Synthesis of 14-hydroxy steroids. Total synthesis of methyl 14β-hydroxy-1,7,17-trioxo-5β,8-androstene-10β-oate and related compounds

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Received April 24, 1990

RÉJEAN RUEL and PIERRE DESLONGCHAMPS. Can. J. Chem. **68**, 1917 (1990).

The total synthesis of the title compound **22** and methyl 14α-hydroxy-5β,13α,8-androstene-1,7,17-trioxo-10β-oate **21** isomer is reported. We also describe the 1,6-Michael addition of 2-methyl-1,3-cyclopentanedione on dienone **14** and the protic ammonium salt catalyzed intramolecular Michael addition of cyclic β-ketoester on the conjugated acetylenic ketone **13**.

Key words: cardenolides, steroid synthesis, aldol, Michael addition.

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On rapporte la synthèse totale des isomères 13α,14α **21** et 13β,14β **22** du 14-hydroxy-5β,8-androstene-1,7,17-trioxo-10β-oate de méthyle. Nous décrivons l'addition de Michaël-1,6 de la 2-méthyl cyclopentane-1,3-dione sur la diènone **14** de même que l'addition de Michäel intramoléculaire du β-cétoester cyclique sur la cétone acétylénique conjuguée **13**, cette dernière addition étant catalysée par un sel d'ammonium protique.

Mots clés : cardénolides, synthèse des stéroïdes, aldol, addition de Michaël.

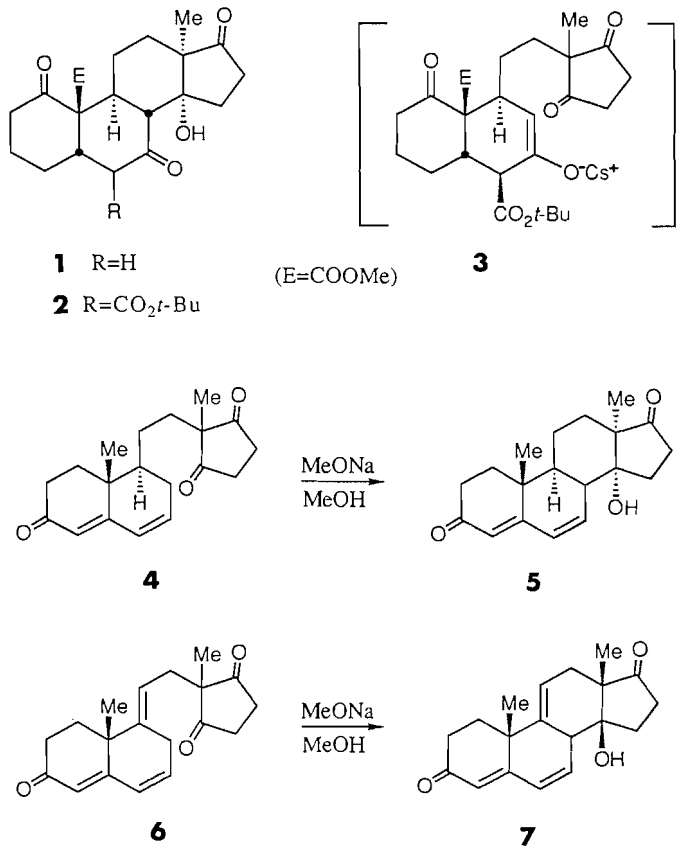
Introduction

We have previously reported the synthesis of 14α-hydroxy steroid **1** (Scheme 1) using a new stereocontrolled anionic polycyclization method (1). Base-catalyzed aldol condensation involving the cesium enolate **3** led to bis-β-ketoester **2**, which was transformed to steroid **1** upon selective decarboxylation of the *tert*-butyl ester (PTSA, C_6H_6, 80°C). A single-crystal X-ray analysis revealed that the 14-hydroxy substituent in steroid **1** had an α configuration. This configuration was, however, opposite to the 14β-hydroxy substituent normally found in cardioactive steroids (2).

It then came to our attention that in Valenta's modified Torgov sequence (3) the closure of ring C effected by base-catalyzed aldol condensation on dienone **4** led to the 14α-hydroxy steroid **5**. On the other hand, when the aldol condensation involved the anion formed from the trienone system in **6** bearing a C9–C11 (steroid numbering) olefin, the 14β-hydroxy steroid **7** was the only product formed. Based on these results, we expected the preferential formation of a 14β-hydroxy steroid from the aldol condensation that would involve an enolate related to **3** but bearing a conjugated double bond between carbons C9 and C11. This account describes the synthesis of this aldol precursor as well as the results observed during the aldol condensation.

Results and discussion

The synthesis of *cis*-bicyclic dienone **14** is depicted in Scheme 2. The β-ketoester **8** was first obtained by treatment of 2-carbomethoxy-2-cyclohexenone (4) with allyltrimethylsilane and titanium tetrachloride (5). The dimethyl ketal **9** was then formed by treatment of **8** with methanol containing *p*-toluenesulfonic acid and methyl orthoformate. Subsequent ozonolysis led to the aldehyde **10** and, like its olefinic precursor **9**, this aldehyde **10** existed as a 2:1 *trans/cis* mixture of isomers that was used without separation. These isomers could be separated and were in fact isolated as pure compounds for the purpose of characterization (see Experimental). The acetylide formed from *n*-butyllithium (THF, −78°C) and the *O*-tosyl derivative of commercially available 3-butyn-1-ol was then added to



SCHEME 1

aldehyde **10** and the resulting propargylic alcohol **11** was oxidized with Jones reagent (5 min, 0°C, Me_2CO) to the ynone **12**. It should be pointed out here that in these conditions the dimethyl ketal protecting group was not hydrolyzed. Transacetalization of dimethyl ketal **12** (12 h, 23°C, Me_2CO, PTSA) then yielded β-ketoester **13**.

Previous reports from this laboratory described in a systematic study the intramolecular Michael addition of cyclic β-ketoesters on conjugated acetylenic (6) and olefinic (7) ketones. Cesium carbonate was the base used for these stereocontrolled

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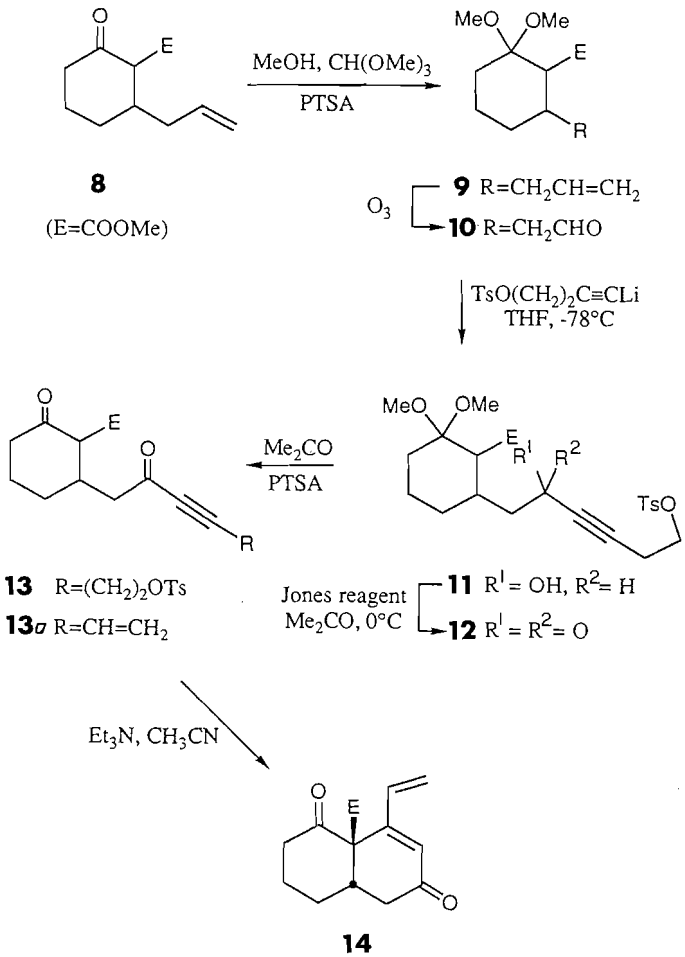
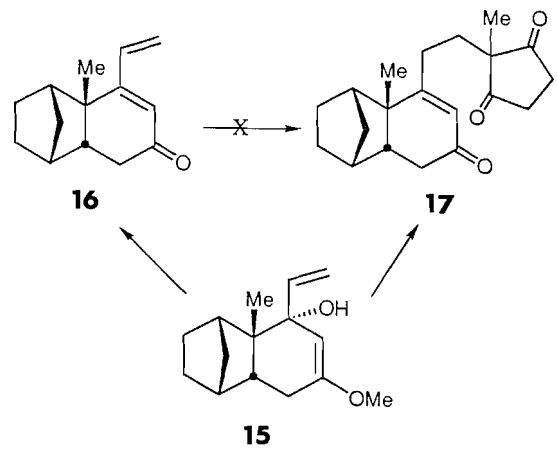


SCHEME 2



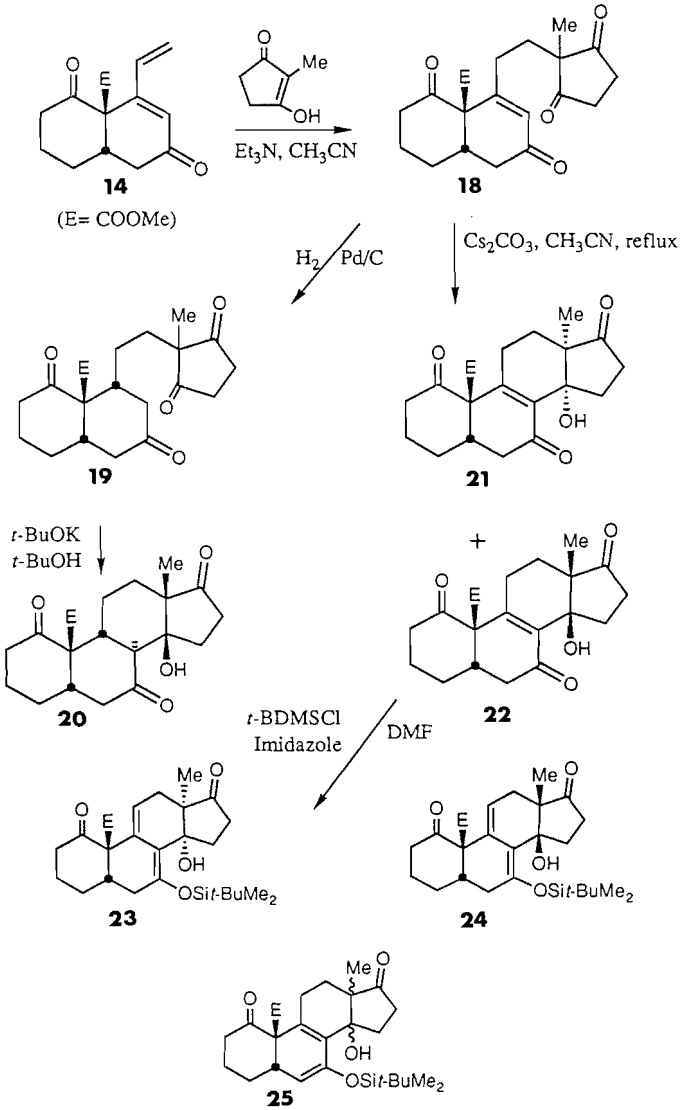
SCHEME 3

processes, which yielded specifically *cis*-decalin products. Using the conditions described (6, 7), we were, however, unable to achieve the Michael addition on acetylenic ketone **13** and obtained mainly decomposition products. This problem was solved when we found complementary experimental conditions very effective for the desired intramolecular Michael addition. When triethylamine (3 equiv.) was indeed added to a solution of β-ketoester **13** in acetonitrile, the *cis*-decalin dienone **14** (74%) was obtained after completion of the reaction. The first intermediate formed in the reaction was the elimination product **13***a*. This β-ketoester **13***a* was in fact spontaneously produced in the reaction mixture and transformed, after 3 h in acetonitrile at room temperature, to the Michael addition product **14**. If, however, acetonitrile was replaced by the less polar solvent methylene chloride (8), only the elimination product **13***a* was obtained from tosylate **13** after the same period of time. This elimination process generated a triethylammonium salt that catalyzed the intramolecular Michael addition, as the following results clearly indicate. When the elimination product **13***a* was submitted to the reaction conditions (Et_3N, CH_3CN) but without any protic ammonium salt, the Michael adduct **14** was formed, but with a modest 50% yield, while completion of the reaction required 2 days. On the other hand, when triethylammonium hydrochloride (1 equiv.) was added to a solution of **13***a* and triethylamine (2 equiv.) in acetonitrile, the formation of the Michael adduct **14** was completed after only 3 h and proceeded with better yield (74%). The synthesis of dienone **14** thus required seven steps and the overall yield was 30%.

Having the dienone **14** in our hands, only the 1,6-Michael addition of 2-methyl-1,3-cyclopentanedione (for a related 1,8-Michael addition, see ref. 9) remained to be done in order to get the requisite aldol condensation precursor of the steroid. Dienone **14** resembles Yates' bridged-ring dienone **16** (Scheme 3), which arose upon attempted purification on silica gel of allylic alcohol **15** (10). Yates *et al.* also reported the synthesis of enone **17**, through their modified Torgov sequence, from allylic alcohol **15**, but attempts to synthesize enone **17** from the Michael addition of 2-methyl-1,3-cyclopentanedione on dienone **16** were uniformly unsuccessful (10). Bearing this in mind, we were pleased to find that the Michael addition of 2-methyl-1,3-cyclopentanedione on our dienone **14** (in CH_3CN) took place cleanly and efficiently (80% yield) to give enone **18** (Scheme 4) when triethylamine was used as the base. It should be pointed out here that since the experimental conditions used (Et_3N, CH_3CN) for this Michael addition are essentially the same as required for the previously described intramolecular Michael addition (**13** → **14**), enone **18** could be synthesized in a "one pot" procedure from ynone tosylate **13** in 65% yield. We have investigated here again whether a protic ammonium salt would enhance the efficiency of this Michael addition, that is, if the reaction **14** → **18** would be also catalyzed by the protic salt as was the case for intramolecular Michael reaction **13***a* → **14**. For the 1,6-Michael addition leading to enone **18**, however, we found no appreciable effect when a protic ammonium salt ($Et_3NH^+Cl^-$) was added to the reaction mixture. The absence of catalysis by the protic ammonium salt may not be surprising if one considers the inherent acidity of the nucleophile 2-methyl-1,3-cyclopentanedione ($pK_a \sim 9$), which could itself catalyze the Michael reaction.

Hydrogenation of enone **18** gave the dihydro compound **19** where hydrogen has approached the less-hindered β face of the cyclohexenone ring. Aldol condensation (*t*-BuOK, *t*-BuOH–THF) of tetraketone **19** then gave 14β-hydroxy steroid **20**. The structure of **20** was predicted, based on related work reported in Professor Yates' elegant synthesis of 1,4-methano bridged steroids (10), and was later confirmed by a single crystal X-ray analysis (11). One should note that steroid **20** has an "unnatural" *syn* relationship between the carbomethoxy group (at C-10) and the C-9 hydrogen atom. Base-catalyzed aldol condensation of enone **18** then led to interesting results. When enone **18** was treated with cesium carbonate in refluxing acetonitrile for 48 h, a 3:2 mixture of 14α- and 14β-hydroxy steroids **21** and **22** was obtained (54% yield). Structures **21** and **22** were also confirmed by single crystal X-ray analysis.[3] No trace of the $\Delta^{9(11)}$-7-keto

[3]A. G. Michel, R. Ruel, and M. Drouin. Unpublished results.



SCHEME 4

steroids corresponding to steroids **21** and **22** could be isolated since, after the aldol condensation, the C9—C11 double bond must rapidly isomerize to the more stable C9—C8 conjugated double bond in **21** (or **22**). This isomerization obviously makes this aldol condensation irreversible.

The 14-hydroxy steroids **21** and **22** could not, however, be separated using low or medium pressure flash chromatography techniques. We could, however, later obtain pure 14-hydroxy steroids **21** and **22** since other quite interesting and unexpected results emerged upon attempted *tert*-butyldimethylsilylation of the tertiary alcohol in **21** or **22**. For example, when *tert*-butyldimethylsilyl chloride was added to a dimethylformamide solution of the 3:2 mixture of steroids **21** and **22** and imidazole, a 19:13:1 mixture of silyl enol ethers **23**, **24**, and **25** was isolated. Whether these silyl enol ethers were formed via an internal S_N2 migration of the "normally expected" silyl ether is not known but none of that silyl ether could be isolated. Technically, this reaction (**21**/**22** → **23**/**24**/**25**) could never be driven to completion but proceeded nevertheless in 67% yield (based upon recovered starting material). We were also pleased to find that 14-hydroxy silyl enol ethers **23** and **24** were easy to separate using flash chromatography techniques. Once the isomers **23** and **24** were separated, regeneration of enone steroids **21** and **22** was the only thing that remained to be done in order to obtain pure steroids. The use of tetrabutylammonium fluoride in THF at −78°C, even for a reaction time as low as 30 s, uniformly led to extensive decomposition. The reasons for this behavior are not quite understood. Among other things, unavoidable traces of hydroxide ions in the ammonium fluoride reagent may, for example, induce retro-Claisen type opening of A-ring β-ketoester. If that process operates, the generated ester enolate would be conjugated with the $\Delta^{8(9)}$-7-keto system of enones **21** and **22** and a complex cascade of reactions could follow. Fortunately, the use of cesium fluoride proved successful. Thus, when silyl enol ether **23** or **24** was treated with cesium fluoride in acetonitrile, the pure hydroxy steroid **21** or **22** was obtained in good yield (73%).

In summary, the enolate derived from the aldol condensation precursor **18** led, although with low selectivity, to the expected 14β-hydroxy steroid **22**. We also found new conditions (Et_3N, $Et_3N^+HCl^-$) for the intramolecular Michael addition of cyclic β-ketoester on acetylenic ketone. Furthermore, our work describes the successful 1,6-Michael addition of 2-methyl-1,3-cyclopentanedione to bicyclic dienone **14** bearing a 9-vinyl-$\Delta^{8(9)}$-7-keto system (steroid numbering).

Experimental

All reactions were carried out under an argon atmosphere unless otherwise noted. Melting points are uncorrected. R_f values were determined by using 5 × 20 cm^2 plates and an equilibrated solvent chamber. Chromatographic separations were made using Merck Kieselgel 60 (230–400 mesh ASTM). The infrared (ir) spectra were taken on a Perkin–Elmer 681 spectrophotometer. The ultraviolet (uv) spectra were registered on a Varian Tecktron 635 spectrophotometer. Mass spectral assays (ms, *m/e*) and peak matching were obtained using a VG Micromass ZAB-1F spectrometer. Proton nmr and carbon nmr spectra were recorded on a Bruker WM-250 instrument. Chemical shifts are reported in δ values relative to chloroform as internal standard. Abbreviations used are m: multiplet, s: singlet, d: doublet, t: triplet, q: quartet, dd: double doublets.

Allyl β-ketoester 8

To a stirred solution of 2-carbomethoxy-2-cyclohexenone (4.13 g, 26.8 mmol) in methylene chloride (55 mL) at −78°C is added titanium tetrachloride (2.8 mL, 28.1 mmol) followed by allyltrimethylsilane (5.8 mL, 37.5 mmol). After stirring for 20 min, aqueous sodium carbonate (20%) is added to the mixture. The aqueous layer is extracted with methylene chloride (3 × 50 mL) and the combined organic layers are washed with brine, dried ($MgSO_4$), filtered, and evaporated to yield 5.3 g of an oil. Flash chromatography of the residue (ethyl acetate/hexane,1:3) yields 4.7 g (90%) of **8** as a colorless oil; R_f 0.26–0.43 (ethyl acetate/hexane,1:4); ir (neat, ν cm^{-1}): 3070, 2935, 2860 (CH), 1745 (C=O ester), 1710 (C=O, ketone) cm^{-1}; ^1H nmr (250 MHz, $CDCl_3$) δ ppm: 5.80–5.68 (1H, m, CH_2=C*H*-), 5.15–4.90 (2H, m, CH_2=CH-), 3.76 (3H, s, CO_2CH_3), 3.16 (1H, d, J = 11.0 Hz, -CO-C*H*-CO_2CH_3), 2.60–1.40 (9H, m, -$(CH_2)_3$-C*H*-CH_2-). Enol form (characteristic signals): 12.36 (>1H, s, enolic H), 3.75 (>3H, s, CO_2CH_3).

Allyl dimethyl ketal 9

To a stirred solution of ketoester **8** (5.1 g, 26.0 mmol) and trimethyl orthoformate (3.7 mL, 33.7 mmol) in methanol (50 mL) at 23°C is added *p*-toluenesulfonic acid (247 mg, 1.3 mmol). After 12 h at 23°C, saturated sodium bicarbonate is added and the mixture is extracted with methylene chloride. The separated aqueous layer is extracted with methylene chloride (3 × 50 mL) and the combined organic layers are washed with brine, dried ($MgSO_4$), filtered, and evaporated to yield 6.3 g of an oil. Flash chromatography of the residue (ethyl acetate/hexane,1:4) yields 5.25 g (84%) of a 2:1 *trans/cis* mixture of dimethyl ketal **9**; R_f 0.36 (**9**-*cis*) and 0.28 (**9**-*trans*) (ethyl acetate/hexane,1:4); ir (neat, ν cm^{-1}): 3070, 2940 (CH), 1740 (C=O ester); ^1H nmr (250 MHz, $CDCl_3$) δ ppm (**9**-*cis*): 5.83–5.72 (1H, m, CH_2=C*H*-), 5.03–4.96 (2H, m, CH_2=CH-), 3.67 (3H, s, -CH_2CH_3),

3.20, 3.15 (6H, 2s, 2 × -OCH_3), 3.04 (1H, dd, J = 4.4, 1.8 Hz, -CH-CO_2CH_3), 2.03–1.34 (9H, m, -(CH_2)$_3$-CH-CH_2-); (**9**-*trans*): 5.78–5.64 (1H, m, CH_2=CH-), 5.02–4.95 (2H, m, CH_2=CH-), 3.68 (3H, s, -CO_2CH_3), 3.21 (6H, s, 2 × -OCH_3), 2.62 (1H, d, J = 6.7 Hz, -CH-CO_2CH_3), 2.21–1.12 (9H, m, -(CH_2)$_3$-CH-CH_2-); ms *m/e*: 242 (M^+), 227 ($M^+ - CH_3$), 211 ($M^+ - OCH_3$). Exact mass calcd. for $C_{13}H_{22}O_4$ (M^+): 242.1518: found 242.1526.

Aldhyde ***10***

Ozone is bubbled into a cold (−78°C) solution of olefin **9** (5.0 g, 20.7 mmol) in methylene chloride (200 mL) until a blue color persists. Argon is then passed through the solution to lower the concentration of ozone, and triphenylphosphine (7.0 g, 26.9 mmol) is added at −78°C. The resulting mixture is stirred for 2 h at room temperature. Concentration under reduced pressure yields the aldehyde **10**, which can be used without purification in the next step. Pure material may be obtained by means of flash chromatography (ethyl acetate/hexane, 7:13), which yields 4.5 g (89%) of aldehyde **10**; R_f 0.13 (**10**-*cis*) and 0.10 (**10**-*trans*) (ethyl acetate/hexane,1:4); (**10**-*cis*): white needles; mp 124–126°C (heptane); (**10**-*trans*): oil; ir (CH_2Cl_2, ν cm^{-1}): 2940, 2830, 2720 (CH), 1740 (C=O ester), 1720 (C=O aldehyde); ^{1}H nmr (250 MHz, $CDCl_3$) δ ppm: (**3**-*cis*): 9.74 (1H, t, J = 1.4 Hz, -CHO), 3.67 (3H, s, -CO_2CH_3), 3.19 (6H, s, 2 × -OCH_3), 3.07 (1H, dd, J = 4.3, 1.7 Hz, -CH-CO_2CH_3), 2.42–1.39 (9H, m, -(CH_2)$_3$-CH-CH_2-), (**3**-*trans*): 9.71 (1H, t, J = 1.5 Hz, -CHO), 3.69 (3H, s, -CO_2CH_3), 3.20–3.19 (6H, 2s, 2 × -OCH_3), 2.70 (1H, d, J = 6.5 Hz, -CH-CO_2CH_3), 2.63–1.15 (9H, m, -(CH_2)$_3$-CH-CH_2-); ms, *m/e*: 229 ($M^+ - CH_3$), 213 ($M^+ - OCH_3$), 201 ($M^+ - CH_2CHO$). Exact mass calcd. for $C_{11}H_{17}O_5$ ($M^+ - CH_3$): 229.1076; found: 229.1074.

Propargylic alcohol ***11***

To a stirred solution of the tosyl derivative of 3-butyn-1-ol (2.0 g, 8.9 mmol) in THF (20 mL) at −78°C is added dropwise a solution of *n*-butyllithium (1.6 M in hexane, 5.1 mL, 8.2 mmol). After stirring for 45 min at −78°C, the solution is transferred, via cannula, to a solution of aldehyde **3** (1.5 g, 6.2 mmol) in THF (35 mL) at − 78°C. The mixture is stirred at −78°C for 1.5 h and quenched with saturated ammonium chloride (50 mL). The aqueous layer is extracted with (1:1) ether/ethyl acetate (5 × 60 mL) and the combined organic layers are washed with brine, dried ($MgSO_4$), filtered, and evaporated to yield crude propargylic alcohol **11** as an oil. Flash chromatography of the residue (ethyl acetate/hexane,3:2) yields 2.1 g (72%) of alcohol **11**; R_f 0.19 (**11**-*cis*) and 0.15 (**11**-*trans*) (ethyl acetate/hexanes,1:1); ir (neat, ν cm^{-1}): 3460 (OH), 2940 (CH), 1735 (C=O ester); ^{1}H nmr (250 MHz, $CDCl_3$) δ ppm: (**11**-*cis*) (diastereomeric mixture): 7.80, 7.36* (4H, 2m, -CH arom.), 4.42* (1H, m, -CH-OH), 4.08* (2H, t, J = 7.0 Hz, -CH_2-OTs), 3.68, 3.66 (3H, 2s, -CO_2CH_3), 3.19, 3.18, 3.15, 3.13 (6H, 4s, 2 × -OCH_3), 3.06, 2.99 (1H, 2dd, J = 5.0, 1.7 Hz, -CH-CO_2CH_3), 2.58, 2.57 (2H, 2t, J = 7.0 Hz, -CH_2CH_2OTs), 2.45* (3H, s, Ar-CH_3), 2.03–1.380* (9H, m, -(CH_2)$_3$-CH-CH_2-); (**11**-*trans*) (diastereomeric mixture): 7.80, 7.36* (4H, 2m, -CH arom.), 4.36* (1H, m, -CH-OH), 4.10, 4.08 (2H, 2t, J = 7.0 Hz, -CH_2-OTs), 3.68* (3H, s, -CO_2CH_3), 3.20, 3.19* (6H, 2s, 2 × -OCH_3), 2.79, 2.71 (1H, 2d, J = 5.8 Hz, -CH-CO_2CH_3), 2.62–2.54* (2H, m, -CH_2-CH_2OTs), 2.45* (3H, s, Ar-CH_3), 2.21–1.17* (9H, m, -(CH_2)$_3$-CH-CH_2-), (*same signal for both diastereomers); ms, *m/e*: 436 ($M^+ - CH_3OH$), 418 ($M^+ - CH_3OH$-H_2O). Exact mass calcd. for $C_{22}H_{28}SO_7$ ($M^+ - CH_3OH$): 436.1556; found: 436.1545.

Ynone dimethylketal ***12***

To a stirred solution of propargylic alcohol **11** (1.0 g, 2.1 mmol) in acetone (15 mL) at 0°C is added dropwise a solution of Jones reagent until the red color persists. After 5 min at 0°C, isopropanol is added until a green mixture is obtained. The mixture is diluted with water and extracted with methylene chloride (4 × 40 mL). The combined organic layers are washed with brine, dried ($MgSO_4$), filtered, and evaporated to yield 965 mg (97%) of an oil. Flash chromatography of the residue (ethyl acetate/hexanes,1:1) yields 926 mg (93%) of a colorless oil; R_f 0.31 (**12**-*cis*) and 0.27 (**12**-*trans*) (ethyl acetate/hexane,1:1); ir (neat, ν cm^{-1}): 2940 (CH), 2210 (C≡C), 1735 (C=O ester), 1657 (C=O ketone); ^{1}H nmr (250 MHz, $CDCl_3$) δ ppm: (**12**-*cis*): 7.80, 7.37 (4H, 2m, -CH arom.), 4.12 (2H, t, J = 6.8 Hz, -CH_2-OTs), 3.68 (3H, s, -CO_2CH_3), 3.20, 3.18 (6H, 2s, 2 × -OCH_3), 3.06 (1H, m, -CH-CO_2CH_3), 2.74 (2H, t, J = 6.8 Hz, -CH_2-CH_2-OTs), 2.46 (3H, s, Ar-CH_3), 2.39 (2H, m, -CH-CH_2-CO-C≡C-), 2.03–1.30 (7H, m, -CH_2-CH_2-CH_2-CH-); (**12**-*trans*): 7.80, 7.37 (4H, 2m, -CH arom.), 4.06 (2H, t, J = 6.8 Hz, -CH_2-OTs), 3.67 (3H, s, -CO_2CH_3), 3.19, 3.18 (6H, 2s, 2 × OCH_3), 2.69 (2H, t, J = 6.8 Hz, -CH_2-CH_2-OTs), 2.68 (1H, m, -CH-CO_2CH_3), 2.46 (3H, s, Ar-CH_3), 2.33 (2H, m, -CH-CH_2-CO-C≡C-), 2.20–1.18 (7H, m, -CH_2-CH_2-CH_2-CH-); ms, *m/e*: 465 (M^+ − H), 438 (M^+ − CO), 434 ($M^+ - CH_3OH$).

Ynone β*-ketoester* ***13***

p-Toluenesulfonic acid (39 mg, 0.2 mmol) is added at 23°C to a stirred solution of ynone dimethylketal **12** (908 mg, 1.95 mmol) in acetone (20 mL). After 36 h at 23°C, water (20 mL) is added and the mixture is extracted with methylene chloride (5 × 25 mL). The combined organic layers are washed with salted sodium bicarbonate and brine, dried ($MgSO_4$), filtered, and evaporated to yield 820 mg of an oil. Flash chromatography of the residue (ethyl acetate/hexane,1:1) yields 736 mg (90%) of a colorless oil; R_f 0.26–0.32 (ethyl acetate/hexane,1:1); ir (neat, ν cm^{-1}): 2940 (CH), 2125 (C≡C), 1745 (C=O ester), 1715 (C=O ketone), 1670 (C=O ynone); ^{1}H nmr (250 MHz, $CDCl_3$) δ ppm: 7.80, 7.36 (4H, 2m, -CH arom.), 4.14 (2H, t, J = 6.8 Hz, -CH_2-OTs), 3.75 (3H, s, -CO_2CH_3), 3.26 (1H, d, J = 10.8 Hz, -CO-CH-CO_2CH_3), 2.76 (2H, t, J = 6.8 Hz, -CH_2-CH_2OTs), 2.60 (2H, m, -CH_2CO), 2.45 (3H, s, Ar-CH_3), 2.27 (2H, m, -CH_2-CO-C≡C-), 2.02 (1H, m, -CH_2-CH-CH_2-), 1.72–1.42 (4H, m, -CH_2-CH_2-CH-). Enol form (characteristic signals): 12.4 (>1H, s, enolic H), 3.76 (>3H, s, -CO_2CH_3), 3.22 (1H, m, -(OH)C=C(E)-CH-CH_2-CO-); ms, *m/e*: 420 (M^+), 402 ($M^+ - H_2O$), 389 ($M^+ - OCH_3$). Exact mass calcd. for $C_{21}H_4SO_7$ (M^+): 420.1243; found: 420.1238. (^{1}H nmr (250 MHz, $CDCl_3$) of the corresponding enol acetate derivative, δ ppm: 7.78, 7.35 (4H, 2m, -CH arom.), 4.13 (2H, t, J = 6.9 Hz, -CH_2-OTs), 3.69 (3H, s, -CO_2CH_3), 3.35 (1H, m, -(OAc)C=C(E)-CH-CH_2-CO-), 2.74 (2H, t, J = 6.9 Hz, -CH_2-CH_2OTs), 2.73 (1H, dd, J = 16.8, 2.9 Hz, -HCH-CO-C≡C-), 2.55 (1H, dd, J = 16.8, 9.9 Hz, -HCH-CO-C≡C-), 2.45 (3H, s, Ar-CH_3), 2.21 (2H, m, -CH_2-(OAc)C=C-), 2.17 (3H, s, -C-CH_3), 1.75–1.57 (4H, m, -CH_2-CH_2-).)

Dienone ***14*** *(and conjugated ynone* **13**a)

To a stirred solution of ynone-tosylate **13** (2.1 g, 5.0 mmol) in acetonitrile (50 mL) at 23°C is added triethylamine (2.1 mL, 15.0 mmol). (Spontaneous elimination of tosylate then leads to conjugated ynone **13***a*.) After stirring for 3 h at 23°C, the mixture is evaporated and purified by flash chromatography (ethyl acetate/hexanes,1:1) and yields 917 mg (74%) of **14** as a viscous liquid; R_f 0.31 (ethyl acetate/hexane,1:1); ir (CH_2Cl_2, ν cm^{-1}): 2960 (CH), 1740 (C=O ester), 1715 (C=O ketone), 1675 (C=O enone); ^{1}H nmr (250 MHz, $CDCl_3$) δ ppm: 6.30 (1H, s, -C=CH-CO), 6.28 (1H, ddd, J = 17.7, 11.2, 0.8 Hz, -HC=CH_2), 5.72 (1H, dd, J = 17.7, 0.8 Hz, -CH=CH-H), 5.43 (1H, dd, J = 11.2, 0.8 Hz, -CH=CH-H), 3.81 (3H, s, -CO_2CH_3), 3.21 (1H, m, -CH_2-CH-CH_2-), 2.69–1.70 (8H, m, -CH_2-CH_2-CH_2-CH-CH_2); ^{13}C nmr (62.9 MHz, $CDCl_3$) δ ppm: 206.4 (s, C=O ketone), 197.0 (s, C=O enone), 170.0 (s, C=O ester), 151.6 (s, CH_2=CH-C=CH-CO), 134.7 (d, -C=CH-CO), 126.0 (d, -CH=CH_2), 121.6 (t, -CH=CH_2), 66.1 (s, C quat.), 53.0 (q, -COCH_3), 42.2 (d, -CH_2-CH-CH_2-), 40.2 (t, CH_2), 40.0 (t, CH_2), 27.1 (t, CH_2), 24.5 (t, CH_2); ms, *m/e*: 248 (M^+), 220 (M^+ − CO). Exact mass calcd. for $C_{14}H_{16}O_4$ (M^+): 248.1049; found: 248.1051. For **13***a*: ir (neat, ν cm^{-1}): 2950 (CH), 2120 (C≡C), 1745 (C=O ester), 1715 (C=O ketone), 1670 (C=O enone); ^{1}H nmr (250 MHz, $CDCl_3$) δ ppm: 5.88 (3H, m, CH olefin), 3.78 (3H, s, -CO_2CH_3), 3.30 (1H, d, J = 12.5 Hz, -CO-CH-CO_2CH_3), 2.84–1.56 (9H, m, -CH_2-CH_2-CH_2CH-CH_2-). Enol form (characteristic signals): 12.4 (>1H, s, enolic H), 3.77 (>3H, s, CO_2CH_3), 3.25 (>1H, m, (OH)C=C(E)-CH-).

Enone ***18***

Upon completion of the reaction **13** → **14** monitored by tlc, 2-methyl-1,3-cyclopentanedione (840 mg, 7.5 mmol) is added to the

reaction mixture at 23°C. The mixture temperature is raised to 40°C and stirred for 36 h. After evaporation and purification by flash chromatography (ethyl acetate/hexane,3:2), 1.17 g of enone **18** (65% from ynone **13**) is isolated as a white solid; mp 110–112°C (MeO*t*-Bu); R_f 0.13 (ethyl acetate/hexane,1:1); ir (CH_2Cl_2, ν cm^{-1}): 2930, 2870 (CH), 1740, 1730 (C=O ester and ketone), 1680 (C=O enone); ^1H nmr (250 MHz, $CDCl_3$) δ ppm: 6.04 (1H, s, -C=C*H*-CO-), 3.85 (3H, s, -CO_2CH_3), 3.16 (1H, m, -CH_2-C*H*-CH_2-), 2.89–2.64 (4H, m, OC-CH_2-CH_2-CO-), 2.39 (12H, m, 6 × -CH_2-), 1.13 (3H, s, -CH_3); ^{13}C nmr (62.9 MHz, $CDCl_3$) δ ppm: 215.4, 215.3 (2s, C=O cyclopentanedione), 205.8 (s, C=O ketone), 196.4 (s, C=O enone), 170.2 (s, C=O ester), 157.2 (s, -*C*=CH-CO-), 127.8 (d, -C=*C*H-CO-), 67.5 (s, -OC-*C*(CH_3)-CO-), 56.0 (s, -OC-*C*-CO_2CH_3), 53.1 (q, -CO_2CH_3), 41.5 (d, -CH_2-*C*H-CH_2), 40.2, 39.2, 34.9, 32.0, 28.4, 27.1, 23.2 (7t, 8 × -CH_2- methylenes in cyclopentanedione are equivalent), 19.4 (q, -*C*H_3); ms, *m/e*: 360 (M^+), 342 ($M^+ - H_2O$). Exact mass calcd. for $C_{20}H_{24}O_6$ (M^+): 360.1573; found: 360.1568.

Tetraketone ***19***

Under an atmosphere of hydrogen, a suspension of enone **18** (590 mg, 1.63 mmol) and 5% palladium on carbon (59 mg, 10% w/w) in methanol (30 mL) is vigorously stirred at 23°C for 3 h. The mixture is filtered on a Celite pad and evaporated. Flash chromatography of the residue (ethyl acetate/hexane,1:1) yields 348 mg (59%) of tetraketone **19** and 83 mg (14%) of 14β-hydroxy steroid **20**. Tetraketone **19**: mp 148–149°C (cyclohexane); R_f 0.16 (ethyl acetate/hexane,1:1); ir (CH_2Cl_2, ν cm^{-1}): 2960 (CH), 1725 (C=O); ^1H nmr (250 MHz, $CDCl_3$) δ ppm: 3.83 (3H, s, -CO_2CH_3), 2.90–1.08 (20H, m, 9 × -CH_2- + 2 × -C*H*-), 1.07 (3H, s, -CH_3); ^{13}C nmr (62.9 MHz, $CDCl_3$) δ ppm: 216.4, 216.0 (2s, C=O cyclopentanedione), 208.3, 207.4 (2s, C=O ketone), 172.6 (s, C=O ester), 64.0 (s, -OC-*C*(CH_3)-CO-), 56.2 (s, -OC-*C*-CO_2CH_3), 52.8 (q, -CO_2CH_3), 41.6 (d, -CH_2-*C*H-CH_2-), 43.7, 41.8, 40.8, 35.1, 33.8, 27.3, 26.0, 21.6 (8t, 9 × -CH_2- methylenes in cyclopentanedione are equivalent), 19.8 (q, -*C*H_3); ms, *m/e*: 362 (M^+), 344 ($M^+ - H_2O$), 330 ($M^+ - CH_3OH$). Exact mass calcd. for $C_{20}H_{26}O_6$ (M^+): 362.1729; found: 362.1727.

14β-Hydroxy steroid ***20***

To a stirred solution of tetraketone **19** (200 mg, 0.55 mmol) in a 1:1 mixture of tetrahydrofuran and *tert*-butanol (8 mL) is added potassium *tert*-butoxide until pH reaches 8–9. (Approximately 3 equivalents are required.) After 3 h at 23°C, saturated ammonium chloride solution is added and the mixture is extracted with methylene chloride (6 × 30 mL). The combined organic layers are washed with brine, dried ($MgSO_4$), filtered, and evaporated to yield 169 mg of an oil. Flash chromatography of the residue (ethyl acetate/hexane,1:1) yields 109 mg (55%) of 14β-hydroxy steroid **20**; mp 169–171°C (petroleum ether 60–110); R_f 0.25 (ethyl acetate/hexane,1:1); ir (CH_2Cl_2, ν cm^{-1}): 3500 (OH), 2940 (CH), 1740 (C=O ester), 1710, 1700 (C=O ketone) cm^{-1}; ^1H nmr (250 MHz, $CDCl_3$) δ ppm: 4.35 (1H, s, -O*H*), 3.80 (3H, s, -CO_2CH_3), 2.94 (1H, m, -CH_2-C*H*-CH_2-), 2.90 (1H, d, J = 12.2 Hz, -OC-C*H*-CH-), 2.88–1.77 (14H, m), 1.58–1.06 (3H, m), 0.99 (3H, s, -C*H*$_3$); ^{13}C nmr (62.9 MHz, $CDCl_3$) δ ppm: 217.7, 213.1, 207.7 (3s, C=O ketone), 172.2 (s, C=O ester), 77.4 (s, -HC-*C*(OH)-CH_2-), 64.1 (s, -OC-*C*-(CH_3)-C-OH), 53.8 (s, -OC-*C*-CO_2CH_3), 52.2 (q, -CO_2-*C*H_3), 52.6, 45.0, 44.4 (3d, 3 × -*C*H-), 43.3, 41.3, 34.6, 31.5, 28.3, 27.7, 23.8, 22.4 (8t, 8 × -CH_2-), 19.5 (q, -*C*H_3); ms, *m/e*: 362 (M^+), 344 ($M^+ - H_2O$). Exact mass calcd. for $C_{20}H_{26}O_6$ (M^+): 362.1729; found: 362.1727.

14-Hydroxy enone steroids ***21*** *and* ***22***

Cesium carbonate (63.2 mg, 0.2 mmol) is added to a solution of enone **18** (350 mg, 0.97 mmol) in acetonitrile (15 mL). The mixture is heated at reflux for 48 h and cooled down to 23°C before filtration on silica gel. Evaporation and flash chromatography of the residue yields 189 mg (54%) of a 3:2 mixture of 14-hydroxy steroids **21** and **22**; R_f 0.22 (ethyl acetate/hexane,1:1); uv (CH_3CN) λ_{max}: 246 nm (ε 6700); ir (CH_2Cl_2, ν cm^{-1}): 3500 (OH), 2950 (CH), 1740 (C=O ester), 1715 (C=O ketone), 1660 (C=O enone). For **21**: mp 151–153°C ($CHCl_3$–heptane); ^1H nmr (250 MHz, $CDCl_3$) δ ppm: 4.27 (1H, s, -O*H*), 3.80 (3H, s, -CO_2-C*H*$_3$), 3.12 (1H, m, -CH_2-C*H*-CH_2-), 2.69–1.47 (16H, m, 8 × -CH_2), 1.10 (3H, s, -C*H*$_3$). For **22**: mp 168–170°C (MeO*t*-Bu); ^1H nmr (250 MHz, $CDCl_3$) δ ppm: 4.39 (1H, s, O*H*), 3.85 (3H, s, -CO_2CH_3), 3.24 (1H, m, -CH_2-C*H*-CH_2-), 2.90–1.20 (16H, m, 8 × -CH_2), 1.05 (3H, s, -C*H*$_3$); ms, *m/e*: 360 (M^+), 342 ($M^+ - H_2O$). Exact mass calcd. for $C_{20}H_{24}O_6$ (M^+): 360.1573; found: 360.1568.

14-Hydroxy silyl enol ether steroids ***23, 24, 25***

To a solution of a 3:2 mixture of enones **21** and **22** (100 mg, 0.28 mmol) and imidazole (47 mg, 0.69 mmol) in freshly distilled dimethylformamide (300 μL) is added *tert*-butyldimethylsilylchloride (58 mg, 0.39 mmol). The mixture is stirred at 23°C for 52 h, quenched with saturated ammonium chloride, and diluted with water (5 mL). The mixture is extracted with 1:1 ether–hexane (5 × 10 mL). The combined organic layers are washed with brine, dried ($MgSO_4$), filtered, and evaporated to yield 107 mg of an oil. Flash chromatography of the residue (ethyl acetate/hexane,1:3) yields **23** (25.0 mg) and **24** (16.7 mg) (37% yield, 67% yield based on recovered starting material) as well as **25** (1.3 mg) and recovered starting material (52.4 mg). For **23**: R_f 0.22 (ethyl acetate/hexane,3:7); ^1H nmr (250 MHz, $CDCl_3$) δ ppm: 5.17 (1H, dd, J = 6.3, 2.5 Hz, -C=C*H*-CH_2-), 4.84 (1H, s, -O*H*), 3.73 (3H, s, -CO_2CH_3), 2.80 (1H, m, -CH_2-C*H*-CH_2-), 2.75–1.65 (14H, m, 7 × CH_2), 1.12 (3H, s, -CH_3), 0.97 (9H, s, -Si-C(CH_3)$_3$, 0.27, 0.20 (6H, 2s, 2 × Si-CH_3). For **24**: R_f 0.19 (ethyl acetate/hexanes,3:7); uv (CH_3CN) λ_{max}: 250 nm (ε 20 800); ir ($CHCl_3$, ν cm^{-1}): 3500 (OH), 2930, 2860 (CH), 1740 (C=O ester), 1705 (C=O ketone); ^1H nmr (250 MHz, $CDCl_3$) δ ppm: 5.18 (1H, dd, J = 6.4, 2.5 Hz, -C=C*H*-CH_2-), 4.61 (1H, s, -O*H*), 3.76 (3H, s, -CO_2CH_3), 2.85 (1H, m, -CH_2-C*H*-CH_2-), 2.75–1.60 (14H, m, 7 × -CH_2), 1.11 (3H, s, -CH_3), 0.99 (9H, s, -Si-C(CH_3)$_3$), 0.29 (6H, s, -Si(CH_3)$_2$); ms, *m/e*: 474 (M^+), 456 ($M^+ - H_2O$), 417 ($M^+ - C_4H_9$). Exact mass calcd. for $C_{26}H_{38}SiO_6$ (M^+): 474.2437; found: 474.2444. For **25** (unseparated mixture of isomers): R_f 0.13 (ethyl acetate/hexane,3:7); ^1H nmr (250 MHz, $CDCl_3$) δ ppm: 5.58 (1H, d, J = 6.4 Hz, -CH-C*H*=C-OSi*t*BDM), 5.27 (1H, d, J = 5.0 Hz, -CH-C*H*=C-OSi*t*BDM), 3.92 (1H, s, -O*H*), 3.87 (1H, s, -O*H*), 3.74 (3H, s, -CO_2-C*H*$_3$), 3.70 (3H, s, -CO_2CH_3), 3.44 (1H, m, -C*H*-CH=C-OSi*t*BDM), 3.25 (1H, m, -C*H*-CH=C-OSi*t*BDM), 2.90–1.60 (14H, m, 7 × -CH_2), 1.21 (3H, s, -C*H*$_3$), 1.18 (3H, s, -C*H*$_3$), 0.99 (9H, s, -SiC(CH_3)$_3$), 0.98 (9H, s, -SiC(CH_3)$_3$, 0.28, 0.26 (6H, 2s, 2 × -Si-C*H*$_3$), 0.28 (6H, s, -Si(CH_3)$_2$).

Cleavage of 14-hydroxy silyl enol ether ***23*** *or* ***24****. Formation of pure 14-hydroxy steroids* ***21*** *and* ***22***

To a solution of silyl enol ether **23** (35.8 mg, 0.08 mmol) in acetonitrile at 23°C is added cesium fluoride (23.0 mg, 0.15 mmol). The mixture is stirred vigorously at 23°C for 15 min, quenched with saturated ammonium chloride, and diluted with water. The mixture is extracted with ethyl acetate and the combined organic layers are washed with brine, dried ($MgSO_4$), filtered, and evaporated to yield 25 mg of an oil. Flash chromatography of the residue (ethyl acetate/hexanes,1:1) yields 19.6 mg (73%) of 14-hydroxy steroid **21**. The same procedure applies for the reaction **24** → **22**.

Acknowledgements

We are grateful to NSERC–Canada and FCAR–Québec for financial support of this work. We also thank NSERCC summer student Dennis Hall (1988) for his technical assistance at an early stage of this work.

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