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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 (\pm) -vitamin D₃ and (\pm) -<u>erythro</u>-juvabione, have been prepared in short steps using stereoselective cleavage reactions of the cyclo-propane 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 (\pm) -vitamin D₃ (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 (\pm)-erythro-juvabione (17) possessing a steroidal type side chain,⁴⁾ by employing the homoconjugate addition of cyanide anion⁵⁾ to methyl 7-methyl-2-oxobicyclo[4.1.0]-heptane-l-carboxylate (8).

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11 R¹=Me, R²=H

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 $4 R^1 = Me, R^2 = H$ 5 R¹ = H, R²=Me

6 n=1, R¹=H, R²=Me 7 n=1, R¹=Me, R²=H 10 R¹=H, R²=Me

8 n=2, R¹ = H, R²=Me

MeO₂C

9 R¹ =Me, R²=H

/H



R¹ ∕Н MeO₂C-MeO

13 R¹=Me, R²=H $14 R^{1} = H, R^{2} = Me$





15

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Me02C

16

20 $R^1 = H$, $R^2 = CO_2 H$ $21 R^1 = CO_2 Me$, $R^2 = CN$ 22 $R^1 = H$, $R^2 = CN$

R²



23



19 $R = N_2$

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, $^{
m 3b)}$ 167 °C $^{
m 3c)}$), 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 $(\pm)-20$ -isocholesterol (2).⁹⁾

Using the above keto ester $(\underline{9})$, we prepared a steroid C/D ring synthon $(\underline{16})$ in two steps. Michael reaction of $\underline{9}$ 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 $(\underline{15})$ in 84% yield. Intramolecular aldol condensation of $\underline{15}$ was carried out with tri-<u>t</u>-butoxyaluminum as base in refluxing benzene for 3 days to produce the cyclohexenone $(\underline{16})^{10}$ in 50% yield. The resulting enone $(\underline{16})$ will be a useful synthon for syntheses of C-18 functionalized steroids.

The bicyclo[4.1.0]heptane derivative (§) was readily prepared from methyl acetoacetate in three steps. Alkylation of the dianion of methyl acetoacetate with 5-bromo-2-pentene¹¹⁾ gave the unsaturated keto ester (18) in 63% yield. After conversion of 18 into the diazo compound (19) by treatment with p-toluene-sulfonyl 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 (±)-<u>erythro</u>-juvabione (17) <u>via</u> 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

- For reviews: D. M. Piatak and J. Wicha, Chem. Rev., <u>78</u>, 199 (1978); J. Redpath and F. J. Zeelen, Chem. Soc. Rev., <u>12</u>, 75 (1983); and for more recent reports: K. Mikami, K. Kawamoto, and T. Nakai, Chem. Lett., <u>1985</u>, 115; idem., Tetrahedron Lett., <u>26</u>, 5799 (1985).
- 2) M. Nakayama, S. Tanimori, and S. Ohira, Synth. Commun., 15, 507 (1985).
- 3) a) B. M. Trost, D. F. Taber, and L. B. Alper, Tetrahedron Lett., <u>1976</u>, 3857;
 b) D. Desmaele, J. Ficini, A. Guingant, and Ph. Kahn, ibid., <u>24</u>, 3079, 3083 (1983); D. Desmaele and S. Tanier, ibid., <u>26</u>, 4941 (1985); c) S. Hatakeyama, H. Numata, and S. Takano, ibid., <u>25</u>, 3717 (1984).
- 4) a) J. Ficini and A. M. Touzin, Tetrahedron Lett., <u>1972</u>, 2093, 2097; b) J. Ficini, J. d'Angelo, and J. Noiré, J. Am. Chem. Soc., <u>96</u>, 1213 (1974); c) D. A. Evans and J. V. Nelson, ibid., <u>102</u>, 774 (1980); d) D. J. Morgans, Jr. and G. B. Feingelson, ibid., 105, 5477 (1983).
- 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(CHCl₃) 2970, 1735 cm⁻¹; ¹³C-NMR(CDCl₃) 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(CCl₄) 2950, 1740 cm⁻¹; 13 C-NMR(CDCl₃) 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., <u>91</u>, 11 (1978).
- 10) 16: MS m/z 306 (M⁺); IR(CHCl₃) 2960, 1730, 1670, 1173 cm⁻¹; ¹H-NMR(CCl₄) 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., <u>47</u>, 3597 (1982).
- 12) 8: MS m/z 182.0974 [Calcd for $C_{10}H_{14}O_3$; 182.0943(M⁺)]; IR(CHCl₃) 1717, 1680 cm⁻¹; ¹H-NMR(CCl₄) & 3.64(3H, s), 2.47-1.50(8H, m), 1.20(3H, d, J=5), ¹³C-NMR (CDCl₃) & 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 (CHCl₃) 3200, 2940, 1710 cm⁻¹; ¹H-NMR(CDCl₃) δ 11.38(1H, brs), 3.10-1.35(10H, m), 1.17(3H, d, J=7); ¹³C-NMR(CDCl₃) δ 211.2(s), 180.7(s), 44.2(2d), 40.9(2t), 28.9(t), 24.7(t), 13.9(q). (Received February 22, 1986)