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A NEW SYNTHESIS OF 25-HYDROXYCHOLESTEROL

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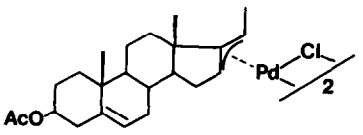
SUMMARY: A simple (η^3-allyl)palladium-based synthesis of 25-hydroxycholesterol is described using a dimetallated coupling reagent.

Recent studies have demonstrated the importance of 25-hydroxycholesterol (7) as an intermediate in the synthesis of the vitamin D_3 metabolite, 25-hydroxycholecalciferol.[1] We have recently described the reaction between (η^3-allylic)Pd(II) halide species and alkenylzirconium complexes which gives rise to 1,4-dienes in high yield; in this context we reported the stereospecific synthesis of either 20(*R*)- or 20(*S*)-cholestan-3-one.[2] Herein we report a direct approach to 7 using this methodology.[2]



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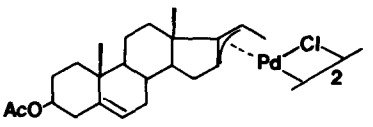

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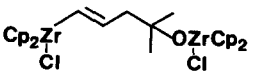
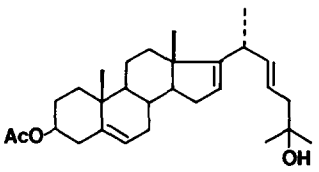


3

(η^3-Allylic)palladium compounds 1 and 2 are readily available[2c] from the corresponding $\Delta^{17,20}$ olefins;[3] *no protection of the* Δ^5 *double bond is necessary.* Using the normal hydrozirconation procedure,[4] 2-methyl-4-pentyn-2-ol[5] and *two* equivalents of Cp_2ZrHCl afforded biszirconated alkenyl compound 3 in 45% yield. In the presence of maleic anhydride[6] reaction[2]



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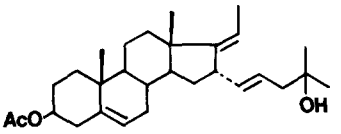

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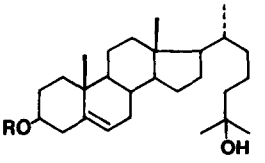
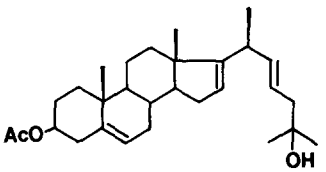


6, R = Ac
7, R = H

between the (*Z*) isomer, 1, and 3 (at -78°C)[7] yielded 4 (20(*R*) configuration, 70% yield) and byproduct 5 (18.4%). Selective hydrogenation of Δ^{16} and Δ^{22} double bonds in 4 afforded 6

(97%), easily hydrolyzed to 25-hydroxycholesterol (7, 97%, overall yield 1 → 7 = 66%). Spectral properties were identical with published data.[8] As expected, a similar coupling



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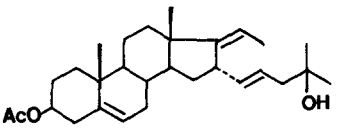

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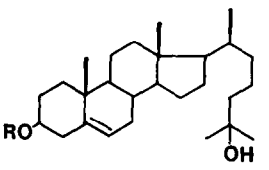

10, R = Ac
11, R = H

reaction using the (*E*) isomer 2 (at -78°C or at room temperature)[9] yielded 8 (20(*S*) configuration, 82%) and 9 (11%). Selective hydrogenation of 8 (to give 10, 95%) and hydrolysis afforded 20(*S*)-25-hydroxycholesterol (11) (96%, overall yield 2 → 11 = 75%). Spectral properties were identical with published data.[8]

PROCEDURES

Sodium chloride (875 mg, 15 mmol), sodium carbonate (875 mg, 8.3 mmol), (15-crown-5, 250 μℓ), and a mixture of the isomeric Δ^{17-20}-olefins (*Z*:*E* = 93:7; prepared from 3-hydroxy-Δ^5-androstan-17-one and ethyl triphenylphosphonium bromide; 1.317 g, 3.85 mmol) were stirred in CH_2Cl_2 (60 mL) for 1 h. Bis(acetonitrile)dichloropalladium (1.38 g, 5.3 mmol) was added as a solid over 1 h, and the suspension was stirred for 48 h. The crude reaction mixture was filtered through Celite. The solvent was removed in vacuo to give an orange oil which was purified by LC (SiO_2, ether/hexanes - 1:1) to yield the (*Z*) isomer 1 (1.614 g, 3.35 mmol, 87%) and the (*E*) isomer 2 (0.130 g, 0.27 mmol, 7%).

1: ^{1}H NMR ($CDCl_3$) δ 1.01 (s, CH_3(18)), 1.05 (s, CH_3(19)); 1.28 (d, *J* = 6.6 Hz, CH_3(21)), 2.03 (s, CH_3COO), 3.68 (br m, H-C(16)), 3.71 (q, *J* = 6.6 Hz, H-C(20)), 4.57 (m, H-C(3)), 5.39 (m, H-C(6)). ^{1}H NMR (C_6D_6) δ 0.64 (s, CH_3(18)), 0.84 (s, CH_3(19)), 1.21 (d, *J* = 6.6, CH_3(21)), 1.77 (s, CH_3COO), 3.32 (br m, H-C(16)), 3.38 (q, *J* = 6.6, H-C(20)), 4.38 (m, H-C(3)), 5.27 (m, H-C(6)).

2: ^{1}H NMR ($CDCl_3$) δ 0.93 (s, CH_3(18)), 1.05 (s, CH_3(19)), 1.12 (d, *J* = 6.6 Hz, CH_3(21)), 2.03 (s, CH_3COO), 4.28 (q, *J* = 6.6 Hz, H-C(20)), 4.39 (br m, H-C (16)), 4.57 (m, H-C(3)), 5.37 (m, H-C(6)). ^{1}H NMR (C_6D_6) δ 0.59 (s, CH_3(18)), 0.84 (s, CH_3(19)), 0.93 (d, *J* = 7 Hz, CH_3(21)), 1.77 (s, CH_3COO), 4.08 (br m, H-C(16)), 4.20 (q, *J* = 7 Hz, H-C(20)), 4.83 (m, H-C(3)), 5.26 (m, H-C(6)).

Cp_2ZrHCl (contaminated by NaCl, 20%, 1.93 g, 6.0 mmol) was added over a period of 3 h to a solution of 2-methyl-4-pentyn-2-ol (294 μℓ, 3.0 mmol) in 70 mL toluene. The yellow solution was filtered and the solvent was evaporated under reduced pressure. The alkenylzirconium compound 3 (824 mg, 1.35 mmol, 45%) was used as a solution in THF (30 mL, 0.045 mmol 3/mL solution)

3: ^{1}H NMR (C_6D_6) δ 1.14 (s, 6), 2.16 (d, 2, J = 5 Hz), 6.00 (s, 10), 6.10 (s, 10), 6.78 and 7.00 (d × t, 1, J = 15 Hz, J' = 5 Hz); other vinylic resonance obscured by Cp.

A THF solution of 3 (10 mL, 0.45 mmol) was added over a period of 2 h to a solution of 1 (160 mg, 0.332 mmol) and maleic anhydride (100 mg, 1 mmol) in 140 mL THF at -78°C. The reaction mixture was allowed to warm to room temperature overnight. The black reaction mixture was filtered through Celite, washed with 1 N aq HCl, and dried with $MgSO_4$; the solvent was evaporated at reduced pressure. LC purification (SiO_2, ether/hexanes - 1:1) yielded a mixture of coupled products 4 and 5 (135 mg, 0.305 mmol, 92%). Separation by LC (SiO_2, ether/hexanes - 1:2) gave 4 (103 mg, 0.233 mmol, 70%) as the major and 5 (27 mg, 0.061 mmol, 18.4%) as the minor product (ratio 4/5 = 3.8/1.

4: ^{1}H NMR ($CDCl_3$) δ 0.81 (s, CH_3(18)), 1.04 (s, CH_3(19)), 1.13 (d, J = 7 Hz, CH_3(21)), 1.20 (s, 6), 2.03 (s, CH_3COO), 2.86 (m, H-C(20)), 4.58 (m, H-C(3)), 5.34 (m, H-C(6)), 5.46 (m, H-C(16), H-C(22) and H-C(23)). ^{1}H NMR (C_6D_6) δ 0.87 (s, CH_3(18)), 0.93 (s, CH_3(19)), 1.12 (s, 6), 1.21 (d, J = 7 Hz, CH_3(21)), 1.76 (s, CH_3COO), 2.47 (m, 2 H-C(24)), 2.89 (m, H-C(20)), 4.83 (m, H-C(3)), 5.34 (m, H-C(6)), 5.47 (m, H-C(16)), 5.57 (m, H-C(22) and H-C(23)).

5: ^{1}H NMR ($CDCl_3$) δ 0.93 (s, CH_3(18)), 1.03 (s, CH_3(19)), 1.20 (s, 6), 1.65 (d × d, J = 7.2 Hz, J' = 1.8 Hz, CH_3(21)), 2.03 (s, CH_3COO), 3.09 (m, H-C(16)), 4.59 (m, H-C(3)), 5.08 (d × q, J = 1.8 Hz, J' = 7.2 Hz, H-C(20)), 5.37 (m, 3). ^{1}H NMR (C_6D_6) δ 0.90 (s, CH_3(18)), 0.92 (s, CH_3(19)), 1.16 (s, 6), 1.72 (d × d, J = 2 Hz, J' = 7.2 Hz, CH_3(21)), 1.77 (s, CH_3COO), 3.16 (m, H-C(16)), 4.79 (m, H-C(3)), 5.29 (m, H-C(6) and d × q, J = 2 Hz, J' = 7.2 Hz, H-C(20)), 5.47 (m, 2).

A suspension of 50 mg, 5% Pd/C in 5 mL EtOH was stirred for 1 h under 1 atm of hydrogen. Compound 4 (85 mg, 0.192 mmol) was added, and hydrogenation was continued to an uptake of 8.6 mL (0.384 mmol) hydrogen (16 min). The solution was filtered, the solvent was removed, and the residue was purified by LC (SiO_2, ether/hexanes - 1:1) to yield 6 (83 mg, 0.186 mmol, 97%). Complex 6 was dissolved in 4 mL saturated K_2CO_3/methanol solution; some drops of water were added and the mixture was stirred overnight. Extraction with ether gave 7 after evaporation of the solvent (73 mg, 0.180 mmol, 97%).

6: ^{1}H NMR ($CDCl_3$) δ 0.68 (s, CH_3(18)), 0.93 (d, J = 5.8 Hz, CH_3(21)), 1.02 (s, CH_3(19)), 1.21 (s, 6), 2.03 (s, CH_3COO), 4.57 (m, H-C(3)), 5.37 (m, H-C(6)). ^{1}H NMR (C_6D_6) δ 0.67 (s, CH_3(18)), 0.94 (s, CH_3(19)), 1.03 (d, J = 6 Hz, CH_3(21)), 1.13 (s, 6), 1.77 (s, CH_3COO), 4.81 (m, H-C(3)), 5.35 (m, H-C(6)).

7: ^{1}H NMR ($CDCl_3$) δ 0.67 (s, CH_3(18)), 0.93 (d, J = 5.5 Hz, CH_3(21)), 1.00 (s, CH_3(19)), 1.20 (s, 6), 3.47 (m, H-C(3)), 5.34 (m, H-C(6)).

The coupling reaction between 2 (40 mg, 0.0830 mmol) with 3 (5 mL THF solution, 0.225 mmol) in the presence of maleic anhydride (25 mg, 0.255 mmol) was done in a manner similar to the reaction involving 1 described above; it yielded (after LC separation) (SiO_2, ether/hexanes - 1:2) 8 (30 mg, 0.0679 mmol, 82%) as the major and 9 (4 mg, 0.0091 mmol, 11%) as the minor product (ratio 8/9 = 7.5/1).

8: ^{1}H NMR ($CDCl_3$) δ 0.81 (s, CH_3(18)), 1.04 (s, CH_3(19)), 1.16 (d, J = 7 Hz, CH_3(21)), 1.19 (s, 6), 2.02 (s, CH_3COO), 2.83 (m, H-C(20)), 4.57 (m, H-C(3)), 5.39 (m, H-C(6), H-C(16), H-C(22), and H-C(23)). ^{1}H NMR (C_6D_6) δ 0.82 (s, CH_3(18)), 0.93 (s, CH_3(19)), 1.14 (s, 6), 1.22 (d, J = 7 Hz, CH_3(21)), 1.76 (s, CH_3COO), 2.86 (m, H-C(20)), 4.79 (m, H-C(3)), 5.31 (m, H-C(6)), 5.50 (m, H-C(16), H-C(22), and H-C(23)).

9: ^{1}H NMR ($CDCl_3$) δ 0.79 (s, CH_3(18)), 1.03 (s, CH_3(19)), 1.19 (s, 6), 1.51 (d × d, J = 2 Hz, J' = 7 Hz, CH_3(21)), 2.02 (s, CH_3COO), 3.30 (m, H-C(16)), 4.57 (m, H-C(3)), 5.17 (d × q, J = 2 Hz, J' = 7 Hz, H-C(20)), 5.39 (m, H-C(6), H-C(22), and H-C(23)). ^{1}H NMR (C_6D_6) δ 0.81 (s, CH_3(18)), 0.92 (s, CH_3(19)), 1.14 (s, 6), 1.58 (d × d, J = 2 Hz, J' = 7 Hz, CH_3(21)), 1.77 (s, CH_3COO), 3.29 (m, H-C(16)), 4.79 (m, H-C(3)), 5.31 (m, H-C(6) and d × q, J = 2 Hz, J' = 7 Hz, H-C(20)), 5.47 (m, H-C(22) and H-C(23)).

Hydrogenation and hydrolysis of 8 (30 mg, 0.0679 mmol) as above afforded 10 (28.5 mg, 0.064 mmol, 95%) and 11 (25 mg, 0.0619 mmol, 96%), respectively.

10: ^{1}H NMR ($CDCl_3$) δ 0.67 (s, CH_3(18)), 0.84 (d, J = 6 Hz, CH_3(21)), 1.01 (s, CH_3(19)), 1.22 (s, 6), 2.03 (s, CH_3COO), 4.58 (m, H-C(3)), 5.36 (m, H-C(6)). ^{1}H NMR (C_6D_6) δ 0.67 (s, CH_3(18)), 0.94 (s, CH_3(19) and d, J = 6 Hz, CH_3(21)), 1.14 (s, 6), 1.76 (s, CH_3COO), 4.80 (m, H-C(3)), 5.36 (m, H-C(6)).

11: ^{1}H NMR ($CDCl_3$) δ 0.68 (s, CH_3(18)), 0.84 (d, J = 6 Hz, CH_3(21)), 1.02 (s, CH_3(19)), 1.22 (s, 6), 3.45 (m, H-C(3)), 5.34 (m, H-C(6)).

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REFERENCES AND NOTES

(1) For example, see: Salmond, W. G.; Sobala, M. C. *Tetrahedron Lett.* 1977, 1695, and references therein.

(2) (a) Temple, J. S.; Schwartz, J. *J. Am. Chem. Soc.* 1980, *102*, 7381.
(b) Hayasi, Y.; Riediker, M.; Temple, J. S.; Schwartz, J. *Tetrahedron Lett.* 1981, 2629.
(c) Temple, J. S.; Riediker, M.; Schwartz, J., unpublished results.

(3) Drehfahl, G.; Ponsold, K.; Schick, H. *Chem. Ber.* 1965, *98*, 604. Wittig Olefination affords a *Z*/*E*-mixture ((*Z*)-isomer/(*E*)-isomer = 93:7). For a high-yield synthesis of the (*E*) isomer see: Reich, H.; Sutter, M.; Reichstein, T. *Helv. Chim. Acta* 1940, *23*, 170.

(4) Carr, D. B.; Schwartz, J. *J. Am. Chem. Soc.* 1979, *101*, 3521.

(5) Mondon, A. *Liebigs Ann. Chem.* 1952, *577*, 181.

(6) The influence of maleic anhydride on coupling regioselectivity has been discussed previously (ref 2).

(7) A significant temperature dependence on the coupling regioselectivity was noted, e.g., at room temperature 4/5 = 2:3.

(8) Narwid, T. A.; Cooney, K. E.; Uskokovic, M. R. *Helv. Chim. Acta* 1974, *57*, 771

(9) No temperature dependence on the regioselectivity for coupling was noted.

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