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A New Synthesis for Δ^{24}-Sterols: Preparation of Cholesta-5,24-dien-3β-ol (Desmosterol)[1a,2]

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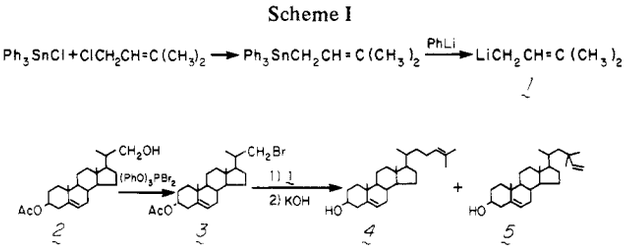
The new synthesis of Δ^{24} unsaturated sterols which involves the coupling reaction between dimethylallyllithium and a bromide is exemplified by the production of cholesta-5,24-dien-3β-ol (desmosterol; **4**) in Scheme I. The anticipated value of the new synthesis is in the preparation of other Δ^{24}- sterols. Reactions such as reductions of double bonds may be performed on the nuclear part of the sterol before the side chain with the labile Δ^{24} bond is added.

In this synthesis of desmosterol, 3β-acetoxy-23,24-dinorchol-5-en-22-ol (**2**), a known compound,[3,4] is converted into 3β-acetoxy-22-bromo-23,24-dinorchol-5-ene (**3**) with $(PhO)_3PBr_2$ in the presence of 1 mol of pyridine. This combination of reagents has been used[5] for the conversion of alkene or alkyne alcohols into bromides.

Preparation of compounds **4** was based on the analogous coupling reaction of allyllithium with 1-iodopentane to give 1-octene.[6] The required dimethylallyllithium reagent (**1**) was prepared by the transmetallation procedure of Seyferth and Weiner[7] involving a triphenyltin intermediate.

Scheme I



The coupling reaction produces the desired product and a minor by-product (**5**, ca. 3:1). The by-product has the same mol wt (as determined by MS) as the main product. The spectral data from **5** which include ^{13}C-NMR, ^{1}H-NMR, and IR determinations support structure **5**. The ^{13}C-NMR peaks at 109.7 and 149.8 ppm downfield from Me_4Si are comparable to the 108.1- and 148.1-ppm values for the vinyl protons of 3,3-dimethyl-1-butene.[8,9] The ^{1}H-NMR spectrum includes vinyl protons with chemical shifts and coupling constants similar to those of model compounds 3,3-dimethyl-1-butene[10] and 17 α-vinylestradiol.[11] The compound absorbs strongly at 907 cm^{-1} which is consistent with the IR absorption of a terminal methylene group. Previous studies[12,13] with allylic Grignard reagents indicate that the products formed are derived from the starting halide and/or the corresponding allylic isomer. This phenomenon appears to be occurring with the dimethylallyllithium in the coupling reaction causing the formation of 23,23-dimethyl-26,27-dinorcholesta-5,24-dien-3β-ol (**5**).

The new synthesis of desmosterol (**4**) is more practical than previously published preparations of this compound. The overall yield of desmosterol from the new synthesis is 14% when the 3β-acetoxy-23,24-dinorchol-5-en-22-ol starting material is prepared from commercially available 3β-acetoxy-23,24-dinorchol-5-en-22-oic acid by the Hayatsu method.[4] Compound **4** is produced from 3β-acetoxychol-5-en-24-oic acid in 9% yield,[14] and from 3β-acetoxy-26-norcholest-5-en-25-one in 36% yield,[15] but 3β-acetoxy-23,24-dinorchol-5-en-22-oic acid is a much more economical starting material. The nickel tetracarbonyl used to prepare π-(dimethylallyl)-nickel bromide in one synthesis[16] is highly toxic, and no yield is reported for the first step (Arndt–Eistert homologation) in another preparation.[16] The latter synthesis also uses 3β-acetoxy-23,24-dinorchol-5-en-22-oic acid as the starting material, and the yield of desmosterol from the homologue is 21%.

The new coupling reaction can be used for preparing Δ^{24} sterols with modified nuclear systems. Reactions such as hydrogenation which the Δ^{24} bond would not survive are performed before the addition of the Δ^{24} bond. The Fagerlund and Idler synthesis of desmosterol[14] can also be adapted for the preparation of other Δ^{24}-sterols. However, the limitations of yield and cost discussed in the synthesis of desmosterol would obtain.

Experimental Section

Melting points were determined on a Hoover Uni-Melt apparatus, under vacuum, and are uncorrected. IR spectra were taken on a Perkin-Elmer Model 521 spectrophotometer equipped with a KBr micropellet attachment. High-resolution MS spectra were determined on an A.E.I.M.S. 30. The ^{1}H-NMR spectrum was determined on a Bruker 270 MHz instrument, and the natural abundance, ^{1}H-decoupled, ^{13}C-NMR spectrum was obtained with an XL-100-15/VFT-100 instrument. The spectra were determined in $CDCl_3$, and chemical shifts are reported downfield from the Me_4Si internal standard. Microanalyses were carried out by M-H-W Laboratories, Garden City, Mich.

Dimethylallyltriphenyltin. This compound was produced from triphenyltin chloride (ICN Pharmaceuticals, Inc., Plainview, N.Y.; 10.9 g, 28.3 mmol) and 1-chloro-3-methyl-2-butene (Eastman, 4.6 g, 44 mmol).[7] The white solid was recrystallized from hexanes (50 mL), and the product (7.2 g, 17.19 mmol, 60.7%) which melted over several degrees was recrystallized from hexanes by removing the solvent at room temperature with nitrogen until crystals began to form. The many-sided irregular crystals melt at 71–72.5 °C and decompose in boiling hexanes: IR (KBr) 3060, 3050, 2964, 2910, 1694, 1657, 1651, 1426, 848, 807, 724, 710, 448 cm^{-1}. Anal Calcd for $C_{23}H_{25}Sn$ (420.147): C, 65.74; H, 5.99. Found: C, 65.82; H, 5.99.

3β-Acetoxy-22-bromo-23,24-dinorchol-5-ene (3). A 250-mL three-neck distilling flask equipped with a dropping funnel, drying tube, nitrogen inlet, and magnetic stirring bar was flame dried under a nitrogen atmosphere. Triphenyl phosphite (Aldrich, 5.4 g, 17.4 mmol) and ether (18 mL, freshly distilled from lithium aluminum

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hydride) were added to the cooled flask, and the solution was cooled on ice. Bromine (2.76 g, 17.2 mmol) was added dropwise with stirring. The ether was removed from the slightly yellow solid by vacuum distillation. The remaining solid was washed with ether which was removed by vacuum distillation while the flask was warmed periodically in a mineral oil bath held below 50 °C. The flask was transferred to an ice–salt bath. Compound **2**[3,4] (0.62 g, 1.65 mmol) in benzene[17] (94 mL, freshly distilled from lithium aluminum hydride) and pyridine (0.14 mL, 1.7 mmol, freshly refluxed in and distilled from BaO) were added to a fresh dropping funnel. The steroid solution was added over 10 min, the flask was allowed to warm to room temperature, and the mixture was stirred for 2 h. The mixture was washed with distilled H_2O (100 mL), and the aqueous layer was washed with benzene (50 mL). The combined benzene layers were warmed in a water bath and the solvent was removed under a stream of nitrogen. The crude material was chromatographed on Alumina F20 (102 g) in benzene–hexanes (increasing polarity from 1:1, v/v). The product (0.34 g, 0.77 mmol, 46.7%, mp 157–159.5 °C), which was eluted with benzene–hexanes 4:1, was rechromatographed on Alumina F20 and recrystallized from distilled MeOH to yield cubes: mp 157.5–158.5 °C; IR (KBr) 580 (CBr) cm^{-1}. Anal. Calcd for $C_{24}H_{37}O_2Br$ (437.452): C, 65.9; H, 8.5; Br, 18.3. Found: C, 65.98, H, 8.65; Br 18.32.

Cholesta-5,24-dien-3β-ol (Desmosterol, 4). A 15-mL three-neck distilling flask equipped with a magnetic stirring bar, dropping funnel, reflux condensor, nitrogen inlet, and drying tube was flame dried under nitrogen. Luer-lok syringes and needles were used for the transfer of all liquids. Lithium wire (2.4 cm, approximately 100 mg, 0.014 g-atom cut into six pieces) was added to the cooled flask, and the lithium was washed with ether (10 and 5 mL, freshly distilled from lithium aluminum hydride) from the dropping funnel. The washings were discarded, and fresh ether (1.2 mL) was added to the lithium. Freshly distilled bromobenzene (0.68 g, 4.3 mmol) was added to ether (2.4 mL) in the dropping funnel, and 10 drops of the mixture was added to the lithium. The remaining mixture was added in two equal portions after 5 and 12 min of stirring. The dark brown cloudy liquid (4 mL) was transferred to a 25-mL three-neck flask equipped with a nitrogen inlet, drying tube, and magnetic stirring bar and containing dimethylallyltriphenyltin (2.2 g, 5.25 mmol) in ether (10.4 mL). A cream-colored precipitate formed quickly, and stirring was discontinued after 5 min. The precipitate was allowed to settle, and the clear brown dimethylallyllithium solution (9 mL) was transferred to a three-neck distilling flask containing **3** (226 mg, 0.51 mmol). The flask was equipped with a reflux condensor, nitrogen inlet, drying tube, magnetic stirring bar, heating mantle, and a dropping funnel which supplies ether to maintain the reaction volume. The mixture was refluxed gently for 6.5 h. Saturated NH_4Cl (pH adjusted to 9 with NH_4OH) was added. The mixture was partitioned between distilled H_2O (20 mL) and ether (30 mL), and the aqueous layer was washed with ether (2 × 30 mL). The combined ether layers were warmed in a water bath, and the solvent was removed under a stream of nitrogen. The oily residue was saponified for 0.5 h with 5% alcoholic KOH (15 mL) and distilled H_2O (20 mL) and hexanes (40 mL) were added. The dried organic layer was chromatographed on a $AgNO_3$/silicic acid/Super-Cel column[18] (88.6 g) in benzene. Desmosterol (79.35 mg, 115–116.5 °C, 0.2 mmol, 39.2%) was rechromatographed on Alumina F20 (49 g) in benzene followed by benzene–EtOAc (1:1, v/v) and recrystallized from distilled MeOH (mp 119–119.5 °C) [lit. mp 120–122,[16] 120.5–121,[15] 117–118 °C[14]]: IR (KBr) 1373, 1056, 1022, 959, 950, 835, 800 cm^{-1}. Anal. Calcd for $C_{27}H_{44}O$: M^+ *m/e* 384.3389. Found: M^+ *m/e* 384.3421.

23,23-Dimethyl-26,27-dinorcholesta-5,24-dien-3β-ol (5). The isomer which is produced in the coupling reaction (26.65 mg, 191–195 °C) was also rechromatographed on Alumina F20 and recrystallized from distilled MeOH (mp 192–194 °C with sublimation): IR (KBr) 1469, 1461, 1457, 1444, 1434, 1378, 1372, 1360, 1290, 1061, 1053, 1023, 1006, 963, 956, 907, 839, 800, 782, 685, 668 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.8 (q, 1, J_{cis} = 7.0 Hz, J_{trans} = 17.2 Hz, $C_{24}CH$=), 5.35 (m, 1, C_6), 4.87 (d, 1, J = 11.7 Hz, C_{25}=$CH_{2_{cis}}$), 4.87 (d, 1, J = 16.25 Hz, C_{25}=CH_2 (trans)); ^{13}C NMR ($CDCl_3$) δ_C 149.8 (C_{24}), 121.86 (C_6), 109.7 (C_{25}). Anal. Calcd for $C_{27}H_{44}O$: M^+ *m/e* 384.3389. Found: M^+ *m/e* 384.3406.

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Registry No.—**1**, 50585-10-9; **2**, 55509-37-0; **3**, 58507-57-6; **4**, 313-04-2; **5**, 65733-48-4; triphenyltin chloride, 639-58-7; 1-chloro-3-methyl-2-butene, 503-60-6; dimethylallyltriphenyltin, 65733-49-5.

References and Notes

(1) (a) This work was supported by NIH Grant No. R01 HL 01875; (b) NIH Predoctoral Fellow. Address correspondence to the Department of Chemistry, the Ohio State University, Columbus, Ohio.
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General Procedure for the Synthesis of Mono-N-acylated 1,6-Diaminohexanes

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Studies in our laboratory required the ready availability of *N*-acrylyl-1,6-diaminohexane and *N*-(2-methylacrylyl)-1,6-diaminohexane in high purity. When attempts were made to prepare *N*-acrylyl-1,6-diaminohexane using the published procedure,[1] a product was isolated which agreed with the reported characteristics of the compound; however, analysis revealed the product to be bis(*N,N'*-acrylyl)-1,6-diaminohexane. In addition, the synthesis of monoacrylated product by reaction of acryloyl chloride and excess 1,6-diaminohexane gave poor yields due both to the preferential formation of the bis(N,N'-acrylated) product and to the similar physical properties of the bases, *N*-acrylyl-1,6-diaminohexane and 1,6-diaminohexane.

The key to the successful synthesis of mono-N-acylated 1,6-diaminohexanes is the protection of one of the amino groups of 1,6-diaminohexane by some readily removable group, particularly when this protecting group also favorably alters the solubility properties of the product so that its separation from the unsubstituted and disubstituted by-products is readily accomplished. Hence the easily removable, hydrophobic *tert*-butyloxycarbonyl[2] (Boc) group was used, which renders *N-tert*-butyloxycarbonyl-1,6-diaminohexane separable from the unreacted diamine and bis(*N,N'-tert*-butyloxycarbonyl)-1,6-diaminohexane.

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