A synthetic approach to 17β-steroidal ethers derived from hydroxymalonic ester

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Abstract. Ethers (**1** and **2**) derived from dimethyl hydroxymalonate and 3-methoxy-1,3,5(10)-estratrien-17β-ol or 17β-hydroxy-4-androsten-3-one have been prepared. The cyclic ethylene acetal of 3-methoxy-1,3,5(10)-estratrien-17-one (**5**) and of 3β-benzyloxy-5-androsten-17-one (**11**) were converted stereoselectively into the corresponding 17β-(2-hydroxy-ethyl) ethers **6** and **12** respectively by $LiAlH_4/AlCl_3$. Upon oxidation, esterification and treatment with lithium diisopropylamide/methyl chloroformate the 17-bis(methoxycarbonyl)methyl esters **1** and **15** were obtained. Catalytic hydrogenolysis of **15**, followed by oxidation gave **2**.

Introduction

The natural hormones, like testosterone or estradiol lack oral activity as they are prematurely inactivated by metabolism. Therefore stable synthetic analogues are used[1,2]. Another way to circumvent this problem is the "pro-drug" approach, whereby the natural hormone is derivatised in such a manner that it will be absorbed in the digestive tract and circumvents or passes the liver without too much degradation, to release in a later stage the natural hormone. Enol ethers[3a-g] and fatty acid esters [4a-b] of estradiol and of testosterone have been used successfully. Our continuous efforts, aiming at synthesizing derivatives of natural hormones which might act as pro-drugs, led us to the synthesis of hitherto unknown mixed ethers of a hydroxymalonic ester and estradiol 3-methyl ether (**1**) and testosterone (**2**).

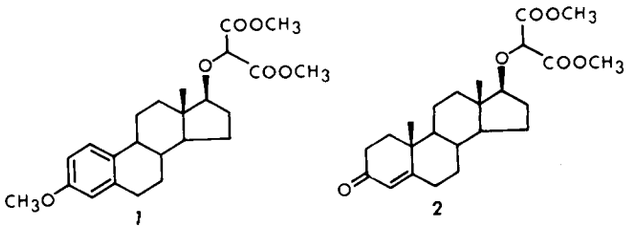


Fig. 1

Synthesis

The preparation of **1** was investigated first, since the parent skeleton contained minimal conflicting functionality. A straightforward synthesis of **1** by reaction of estradiol 3-methyl ether (**3**) with dimethyl bromomalonate (**4a**) in a Wiliamson-like ether synthesis proved to be unsuccesful (NaH in THF, DMSO, DMF or HMPT).

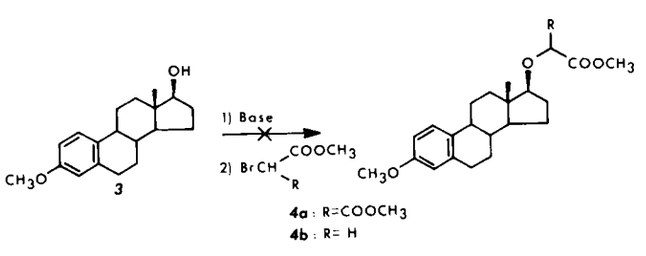
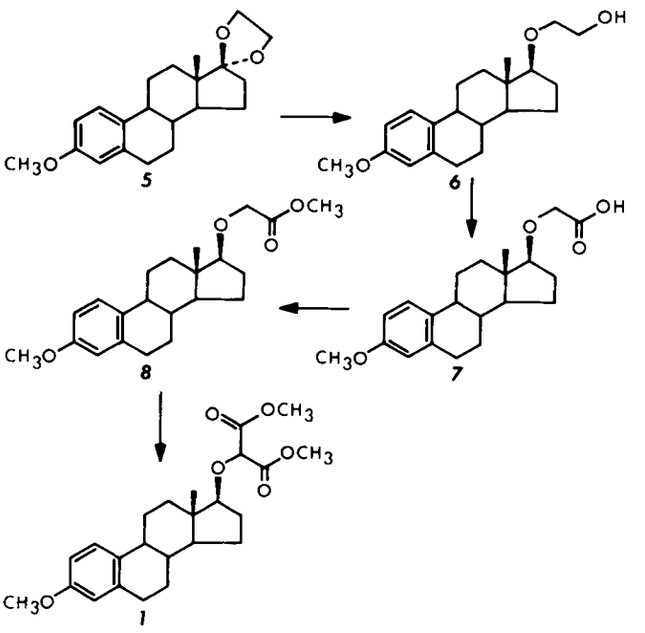


Fig. 2



Scheme 1

The reason for this failure will be the fact that the sterically hindered 17β-alcoholate acts merely as a base rather than as a nucleophile, thereby causing only deprotonation of the malonate. Even methyl/bromoacetate (**4b**) failed to undergo nucleophilic substitution under these conditions. Therefore

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[3a] *A. D. Cross* and *I. L. Harrison*, Steroids **6**, 397 (1965);
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[d] *A. D. Cross, C. Denot, H. Carpio, R. Acevedo* and *P. Crabbé*, Steroids **5**, 557 (1965);
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[g] *A. Ercoli, R. Gardi* and *R. Vitali*, Chem. Ind. 1284 (1962).
[4a] *A. Coert, J. Geelen, J. de Visser* and *J. van der Vlies*, Acta Endocrinol. 789 (1975);
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an alternative approach was employed, which consisted of the stereoselective introduction of a suitable side-chain which lent itself to further chemical modification to the required malonyl unit. It has been shown by *Crabbé* et al.[3d], that treatment of the 17-ethylene acetal of estrone methyl ether (**5**) with a large excess of a mixture of $LiAlH_4$ and $AlCl_3$[5a-g] leads to stereoselective reductive ring opening of the acetal to give **6**.

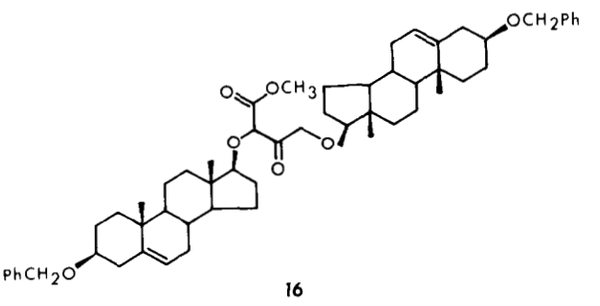
We found that, upon modifying the original prescriptions, compound **6** could be obtained in essentially quantitative yield even in large scale preparation by using only a drastically reduced amount of $LiAlH_4$–$AlCl_3$. Examination of an NMR spectrum showed the 17α proton of **6** unambiguously as a triplet at δ 3.45 (J 9 Hz).

Careful oxidation (see Experimental) of **6** with 8N chromic acid in acetone gave the carboxylic acid **7** in moderate yield (46%).

Esterification of **7** in methanol containing a catalytic amount of sulphuric acid gave the methyl ester **8** in 87% yield. The introduction of an additional methoxy carbonyl group at the α-carbon atom in the side chain by reaction with sodium hydride and an excess of dimethyl carbonate in refluxing benzene[6] failed to give any desired **1**. Alternatively, on treatment of **8** with an equivalent of lithium diisopropylamide in THF at −70° followed by a slight excess of methyl chloroformate the required **1** could be isolated in 53% yield. The preparation of the corresponding testosterone derivative **2** along the lines indicated above was a more circuitous one due to the conflicting functionality in ring A. The commercially available 3β-hydroxy-5-androsten-17-one (androstenolone, **9**) was judged to be a suitable substrate.

Acetalization of **9** with ethylene glycol, to give **10**, followed by protection of the 3β-OH function as benzyl ether with $NaH–PhCH_2Br$ in dimethylformamide gave **11** in 70% over-all yield. Reductive ring opening of the ethylene acetal with $LiAlH_4/AlCl_3$ gave the 17β-(hydroxyethyl)ether **12** in essentially quantitative yield. NMR spectrum showed a triplet of the 17α-H at δ 3.33 (J 8 Hz) which was superimposed on the 3α-H multiplet. Chromic acid oxidation provided the carboxylic acid **13** (43% yield), which was smoothly converted to the corresponding methyl ester **14** in 87% yield in refluxing methanol.

A first attempt to prepare **15**, by means of lithium diisopropylamide and methyl chloroformate at −70°, provided **15** in a disappointingly low yield (~10%). The main product, which was isolated in 56% yield by chromatography turned out to be the ester condensation product **16**.



16

Fig. 3

However, we found that upon rapid addition (~1 min.) of **14** to a cooled solution (−70°) of lithium diisopropylamide in THF followed by a very brief anion formation time (~5 min.) prior to addition of methyl chloroformate, the yield of **15** could be improved significantly to 47%. Debenzylation of **15** by means of a catalytic reduction procedure (5% Pd on charcoal in abs. ethanol) provided **17** without affecting the $\Delta^{5,6}$ double bond.

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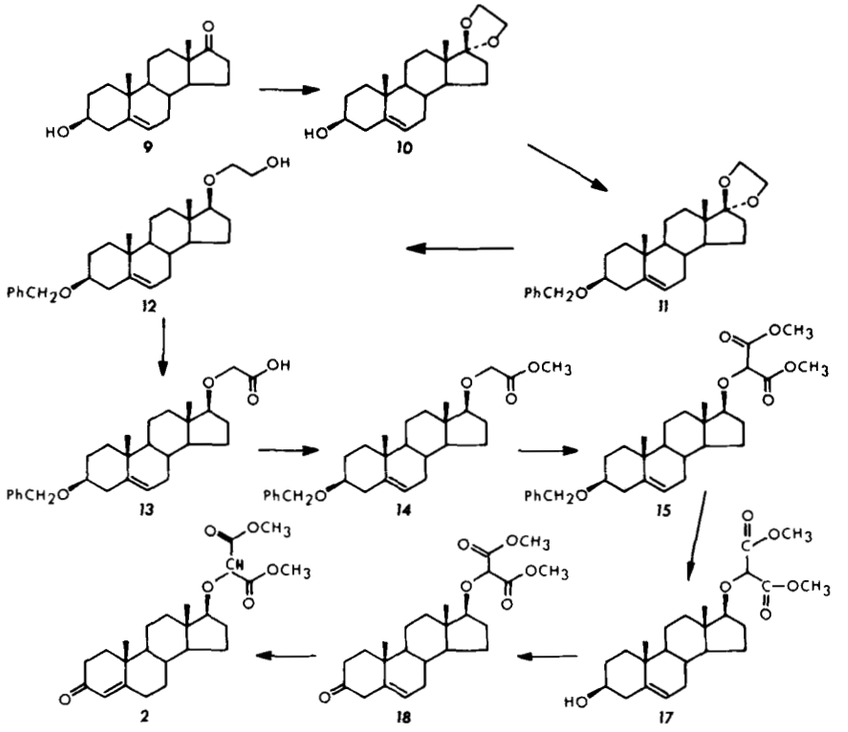

Scheme 2

The oxidation of **17** could be accomplished with pyridinium chlorochromate[7] in methylene chloride to provide the unconjugated ketone **18** in 68% yield. The final conversion of **18** into the conjugated system **2** was brought about by stirring a solution of **18** in toluene for a short time in the presence of neutral alumina[8] (grade I). This gave **2** in 68% yield.

Experimental part

General: Melting points were uncorrected and measured on a Büchi melting point apparatus. ^{1}H-NMR spectra were recorded in $CDCl_3$ solutions on a Varian A-60 spectrometer, using tetramethysilane as an internal standard. For the stereochemical assignment of **6** and of **12** and additional NMR spectrum has been recorded on a Bruker HX-90 E apparatus. The steroid substrates were purchased from Diosynth B.V. (Oss, The Netherlands). Silicagel and aluminum oxide were obtained from Merck (Darmstadt).

2-(3-Methoxy-1,3,5(10)-estratrien-17β-yloxy)ethanol (**6**)

To a solution of 4.39 g (30 mmol) of $AlCl_3$ in 10 ml of dry ether were added in portions 380 mg (10 mmol) of $LiAlH_4$. The mixture was stirred for 1 h and then a solution of 6.36 g (20 mmol) of **5** in 20 ml of dry THF was added drop by drop. The mixture was stirred for 1 h and then excess reagent was destroyed by careful addition of 10 ml of ethyl acetate followed by 20 ml of water and 20 ml of 2N HCl. The product was extracted with ether. The organic phase was washed twice with water, dried and concentrated. The remaining white solid was triturated with a small amount of n-hexane and gave 6.05 g (95%) of **6**; m.p. 108–110° (toluene/hexane) (lit.[3d] 109–110°). NMR: δ 0.83 (s, CH_3), 3.70 (m, OCH_2CH_2OH), 3.80 (s, OCH_3).

2-(3-Methoxy-1,3,5(10)-estratrien-17β-yloxy)acetic acid (**7**)

To a solution of 3.20 g (0.01 mol) of **6** in 100 ml of acetone was added dropwise at room temperature 5.5 ml of 8N chromic acid. The chromic acid should be added at such a rate that after each drop the colour of the reaction mixture was allowed to turn from orange to green. Only on doing so could a satisfactory yield be achieved! After stirring for an additional hour the precipitate was filtered and the filtrate was diluted with 500 ml of water and then extracted with methylene chloride. The formation of emulsions during the extraction could be avoided by slight acidification of the aqueous phase with 2N HCl. The crude product which resulted after washing, drying and concentration of the organic phase was purified by chromatography on a short silicagel column. Chloroform/2% CH_3OH was used as eluent. This gave 1.6 g (46%) of pure **7**; m.p. 167–168° (lit.[3d] 155–159°). NMR: δ 0.85 (s, CH_3), 3.75 (s, OCH_3), 4.12 (s, OCH_2COOH), 3.50 (t, 17α-H).

Methyl-2-(3-methoxyestra-1,3,5(10)-trien-17β-yloxy)acetate (**8**)

A solution of 3.44 g (0.01 mol) of the carboxylic acid **7** in 100 ml of methanol, containing 10 drops of concentrated sulphuric acid, was refluxed for 2 h. After concentrating the mixture on a rotary evaporator, the residue was poured into 100 ml of ice-water. The product was extracted with ether The ethereal phase was washed twice with aq. 10% $NaHCO_3$ solution and twice with water. Upon drying and concentrating, 3.10 g (87%) of essentially pure **8** were obtained; m.p. 81–82° from (iPr_2O). NMR: δ 0.83 (s, CH_3), 3.50 (m, 17α-H), 3.73 (s, 2 × OCH_3), 4,12 (s, CH_2COOCH_3).

Dimethyl-2-(3-methoxy-1,3,5(10)-estratrien-17β-yloxy)malonate (**1**)

A solution of 1 mmol of lithium diisopropylamide was prepared by addition of 650 ul of a 15%-solution of butyllithium in hexane to a solution of 150 ul of diisopropylamine in 3 ml of dry THF (freshly distilled from $LiAlH_4$) under an N_2 atmosphere. The colourless solution was cooled to −70° and a solution of 356 mg (1 mmol) of **8** in 2 ml of dry THF was introduced by syringe in one minute. After stirring for an additional 10 min at −70°, 91.5 mg (80 µl) of methyl chloroformate were added dropwise. After stirring for an additional 10 min at −70° the reaction mixture was warmed quickly to room temperature. Then 25 ml of water were added and the product was extracted with ether. The crude product which was obtained after washing, drying and concentration of the organic phase could be purified easily by column chromatography on silicagel, using toluene-5% ethyl acetate as eluent. (Rf **1**: 0.32: Rf **8**: 0.29, measured in hexane/acetone 8 : 2). This gave 220 mg (53%) of **1**; m.p. 92–94°. Analysis $C_{24}H_{32}O_6$; calcd. C, 68.26; H, 7.69; found C, 67.98; H, 7.61. NMR: δ 0.85 (s, CH_3), 3.53 (t, 17αH, 3.77 (OCH_3), 3.80 (s, $COOCH_3COOCH_3$), 4.60 (s, $CH(COOCH_3)_2$). $[\alpha]_D^{20}$ (CH_2Cl_2) +43° (c 1.00); UV (ethanol) λ_{max}: 280 nm (ε 197 mol^{-1} m^2).

3β-Hydroxy-5-androsten-17-one, cyclic 1,2-ethylene acetal (**10**)

A solution of 2.88 g (0.0100 mol) of androstenolone **9** in 100 ml of toluene, containing 100 mg of p-toluenesulphonic acid and 25 ml of ethylene glycol was refluxed with stirring under continuous removal of water by means of a Dean-Stark trap. After 4 hours, the organic phase was washed twice with 10% aq. $NaHCO_3$ solution and twice with water. After drying and evaporation of the solvent 3.10 g (93%) of **10** were obtained as a colourless solid; m.p. 160–163°. NMR: δ 0.85 (s, 18-CH_3), 1.00 (s, 18-CH_3), 1.00 (s, 19-CH_3), 3.50 (m, 3α-H), 3.87 (m, OCH_2CH_2O), 5.30 (d, H-6).

3β-Benzyloxy-5-androsten-17-one, cyclic 1,2-ethylene acetal (**11**)

To a solution of 6.6 g (0.020 mol) of **10** in 30 ml of DMF were added 1.1 g (0.022 mol) of NaH (55% dispersion in mineral oil). The mixture was heated with stirring to the temperature where rapid effervescence of hydrogen was observed (85°–90°) and then kept for 1/2 h at this temperature. Then at 0°, a solution of 3.40 g (0.020 mol, 2.36 ml) of benzyl bromide in 10 ml of DMF was added drop by drop. After stirring for an additional hour the mixture was poured in to 150 ml of water and the product was extracted with ether. The crude product, which was obtained after washing, drying and concentrating of the organic phase, was filtered through a short silicagel column (toluene/5% ethyl acetate) to give 6.0 g (71%) of **11**; m.p. 132–134° (toluene/hexane). NMR: δ 0.88 (s, 18-CH_3), 1.06 (s, 3, 19-CH_3), 3.89 (s, OCH_2CH_2O), 4.60 (s, OCH_2Ph), 5.38 (m, H-6).

2-(3β-Benzyloxy-5-androsten-17β-yloxy)ethanol (**12**)

The reductive opening of the ethylene acetal was carried out in essentially the same way as described for **6**. To a solution of 4.30 g (30 mmol) of $AlCl_3$ in 10 ml of dry ether were added 380 mg (10 mmol) of $LiAlH_4$ followed by a solution of 8.4 g (20 mmol) of **11** in 15 ml of dry THF. Work-up afforded 8.10 g (96%) of essentially pure **12**; m.p. 104–106° (ether/hexane). NMR: δ 0.80 (s, 18-CH_3), 1.05 (s, 19-CH_3), 3.60 (m, OCH_2CH_2O), 4.60 (s, 2, OCH_2Ph).

2-(3β-Benzyloxy-5-androsten-17β-yloxy)acetic acid (**13**)

To a solution of 4.24 g (0.01 mol) of **12** in 250 ml of acetone 5.5 ml of 8N chromic acid were added dropwise in a similar fashion as described for **7**. After stirring for an additional 1/2 h the precipitate was removed by filtration through celite. The filtrate was concentrated to about one third of the original volume and then diluted with 300 ml of water. After acidification to pH ~ 2 with 2N HCl the product was extracted with methylene chloride. The crude product, which remained after washing, drying and concentrating of the organic phase, was purified by chromatography on a short silicagel column ($CHCl_3$/2% CH_3OH as eluent). This gave 2.31 g (43%) of **13**; m.p. 133–136° (ether); NMR: δ 0.80 (s, 18-CH_3), 1.03 (s, 19-CH_3), 4.10 (s, OCH_2COO), 4.55 (s, 2, OCH_2Ph).

Methyl-2-(3β-benzyloxyandrost-5-en-17β-yloxy)acetiate (**14**)

A solution of 4.38 g (0.01 mol) of the carboxylic acid **13** in 100 ml of methanol, containing 10 drops of conc. H_2SO_4, was refluxed for 1 h. Most of the methanol was then removed on a rotary evaporator, and the residue was poured out into 100 ml of water. The product was extracted with ether. The etheral phase was successively washed with 10% aq. $NaHCO_3$ solution and water and then dried and concentrated to give crude **14**. Upon passing the crude product through a short silicagel column (toluene/5% ethyl acetate as eluent), 3.90 g (86%) of pure ester **14** were obtained; m.p. 148–149°. NMR: δ 0.80 (s, 18-CH_3), 1.02 (s, 19-CH_3), 3.69 (s, OCH_3), 4.07 (s, OCH_2COO), 4.52 (s, OCH_2Ph).

[7] *E. J. Corey* and *J. W. Suggs*, Tetrahedron. Lett. 2647 (1975).

[8] The chemical properties of this reagent have been reviewed recently: *G. H. Posner*, Angew. Chem. **90**, 527 (1978).

Dimethyl-2-(3β-benzyloxy-5-androsten-17β-yloxy)malonate (**15**)

To a cooled solution (−70°) of 4 mmol of lithium diisopropylamide in THF (prepared from 0.6 ml of diisopropylamine and 2.6 ml of 15%-butyllithium in 5 ml of dry THF) was added dropwise within 1 minute a solution of 1.81 g (4 mmol) of **14** in 3 ml of THF. After stirring for an additional 5 minutes at −70°, methyl chloroformate (0.32 ml, 4 mmol) was introduced dropwise by syringe. Stirring was prolonged for 10 minutes and then the reaction mixture was warmed quickly to room temperature. After the addition of 20 ml of water the product was extracted with ether. The pure product was isolated by chromatography on silicagel, using hexane/5% ethyl acetate as eluent. This gave 0.95 g (47%) of **15**, which solidified on treatment with hexane/diisopropyl ether; m.p. 98–101° (ether/hexane). N...R: δ 0.85 (s, 18-CH_3), 1.03 (s, 19-CH_3), 3.80 (s, OCH_3), 4.55 (s, 3H, OCH_2Ph and $CH(COOCH_3)_2$, 5.30 (m, H-6).

The side-product **16** which was isolated, melted at 98–101°. NMR for **16**: δ 0.80 and 0.83 (s, 6H, 2 × 18-CH_3, 1.05 (s, 6H, 2 × 19-CH_3, 3.78 (s, OCH_3), 4.30 (d, $CO-CH_2-O$), 4.55 (s, 5H, 2 × $PhCH_2O$ and CO−CH−CO), 5.30 (m, 2H-6 H-6).

R_f value in toluene/ethyl acetate (9 : 1) for **15**: 0.48; for **16**: 0.52.

Dimethyl-2-(3β-hydroxy-5-androsten-17β-yloxy)malonate (**17**)

A solution of 4.54 g (0.01 mol) of **15** in 30 ml of a mixture of abs. ethanol/THF (3/1) was hydrogenated in the presence of 400 mg of 5% palladium on charcoal. After 1/2 h the calculated amount of H_2 (~250 ml) had been taken up. The catalyst was removed by filtration over Celite. Upon concentrating the solution 4.05 g (95%) of essentially pure **17** were obtained as a colourless solid; m.p. 99–101° (toluene). NMR: δ 0.85 (s, 18-CH_3), 1.01 (s, 19-CH_3), 3.45 (m, 2H, 3αH and 17αH), 3.80 (s, 2 × OCH_3), 4.54 (s, $CH(COOCH_3)_2$), 5.30 (m, H-6).

Dimethyl-2-(3-oxo-5-androsten-17β-yloxy)malonate (**18**)

The oxidation was performed by addition of 2.5 g of pyridinium chlorochromate to a solution of 2.10 g (5 mmol) of **17** in 30 ml of methylene chloride. The progress of the reaction was monitored by tlc. After 2 h, 120 ml of ether were added to the reaction mixture. The organic layer was decanted from the precipitates, and then passed through a short Florisil column. Ether was used as eluent. Concentration of the eluate gave 1.0 g (48%) of **18**; m.p. 125–127°. NMR: δ 0.87 (s, 18-CH_3), 1.21 (s, 19-CH_3), 3.80 (s, OCH_3OCH_3), 5.30 (m, H-5), 4.54 (s, 1, $CH(COOCH_3)_2$).

Dimethyl-2-(3-oxo-4-androsten-17β-yloxy)-malonate (**2**)

To a stirred solution of 627 mg (1.5 mmol) of crude **18** in 5 ml of toluene was added 1 g of neutral alumina (act. I). The isomerization was followed by tlc. After 2 h, the alumina was filtered and the filtrate was concentrated. The residue was crystallized from diisopropyl ether to give 420 mg (68%) of analytically pure **2**; m.p. 89–91°. NMR: δ 0.87 (s, 18-CH_3), 1.20 (s, 19-CH_3), 3.40 (d, 17αH), 3.80 (s, 2 × OCH_3), 4.50 (s, $CH(COOCH_3)_2$), 5.70 (broad s, H-4). Analysis $C_{24}H_{34}O_6$; calcd. C, 68.59; H, 8.21; found C, 68.40; H, 8.23. $[\alpha]_D^{20}$ (CH_2Cl_2) +83° (c = 1.00); UV (ethanol λ_{max} 240 nm (ε 1670) mol^{-1} m^2).

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Sulfenylated cyclic β-keto esters and cyclic β-diketones; synthesis and reactions with nucleophiles

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Abstract.—Quenching the enolates of cyclic β-diketones or 2-oxocycloalkanecarboxylates with phenylsulfenyl chloride or methylsulfenyl chloride produces the corresponding α-sulfenylated products. Nucleophilic attack on these α-sulfenylated 1,3-dicarbonyl compounds produces regiospecific sulfenylated linear dicarboxylic acids, acid esters, diesters or oxo esters suitable for further chemical transformation, this has been demonstrated in the synthesis of the queen substance of the honoy bee. In some cases recyclization of the intermediate enolates was observed to regiospecific sulfenylated cyclohexenones.

Introduction

α-Sulfenylated carbonyl compounds have found extensive applications in organic synthesis[1]. In the more intriguing reaction sequences the sulfenyl group stays in the molecule in order to direct or facilitate specific transformations at several stages of the synthetic pathway. This is beautifully illustrated by *Trost* et al.[2] in the oxidative cleavage of 2,2-dithiocycloalkan-1-ols to functionalized α-mercapto thio esters which can be used for further chemical elaboration.

We wish here to report the synthesis of sulfenylated cyclic β-dicarbonyl compounds and their reactions with nucleophiles. Especially the ring cleavage reactions to a variety of functionalised α-sulfenylated esters, illustrate the multiple role of the sulfenyl group in this reaction sequence.

[1] *B. M. Trost*, Chem. Rev. **78**, 363 (1978).

[2] *B. M. Trost* and *K. Hiroi*, J. Am. Chem. Soc. **98**, 4313 (1976).