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SYNTHETIC INTERMEDIATES DERIVED FROM TRITERPENOIDS BY THE RETRO-MICHAEL REACTION IN THE VAPOUR PHASE

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ABSTRACT : *Retro-Michael reactions were performed by super-heated steam distillation of 1,5-diketones with a basic catalyst. Dammarane, hopane and lupane derivatives gave yields in the range of 85 to 100% using sodium hydroxide deposited on glass wool as a catalyst.*

It is possible to obtain molecules with well defined stereochemistry from known natural products by a retro-Michael reaction of 1,5-diketones. This degradative approach, however, results in a large decrease in product weight. As an example, in the synthetic scheme A in figure 1, even when the reaction is complete, 33% of the original weight is lost. Utilization of this degradative approach is therefore valuable for synthesis only if high yields are obtained.

The retro-Michael reaction works well for aromatic ketones[1]. However, for alicyclic ketones rather drastic reaction conditions (potassium hydroxide in diethylene glycol at 200°C) are required ; they lead to poor or moderate yields, as shown in the case of 3-acetoxy-13,17-seco-dammarane-13,17-dione[2] and 6-acetoxy-17,21-secozeorinane-17,21-dione[3]. With the same procedure Baddeley et al.[4] obtained a pure alcohol in 18% yield from 4,5-secolupane-3,5-dione. However, carrying out a vacuum distillation of the latter (350°C/0.15 mm) through an alkaline glass column, these authors obtained a 55% yield of the expected ketone.

As high temperatures and prolonged contact times seemed to be responsible for the poor or moderate yields obtained in the above experiments, we planned to carry out this reaction in the vapour phase with a reduced contact time between catalyst and reagent. By using a super-heated steam distillation device coupled with an oven containing a basic catalyst, we could indeed show that triterpenoid 1,5-diketones undergo retro-Michael reactions in high yields.

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RESULTS AND DISCUSSION

Table 1 shows the experimental conditions employed and the results obtained from more than fifty retro-Michael reactions carried out on (20ξ)-13,17-secodammarane-13,17-dione 2 (Figure 1, scheme A). The set-up used for these reactions is described in the experimental part.

Table 1

Reaction parameters for the retro-Michael reaction of (20ξ)-13,17-secodammarane-13,17-dione 2.

Catalyst[a]	Catalyst temperature °C	Transformed product (%)	Yield[b] 3 + 4	Less stable isomer 4 (%)
Na_2CO_3	280	11	95	7
Al_2O_3(n)	200	100	37	11
Al_2O_3(b)	200	91	74	14
	280	96	71	13
NaOH	150	34	63	7
	200-280°C[c]	95-100	85-100	10-11

a. See experimental part for preparation and use

b. Percentage of 3 + 4 after sublimation relative to transformed product.

c. Optimal conditions at 250°C.

With a contact time between the starting diketone and the catalyst of less than half a second, the yields obtained were satisfactory when the catalyst had a basicity at least equal to that of sodium carbonate. Even for sodium hydroxide the lower limit for the reaction temperature was of the order of 200°C.

Alumina gave a secondary catalytic effect producing dehydrogenated ketones. With "neutral" alumina these secondary products represented 50% of the reaction products, while basic alumina gave only traces.

When the catalyst was used for the first time with low quantities of diketone (∿ 50 mg) reduced yields and conversions were usually obtained, although normal yields and conversions were observed in subsequent reactions with the same catalyst. This difference could be due to the deactivation of adsorbtive sites during the early stages of the first reaction.

With diketone 2 almost the same ratio between the epimers was observed in all cases : 90% of ketone 3 to 10% of ketone 4. For the other two, 17,21-secohopane-17,21-dione 7 and 4,5-seco-lupane-3,5-dione 10, only one product was detected. This is certainly due to differences in steric repulsion. While 4 has only 1,3 CH_3-H diaxial interactions, the less stable epimers of 8 and 11 suffer from 1,3 CH_3-CH_3 diaxial interactions.

Several reactions with 17,21-secohopane-17,21-dione 7 were performed with NaOH as a catalyst at 280°C, and gave 95% yield of the expected product 8. Under the same conditions more than 2 g of 11 were prepared from 10 in less than an hour by increasing the water vapour flow. The latter was obtained by using a stronger heating rate of the water, as well as larger transfer lines.

The ketones formed by the retro-Michael reactions were subsequently reduced to the corresponding tri- and tetracyclic hydrocarbons[5,6] or used as synthons for the preparation of other tricyclic terpanes[7]. Most of these hydrocarbons were identified as biological markers occurring in sediments and petroleums[8,9].

CONCLUSIONS

A method has been described to carry out the retro-Michael reaction of non-activated triterpenoid 1,5-diketones in high yields. The diketone is steam distilled over a solid catalyst with short contact time. Vapour/solid heterogeneous catalysis by sodium hydroxide impregnated glass wool at 250°C are the most efficient reaction conditions (~100% conversion with 85-100% yield). The only limitation of the present method is the need to have a starting material which can be steam distilled. Furthermore the reaction can easily be upscaled from the milligram to the gram range.

The method has been successfully used for the preparation of novel polycyclic terpanes occurring in geological samples.

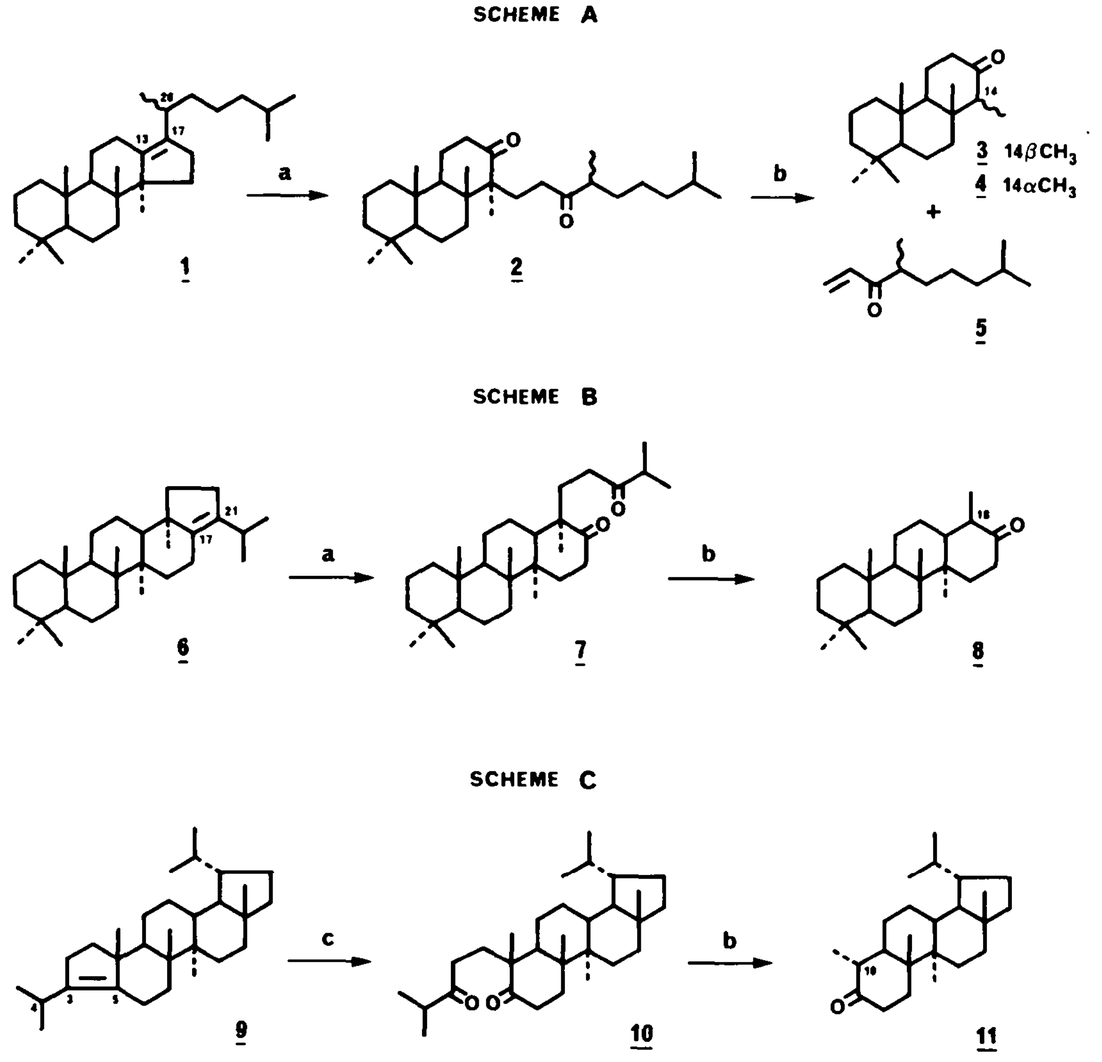

Figure 1. Ketones obtained by retro-Michael reactions from cyclopentene containing triterpenes.
a : $RuO_2/NaIO_4$, b : retro-Michael, c : RuO_4

EXPERIMENTAL

Water was distilled from a 500 ml flask via a heated tubing into a heated 25 ml flask containing the starting diketone in the liquid state. The steam distilled material was passed through a basic catalyst containing glass column (15 x 1.6 cm) heated in a tubular oven. At the outlet of the column the reaction products were trapped using a water condenser.

The reaction conditions are described in Table 1. Typically, the water flux was about 5 ml/min, corresponding to a vapour flux of about 6 l/min and, consequently, a contact time with the catalyst of less than half a second.

Preparation of the catalysts :

Sodium hydroxide catalyst : The catalyst was prepared by passing through a loosely packed column (15 x 1.6 cm) of glass wool 15 ml of a normal solution of sodium hydroxide (Prolabo P.A.). After 15 minutes the excess solution was removed under vacuum (ca. 20 mm Hg). The wet catalyst in the column was further dried in an oven at 200°C. The lifetime of the catalyst was increased when stored dry or at temperatures above 200°C.

Sodium carbonate catalyst : The catalyst was prepared as above, employing a saturated solution of sodium carbonate (Prolabo P.A.).

Alumina catalyst : Neutral alumina (2 g, act. I, 0.063-0.200 mm, Merck art. 1077) was dispersed in distilled water and mixed with 2 g of glass wool. After decanting and filtering, the solid phase was introduced in the reaction tube. Excess water was removed under vacuum and drying was performed in the oven.

Basic alumina catalyst : The catalyst was prepared by passing through a column (1.6 cm internal diameter) of neutral alumina (Merck art. 1077 ; 4 g) plugged with glass wool (1 g), 5 ml of a 5% sodium hydrogenocarbonate solution. After 15 minutes the excess solution was removed under vacuum and drying was performed in the oven.

Analysis of the products was made by gas-phase chromatography and the relative percentage of the isomers was calculated from the area of the chromatographic peaks (Hewlett Packard GC mod 417 coupled with a Hewlett Packard automation system mod 3385A ; glass capillary column (28 m x 0.3 mm) coated with a polymethylsiloxane stationary phase (film thickness 0.4 x 10^{-3} mm). Electron ionization mass spectrometry was performed on a double focusing Thomson THN 208 mass spectrometer ; GC-MS on a LKB 9000S coupled with a PDP 11/10 calculator and a LKB 1130 interface. Ultra-violet measurements were performed on a JOBIN YVON DUOSPAC model 203 spectrophotometer and circular dichroism on a JOBIN YVON DICHROGRAPH R.J. MARK III. ^{1}H-NMR was performed on a CAMECA 250 (250 MHz) or a BRUKER WP 200 SY (200 MHz).

(20ξ)-dammar-13(17)-ene 1 - Prepared from dipterocarpol as described by Tori et al.[10] Colorless oil. Anal. Found : C, 87.34 ; H, 12.84. Calc. for $C_{30}H_{52}$: C, 87.29 ; H, 12.70%. EIMS (probe) 70eV, m/z (rel. int.) : 412 M^+(42), 397(7), 299(32), 231(32), 220(30), 206(25), 205(44), 191(100).

(20ξ)-13,17-secodammarane-13,17-dione 2 - Typical preparation after Piatak et al.[11] Ruthenium dioxide (60 mg) was stirred with sodium metaperiodate (600 mg) and 3 ml of water, until a yellow suspension was obtained to which 3 ml of acetone were added. A solution of 1 (881 mg) in acetone was saturated with water and added dropwise over the yellowish suspension. The reaction mixture turned immediately brownish-black. The ruthenium tetroxide was regenerated by means of periodical additions of a saturated sodium metaperiodate solution. This was shown by the yellowish colour that appeared in the reaction mixture. If an oily phase was formed, it was useful to add acetone until it disappeared. After the end of addition (5-6 h), the starting olefin had virtually disappeared as checked by TLC. The reaction was quenched by isopropanol. After vacuum concentration, the residue was chromatographed over a short silica gel column. Elution with hexane gave 32 mg of compound 1. Elution with hexane/ether 7:3 gave 886 mg (93% yield) of compound 2 as a colorless oil (shown by GC and GC-MS to be a 50:50 mixture of both possible isomers). Purification was performed by TLC (Merck Kieselgel 60 F_{254}, 0.25 mm plates, hexane/ether 9:1 as eluting solvent). Anal. Found : C, 81.14 ; H, 11.79. $C_{30}H_{52}O_2$ requires : C, 81.02 ; H, 11.78%. EIMS (probe) 70eV, m/z (rel. int.) : 444 M^+(45), 429(4), 426(4), 411(7), 360(7), 331(24), 289(15), 253(85), 191(100).

(14ξ)-des-D-dammaran-13-ones 3 + 4 - Typically, the diketone 2 (178 mg) was introduced in the steam-distilling flask. After stabilization of the oven temperature at 250°C, the line between the boiler and the steam-distilling flask was heated at 300°C. The temperature of the line between the steam-distilling flask and the oven was set to a reading of 250°C on the thermometer inserted into the flask. When the formation of oily droplets ceased in the condenser (*ca* 1/2 - 1 h) the reaction was complete. The condenser and the receiving flask were rinsed with ether. The combined ethereal extracts were concentrated on a rotatory evaporator to a residue weighing 120 mg, which after sublimation (110°C, 0.1 mm) gave 109 mg of a mixture of 3 + 4.

3 was purified by repeated crystallization from methanol/ether. M.p. 123.5°-124°C (white needles). Anal. Found : C, 82.50 ; H, 11.52. $C_{19}H_{32}O$ requires : C, 82.54 ; H, 11.67%. EIMS (probe) 70eV, m/z (rel. int.) : 276 M^+(28), 261(8), 258(2), 243(7), 234(4), 205(8), 204(8), 192(21), 191(100), 177(11), 163(8), 149(11), 137(27), 125(14), 123(29), 109(21), 95(24), 81(26), 69(25), 55(17). UV λ_{max} (isooctane) : 296 nm. Circular dichroism shows a strong positive effect when compared with 4, as expected. ^{1}H-NMR (250 MHz, $CDCl_3$) : δ 0.73 (3H, s), 0.82 (3H, s), 0.87 (3H, d, J=5.8 Hz), 0.87 (3H, s), 0.88 (3H, s).

4 was isolated from a mixture with 30% (3) by preparative TLC (Merck Kieselgel 60 F_{254}, 0.25 mm plates ; eluting solvent hexane-ether 9:1). Crystallized from methanol-ether, m.p. 92-9[illegible]°C (white needles). HRMS M^+, m/z : 276.2453 ; $C_{19}H_{32}O$ requires 276.2453. EIMS (probe) 70eV, m/z (rel. int.) : 276 M^+(33), 261(10), 243(7), 234(5), 205(8), 204(8), 192(21), 191(100), 177(11), 163(6), 149(10), 137(24), 123(26), 109(19), 95(20), 81(26), 69(19). UV λ_{max} (isooctane) : 297 nm. Circular dichroism shows a very weak positive effect when compared with ketone 3. ^{1}H-NMR (250 MHz, $CDCl_3$) : δ 0.82 (3H, s), 0.86 (3H, s), 0.88 (3H, s), 0.93 (3H, s), 1.10 (3H, d, J=7.2 Hz).

5 : concentration of the ether distilled in the rotatory evaporator gave 5 in non-quantitative recovery. Characterized by GC-MS.

Hop-17,21-ene 6 - Prepared from hydroxyhopanone according to Dunstan *et al.*[12] and Corbett and Wilkins[13]. EIMS (probe) 70eV, m/z (rel. int.) : 410 M^+(48), 395(20), 367(100), 273(7), 231(68), 203(15), 191(65), 189(46). ^{1}H-NMR (250 MHz, $CDCl_3$) : δ 0.79 (3H, s), 0.82 (3H, s), 0.84 (3H, s), 0.85 (3H, s), 0.92 (3H, d, J=7 Hz), 0.93 (3H, s), 0.98 (3H, d, J=7 Hz), 1.04 (3H, s), 2.64 (1H, septet, J=7 Hz).

17,21-Secohopane-17,21-dione 7 - Prepared as described for 2 ; 250 mg of 6, 500 ml acetone, 45 mg RuO_2 in 100 ml acetone, 400 mg $NaIO_4$. After purification by flash chromatography on silica, 251 mg of 7 were obtained (93% yield). M.p. 97.5-98.5°C (CH_3OH/CH_2Cl_2), lit. 98-99°C[14]. EIMS (probe) 70eV, m/z (rel. int.) : 442 M^+(25), 427(14), 424(14), 409(2), 399(10), 357(5), 344(30), 300(5), 191(100). ^{1}H-NMR (250 MHz, $CDCl_3$) : δ 0.80 (3H, s), 0.84 (3H, s), 0.85 (3H, s), 1.00 (3H, s), 1.01 (3H, s), 1.05 (3H, s), 1.07 (3H, d, J=6.8 Hz), 1.08 (3H, d, J=6.8 Hz), 2.13-2.49 (4H), 2.59 (1H, septet, J=6.8 Hz).

(18αH)-Des-E-hopan-17-one 8 - Prepared as described for 3 + 4. 200 mg of 7. Catalyst temperature 280°C. 95% yield of 8. M.p. 181.5-182°C (CH_3OH/CH_2Cl_2). HRMS M^+, m/z : 344.3069 ; $C_{24}H_{44}O$ requires 344.3079. EIMS (GC) 70eV, m/z (rel. int.) : 344 M^+(42), 329(13), 326(3), 206(10), 191(87), 81(100). ^{1}H-NMR (250 MHz, $CDCl_3$) : δ 0.80 (3H, s), 0.85 (3H, s), 0.86 (3H, s), 0.96 (3H, s), 0.97 (3H, d, J=7 Hz), 1.20 (3H, s), 2.14-2.51 (3H).

5(4→3)abeo-lup-3(5)-ene 9 - Prepared from lupanol as described by Nowak et al.[15] EIMS (GC) 70eV, m/z (rel. int.) : 410 M^+(24), 395(17), 367(100), 273(6), 259(3), 245(3), 231(29), 217(4), 203(5), 191(5), 189(11), 175(19), 161(29), 150(16), 137(23), 136(53), 135(45), 123(17), 121(48). ^{1}H-NMR (250 MHz, $CDCl_3$) : δ 0.76 (3H, d, J=7 Hz), 0.77 (3H, s), 0.84 (3H, d, J=7 Hz), 0.86 (3H, s), 0.90 (3H, s), 0.92 (3H, d, J=7 Hz), 0.98 (3H, d, J=7Hz), 1.12 (3H, s), 2.64 (1H, septet, J=7 Hz).

4,5-Secolupane-3,5-dione 10 - To 4 mg of 9 in 0.5 ml of carbon tetrachloride, an excess of a solution of ruthenium tetroxide in the same solvent was added dropwise. After half an hour the reaction product was filtered through active charcoal, and gave after purification by TLC 4 mg of a colorless oil[4] (91% yield) of 10. ^{1}H-NMR (250 MHz, $CDCl_3$) : δ 0.77 (3H, d, J=7 Hz), 0.77 (3H, s), 0.85 (3H, d, J=7 Hz), 0.96 (3H, s), 1.04 (3H, s), 1.07 (3H, d, J=7 Hz), 1.08 (3H, d, J=7 Hz), 1.12 (3H, s), 2.14-2.50 (4H), 2.60 (1H, septet, J=7 Hz).

(10βH)-Des-A-lupan-5-one 11 - Prepared as described for 8. M.p. 171-172°C (CH_3OH/CH_2Cl_2), lit. 174°C[4]. EIMS (GC) 70eV, m/z (rel. int.) : 344 M^+(58), 329(21), 301(47), 231(21), 218(15), 206(48), 191(41), 177(21), 163(74), 151(41), 149(51), 138(81), 123(100), 109(60), 107(47), 95(95), 81(91), 69(75), 55(96). ^{1}H-NMR (200 MHz, $CDCl_3$) : δ 0.77 (3H, d, J=6.8 Hz), 0.81 (3H, s), 0.86 (3H, d, J=6.8 Hz), 0.93 (3H, s), 0.98 (3H, d, J=6.5 Hz), 1.27 (3H, s), 2.19-2.56 (3H).

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