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STEREOSELECTIVE SYNTHESES OF STEROID SIDE CHAINS. EFFICIENT SYNTHESES OF (2RS,3RS)-2-METHYL-3-[(1RS)-1,5-DIMETHYLHEXYL]CYCLOPENTANONE AND (2RS)-2-[(1RS)-3-OXOCYCLOHEXYL]PROPANOIC ACID

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The title compounds, key intermediates in the syntheses of (±)-vitamin D_3 and (±)-erythro-juvabione, have been prepared in short steps using stereoselective cleavage reactions of the cyclopropane derivatives.

The stereoselective syntheses of steroid side chains have attracted much attention, and numerous methodologies have been developed.[1] We previously reported the synthesis of (2RS,3RS)-2-methyl-3-[(1RS)-1,5-dimethylhexyl]cyclopentanone (4),[2] the key intermediate in synthesis of (±)-vitamin D_3 (1),[3] from methyl 6-methyl-2-oxobicyclo[3.1.0]hexane-1-carboxylate (6) in eight steps containing steleoselective homoconjugate addition of homocuprate. In this paper we wish to describe a more direct approach for the synthesis of 4 from the same starting material (6) in only three steps using the following cuprous iodide-mediated homoconjugate addition of the Grignard reagent. In addition, the paper deals with a preparation of (2RS)-2-[(1RS)-3-oxocyclohexyl]propanoic acid (20), the key intermediate in synthesis of the naturally occurring juvenile hormone (±)-erythro-juvabione (17) possessing a steroidal type side chain,[4] by employing the homoconjugate addition of cyanide anion[5] to methyl 7-methyl-2-oxobicyclo[4.1.0]-heptane-1-carboxylate (8).

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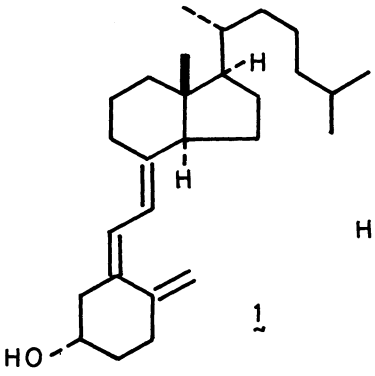

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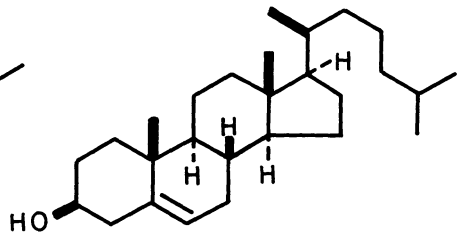

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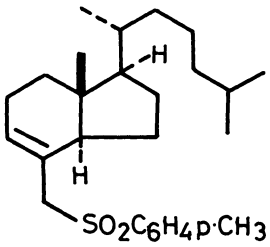

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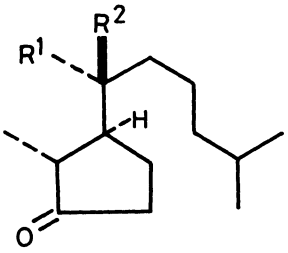
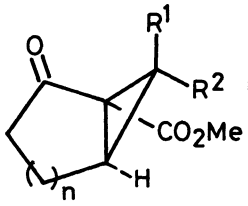


4 R^1 = Me, R^2 = H

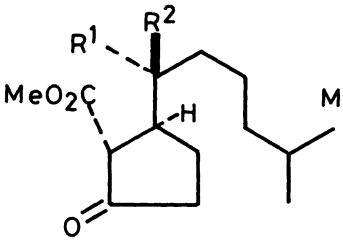
5 R^1 = H, R^2 = Me



6 n = 1, R^1 = H, R^2 = Me

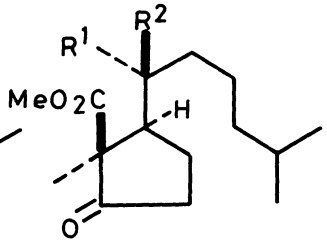
7 n = 1, R^1 = Me, R^2 = H

8 n = 2, R^1 = H, R^2 = Me



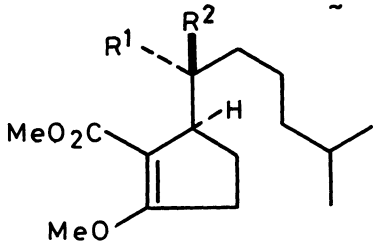
9 R^1 = Me, R^2 = H

10 R^1 = H, R^2 = Me



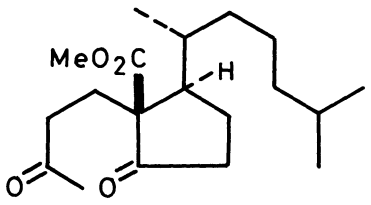
11 R^1 = Me, R^2 = H

12 R^1 = H, R^2 = Me



13 R^1 = Me, R^2 = H

14 R^1 = H, R^2 = Me



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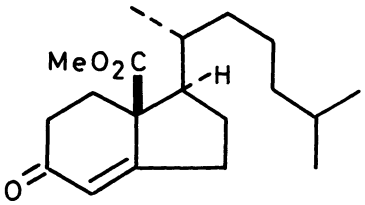

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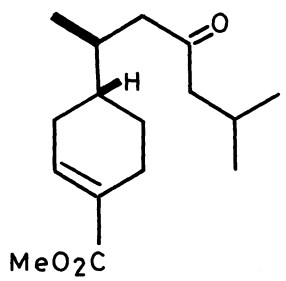

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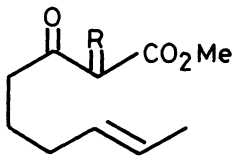
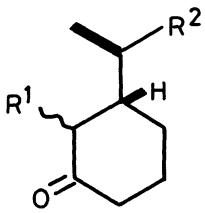


18 R = H_2

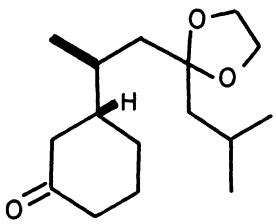
19 R = N_2



20 R^1 = H, R^2 = CO_2H

21 R^1 = CO_2Me, R^2 = CN

22 R^1 = H, R^2 = CN



23

The bicyclo[3.1.0]hexane derivative (6)[6] was treated with 4-methylpentylmagnesium bromide in the presence of catalytic amount of cuprous iodide in tetrahydrofuran at -20 °C for 30 min to produce the keto ester (9) in 43% yield. Methylation of 9 with methyl iodide and potassium carbonate in acetone at reflux for 5 h afforded the C-methylated product (11) and the O-methylated one (13), which were separated easily by silica-gel chromatography, in a ratio ca. 6:1, respectively. By demethoxycarbonylation of 11 with sodium cyanide and hexamethylphosphoric triamide at 75 °C for 3 h, the desired cyclopentanone (4), mp 157 °C (semicarbazone) (lit. 157 °C,[3b] 167 °C[3c]), was obtained in 53% yield. The spectral data of 4[7] were identical with those recorded in the literatures.[2,3] Alternatively, along the same reaction sequence, the C-1' epimer (5),[8] mp 166-167 °C (semicarbazone), was synthesized from the corresponding methyl isomer (7)[5] via 10 and 12 in about the same yield as 4. The conversion of 4 into the C/D ring fragment of vitamin D_3 (3) had been already reported,[3b] and 5 will be a potential synthon for synthesis of (±)-20-isocholesterol (2).[9]

Using the above keto ester (9), we prepared a steroid C/D ring synthon (16) in two steps. Michael reaction of 9 with methyl vinyl ketone in methanol was performed in the presence of catalytic amount of sodium methoxide at 0 °C to room temperature for 3 h, yielding the single diketone (15) in 84% yield. Intramolecular aldol condensation of 15 was carried out with tri-t-butoxyaluminum as base in refluxing benzene for 3 days to produce the cyclohexenone (16)[10] in 50% yield. The resulting enone (16) will be a useful synthon for syntheses of C-18 functionalized steroids.

The bicyclo[4.1.0]heptane derivative (8) was readily prepared from methyl acetoacetate in three steps. Alkylation of the dianion of methyl acetoacetate with 5-bromo-2-pentene[11] gave the unsaturated keto ester (18) in 63% yield. After conversion of 18 into the diazo compound (19) by treatment with p-toluenesulfonyl azide/triethylamine, 19 was refluxed in benzene for 20 h with bis(2,4-pentanedionato)copper to form the bicyclic β-keto ester (8)[12] in 36% yield from 18. The cyclopropane derivative (8) was treated with sodium cyanide in dimethyl sulfoxide (DMSO) at 70 °C for 5 h under nitrogen atmosphere to give the cyano keto ester (21) in 70% yield. Transformation of 21 by heating with sodium chloride in wet DMSO at 165 °C for 2 h afforded the cyano ketone (22) in 83% yield.. The final hydrolysis of 22 in acidic conditions (20% aqueous sulfuric acid/acetic acid

6:1, 100 °C, 40 h) furnished the desired keto acid (20), mp 77-77.5 °C (lit. 76 °C,[4b] 77-78 °C,[4c] 76-77 °C[4d]), in 65% yield. The spectral data of 20[13] were coincident with those reported in the literatures.[4] The compound (20) had been converted to (±)-erythro-juvabione (17) via 23 by an efficient sequence.[4b]

The efficiency of the homoconjugate addition described in this and our previous reports[2,5,6] is appealing, and further synthetic studies of the other natural products applying this method are now in progress.

References

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5) M. Nakayama, S. Ohira, S. Takata, and K. Fukuda, Chem. Lett., 1983, 147.

6) M. Nakayama, S. Tanimori, M. Hashio, and Y. Mitani, Chem. Lett., 1985, 613.

7) 4: MS m/z 210.1986 [Calcd for $C_{14}H_{26}O$: 210.1985(M^+)]; IR($CHCl_3$) 2970, 1735 cm^{-1}; ^{13}C-NMR($CDCl_3$) δ 221.8(s), 50.3(d), 46.9(d), 39.3(t), 37.3(t), 34.7(d), 32.6(t), 28.0(d), 25.3(t), 23.3(t), 22.8(q), 22.5(q), 17.8(q), 14.1(q).

8) 5: MS m/z 210 (M^+); IR(CCl_4) 2950, 1740 cm^{-1}; ^{13}C-NMR($CDCl_3$) δ 221.2(s), 48.9 (d), 47.0(d), 39.1(t), 37.1(t), 35.4(d), 33.1(t), 27.9(d), 25.2(t), 24.2(t), 22.5(q), 21.2(q), 14.0(q), 12.9(q).

9) B. A. Teicher, N. Koizumi, M. Kreeda, and P. Talalay, Eur. J. Biochem., 91, 11 (1978).

10) 16: MS m/z 306 (M^+); IR($CHCl_3$) 2960, 1730, 1670, 1173 cm^{-1}; ^{1}H-NMR(CCl_4) δ 5.59(1H, t, J=2), 3.63(3H, s), 3.29-0.99(17H, m), 0.89(9H, d, J=6).

11) R. M. Coats, P. D. Senter, and W. R. Baker, J. Org. Chem., 47, 3597 (1982).

12) 8: MS m/z 182.0974 [Calcd for $C_{10}H_{14}O_3$; 182.0943(M^+)]; IR($CHCl_3$) 1717, 1680 cm^{-1}; ^{1}H-NMR(CCl_4) δ 3.64(3H, s), 2.47-1.50(8H, m), 1.20(3H, d, J=5), ^{13}C-NMR ($CDCl_3$) δ 202.6(s), 168.6(s), 52.1(q), 42.7(s), 37.6(t), 31.6(t), 25.3(d), 21.2(d), 19.3(t), 13.9(q).

13) 20: Found: C, 63.51; H, 8.29%. Calcd for $C_9H_{14}O_3$: C, 63.40; H, 8.59%; IR ($CHCl_3$) 3200, 2940, 1710 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 11.38(1H, brs), 3.10-1.35(10H, m), 1.17(3H, d, J=7); ^{13}C-NMR($CDCl_3$) δ 211.2(s), 180.7(s), 44.2(2d), 40.9(2t), 28.9(t), 24.7(t), 13.9(q).

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