scraped off the glass plate and extracted with acetone. Infrared spectrum of compounds were recorded with sodium

(5) Behrens, C. H.; Sharpless, K. B. *Aldrichim. Acta* **1983**, *16*, 67.
(6) Roush, W. R.; Adam, M. A.; Peseckis, S. M. *Tetrahedron Lett.* **1983**, 1377.

(7) The X-ray analysis was carried out by J. F. Blount of Hoffmann-LaRoche Inc., Nutley, NJ, and is gratefully acknowledged.

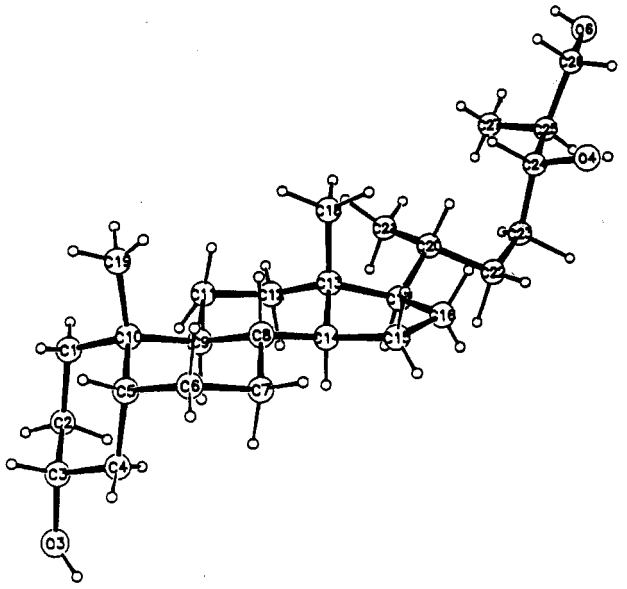


Figure 1. Compound 11.

chloride windows as a film if syrupy or as a potassium bromide disk if crystalline, with a Perkin-Elmer Infracord. UV spectra were determined for acetonitrile solutions on a Perkin-Elmer 202 spectrometer. The NMR spectra were obtained in deuteriochloroform solution by using as internal reference tetramethylsilane and were recorded on a 90-MHz Varian EM-390 spectrometer.

(*E*)-Methyl 3α-[(Tetrahydropyranyl)oxy]-(5β)-24-norcholest-24-en-26-oate (4e). Methyl (triphenylphosphoranylidene)acetate (10 g, 0.03 mol), recrystallized from ethyl acetate (mp 167–169 °C), was suspended in dry benzene (50 mL), and the aldehyde **3** (5.8 g, 0.01 mol) in dry benzene (50 mL) was added all at once and the reaction mixture refluxed for 2 h in a nitrogen atmosphere. Benzene was distilled off and the semicrystalline solid dissolved in a minimum amount of methylene chloride and flash-chromatographed on a silica gel column with 10% ethyl acetate/hexane. The conjugated esters were further purified on 2000-μm prepartive TLC plates (5× recycled with 5% ethyl acetate/hexane). The upper band gave the *Z*-conjugated ester **4z** [0.12 g (2%)] as an oil: IR, ν 1720 (C=O), 1640 (C=C), 1175 (ester), 1020, 980 (THP ether) cm^{-1}; ^1H NMR δ 0.66 (3 H, s, 18-CH_3), 0.92 (3 H, s, 19-CH_3), 0.94 (3 H, d, J = 7 Hz, 21-CH_3), 3.53 (2 H, br m, $w/2$ = 21 Hz, TPH ether), 3.70 (3 H, s, 26-CO_2CH_3), 3.93 (1 H, br m, $w/2$ = 15 Hz, 3-H), 4.73 (1 H, m, $w/2$ = 9 Hz, THP ether), ABX system H_A 6.21 (1 H, dt, J_{AB} = 12 Hz, J_{AX} = 7 Hz, 24-H), H_B 5.77 (1 H, d, J_{AB} = 12 Hz, 25-H). Anal. Calcd for $C_{32}H_{52}O_4$: C, 76.75; H, 10.47. Found: C, 76.79; H, 10.51.

The lower band gave the *E*-conjugated ester **4e**: 5.2 g (82%); mp 110–112 °C (methanol); IR ν 1720 (C=O), 1650 (C=C), 1250, 1160 (ester), 1030, 980 (THP ether cm^{-1}; ^1H NMR δ 0.64 (3 H, s, 18-CH_3), 0.90 (3 H, s, 19-CH_3), 0.92 (3 H, d, J = 6 Hz, 21-CH_3), 3.50 (2 H, br m, $w/2$ = 27 Hz, THP ether), 3.70 (3 H, s, 26-CO_2CH_3), 3.84 (1 H, br m, $w/2$ = 15 Hz, 3-H), 4.72 (1 H, m, $w/2$ = 10 Hz, THP ether), ABX system H_A 6.93 (1 H, dt, J_{AB} = 15 Hz, J_{AX} = 7 Hz, 24-H), H_B 5.80 (1 H, d, J_{AB} = 15 Hz, 25-H). Anal. Calcd for $C_{32}H_{52}O_4$: C, 76.75; H, 10.47. Found: C, 76.78; H, 10.46.

(*E*)-3α-[(Tetrahydropyranyl)oxy]-(5β)-27-norcholest-24-en-26-ol (5). To the *E*-conjugated ester **4e** (5.1 g, 10 mmol) in anhydrous ether (20 mL) at −70 °C was added diisobutylaluminum hydride in hexane (25 mL, 1.0 M, 25 mmol). The mixture was allowed to warm to room temperature and was stirred for 2 h. The progress of the reaction was followed by TLC. At the end of the reaction, the mixture was cooled in an ice bath and dilute hydrochloric acid (100 mL, 1 N) was slowly added. After the mixture was stirred for 15 min, the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed successively with water, saturated sodium bicarbonate, and water and dried over anhydrous magnesium sulfate. Evaporation of the solvents gave an oil that was chromatographed on a silica gel column (15% ethyl acetate/hexane) to give the oily allylic alcohol **5**: IR ν 3400 (OH), 1680 (C=C), 1020, 980 (THP ether) cm^{-1}; ^1H NMR δ 0.62 (3 H, s, 18-CH_3), 0.90 (3 H, s, 19-CH_3), 0.91 (3 H, d, 21-CH_3), 3.57 (2 H, br m, $w/2$ = 21 Hz, THP), 3.90 (1 H, br m, $w/2$ = 15 Hz, 3-H), 4.08 (2 H, d, J = 3 H Hz, 26-Ch_2OH), 4.73 (1 H, m, $w/2$ = 9 Hz, THP), 5.67 (2 H, m, $w/2$ = 9 Hz, 24- and 25-H). Anal. Calcd for $C_{31}H_{52}O_3$: C, 78.76; H, 11.09. Found: C, 78.78; H, 11.10.

(24*R*,25*R*)-24,25-Epoxy-3α-[(tetrahydropyranyl)oxy]-(5β)-27-norcholestan-26-ol (6). A 250-mL round-bottom flask, equipped with a Teflon-coated magnetic stirring bar, was flame-dried and flushed with nitrogen. The flask was charged with anhydrous methylene chloride (60 mL, distilled from calcium hydride) and cooled in a −20 °C bath. The following liquids were added sequentially with a syringe: titanium tetraisopropoxide (1.76 mL, 6.0 mmol); (−)-diethyl D-tartarate (1.02 mL, 6.0 mmol), stirred for 5 min before the next addition; allylic alcohol **5** (2.78 g, 5.9 mmol) in dry methylene chloride (5 mL); finally, anhydrous *tert*-butyl hydroperoxide[8] (3 mL, 4.2 M solution in metylene chloride, 12.5 mmol). The resulting homogeneous solution was stored overnight in a freezer (∼−20 °C) in the sealed reaction vessel (serum cap). The progress of the reaction was monitored by TLC. After completion, the reaction mixture was quenched with 10% aqueous tartaric acid (50 mL) and stirred for 30 min at −20 °C and then at room temperature for 1 h. The organic layer was separated and the aqueous layer extracted with methylene chloride (2 × 20 mL). The combined methylene chloride solution was washed with water and evaporated to afford a colorless oil. This residue was diluted with ether (150 mL), cooled in an ice bath, and stirred vigorously with a 1 N sodium hydroxide solution (60 mL) for 30 min. The ether phase was separated, washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated. The oil was chromatographed on silica gel and eluted with 20% EtOAc in benzene to afford the epoxide **6**: 2.08 g (72%); $[\alpha]^{25}_D$ +42 ± 2° (*c* 1.20, methanol); IR ν 3450 (OH), 1130, 1110 (epoxide), 1025, 980 (THP ether), 920, 880, 870, 820 (epoxide) cm^{-1}; ^1H NMR δ 0.62 (3 H, s, 18-CH_3), 0.88 (3 H, s, 19-CH_3), 0.90 (3 H, d, J = 6 Hz, 21-CH_3), 2.90 (2 H, m, $w/2$ = 12 Hz, 24- and 25-H), 3.60 (2 H, br m, $w/2$ = 30 Hz, TPH ether), 3.64 (2 H, d, J = 5 Hz, 26-H), 3.90 (1 H, m, $w/2$ = 18 Hz, 3-H), 4.73 (1 H, m, $w/2$ = 9 Hz, THP ether). Anal. Calcd for $C_{31}H_{52}O_4$: C, 76.18; H, 10.72. Found: C, 76.22; H, 10.73.

(24*R*,25*S*)-3α-[(Tetrahydropyranyl)oxy]-5β-cholestane-24,26-diol (9). To a stirred suspension of cuprous iodide (485 mg, 2.5 mmol) in anhydrous tetrahydrofuran (10 mL) at 0 °C was added methyllithium (5.3 mL, 1.4 M in ether, 7.5 mmol). The clear brownish solution was stirred for 20 min at 0 °C and then cooled to −20 °C (dry ice/CCl_4). A dry tetrahydrofuran solution (5 mL) of the epoxide **6** (600 mg, 1.2 mmol) was added dropwise and the reaction mixture allowed to stir at −20 °C for 2 h. The reaction was quenched with saturated aqueous ammonium chloride (20 mL). After $1^1/_2$ h of vigorous stirring at room temperature, sufficient water was added to dissolve the precipitated salt. The deep blue solution was extracted with methylene chloride (3 × 30 mL). The combined organic extracts were washed with water, dried over anhydrous sodium sulfate, and evaporated in vacuo to give a solid. Analytical HPLC of the crude material with a Waters μ-Porasil column (20% ethyl acetate/hexane, 2.0 mL/min, five cycles) indicated equal amounts of **8** and **9**.

The crude solid was chromatographed on several 250-μm preparative TLC plates (run 5×, 30% ethyl acetate/hexane) and gave two very closely moving bands. The less polar band was isolated and determined as the diol **8** [220 mg (35%)] by the periodate method. To the diol **8** in tetrahydrofuran (5 mL) was added sodium metaperiodate (100 mg, 0.46 mmol) in 10% aqueous tetrahydrofuran (2 mL). The reaction mixture was stirred vigorously for 4 h, quenched with water (20 mL), and then extracted with methylene chloride (3 × 20 mL). The organic extract was washed with water and dried over anhydrous magnesium sulfate and the solvent then evaporated to give the unreacted diol **8** [210 mg (95%)] as white crystals: mp 122–123 °C (ethyl acetate; $[\alpha]^{25}_D$ +42 ± 2° (*c* 1.10, MeOH); IR ν 3400 (OH), 1020, 980 (THP ether) cm^{-1}; ^1H NMR δ 0.64 (3 H, s, 18-CH_3), 0.88 (3 H, d, J = 7 Hz, 27-CH_3), 0.90 (3 H, s, 19-CH_3), 0.91 (3 H, d, J = 6 Hz, 21-CH_3),

(8) Langhals, H.; Fritz, E.; Mergelsberg, I. *Ber.* **1980**, *113*, 3662.

3.56 (3 H, br m, $w/2$ = 27 Hz, THP and 24-H), 3.68 (2 H, d, J = 7 Hz, 26-CH_2OH), 3.90 (1 H, br m, $w/2$ = 18 Hz, 3-H), 4.74 (1 H, m, $w/2$ = 8 Hz, THP). Anal. Calcd for $C_{32}H_{56}O_4$: C, 76.14; H, 11.18. Found: C, 76.13; H, 11.21.

Diol **9** (89 mg, 0.18 mmol) was treated with sodium metaperiodate (50 mg, 0.23 mmol) by a procedure similar to that for diol **8**. Worked up as described above, there was obtained the aldehyde **10** [68 mg (72%)] as an oil: IR ν 2700, 1720 (CHO), 1030, 980 (THP ether) cm^{-1}; ^{1}H NMR δ 0.65 (3 H, s, 18-CH_3), 0.93 (3 H, s, 19-CH_3), 0.94 (3 H, d, J = 7 Hz, 21-CH_3), 1.10 (3 H, d, J = 7 Hz, 24-CH_3), 3.53 (2 H, br m, $w/2$ = 20 Hz, THP - *H*), 3.90 (1 H, br m, $w/2$ = 14 Hz, 3-H), 4.73 (1 H, m, $w/2$ = 14 Hz, 3-H), 4.73 (1 H, m, $w/2$ = 9 Hz, THP-H). Anal. Calcd for $C_{31}H_{52}O_3$: C, 78.76; H, 11.09. Found: C, 78.80; H, 11.13.

(24*R*,25*S*)-5β-Cholestane-3α,24-26-triol (11). Diol **8** (95 mg, 0.19 mmol) was suspended in methanol (20 mL) followed by the addition of *p*-toluenesulfonic acid (36 mg, 0.20 mmol). The reaction was allowed to proceed at room temperature for 2 h, while progress was followed by TLC. It was then worked up by concentrating the reaction mixture in vacuo, maintaining the bath temperature below 40 °C. Dilution with methylene chloride (100 mL) washing successively with 5% sodium bicarbonate, water, and brine, and drying over anhydrous sodium sulfate followed by evaporation of solvents yielded a crude white solid material. This was purified on preparative TLC (2 × 10% methanol/methylene chloride). Extraction of the product from the silica gel yielded the triol **11** [63.4 mg (80%)] as white crystals: mp 169-170 °C (ethyl acetate); $[\alpha]^{25}_D$ +40 ± 2° (*c* 0.27, methanol); IR ν 3400 (OH) cm^{-1}; ^{1}H NMR δ 0.67 (3 H, s, 18-CH_3), 0.87 (3 H, d, J = 7 Hz, 27-CH_3), 0.93 (3 H, s, 19-CH_3), 0.93 (3 H, d, J = 7 Hz, 21-CH_3), 3.50 (4 H, br m, $w/2$ = 21 Hz, 3-H, 24-H, 26-H). Anal. Calcd for $C_{27}H_{48}O_3$: C, 77.09; H, 11.50. Found: C, 77.08; H, 11.54.

Uranium-Mediated Methylenation of Carbonyl Compounds

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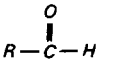
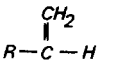
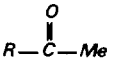
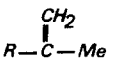
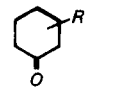
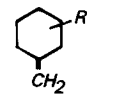
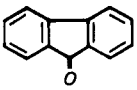
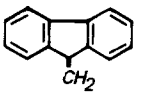
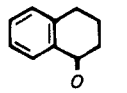
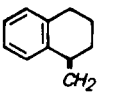
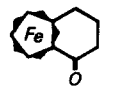
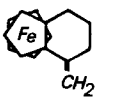
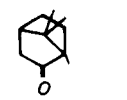
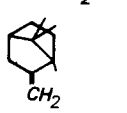
The direct methylenation of carbonyl compounds via phosphorus ylides[1] shows some limitations: as an example, poor yields were obtained from cyclic or sterically hindered ketones.[2] A major advance in this area occurred when new techniques using alkyltitanium,[3] zinc-alkylidenealuminium,[4] zinc-alkylidenetitanium,[5] or titanium-alkylidenealuminium (Tebbe reactif)[6] were used. Moreover, several papers reported Wittig-like reactions with both group 4[7] and 5[8] alkylidenes and group 6 alkylidenes complexes.[9] We report here a rapid, clean, and high-yield methylenation reaction of a wide range of both aldehydes and ketones using an uranium metallacycle:

Table I. Representative Reactions of Aldehydes and Ketones with $[(Me_3Si)_2N]_2\overline{UCH_2SiMe_2NSiMe_3}$ (1)

entry	substrate		product[a]	yield,[b] %
A		R = Ph; Fc;[c] *n*-C_8H_{17}		75; 92, 90
B		R = Ph; Fc;[c] *n*-C_8H_{17}		85; 90; 70
C		R = 4-*t*-Bu		90
D		R = 3,3,5,5-Me_4		90
E				85
F				88
G				90
H				85

[a] All products afforded satisfactory NMR and analytical data. [b] Yields cited were on isolated olefinic products. [c] Fc = $C_5H_5FeC_5H_4$.

$((Me_3Si)_2N)_2\overline{UCH_2SiMe_2NSiMe_3}$ (1).[10]

Experimental Section

All operations using the air- and moisture-sensitive metallacycle **1** were carried out in Schlenk-type vessels under purified argon.

The solvents were thoroughly dried and deoxygenated and distilled under argon prior to use.

NMR spectra were obtained on JEOL FX 100 or BRUCKER 400-W spectrometers in C_6D_6 at 25 °C. Chemical shifts are reported in ppm from the external standard tetramethylsilane.

General Procedure for the Methylenation Reaction. A solution of 1 mmol of the carbonyl compound in 2 mmL of pentane was added dropwise (1 min) at room temperature to 1.1 mmol of **1** (0.25 M) in pentane.

(a) The reaction was immediately quenched by addition of 2 mL of diluted (1 M) HCl.[12] The organic layer was washed twice with 1 mL of water, diluted with 10 mL of pentane, and dried on sodium sulfate. After removal of the solvent, the crude vinyl compound was purified by chromatography on a short column of neutral alumina (pentane as eluant): 75-90% yield.

(b) After removal of the solvent, the brown powder was washed twice with 1 mL of pentane at -70 °C, affording the metallacycle **2** in good yield (80-90%). Analysis by NMR revealed the product to be >95% pure. After redissolution in pentane, **2** can be hydrolyzed as described above.

Results and Discussion

The crystalline metallacycle **1** was synthesized in high yield (>95%) in an one-step synthesis according to our

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(12) Workup with water or 10% aqueous Na_2CO_3 afforded similar yields. Nevertheless, free $HN(SiMe_3)_2$ and the remaining "UOH" products were best eliminated with aqueous HCl.

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