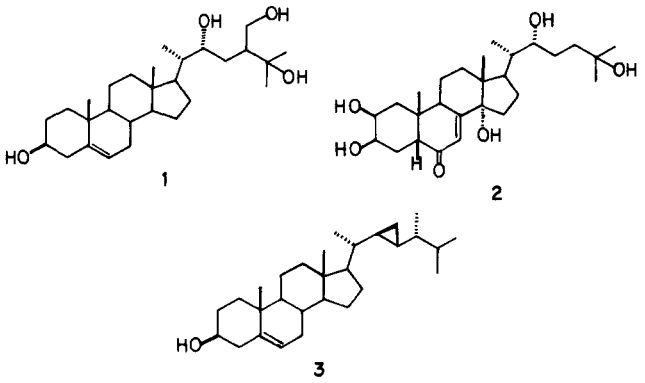
Stereocontrolled Construction of Oxygenated Steroidal Side Chains. Synthesis and Stereochemistry of Depresosterol

Eiichi Nakamura* and Isao Kuwajima*

Contribution from the Department of Chemistry, Tokyo Institute of Technology, Meguro, Tokyo 152, Japan. *Received July 5, 1984*

Abstract: Depresosterol (**1**), a marine sterol with a highly oxygenated side chain, has been synthesized, relying on the stereoselective 1,2-addition reaction of the alkoxydichlorotitanium homoenolate **6** and the introduction of the C(28) substituent to the lactone **13**. Synthesis of both of the two possible C(24) epimers elucidated the previously unassigned C(24) stereochemistry as *R* and also confirmed the (20*S*,22*R*) configuration. Concise syntheses of viable precursors to ecdysone (**2**) and demethylgorgosterol (**3**) have also been achieved.

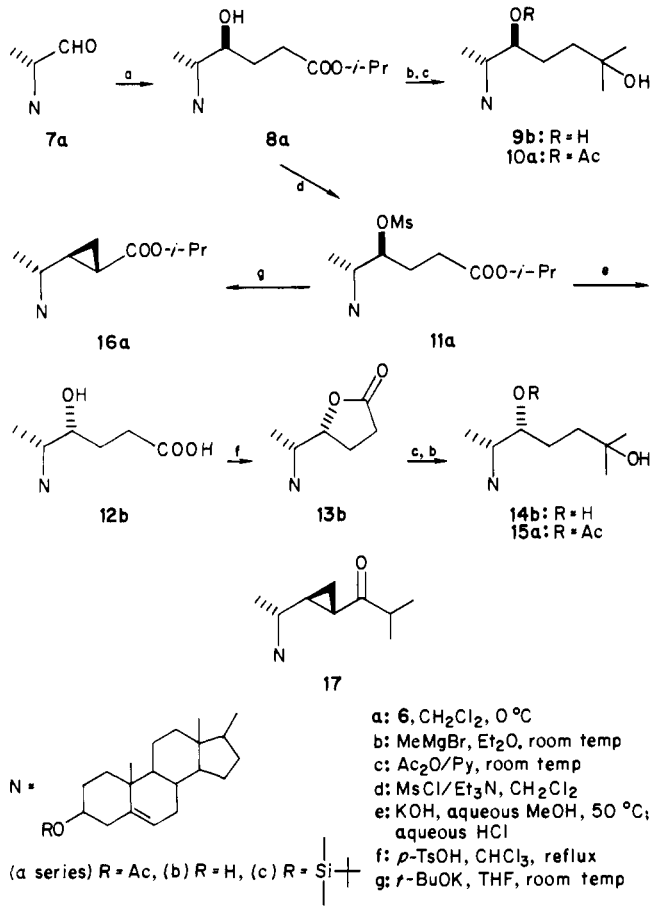
Two significant departures of marine sterols from the sterols of terrestrial origin involve the unusual oxygenation (e.g., **1**) and alkylation (e.g., **3**) of the side chain.[1] Given their difficult



accessibility from natural sources as well as the rapidly growing interests in their biological activities, inter alia, cytotoxicities,[1b] they are attractive targets for synthesis. Only a few known synthetic methods,[2a] however, meet the required stereorationality and the flexibility in functionalizing centers remote from the steroidal nucleus.[2b] We have developed, through the novel homoenolate chemistry,[3] an effective new strategy to achieve such a goal, which has been applied to some specific targets to examine its potentiality.

Depresosterol (**1**), an amorphous solid isolated from a soft coral *Lobophytum depressum*, possesses one of the most highly oxygenated side chains known, whose biological significance is yet to be established.[4] The fact that various parts of the oxygenation pattern in **1** are found among important steroids (e.g., ecdysone (**2**),[5] vitamin D_3 metabolites,[6] and antitumor steroids[7]) also made this molecule an ideal prototype to work on. Since the stereochemistry of the side chain has not been assigned unambiguously, we have chosen to clarify this by chemical synthesis. A short route to a precursor of demethylgorgosterol (**3**),[8] a marine sterol with an unusual alkylation pattern, has also been developed.

Scheme I



The synthesis started from the "homo-Reformatsky" coupling of the aldehyde **7a** and a homoenolate of isopropyl propionate (Scheme I). The trichlorotitanium complex **5** prepared from the cyclopropane **4**[3a] was not reactive enough for this sterically hindered aldehyde. After considerable experimentation, the alkoxytitanium complex **6**[9] prepared by adding half an equivalent of $Ti(OiPr)_4$ to **5** has proven suitable for the desired condensation (eq 1). Thus, condensation reaction at 0 °C in methylene chloride gave the expected[2a] Cram adduct **8a** (mp 150.5–151.5 °C) in ca.

(1) (a) Reviews: Schmitz, F. J. In "Marine Natural Products"; Scheuer, Ed.; Academic Press: New York, 1978; Vol. 1, p 241. Djerassi, C.; Arlson, R. M. K.; Popov, S.; Varkony, T. H. In "Marine Natural Product Chemistry"; Faulkner, D. J., Fenical, W. H., Eds.; Prenum Press: New York, 1977; p 111. (b) Guyot, M.; Morel, E.; Belaud, C. *J. Chem. Res., Synop.* **1983**, 188.

(2) (a) Reviews: Piatak, D. M.; Wicha, J. *Chem. Rev.* **1978**, *78*, 199. (b) Claisen rearrangement is almost the only one useful for the purpose: See for a recent example: Fujimoto, Y.; Kimura, M.; Terasawa, T.; Khalifa, F. A. M.; Ikekawa, N. *Tetrahedron Lett.* **1984**, *25*, 1805.

(3) (a) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1977**, *99*, 7360; **1983**, *105*, 651. (b) Ibid. **1984**, *106*, 3368. (c) Nakamura, E.; Shimada, J.-i.; Kuwajima, I. *Organometallics*, in press.

(4) Carmely, S.; Kashman, Y. *Tetrahedron* **1981**, *37*, 2397. The natural sample is currently unavailable: Y. Kashman, private communication.

(5) Review: Bergamasco, R.; Horn, D. H. S. In "Progress in Ecdysone Research"; Hoffmann, J. A.; Ed.; Elsevier/North Holland Biomedical Press: Amsterdam, 1980; pp 299–324.

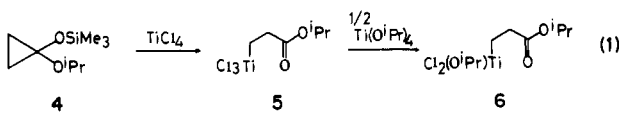
(6) Review: Norman, A. W., Schaefer, K., Herrath, D. v., Grigoleit, H.-G., Eds. "Vitamin D Chemical, Biochemical and Clinical Endocrinology of Calcium Metabolism"; Gruyter: Berlin, 1982.

(7) Cheng, K.-P.; Bang, L.; Ourison, G.; Beck, J.-P. *J. Chem. Res., Synop.* **1979**, 84 and references therein.

(8) Schmitz, F. J.; Pattabhiraman, T. *J. Am. Chem. Soc.* **1970**, *92*, 6073.

(9) The structure of **6** has been deduced by spectroscopic studies. Unlike the original **5**, **6** also reacts smoothly with ketones: H. Oshino, unpublished results.

0002-7863/85/1507-2138$01.50/0



(1)

4 5 6

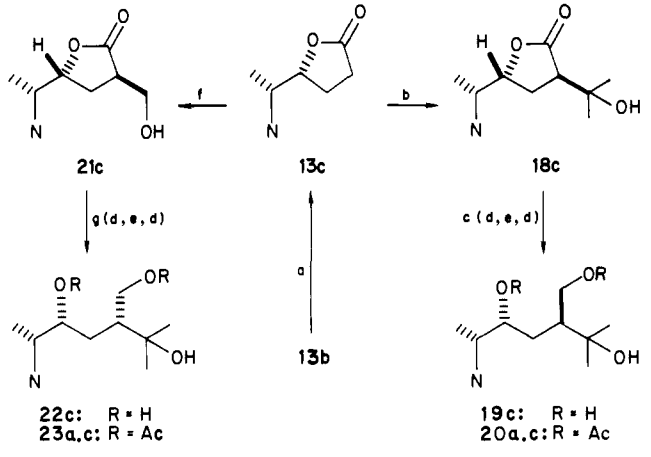
60% yield as a major diastereomer (>6:1). The C(22) configuration of **8a** was proven to be 22(*S*) by conversion into the known diacetate **10a**.[10] The value of the new homoenolate **6** resides in its enhanced nucleophilicity as well as its ability to afford the hydroxy ester free from the lactonized product. This latter point turned out to be crucial for the successful synthesis of **1** (vide infra). Followup studies revealed that **6**, being more reactive than the original **5**, is suitable for general synthetic use.[9]

An inversion of the C(22) configuration was now required in order to arrive at the 22(*R*) configuration which has been assigned.[4] The virtue of the homoenolate chemistry emerged at this point, allowing this difficult inversion reaction[11] to proceed with ease. Thus, **7a** was mesylated (**11a**, 93%) and then the terminal ester group hydrolyzed with KOH in hot aqueous MeOH. Acid-catalyzed lactonization of **12b** then provided the (22*R*)-lactone **13b** (90% from **11a**) as the sole product. The C(22) stereochemistry was proved by completion of a concise synthesis of the ecdysone side chain (**14b**).[12] The whole sequence could also be accomplished in a comparative overall yield in the corresponding series of compounds with 3,5α-cyclo-6β-methoxy protection.

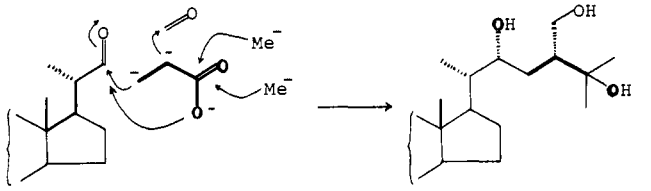
Stereoselective introduction of the C(28) hydroxymethyl group was then performed in a controlled manner by taking advantage of the steric bias[13] imposed on the lactone ring of **13** by the bulky steroidal nucleus (Scheme II). Thus, **13b** was silylated, and then **13c** (mp 214–215 °C) was enolized with lithium diisopropylamide (LDA) at −78 °C. The enolate was trapped with acetone (latent C(25)–(27)) to afford **18c** (87%) as a sharp melting solid (mp 172.5–173.5 °C), in which all the required carbon had been installed. The C=O stretching band of the IR spectrum appeared as low as 1735 cm^{-1} owing to internal hydrogen bonding, which has been observed for the naturally derived material.[4] The lactone carbonyl was reduced ($LiAlH_4$) to obtain the (24*S*)-diol **19c**. The side chain region of the ^{13}C NMR of the diacetate **20c** was clearly different from that of the natural depresosterol triacetate, and the 270-MHz ^1H NMR spectrum of the synthetic triacetate **20a** differed markedly from the natural one for the crucial C(28) methylene signals. We, therefore, turned to the possibility of synthesizing the 24(*R*) isomer.

Since the inversion of the C(24) configuration[13] in **18c** appeared impossible, we introduced the latent C(28) first. Thus, the enolate of **13c** was quenched with gaseous formaldehyde at −78 °C to obtain **21c** (70%). Although MeMgBr could deliver only one methyl group to the unreactive lactone carbonyl, MeLi in hot THF did convert **21c** to the (21*R*)-diol **22c**, which was then transformed to the diacetate **23c** (46% from **21C** + 5% of **19c**). Unlike the case of the 24(*S*) isomer, the ^{13}C NMR spectrum of **23c** was identical with that of the depresosterol triacetate except for the A-ring region. Appropriate exchange of protection afforded the triacetate **23a**, whose spectral properties, including the 270-MHz ^1H NMR, were identical with those of the natural sample. Conversion of **23a** to depresosterol (**1**) by simple hydrolysis is known.[4] The first total synthesis of depresosterol was thus finished and allowed the assignment of the 20(*S*), 22(*R*), 24(*R*) configuration to natural depresosterol. The synthesis of 22(*S*) epimers,

Scheme II



Scheme III



not required for the present purpose, would also be achieved readily via **8a**.

The mesylate **11a** serves also as a precursor to demethylgorgosterol (**3**) (Scheme I). Thus, **11a** was treated with potassium *tert*-butoxide in THF to give (22*R*,23*S*)-cyclopropanecarboxylate (**16a**) (67%), elaboration of which into **3** would involve a straightforward route via **17**, following a sequence due to Djerassi.[14]

In summary, we have developed a new approach to functionalize steroid side chains with a significant control of the stereoselection. The present synthetic scheme is a good representation of the potentialities of metal homoenolates in organic syntheses. As illustrated by Scheme III, the whole elements of the homoenolate moiety have been efficiently exploited. Suitable modification of this basic planning would make accessible further structural variations of side chains, including the intriguing 24-dialkylated steroids.[15]

Experimental Section

General Data. All the reactions dealing with air- and moisture-sensitive compounds were carried out in a dry reaction vessel under nitrogen or argon. Liquid samples were introduced either neat via a microsyringe or in a organic solvent via a hypodermic syringe. Routine chromatographic purification was achieved by flash chromatography[16] by using purified Wako C-300 silica gel. ^1H NMR spectra were taken at 60 MHz on a Hitachi R24B spectrometer. ^{13}C NMR spectra were taken at 22.25 MHz on a JEOL FX90Q instrument. This instrument was also used for 90-MHz ^1H NMR in cases so indicated. Spectra are reported in parts per million from internal tetramethylsilane. IR spectra were recorded on a Hitachi 260-10 instrument; absorptions are reported in inverse centimeters.

Ethereal solvents were distilled from benzophenone ketyl immediately before use. CH_2Cl_2 was distilled successively from P_2O_5 and K_2CO_3 and stored over molecular sieves under nitrogen. Hexane was distilled from $LiAlH_4$ under nitrogen and stored over potassium mirror. Titanium reagents were distilled and stored under nitrogen.

(10) The initial product **9b** was acetylated for spectral comparison. (a) Trost, B. M.; Matsumura, Y. *J. Org. Chem.* **1977**, *42*, 2036. (b) Hirano, Y.; Ikekawa, N.; Tanaka, Y.; DeLuca, H. F. *Chem. Pharm. Bull.* **1981**, *29*, 2254. (c) Mori, H.; Shibata, K.; Tsuneda, K.; Sawai, M. *Tetrahedron* **1971**, *27*, 1157.

(11) The difficult accessibility of C(22) position is wellknown. The C(22) inversion has previously been achieved with potassium superoxide: Ishiguro, M.; Saito, H.; Sakamoto, A.; Ikekawa, N. *Chem. Pharm. Bull.* **1978**, *26*, 3715.

(12) Due to extreme insolubility of **14b**, it was converted to **15b** for spectral comparison with an authentic sample (ref 10b).

(13) Review: Takano, S.; Ogasawara, K. *J. Syn. Org. Chem. Jpn.* **1982**, *40*, 1037. Takano, S.; Tamura, H.; Ogasawara, K.; Nakagawa, Y.; Sakai, T. *Chem. Lett.* **1982**, *933*. Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1979**, 3315.

(14) (a) Walkup, R. D.; Anderson, G. D.; Djerassi, C. *Tetrahedron Lett.* **1979**, 767. (b) Ishiguro, M.; Akaiwa, A.; Fujimoto, Y.; Sato, S.; Ikekawa, N. *Tetrahedron Lett.* **1979**, 763. (c) Sato, S.; Akaiwa, A.; Fujimoto, Y.; Ishiguro, M.; Ikekawa, N. *Chem. Pharm. Bull.* **1981**, *29*, 406.

(15) Li, L. N.; Sjostrand, U.; Djerassi, C. *J. Org. Chem.* **1981**, *46*, 3867.

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

Isopropyl (3β,22*R*)-3-Acetoxy-22-hydroxy-26,27-bis(norcholest-5-en-25-oate) (8a). To a solution of $TiCl_4$ (660 μL, 6.00 mmol) in 15 mL of hexane was added the cyclopropane **4**[17] (1.24 mL, 6.00 mmol) with stirring, and the mixture was let to stand for 30 min at room temperature. The supernatant was removed by a syringe. The purple crystals of **5** were dissolved in 7 mL of methylene chloride, $Ti(O\text{-}i\text{-}Pr)_4$ (743 μL, 2.5 mmol) was added at 0 °C, and the mixture was stirred for 10 min.

To this reddish solution was added the aldehyde **7a**[18] (931 mg, 2.50 mmol) in several portions during 30 s. The dark red reaction mixture was stirred for 4 h at 0–5 °C, diluted with ether, and poured into a ice-water mixture. After extraction with ether, the combined organic layer was washed twice with water, once with 1 N HCl, saturated $NaHCO_3$, and finally with saturated NaCl. The crude product was purified by column chromatography to obtain 170 mg (18%) of the starting **7a** and 729 mg (60%) of the title hydroxyester, consisting of 85–90% 22 (*S*) epimer as estimated by ^{13}C NMR. Recrystallization from hexane gave an analytical sample: mp 150.5–151.5 °C (needles); IR ($CHCl_3$) 3500 (br), 1720 (s), 1255 (m), 1210 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.68 (s), 1.01 (s), 1.20 (d, J = 6 Hz), 1.98 (s), 3.5–3.8 (m, 1 H), 4.3–4.5 (m, 1 H), 4.62 (qq, J = 6 Hz), 4.9–5.1 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 173.6, 170.4, 139.7, 122.5, 73.9, 73.2, 67.6, 56.6, 52.6, 50.0, 42.3, 40.9, 39.7, 38.1, 37.0, 36.6, 35.8, 32.1, 31.9, (br), 30.6, 27.8, 24.2, 212.8, 21.4, 21.0, 19.3, 11.8.

Anal. Calcd for $C_{30}H_{48}O_4$: C, 73.73; H, 9.90. Found; C, 73.89, H, 9.93.

The hydroxyester was lactonized by heating with *p*-toluenesulfonic acid to give the corresponding (22*S*)-lactone as fluffy crystals mp 214–215.5 °C (dec. EtOAc/hexane).

Anal. Calcd for $C_{27}H_{42}O_5$: C, 75.66, H, 9.41. Found: C, 75.64; H, 9.65.

(3β,22*S*)-Cholest-5-ene-3,22,25-triol 3,22-Diacetate (10a). To a solution of 123 mg (0.25 mmol) of the 22-hydroxyester **8a** in 2 mL of THF was added a 1.36-mL solution of methylmagnesium bromide in ether (1.29 M, 1.75 mmol). The mixture was quenched by 1 N HCl, and the organic layer was extracted with a large amount of chloroform to obtain 126 mg of the crude **9**, which was acetylated with 1 mL of acetic anhydride in 1.5 mL of pyridine for 1.5 h. The volatile material was removed in vacuo, and the residue was partitioned between ether and water. Chromatographic purification gave 108 mg of the title compounds (84%). One recrystallization from hexane gave an analytical sample: mp 168.5–170 °C; IR ($CHCl_3$) 1703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.68 (s), 1.02 (s), 1.20 (s), 2.00 (s), 4.2–5.0 (m, 2 H), 5.1–5.3 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 171.1, 170.3, 139.8, 122.7, 76.98 74.2, 70.7, 56.8, 52.9, 50.3, 42.5, 40.0, 39.4, 38.3, 37.3, 36.8, 32.2, 29.6, 29.5, 28.3, 28.0, 27.3, 24.5, 21.5, 21.4, 19.5, 13.0, 11.9.

Anal. Calcd for $C_{31}H_{50}O_5$: C, 74.06; H, 10.02. Found: C, 74.12; H, 10.13.

Isopropyl (3β,22*S*)-3-Acetoxy-22-methanesulfonyloxy-26,27-bis(norchlest-5-en-25-oate) (11a). To a solution of the alcohol **8a** (127 mg, 0.259 mmol) in 1 mL of methylene chloride at 0 °C was added triethylamine (46 μL, 0.33 mmol) and methanesulfonyl chloride (24 μL, 0.30 mmol). After 10 min, water was added and the organic layer was extracted with ether. Drying, concentration, and chromatographic separation (1 g of silica gel, 10% ethyl acetate in hexane) gave 137 mg (93%) of the title mesylate. Recrystallization gave an analytical sample as fine needles: mp 132–132.5 °C; IR ($CHCl_3$) 1725 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.7 (s 3 H), 1.01 (s, 3 H), 1.22 (d, 6 H, J = 6 Hz), 1.97 (s, 3 H), 2.97 (s, 3 H), 4.2–5.3 (m, 3 H, involving qq, J = 6 Hz at 4.90).

Anal. Calcd for $C_{31}H_{50}O_7S$: C, 65.69; H, 8.89. Found: 65.63; H, 8.70.

(3β,22*R*)-3-(*tert*-Butyldimethylsiloxy)-22-hydroxy-26,27-bis(norchlest-5-en-25-oic Acid) Lactone (13c). The mesylate **11a** (320 mg, 0.579 mmol) was added to a solution of 0.15 g of KOH in 5.5 mL of 30% aqueous MeOH and 2 mL of THF. The mixture turned homogeneous when heated, and the reflux was continued for 3 h. The reaction mixture was concentrated to a volume of ca. 1.5 mL and acidified with 2 M HCl. The precipitated acid was collected by filtration (195 mg). The crude acid was heated in 5 mL of $CHCl_3$ with ca. 10 mL of *p*-toluenesulfonic acid for 2 h. The insoluble acid dissolved as the reaction proceeded. The insoluble material was removed by filtration to give 210 mg (ca. 90% overall yield) of the lactone **13**: mp 198–199 °C (ethyl acetate/hexane); IR (KBr) 1775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.72 (s), 0.91 (d, J = 6.5 Hz), 1.00 (s), 3.2–3.6 (m), 4.3–4.6 (m) 5.1–5.3 (m).

The crude hydroxy lactone **13b** (210 mg) was treated with *tert*-butyldimethylsilyl chloride (0.43 mL of a 2.11 M hexane solution, 0.9 mmol) and (dimethylamino)pyridine (147 mg, 1.2 mmol) in a mixture of THF (1 mL) and 0.5 mL of DMF. After 16 h, the solvent was removed in vacuo and the residue was filtered through SiO_2. Purification of the crude product by column chromatography gave 232 mg (80%) of the silyl lactone (R_f 0.57, 15% ethyl acetate in hexane, two developments) contaminated by a trace amount of the 22 epimer to obtain 129 mg of a pure sample as shining plates: mp 214–215 °C; IR (KBr) 1775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s), 0.71 (s), 0.87 (s), 0.99 (s), 3.1–3.7 (m), 4.3–4.7 (m), 5.1–5.3 (m).

Anal. Calcd for $C_{31}H_{51}O_3Si$: C, 74.35; H, 10.47. Found: C, 74.45; H, 10.33.

(3β,22*R*)-Cholest-5-ene-3,22,25-triol 3,22-Diacetate (15a). The lactone **13b** obtained from 72 mg of the mesylate **11a** was dissolved in Ac_2O (1 mL), pyridine (0.5 mL) was added after 2 h, and the mixture was stirred overnight. After concentration in vacuo, the residue was filtered through a short column of silica gel with ether as eluent to obtain the crude **13a** (56 mg, 100%): IR ($CHCl_3$) 1763, 1723 cm^{-1}; MS m/e 368 (M^+ – AcOH).

This material was dissolved in 1.5 mL of THF, and 0.71 mL of 1.29 M methylmagnesium bromide in ether (0.92 mmol) was added at 0 °C. After 10 min at room temperature, 2 mL of 1 N HCl was added, the organic solvent was removed, and the suspension was filtered to obtain the crude triol **14b** (50 mg, 91%) as pale yellow crystals: mp 217–221 °C (lit. mp 224–227 °C,[10b] mp 253–255 °C).[10a]

A 45-mg portion of **14b** was treated with 0.5 mL of Ac_2O and 0.5 mL of pyridine for 19 h. After concentration in vacuo, the residue was chromatographed to give 29 mg of (3β,22*R*)-diacetate **15b**. The ^{13}C NMR of this compound was superimposible on an authentic spectrum: mp 147–148 °C (ether/hexane) (lit. mp 150–152.5 °C;[10b] mp 150 °C);[10a] IR ($CDCl_3$) 1720 (s), 1370 (m), 1255 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.67 (s), 1.00 (s), 1.20 (s), 1.99 (s), 4.2–4.9 (m, 2 H), 5.1–5.3 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 171.3, 170.8, 140.0, 123.0, 77.78 74.3, 71.0, 56.6, 53.3, 50.3, 43.1, 40.9, 40.1, 39.5, 38.5, 37.48 37.0, 32.28 30.0, 29.5, 28.2, 27.4, 24.6, 22.2, 21.8, 21.4, 29.7, 13.5, 12.8.

(3β,22*R*,24*S*)-3-(*tert*-Butyldimethylsilyl)-22,28-diacetoxy-25-hydroxycholest-5-ene (20c). The silyl lactone **13c** (25.0 mg, 0.050 mmol) was lithiated by 0.07 mmol of LDA as described for **23c**, and acetone (15 μL, 0.20 mmol) was added at −78 °C. After 5 min, the mixture was quenched by adding 30 μL of acetic acid in 0.1 mL of THF and then 0.3 mL of water, and the adduct was isolated by extractive workup was chromatographed to obtain 19.5 mg of a pure sample of **18c** as a white solid (87%): mp 172.5–173.5 °C; IR ($CHCl_3$) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s), 0.72 (s), 0.89 (s), 0.91 (d, J = 6.5 Hz), 1.26 (s), 1.29 (s), 3.53 (br s), 4.56 (ddd, J = 4, 5.5, 8 Hz), 5.15–5.35 (m).

The hydroxylactone **18c** (19.0 mg, 0.034 mmol) was reduced with 7 mg of $LiAlH_4$ in 0.5 mL of THF at 20 °C to give 13 mg of the crude triol which showed a single spot on TLC. The compound was treated with 0.1 mL of acetic anhydride in 0.3 mL of pyridine at 75 °C for 3.5 h. Chromatographed purification gave the title ester **23c** (8.5 mg, 39%) as a viscous oil in addition to impure 24(*R*) epimer **20c** (4 mg, <18%): MS (20 eV) m/e (rel intensity) 644 (M^+ – 2, 7), 589 (30), 571 (28), 529 (40), 377 (85), 253 (75), 255 (50), 171 (100), 123 (90), 111 (85). FAB mass spectrum using glycerine matrix also indicated the molecular weight of 644. ^1H NMR ($CDCl_3$, 90 MHz) δ 0.06 (s), 0.68 (s), 0.89 (s), 1.00 (s), 1.22 (s), 1.24 (s), 2.05 (s), 2.06 (s), 3.25–3.65 (m, 1 H, H(3)), 4.07 (dd, J = 4.4, 11.3 Hz, H(28)), 4.24 (dd, J = 4.0, 11.3 Hz, H(28)), 5.02 (br d, J = 10.5 Hz, H(22)), 5.28 (br d, J = 4.0 Hz, H(6)); ^{13}C NMR ($CDCl_3$) δ −4.50, 11.9, 12.9, 18.3, (Bu–Si), 19.45, 21.1, 21.4, 24.2, 24.4, 25.7 (23), 26.0 (*t*-Bu), 27.0, 27.5, 28.2 (26), 32.0, 32.18 36.6, 37.5, 39.1, 39.9, 42.8, 44.4, (24), 50.3, 53.0, 56.6, 65.2 (28), 72.4 (25), 72.7, 74.7 (22), 121.0, 141.6, 170.6.

24-Epidepresosterol Triacetate (20a). The 3-siloxy product **23c** (2.0 mg) was dissolved in a mixture of acetic acid (30 μL), water (20 μL), and THF (50 μL) and kept for 2 days at room temperature. Volatile material was removed in vacuo, and the residue was treated with a mixture of acetic anhydride (20 μL) and pyridine (30 μL) for 1 day at room temperature. After concentration the residue was chromatographed to give 1.80 mg of the title compd. (R_f 0.5, 50% ethyl acetate in hexane). The side chain region of the 90-MHz ^1H NMR spectrum was identical with that of **20c**. The C(28) methylene signal on the 270-MHz ^1H NMR spectrum was different from that of the natural depresosterol: ^1H NMR ($CDCl_3$, 90 M Hz) δ 0.680 (s), 0.938 (d, J = 7.7 Hz), 1.017 (s), 1.213 (s), 1.239 (s), 2.030 (s), 2.038 (s), 2.059 (s), 2.326 (br d, J = 7.7 Hz), 4.080 (dd, J = 4.3, 11 Hz), 4.271 (dd, J = 4 Hz, 11 Hz), 4.41–4.78 (m), 5.014 (br d, J = ca. 10.5 Hz), 5.353 (br d, J = 4 Hz).

(3β,22*R*,24*R*)-3-(*tert*-Butyldimethylsilyloxy)-22,28-diacetoxy-25-hydroxycholest-5-ene (23c), The silyl lactone **13c** (25.0 mg, 0.050 mmol)

(17) The procedure reported for the preparation of the corresponding ethoxycyclopropane was employed with sucess. (a) Rülmann, K. *Synthesis* **1971**, 236. (b) Salaün, J.; Marguerite, J. *Org. Synth.*, in press.

(18) Available either from bis(norchlolenic acid) acetate (Steraloids, Inc.: ClCOOEt, Et_3; $NaBH_4$; pyridinium chlorochromate) or from pregnenolone acetate: Batcho, A. D.; Berger, D. E.; Devoust, S. G.; Wovkulich, P. M.; Uskokovic, M. R. *Helv. Chim. Acta* **1981**, *64*, 1682.

in 0.4 mL of warm THF was added during 45 s to a solution of LDA (prepared from 44 μL of 1.58 M BuLi, 0.070 mmol, and 12 μL of diisopropylamine, 0.080 mmol) in 0.4 mL of THF at −78 °C. The mixture was stirred for 5 min at −78 °C and for 10 min at −10 °C and finally cooled to −78 °C. Gaseous formaldehyde (from 18 mg of paraformaldehyde depolymerized at 150 °C) was introduced for 10 min and after 5 min 1 N HCl. The reaction mixture was extracted with ether/chloroform mixture to furnish 18.5 mg of the hydroxylactone **21c** (70%) and 1 mg of the starting material after chromatographic purification: iR ($CHCl_3$) 1750 cm^{-1}; ^1H NMR δ 0.05 (s), 0.72 (s), 0.87 (s), 0.88 (d, J = 6.5 Hz), 1.00 (s), 3.1–3.7 (m), 3.7–4.1 (m), 4.3–4.8 (m), 5.1–5.3 (m).

To a solution of the lactone **21c** (17 mg, 0.032 mmol) in 0.5 mL of THF at −78 °C was added 0.2 mL of 2.1 M methyllithium, and the mixture was then warmed at 45 °C for 1 h. Methanol (0.3 mL) was added, and the mixture was concentrated. Pyridine (0.3 mL) and 0.2 mL of acetic anhydride were added, and the mixture was heated at 80 °C for 1.5 h until the initially formed monoacetate was completely converted to the diacetate. Purification of the crude product obtained after concentration gave 9.5 mg of the title diacetate **23c** (46%) as a solid (R_f 0.60, 50% ethyl acetate in hexane): MS (20 eV), m/e (rel intensity) 645 (M^+ − 1), 589 (50), 571 (26), 529 (35), 377 (55), 255 (53), 253 (45), 171 (100), 123 (74), 111 (76). FAB mass spectrum using a glycerin matrix also indicated the molecular weight of 645. ^1H NMR ($CDCl_3$, 90 MHz) δ 0.06 (s, 6 H), 0.67 (s, 3 H), 0.89 (s), 0.99 (s), 1.22 (s), 1.25 (s), 2.04 (s), 2.06 (s), 3.2–3.75 (m, 1 H), 3.8–4.4 (m centered at 4.12, 2 H), 5.03 (br d, J = 10.5 Hz), 5.29 (br d, 2 H, J = 4.0 Hz); ^{13}C NMR ($CDCl_3$) δ − 4.5, 11.9, 13.0, 18.3 (Bu–Si), 19.5, 21.1, 21.5, 24.4, 25.2 (23), 26.0 (t-Bu), 27.2 (27, 16), 28.4 (26), 32.0, 32.1, 36.6, 37.4, 39.7, 39.8, 42.9, 46.4 (24), 50.3, 53.1, 56.5, 65.9 (28), 72.7 (25), 77.7 (22), 121.0, 141.6, 170.8, 171.0.

Depresosterol Triacetate (23a). The 3-siloxy compound **23c** (3.0 mg) was dissolved in a mixture of acetic acid (30 μL), water (20 μL), and THF (50 μL) and kept for 2 days at room temperature. Volatile material was removed in vacuo and the residue was treated with a mixture of acetic anhydride (20 μL) and pyridine (30 μL) for 1 day at room temperature. After concentration, the residue was chromatographed to give 2.5 mg of the title compound as a solid (R_f 0.65, 50% ethyl acetate in hexane), which was identical with an authentic sample by the 270-MHz ^1H NMR and EI-MS spectra. The 90-MHz ^1H NMR of **23a** was identical with the silylated **23c** except for the signals due to the A-ring region.

Acknowledgment. We thank Prof. Y. Kashman for the 270-MHz ^1H NMR spectrum of the natural depresosterol, Prof. N. Ikekawa and Dr. Y. Fujimoto for helpful discussion and for the provision of steroidal aldehydes and the authentic spectra of **10a** and **15a**, Prof. O Mitsunobu for the measurement of 270-MHz spectra, and N. Nakayama for the measurement of mass spectra. Financial support from the Ministry of Education, Science, and Culture is deeply acknowledged.

Registry No. **1**, 77517-54-5; **4**, 84098-44-2; **5**, 84098-53-3; **7a**, 10211-88-8; **8a**, 94956-26-0; **8a** lactone, 95042-54-9; **9b**, 63163-38-2; **10a**, 79435-62-4; **11a**, 94956-27-1; **12b**, 94956-28-2; **13a**, 95042-55-0; **13b**, 95042-56-1; **13c**, 94956-29-3; **14b**, 63160-61-2; **15a**, 63160-62-3; **16a**, 94978-08-2; **18c**, 94956-30-6; **20a**, 94956-31-7; **20c**, 94956-32-8; **21c**, 94956-33-9; **23a**, 95042-57-2; **23c**, 94956-34-0; $TiCl_4$, 7550-45-0; Ti(O-*i*-Pr)$_4$, 546-68-9; methyl bromide, 74-83-9; *tert*-butyldimethylsilyl chloride, 18162-48-6; acetone, 67-64-1; methyllithium, 917-54-4.

Synthesis of 14-Membered P_2S_2 and P_3S Macrocycles Which Contain the 1-Thio-2-(phenylphosphino)benzene Moiety. Determination of Stereochemistries of the Free Ligands and of a Pt(II) Complex

Evan P. Kyba,* Clyde N. Clubb, Steven B. Larson, Victor J. Schueler, and Raymond E. Davis*

Contribution from the Department of Chemistry, The University of Texas at Austin, Austin, Texas 78712. *Received July 30, 1984*

Abstract: Three new 14-membered tetradentate (P_3S and two P_2S_2) macrocycles have been synthesized and isolated as pairs of isomers. All the isomers were separated and fully characterized, and their stereochemistries were determined or assigned. The new ligands are *cis*- and *trans*-13,17-diphenyl-13,17-diphospha-2,6-dithiatricyclo[16.4.0.0^{7,12}]docosa-7(12),8,10,1-(18),19,21-hexaene (**3C** and **3T**), *cis*- and *trans*-6,17-diphenyl-6,17-diphospha-2,13-dithiatricyclo[16.4.0.0^{7,12}]docosa-7-(12),8,10,1(18),19,21-hexaene (**4C** and **4T**), and *cis,cis*- and *cis,trans*-6,13,17-triphenyl-6,13,17-triphospha-2-thiatricyclo-[16.4.0.0^{7,12}]docosa-7(12),8,10,1(18),19,21-hexaene (**5C** and **5T**). The synthesis of **4C,T** involved the use of an S–H protecting group, CH_2OMe, which is removed quantitatively with *n*-butylthiolate in DMF. The stereochemistry of **3T** was established by a single-crystal X-ray diffraction study and that of **4C** by an X-ray study of the complex **4C**·$Pt^{II}(PF_6)_2$. The latter was a classical square-planar complex, with essentially equal Pt–S and Pt–P bond lengths, in the range 2.287–2.297 Å. The stereochemistries of **5C,T** were assigned by the comparison of the physical and spectroscopic properties with those of **3C,T**, **4C,T** as well as those of the analogous **14**-P_4**C,T** species. Crystal structures at −110 °C have been determined for **3T** and **18**. X-ray data were collected on a Syntex $P2_1$ autodiffractometer and refined by the full-matrix least-squares method. For **3T** as hexagonal plates from ethyl acetate, a = 13.4358 (22) Å, b = 14.2137 (14) Å, c = 14.0314 (21) Å, β = 93.903 (11)°, monoclinic, $P2_1/c$, Z = 4, R = 0.0520, and R_w = 0.0567 for 3383 reflections with $|F_o| \geq 6\sigma_{|F_o|}$. The structure is severely disordered, with only one PPh and one $(CH_2)_3$ chain ordered. For **18**·C_6H_6, a = 12.629 (5) Å, b = 15.304 (3) Å, c = 20.714 (6) Å, β = 104.76 (4)°, monoclinic, $P2_1/c$, Z = 4, R = 0.0530, R_w = 0.0437 for 6061 reflections with $|F_o| \geq 4\sigma_{|F_o|}$. Coordination about Pt is square planar with nearly equal Pt–P (2.297 and 2.293 Å) and Pt–S (2.296 and 2.287 Å) bond lengths. The angle S–Pt–S is 179.3°, while P–Pt–P is 170.7°. Both $\overline{SPtP(CH_2)_2CH_2}$ rings adopt the chair conformation.

Several years ago we described the synthesis and structures of several tetradentate 14-membered macrocycles which contained *tert*-phosphino sites of general type **1**.[2] One of our goals for these ligands was the systematic modification of the properties of a

0002-7863/85/1507-2141$01.50/0