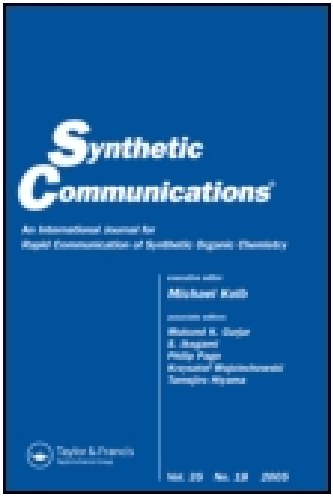

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MONTMORILLONITE CLAY CATALYSIS. PART 15[1] BACKBONE REARRANGEMENT OF 4,4-DIALKYLCHOLEST-5-ENES CATALYZED BY MONTMORILLONITE K-10

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Abstract: In the presence of montmorillonite K-10 4,4-dialkylcholest-5-enes undergo backbone rearrangement to give (20R)- and (20S)-4,4-dialkyl-5β,14β-dimethyl-18,19-dinor-8α,9β,10α-cholest-13(17)-enes in high yields.

Under acidic conditions, cholest-5-ene undergoes a backbone rearrangement leading to 5β,14β-dimethyl-18,19-dinor-8α,9β,10α-cholest-13(17)-enes.[2-4] $\Delta^{13(17)}$–Rearranged sterenes have also been discovered in immature sediments where they are presumably formed by rearrangement of cholestenes catalysed by clay minerals.[2-5] Furthermore, laboratory experiments have shown that montmorillonite clays are the most efficient catalysts for converting cholestenes into backbone rearranged products.[6-8] Recently, we have demonstrated that steric hindranced, 4,4-dimethylcholest-5-ene can also give the corresponding rearranged products in excellent yield catalyzed by montmorillonite K-10.[9] To clarify the

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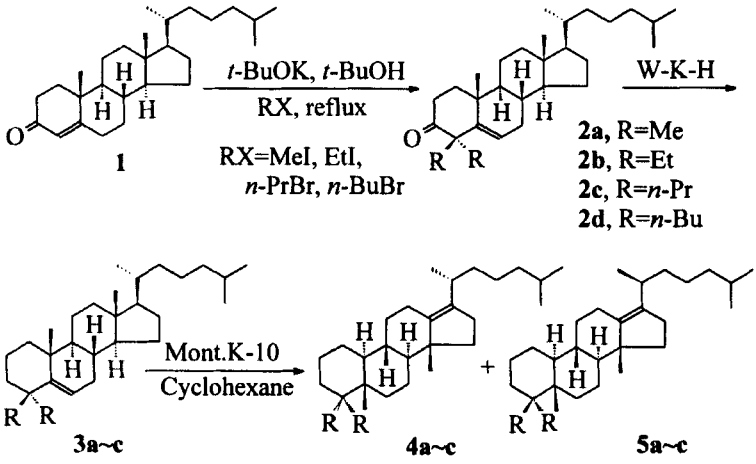

Scheme 1

effect of 4,4-dialkyl groups in the backbone rearrangement of cholest-5-enes, we report herein the backbone rearrangement of 4,4-dialkylcholest-5-enes (**3a~c**) catalyzed by montmorillonite K-10.

As shown in **Scheme 1**, the 4,4-dialkylation of cholest-4-en-3-one (**1**) was achieved by excess alkyl halides in *t*-BuOH in the presence of *t*-BuOK.[10] In this series of reactions, though the substituting groups were much larger successively, the reaction time and the yield did not change obviously (**2a**, 86 %; **2b**, 85 %; **2c**, 89 %; **2d**, 86 %). Reduction of 4,4-dimethylcholest-5-en-3-one (**2a**) by Huang Minlon's method[11] afforded 4,4-dimethylcholest-5-ene (**3a**) in 88 % yield. However, ketones (**2b~d**) were very difficult to be reduced because of the steric hindrance of the 4,4-dialkyl groups. The yield of **3b** and **3c** was less than 45 % (conversion *ca* 80 %) and **2d** could not be reduced by Huang Minlon's method even under much longer time. Other reductive methods were also tried to obtain **3d** from **2d**. There is nearly no anticipated product by Clemenson reduction of

Table 1 Backbone rearrangement of **3a~c** catalyzed by montmorillonite K-10.

R	Temp. (°C)	Time	**4** (20R) Yield(%)	**5** (20S) Yield(%)
*H	20	60 min	47	46
Me	rt.	40 min	53	45
Et	81	1.5 h	50	47
n-Pr	81	4 h	43	38

*Literature[6] result.

2d.[12] By employing $LiAlH_4$-$AlCl_3$[13] or $NaBH_4$-$AlCl_3$[14] as reductant, a pair of epimeric 4,4-dibutylcholesterols were afforded. Thus the backbone rearrangement were carried out by using compounds **3a~c** as substrates.

As shown in **Table 1**, In the presence of montmorillonite K-10, by employing cyclohexane as solvent, the rearrangement of **3a~c** gave corresponding (20R)- and (20S)-4,4-dialkyl-5β,14β-dimethyl-18,19-dinor-8α,9β,10α-cholest-13(17)-enes (**4a~c** and **5a~c**). 4,4-Dimethylcholest-5-ene (**2a**) underwent this rearrangement reaction to provide the two products (**4a** and **5a**) in excellent yield (combined 98 %) at room temperature in only 0.7 h. When the substituting groups at C-4 were two ethyls, higher temperature (refluxing temperature of cyclohexane) and longer reaction time (1.5 h) were needed for completion of the reaction. The combined yield decreased to 93 %. More steric hindranced 4,4-dipropylcholest-5-ene was employed as the substrate, much longer reaction time (4 h) was needed and the combined yield decreased to 81%. It was worth noting that the amounts of the two epimers were not equal. Although the ratio of (20R)-epimer (**4**) and (20S)-epimer (**5**) was approximately 1:1, the yield of **4** was a little more than that of **5**. The R_f value of **5a~c** were longer than those of **4a~c** on 10 % $AgNO_3$-silica TLC. The mixture (**4** and **5**) could be separated successfully on a 10 % $AgNO_3$-silica gel column chromatography with petroleum ether-toluene (20:1, v/v) as eluant.

The structures of the new compounds (**2c~d**, **3b~c**, **4b~c**, **5b~c**) were established by ^{1}H and ^{13}C–DEPT NMR and mass spectra. The NMR assignments for the new compounds were compared with those of the analogues compounds.[9] The chemical shift of 21-Me in **4a~c** appeared at 0.942~0.947 ppm, whereas that of **5a~c** at 0.898~0.902 ppm. The mass spectra of the backbone rearranged cholestenes (**4a~c** and **5a~c**) all shown [M^{+}-113] as base peak, these are agreed well with their reported analogues.[5, 9]

In conclusion, we have shown that montmorillonite K-10 worked very well for the backbone rearrangement of 4,4-dialkylcholest-5-enes. Steric hindranced substrates, even for 4,4-dipropylcholest-5-ene, also gave the corresponding rearranged products in high yield (81 %). Although the larger substituting groups are, the longer reaction time and higher temperature are needed and the lower yield.

EXPERIMENTAL

Melting points were uncorrected. IR spectra were recorded on a PE-983G spectrometer as liquid films. ^{1}H and ^{13}C-DEPT NMR spectra were measured on Varian-INOVA-500, Bruker AM-400, or Bruker AC-80 spectrometers by using $CDCl_3$ as solvent and TMS as internal standard. Mass spectra were determined on a VG-7070E spectrometer (EI, 70 eV). Montmorillonite K-10 was purchased from Aldrich.

Cholest-4-en-3-one (**1**) was obtain from the oxidation of cholesterol by Oppenauer's method[15] in 85 % yield, mp 81.5~82.5 °C.

4,4-Dialkylcholest-5-en-3-one (2a~d)

A typical procedure. **4,4-Dibutylcholest-5-en-3-one (2d)**: Potassium (0.79 g, 20 mmol) was dissolved in warm anhydrous *t*-butanol (20 ml). A solution of

cholest-4-en-3-one (1.01 g, 2.63 mmol) in anhydrous *t*-butanol (20 ml) was added and the mixture was refluxed for 1 h. Then a solution of *n*-BuBr (1.7 ml, 2.1 g, 15 mmol) in anhydrous *t*-butanol (20 ml) was added dropwise (20 min). The mixture was refluxed for 1.5 h. After cooling, the mixture was neutralised with 2 N hydrochloric acid and extracted with diethyl ether (3 x 30 ml). The extracts were washed with brine and dried over $MgSO_4$ and the solvent was evaporated. The residue was chromatographied on a silica gel column to afford the product **2d** (1.12 g, 86 %) as white solid (mp: 66~67 °C). IR ν_{max}: 3030(6-H), 1704(C=O) cm^{-1}; ^1H NMR (80 MHz) δ: 0.70(3H, s, 18-Me), 0.83(3H, s, 19-Me), 0.87(6H, d, J = 5.6 Hz, 26,27-diMe), 0.90(3H, d, J = 6.0 Hz, 21-Me), 5.40(1H, m, 6-H) ppm; MS m/z (%): 496(M^+, 6), 442(100), 312(9), 159(13), 116(13), 92(22), 72(33).

4,4-Dimethylcholest-5-en-3-one (2a):

Cholest-4-en-3-one (1.00 g, 2.60 mmol) provided **2a** (0.92 g, 86 %), mp 177.5~180 °C, lit.[10] 176~177 °C.

4,4-Diethylcholest-5-en-3-one (2b):

Cholest-4-en-3-one (1.02 g, 2.66 mmol) provided **2b** (0.99 g, 85 %), mp 94~96 °C, Lit.[16] 94.5~95.0 °C; IR ν_{max}: 3030(6-H), 1709(C=O) cm^{-1}; ^1H NMR (80 MHz) δ: 0.69(3H, s, 18-Me), 0.83(3H, s, 19-Me), 0.86(6H, d, J = 5.4 Hz, 26,27-diMe), 0.91(3H, d, J = 7.0 Hz, 21-Me), 5.39(1H, m, 6-H) ppm; MS m/z (%): 440(M^+, 70), 425(10).

4,4-Dipropylcholest-5-en-3-one (2c):

Cholest-4-en-3-one (0.94 g, 2.45 mmol) provided **2c** (1.02 g, 89 %), mp 91~93 °C; IR ν_{max}: 3035(6-H), 1705(C=O) cm^{-1}; ^1H NMR (80 MHz) δ: 0.69(3H, s, 18-Me), 0.82(3H, s, 19-Me), 0.86(6H, d, J = 6.0 Hz, 26,27-diMe), 0.91(3H, d, J = 6.6 Hz, 21-Me), 5.40(1H, m, 6-H) ppm; MS m/z (%): 468(M^+, 10), 426(100), 180(16).

4,4-Dialkylcholest-5-ene (3a~c)

A typical procedure.[11] **4,4-Dimethylcholest-5-ene (3a)**: A mixture of **2a** (1.50 g, 3.64 mmol), hydrazine hydrate (50 %, 30 ml), *n*- butanol (60 ml), ethyleneglycol (100 ml) and potassium hydroxide (3.86 g) was heated at refluxing temperature for 1.5 h. The condenser was then removed and water, *n*-butanol and excess hydrazine was distilled until the temperature reached 230 °C. Then the mixture was heated at refluxing temperature for another 1.25 h. After cooling, the mixture was diluted with water (150 ml) and neutralised with 2 N hydrochloric acid, and extracted with diethyl ether (4 x 90 ml). The extracts was washed with saturated aqueous Na_2CO_3 (300 ml) and water (300 ml) and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographied on a 10 % $AgNO_3$-silica gel column eluted with petroleum ether-toluene (20:1, v/v) to give **3a** (1.27 g, 88 %) as a crystalline solid, mp 72~73 °C.

4,4-Diethylcholest-5-ene (3b):

4,4-Diethylcholest-5-en-3-one (0.60 g, 1.36 mmol) provided **3b** (0.150 g, 32 % net yield based on 80 % conversion of **2b**) as colourless oil. ^{1}H NMR (80 MHz) δ: 0.67(3H, s, 18-Me), 0.86(6H, d, J =6.1 Hz, 26,27-diMe), 0.90(3H, d, J = 6.4 Hz, 21-Me), 1.01(3H, s, 19-Me), 5.20(1H, m, 6-H) ppm; MS m/z (%): 426(M^+, 3), 397(100), 315(5), 189(8), 149(15), 95(35).

4,4-Dipropylcholest-5-ene (3c):

4,4-Dipropylylcholest-5-en-3-one (100 mg, 0.214 mmol) provided **3c**(36 mg, 42 % net yield based on 88 % conversion of **2c**) as colourless oil. ^{1}H NMR (500 MHz) δ: 0.662(3H, s, 18-Me), 0.860, 0.867(6H, 2d, J = 6.5 Hz, 26,27-diMe), 0.912(3H, d, J = 6.5 Hz, 21-Me), 1.008(3H, s, 19-Me), 5.209(1H, dd, J = 4.5, 3.5 Hz, 6-H) ppm; MS m/z (%): 454(M^+, 4), 425(6), 411(100), 369(4), 147(15), 57(35).

The backbone rearrangement of 4,4-dialkylcholest-5-enes

A typical procedure.[8] Rearrangement of 4,4-dimethylcholest-5-ene (**3a**): A mixture of **3a** (1.27 g, 3.19 mmol), montmorillonite K-10 (1.20 g) and cyclohexane (20 ml) was stirred at room temperature for 0.7 h. The clay was removed by filtration and the solvent was evaporated under reduced pressure to give an colourless oil. This was chromatographied on a 10 % $AgNO_3$-silica gel column, eluted with petroleum ether-toluene (20:1, v/v), to give **5a** (0.57 g, 45 %) as colourless oil and **4a** (0.67 g, 53 %) as a colourless crystal, mp 62~63.5 °C (petroleum ether) successively. The ^{1}H NMR data agreed well with that reported.[9]

4,4-Diethylcholest-5-ene (**3b**) (0.105 g, 0.246 mmol) provided **4b** (53 mg, 50 %) and **5b** (45 mg, 43 %) both as colourless oil. **4b**, ^{1}H NMR (400 MHz) δ: 0.804(3H, t, J = 7.5 Hz, 4-Et-CH_3), 0.829, 0.834(6H, 2d, J = 6.4 Hz, 26, 27-di-Me), 0.842(3H, t, J = 7.2 Hz, 4-Et-CH_3), 0.870(3H, s, 5β-Me), 0.902(3H, s, 14β-Me), 0.944(3H, d, J = 7.0 Hz, 21-Me) ppm; ^{13}C NMR (100 MHz) δ: 9.46 (4α–Et-CH_3), 10.71(4β-Et-CH_3), 15.74(5β-Me), 18.11(14β-Me), 20.27(21), 22.02(7), 22.44(4α-Et-CH_2), 22.48(2), 22.58(26), 22.70(27), 23.15(12), 24.70(1), 25.43(23), 27.64(4β-Et-CH_2), 27.76(16), 27.98(25), 29.58(6), 31.40(20), 32.09 (11), 32.77(3), 35.78 (22), 37.19(9), 37.91(15), 39.01(24), 40.30(4), 40.95 (5), 44.93(10), 54.81(8), 56.16(14), 133.68 (17), 141.38(13) ppm; MS m/z (%): 426(M^+, 15), 410(25), 396(5), 313(100), 285(5), 147(10), 95(15), 55(25). **5b**, ^{1}H NMR (400 MHz) δ: 0.809(3H, t, J = 7.5 Hz, 4-Et-CH_3), 0.842(3H, t, J =7.2 Hz, 4-Et-CH_3), 0.858, 0.864(6H, 2d, J = 6.4 Hz, 26, 27-Me), 0.866(3H, s, 5β-Me), 0.898(3H, d, J = 7.0 Hz, 21-Me), 0.901(3H, s, 14β-Me) ppm; ^{13}C NMR (100 MHz) δ: 9.46 (4α–Et-CH_3), 10.73(4β-Et-CH_3), 15.75(5β-Me), 17.99(14β-Me), 19.73(21), 22.04(7), 22.45(4α-Et-CH_2), 22.49(2), 22.66(26), 22.77(27), 23.00(12), 24.72(1), 25.59(23), 27.67(4β-Et-CH_2), 27.91(25), 28.00(16), 29.58(6), 31.62(20),

32.12(11), 32.77(3), 35.60(22), 37.20(9), 37.94(15), 39.09(24), 40.30(4), 40.97(5), 44.96(10), 56.17(14), 55.17(8), 133.73(17), 141.20(13) ppm. MS m/z (%): 426(M^+, 15), 411(30), 397(5), 313(100), 285(5), 147(10), 95(15), 55(25).

4,4-Dipropylcholest-5-ene (**3c**) (23 mg, 0.051 mmol) provided **4c** (10 mg, 43 %) and **5c** (8.7 mg, 38 %) both as colourless oil. **4c**, ^{1}H NMR (400 MHz) δ: 0.828, 0.834(6H, 2d, J = 6.5 Hz, 26, 27-di-Me), 0.831(3H, t, J = 6.6 Hz, 4-*n*-Pr-CH_3), 0.870(3H, s, 5β-Me), 0.877(3H, t, J = 6.4 Hz, 4-*n*-Pr-CH_3), 0.888 (3H, s, 14β-Me), 0.942 (3H, d, J = 6.8 Hz, 21-Me) ppm; MS m/z (%): 454(M^+, 10), 439(30), 411(5), 341(100), 147(10), 121(10), 95(15), 55(17). **5c**, oil, ^{1}H NMR (400 MHz) δ: 0.833(3H, t, J = 6.8 Hz, 4-*n*-Pr-CH_3), 0.860, 0.867(6H, 2d, J = 6.6 Hz, 26, 27-di-Me), 0.868 (3H, s, 5β-Me), 0.889(3H, t, J = 6.8 Hz, 4-*n*-Pr-CH_3), 0.890(3H, s, 14β-Me), 0.899(3H, d, J = 7.2 Hz, 21-Me) ppm; MS m/z (%): 454(M^+, 10), 439(30), 411(20), 341(100), 147(12), 121(20), 95(18), 55(20).

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