THE RETRO-MICHAEL REACTION OF 1,5-DICARBONYL COMPOUNDS: SCOPE AND LIMITATION

Jian-Xin WANG and Tong-Shuang LI[1,*]

Department of Chemistry, Hebei University, Baoding 071002, Hebei Province, China; e-mail: [1] orgsyn@mail.hbu.edu.cn

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Under catalysis of NaOH or KOH adsorbed on glass wool and by using steam distillation, (20*R*,*S*)-4,4,5,14-tetramethyl-18,19-dinor-13,17-seco-5β,8α,9β,10α,14β-cholestane-13,17-dione (**1**) and 3,14-dioxo-14,15-seco-5α-cholestan-15-al (**4**) gave good yield (>59%) of the corresponding tricyclic compounds (**8a**, **8b** and **10a**) *via* a retro-Michael reaction at 250 °C. While 5-oxo-4-nor-3,5-secocholestan-3-oic acid (**6**) and ethyl 5-oxo-4-nor-3,5-secocholestan-3-oate (**7**) afforded low yield (<15%) of the retro-Michael cleavage products (**12a**, **12b**) at the same conditions. Thus, the retro-Michael reaction worked well for 1,5-diketones and 1,5-keto aldehydes but gave poor yield for 1,5-keto esters and 1,5-keto acids.

Key words: Retro-Michael reaction; Tricyclic compounds; Dicarbonyl compounds; Steroids; Terpenoids.

Methylated tricyclic terpanes are important novel biomarkers recently discovered from a boghead sample in Shuicheng, western Guizhou of China[1]. In connection with our synthesis of this series of methylated tricyclic terpanes, the retro-Michael reaction of 1,5-dicarbonyl compounds derived from cholestane or dammarane is projected to be employed as a key step. Literature search shows that this reaction works well for aromatic 1,5-diketones in the inlet of mass spectrometer[2]. For alicyclic ketones, however, drastic conditions are needed and lead to poor or moderate yields[3–5]. Recently, Albrecht *et al.* developed an improved approach by using steam distillation of 1,5-diketones with sodium hydroxide adsorbed on glass wool as a catalyst and obtained high yields of the products[6]. Up to the present time, the utilization of this degradative manner in synthesis has been only limited to 1,5-diketone compounds[7]. We report herein the investigation of the scope and limitation of retro-Michael reaction of 1,5-dicarbonyl compounds.

EXPERIMENTAL

Melting points were measured on an XT4 Kofler hot stage and were uncorrected. IR spectra were recorded on a PE-983G spectrometer as liquid films by using $CDCl_3$ as solvent; wavenumbers in cm^{-1}. ^1H and ^{13}C NMR spectra were measured on Bruker AM-400 or AC-80 spectrometers by using TMS as internal standard and $CDCl_3$ as solvent unless otherwise stated. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. Mass spectra were determined on a VG-7070E spectrometer (EI, 70 eV). Thin-layer chromatography (TLC) was performed on silica gel-60H (Merck). (20*R*,*S*)-4,4,5,14-Tetramethyl-18,19-dinor-13,17-seco-5β,8α,9β,10α,14β-cholestane-13,17-dione (**1**) was prepared from cholesterol (**2**) according to literature[8] in an overall yield of 31%. 14,15-Dioxo-14,15-seco-5α-cholestan-3β-yl acetate (**3**) and 3,14-dioxo-14,15-seco-5α-cholestan-15-al (**4**) were synthesized from cholesterol (**2**) in five and seven steps in overall yields of 20 and 16%, respectively, as described by Li *et al.*[9]. Ozonization of cholest-4-en-3-one (**5**) according to literature[10] provided 5-oxo-4-nor-3,5-secocholestan-3-oic acid (**6**).

Ethyl 5-Oxo-4-nor-3,5-secocholestan-3-oate[11] (**7**)

To a solution of **6** (0.45 g, 1.1 mmol) in DMSO (15 ml) was added potassium hydroxide (0.25 g, 4.5 mmol) and then followed by ethyl iodide (0.19 ml, 0.36 g, 2.3 mmol). The solution was stirred at 60 °C for 2 h and after cooling, the mixture was poured into water (70 ml). The solution was extracted with ether (2 × 40 ml) and CH_2Cl_2 (3 × 30 ml). The combined organic phase was dried ($MgSO_4$) and evaporated to dryness. The residue was chromatographied on silica gel with light petroleum–ether (8 : 1) as eluent to afford the title compound **7** (0.36 g, 75%) as a colourless oil. IR: 2 950, 2 835, 1 735, 1 700, 1 460, 1 420, 1 375, 1 295, 1 195, 930. ^1H NMR (80 MHz): 0.72 s, 3 H (3 × H-18); 0.85 d, 6 H, *J* = 6.6 (3 × H-26 and 3 × H-27); 0.90 d, 3 H, *J* = 5.4 (3 × H-21); 1.10 s, 3 H (3 × H-19); 1.24 t, 3 H, *J* = 7.1 ($OCH_2C\mathbf{H}_3$); 4.11 q, 3 H, *J* = 7.1 ($OC\mathbf{H}_2CH_3$). For $C_{28}H_{48}O_3$ (432.7) calculated: 77.7% C, 11.2% H; found: 77.5% C, 11.5% H.

General Procedure for the Retro-Michael Reaction

The catalyst was prepared by passing a solution of 30% sodium (compounds **1**, **3** and **4**) or potassium (compounds **6** and **7**) hydroxide through a column (20 × 2 cm) loosely packed with glass wool and then the column was heated by a tubular oven at 210 °C for 3 h. Steam was successively introduced to the preheating tube (210 °C), the inlet and the catalysis tube. After stabilization of the catalysis tube temperature at 250 °C and reaching the rate of condensation of water to 5 ml/min, the starting material dissolved in small quantity of ether was injected into the inlet. The rate and the temperature of the catalysis tube (250–260 °C) was kept until no oil was appeared in the condenser. The obtained water solution was extracted with ether (4 times) and the combined extracts were dried ($MgSO_4$) and concentrated to give the crude product. This was further separated by silica gel column chromatography.

Compound **1** (98.5 mg, 0.229 mmol) afforded *4,4,5,14-trimethyl-des-D-5*β*,8*α*,9*β*,10*α*,14*α*-androstan-13-one* (**8a**; 37.2 mg, 57%) and *4,4,5,14-trimethyl-des-D-5*β*,8*α*,9*β*,10*α*,14*β*-androstan-13-one* (**8b**; 9.6 mg, 16%). Compound **8a**, m.p. 91–93 °C (colourless needles from ethanol). TLC: R_F 0.33 (light petroleum–ether, 5 : 1), silica gel-60H. IR: 2 986, 2 957, 2 880, 1 708, 1 448, 1 378, 1 195, 1 175, 1 130, 965, 938. ^1H NMR (80 MHz): 0.81 s, 3 H (Me-5β); 0.93 s, 6 H (Me-4α and Me-4β); 0.98 d, 3 H, *J*(Me,14) = 6.5 (Me-14α). ^1H NMR (400 MHz, C_6D_6):

0.773 s, 3 H (Me-4α); 0.794 s, 3 H (Me-4β); 0.874 s, 3 H (Me-5β); 1.058 d, 3 H, *J*(Me,14) = 6.5 (Me-14α). ^{13}C NMR (100 MHz, C_6D_6): 11.56 (q), 14.90 (q), 22.53 (q), 22.65 (t), 25.03 (t), 25.57 (q), 26.83 (t), 31.44 (t), 32.63 (t), 36.28 (s), 37.27 (t), 38.52 (s), 41.21 (d), 41.27 (t), 43.68 (d), 49.50 (d), 50.30 (d), 210.22 (s). MS, *m/z* (%): 262 (M^+, 94), 247 (6), 205 (9), 190 (6), 177 (100), 149 (26), 135 (15), 121 (19), 107 (17), 95 (21), 81 (23). For $C_{18}H_{30}O$ (262.4) calculated: 82.4% C, 11.5% H; found: 82.1% C, 11.8% H. Compound **8b**, m.p. 177–180 °C (colourless plates from ethanol). TLC: R_F 0.26 (light petroleum–ether, 5 : 1). IR: 2 928, 2 860, 1 710, 1 460, 1 430, 1 375, 1 010, 760, 730. ^{1}H NMR (80 MHz, CD_3COCD_3): 0.82 s, 3 H (Me-5β); 0.96 s, 6 H (Me-4α and Me-4β); 1.10 d, 3 H, *J*(Me,14) = 7.3 (Me-14β). ^{1}H NMR (80 MHz, C_6D_6): 0.75 s, 3 H (Me-4α); 0.77 s, 3 H (Me-4β); 0.81 d, 3 H, *J*(Me,14) = 7.3 (Me-14β); 0.88 s, 3 H (Me-5β). MS, *m/z* (%): 262 (M^+, 89), 247 (5), 205 (9), 190 (9), 177 (100), 149 (45), 135 (15), 121 (18), 107 (16), 95 (21), 81 (24). For $C_{18}H_{30}O$ (262.4) calculated: 82.4% C, 11.5% H; found: 82.6% C, 11.7% H.

Compound **3** (122.4 mg, 0.266 mmol) afforded *14-oxo-des-D-13α-androstan-3β-yl acetate* (**9a**; 14.9 mg, 19%), *14-oxo-des-D-androstan-3β-yl acetate* (**9b**; 5.5 mg, 7%), *3β-hydroxy-des-D-13α-androstan-14-one* (**9c**; 14.9 mg, 22%) and an unseparated mixture (11.1 mg, 18%). Compound **9a**, m.p. 136–138 °C (colourless needles from light petroleum). TLC: R_F 0.49 (light petroleum–ether, 3 : 1). IR: 2 940, 2 868, 1 730, 1 700, 1 450, 1 365, 1 230, 1 130, 1 028, 885. ^{1}H NMR (80 MHz): 0.89 s, 3 H (Me-10β); 1.00 d, 3 H, *J*(Me,13) = 6.2 (Me-13α); 2.02 s, 3 H (CH_3CO_2); 4.68 m, 1 H (H-3α). ^{13}C NMR (100 MHz): 11.72 (q), 14.47 (q), 21.39 (q), 24.95 (t), 25.62 (t), 27.25 (t), 27.39 (t), 33.72 (t), 35.36 (t), 36.32 (s), 36.70 (t), 43.53 (d), 44.96 (d), 49.46 (d), 55.35 (d), 73.25 (d), 170.59 (s), 214.29 (s). MS, *m/z* (%): 292 (M^+, 12), 232 (100), 217 (15), 199 (11), 178 (78), 134 (63), 108 (61), 93 (50), 81 (44), 67 (41). For $C_{18}H_{28}O_3$ (292.4) calculated: 73.9% C, 9.65% H; found: 73.7% C, 9.8% H. Compound **9b** (colourless oil). TLC: R_F 0.39 (light petroleum–ether, 3 : 1). IR: 2 940, 2 868, 1 730, 1 700, 1 445, 1 360, 1 250, 1 125, 1 038, 895. ^{1}H NMR (80 MHz): 0.90 s, 3 H (Me-10β); 1.17 d, 3 H, *J*(Me,13) = 7.3 (Me-13β); 2.02 s, 3 H (CH_3CO_2); 4.67 m, 1 H (H-3α). MS, *m/z* (%): 292 (M^+, 9), 232 (100), 217 (15), 199 (15), 178 (96), 134 (74), 108 (72), 93 (72), 79 (61), 67 (41). For $C_{18}H_{28}O_3$ (292.4) calculated: 73.4% C, 9.65% H; found: 74.1% C, 9.9% H. Compound **9c**, m.p. 116–117 °C (colourless needles from ethanol). TLC: R_F 0.10 (light petroleum–ether, 5 : 1). IR: 3 430, 2 940, 2 860, 1 700, 1 435, 1 370, 1 245, 1 130, 1 070, 1 045. ^{1}H NMR (80 MHz): 0.88 s, 3 H (Me-10β); 0.99 d, 3 H, *J*(Me,13) = 6.2 (Me-13α); 3.60 m, 1 H (H-3α). ^{13}C NMR (100 MHz): 11.93 (q), 14.49 (q), 25.02 (t), 25.70 (t), 27.37 (t), 31.35 (t), 35.46 (t), 36.35 (s), 36.96 (t), 37.68 (t), 43.71 (d), 44.99 (d), 49.56 (d), 55.55 (d), 70.96 (d), 214.52 (s). MS, *m/z* (%): 250 (M^+, 89), 232 (55), 217 (13), 199 (12), 189 (11), 178 (38), 159 (15), 147 (23), 134 (23), 125 (36), 120 (47), 108 (100), 93 (57), 81 (51), 69 (49), 55 (62). For $C_{16}H_{26}O_2$ (250.4) calculated: 76.7% C, 10.5% H; found: 76.5% C, 10.3% H.

Compound **4** (203.6 mg, 0.489 mmol) afforded *des-D-5α,13α-cholestane-3,14-dione* (**10a**; 71.9 mg, 59%) and *(2E,4R)-4,8-dimethylnon-2-en-1-al* (**11**; 30.5 mg, 55%). Compound **10a** (colourless oil). TLC: R_F 0.37 (light petroleum–ether, 4 : 1). IR: 2 928, 2 864, 1 706, 1 442, 1 364, 1 220, 1 160, 1 122. ^{1}H NMR (80 MHz): 1.01 d, 3 H, *J*(Me,13) = 6.2 (Me-13α); 1.08 s, 3 H (Me-10β). MS, *m/z* (%): 248 (100), 230 (13), 215 (13), 190 (26), 124 (72), 108 (33), 95 (33), 81 (48), 67 (44), 55 (72). For $C_{16}H_{24}O_2$ (248.4) calculated: 77.4% C, 9.7% H; found: 77.6% C, 9.8% H. Compound **11** (colourless oil). TLC: R_F 0.60 (light petroleum–ether, 4 : 1). ^{1}H NMR (400 MHz): 0.84 d, 6 H, *J*(8,9) = *J*(Me,8) = 6.0 (3 × H-9 and Me-8); 1.04 d, 3 H, *J*(Me,4) = 6.6 (Me-4); 6.05 ddd, 1 H, *J*(2,3; 1,2; 2,4) = 15.6, 7.7, 0.9 (H-2); 6.74 dd, 1 H, *J*(2,3) = 15.6, *J*(3,4) = 7.3 (H-3); 9.48 d, 1 H, *J*(1,2) = 7.7 (H-1).

Compound **6** (130.9 mg, 0.324 mmol) afforded **12a** (2.5 mg, 4%) and **12b** (only detected on TLC).

Compound **7** (99.7mg, 0.231 mmol) afforded *des-A-10α-cholestan-5-one* (**12a**; 2.9 mg, net yield 13%), *des-A-cholestan-5-one* (**12b**; 0.5 mg, 2%) and recovered **7** (70.2 mg). Compound **12a**, m.p. 60.5–62 °C (colourless needles from light petroleum) (ref.[12a], 61–62 °C; ref.[12b], 62–63 °C). TLC: R_F 0.32 (light petroleum–ether, 5 : 1). IR: 2 928, 2 856, 1 700, 1 450, 1 371, 1 158, 840. ^{1}H NMR (80 MHz): 0.75 s, 3 H (3 × H-18); 0.87 d, 6 H, J = 6.0 (3 × H-26 and 3 × H-27); 0.93 d, 3 H, J = 6.2 (3 × H-21); 1.00 d, 3 H, J = 6.6 (Me-10α). MS, *m/z* (%): 332 (M^+, 100), 317 (2), 304 (2), 275 (7), 360 (7), 247 (6), 217 (11), 201 (11), 192 (13), 177 (99), 163 (11), 150 (20), 136 (26), 121 (22), 110 (26), 95 (22), 81 (22), 69 (22), 55 (43). Compound **12b**, m.p. 79–81 °C (colourless needles from light petroleum). TLC: R_F 0.25 (light petroleum–ether, 5 : 1). IR: 2 930, 2 865, 1 705, 1 465, 1 379, 1 170, 741. ^{1}H NMR (400 MHz): 0.727 s, 3 H (3 × H-18); 0.864 d, 0.868 d, 2 × 3 H, J = 6.6 (3 × H-26 and 3 × H-27); 0.918 d, 3 H, J = 6.5 (3 × H-21); 1.118 d, 3 H, J = 7.2 (Me-10β); 2.214 dt, 1 H, J(6α,6β) = 14.0, J(6α,7α) = J(6α,7β) = 4.9 (H-6α); 2.382 m, 1 H (H-10α); 2.515 td, 1 H, J(6α,6β) = 14.0, J(6β,7α) = J(6β,7β) = 6.5 (H-6β). MS, *m/z* (%): 332 (M^+, 65), 317 (4), 260 (7), 219 (7), 192 (15), 177 (100), 136 (26), 95 (30), 55 (54).

Conversion of **8b**, **9b** or **12b** to more Stable Epimers **8a**, **9a** or **12a**

A mixture of **8b** (or **9b**, or **12b**) (0.5 mg) in ethanol (0.5 ml) and acetic acid (1 drop) was stirred at room temperature for 1 h. TLC analysis showed that **8b** (or **9b**, or **12b**) was transformed to **8a** (or **9a**, or **12a**).

RESULTS AND DISCUSSION

Modification of Albrecht's et al. Apparatus

The Albrecht's method[6] with (20*R*,*S*)-4,4,5,14-tetramethyl-18,19-dinor-13,17-seco-5β,8α,9β,10α,14β-cholestane-13,17-dione (**1**) as a substrate proved to be impractical as the starting material was not efficiently carried into the catalysis tube in a reasonable time. The work-up for the extraction of the products was troublesome because of the large quantity of the water solution obtained. Therefore, the apparatus for this reaction was modified by introducing an inlet between the preheating tube and the catalysis tube (Fig. 1). The 1,5-dicarbonyl compounds dissolved in ether could be injected into the inlet after the steam going smoothly.

Retro-Michael Reaction of 1,5-Dicarbonyl Compounds

Compound **1** was introduced into the inlet of the reactor (see Scheme 1) to give a mixture of tricyclic ketones **8a** (57%) and **8b** (16%) in a combined isolated yield of 73%. Compounds **8a** and **8b** could be separated by silica gel column chromatography. Ketones **8a** and **8b** were epimers at C-14 and

their structure was characterized by IR, ^{1}H NMR and ^{13}C NMR spectra. Their ^{1}H NMR spectra showed doublets at 1.058 (J = 6.5) and at 0.81 (J = 7.3) ppm assigned to 14α-Me and 14β-Me in **8a** and **8b**, respectively. These assignments were consistent with the similar compounds[6]. Mass spectra of both **8a** and **8b** showed a base peak at *m/z* 177 (M^+ – ring – C). The less stable epimer **8b** could be converted to the more stable epimer **8a** under acid conditions. The α,β-unsaturated ketone arising from side chain was not collected due to its small yield and volatility but it could be detected on TLC.

The retro-Michael reaction of **3** resulted in a complex mixture from which **9a** (19%), **9b** (7%) and **9c** (22%) were isolated and characterized. Compounds **9a** and **9b** were two epimers of the expected ketones and **9c** was a hydrolysis product of **9a** as confirmed by its IR, ^{1}H NMR and ^{13}C NMR spectra. The ^{1}H NMR spectra of **9a** and **9c** showed doublets at 1.00 (J = 6.2) and at 0.99 ppm (J = 6.2) assigned to 13α-Me in **9a** and **9c**, respectively. The ^{1}H NMR spectrum of epimer **9b** displayed a doublet at 1.17 ppm (J = 7.3) assigned to 13β-Me. The above coupling constants were consistent with those of **8a** and **8b**, respectively. Both **9a** and **9b** showed an acetoxy methyl at 2.02 ppm as singlet. The less stable epimer **9b** could be smoothly converted to **9a** under acid conditions. The mass spectra of **9a** and **9b** indicated base peak at *m/z* 232 (M^+ – AcOH), whereas that of **9c** showed *m/z* 232 ($M^+ - H_2O$). It is worth noting that the less polar product (18%) of the retro-Michael reaction of **3** was still a complex mixture of, presumably, the hydrolysis-dehydration or dehydration products of **9a** and **9b** or **9c** with double bond isomers in ring A and epimers at C-13.

After substitution of 3β-acetoxy group with a carbonyl, ketone **4** worked well under retro-Michael reaction conditions and cleanly gave tricyclic diketone **10a** with an isolated yield of 59%. The less stable epimer was not

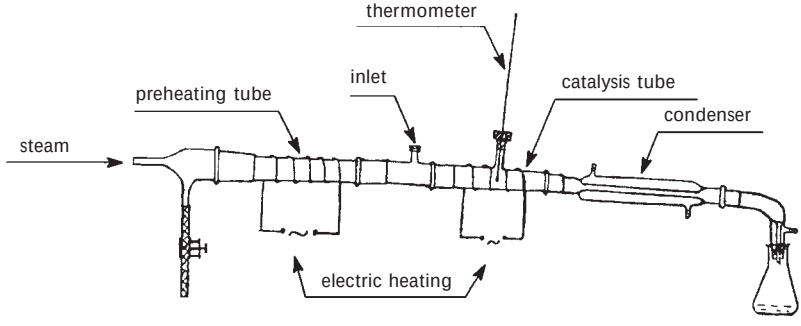
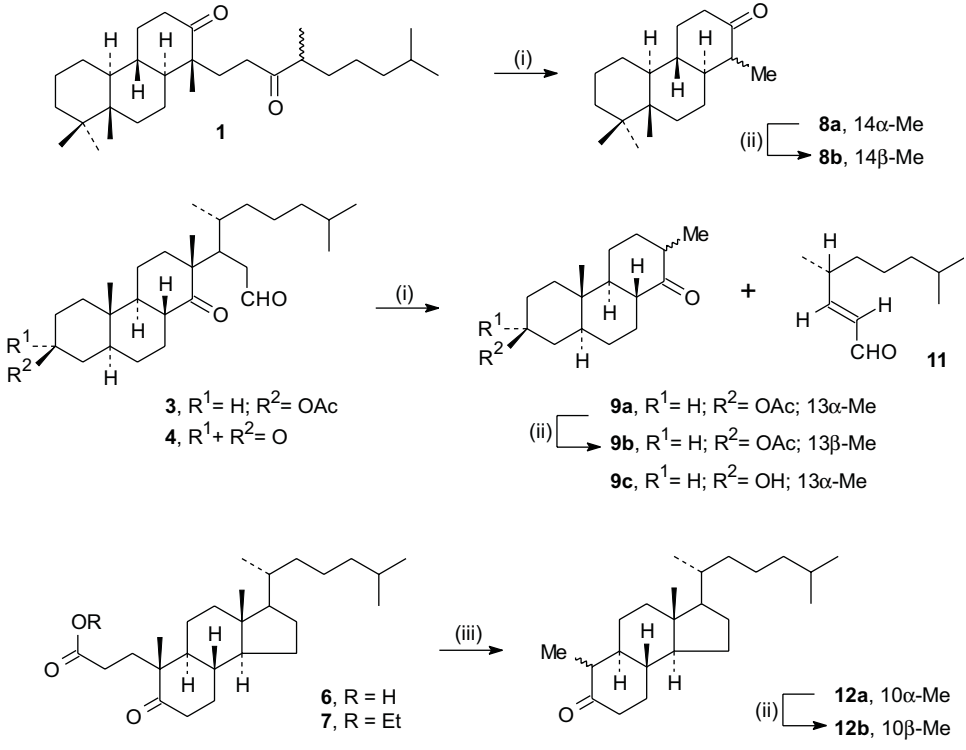


FIG. 1
The apparatus for retro-Michael reaction

isolated. The ^{1}H NMR spectrum of **10a** showed doublet at 1.01 ppm (J = 6.2) assigned to the 14α-Me. The mass spectrum of **10a** indicated a base peak at m/z 248 (M^+). These results demonstrated that the retro-Michael reaction of **4** worked better than that of substrate **3**. The other product (2*E*,4*R*)-4,8-dimethylnon-2-en-1-al (**11**) from compounds **3** and **4** was collected and characterized by ^{1}H NMR spectrum. The ^{1}H NMR of **11** showed a doublet at 9.48 ppm (J = 7.7) assigned to the aldehyde proton. The signals at 6.05 ddd ppm (J = 15.6, 7.7 and 0.9) and 6.74 dd ppm (J = 15.6 and 7.3) were assigned to H-2 and H-3, respectively. The Me-4 resonated at 1.04 d ppm (J = 6.6) whereas Me-8 and H-9 at 0.84 d ppm (J = 6.0). This compound was obtained by Cornforth *et al.* on their studies of the structure of cholesterol[13].

The retro-Michael reaction of acid **6** gave a low conversion rate (<30%) and a very poor yield (4%) of **12a** and **12b**, whereas for the ethyl ester **7**, a little better yield of **12a** and **12b** (combined 15%) was obtained. Melting



SCHEME 1

point of **12a** was consistent with the literature[12]. The ^{1}H NMR spectra of **12a** and **12b** showed doublets at 1.00 ppm (J = 6.6) and 1.118 ppm (J = 7.2) which were assigned to the 10α- and 10β-Me in **12a** and **12b**, respectively. The coupling constants were consistent with those of the above obtained compounds (**8a** and **8b**, **9a** and **9b**, and **10a**). The mass spectra of **12a** and **12b** showed their molecular ions in high abundance. For **12a** the base peak was *m/z* 332 (M^+) and *m/z* 177 (M^+ – ring – C) was in a relative abundance of 99%, while for **12b** *m/z* 177 (M^+ – ring – C) was a base peak with the molecular ions (*m/z* 332) in 65% intensity. The conversion of **12b** to **12a** could be also achieved under acid conditions. The low conversion rate of **6** and **7** and poor cleavage yield were probably due to their lower volatility and less active α-H to carboxyl or ester group in **6** and **7**.

From the above results, we can conclude that the retro-Michael reaction of 1,5-dicarbonyl compounds works well for 1,5-diketones and 1,5-keto aldehydes, however, for 1,5-keto esters and 1,5-keto acids gives only poor yields.

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