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Hemisynthesis of (20S,24R)-20,24-Epoxy-3β,16β,25-Trihydroxy-6-Oxo-5α-Cholestane 16-Acetate from Diosgenin

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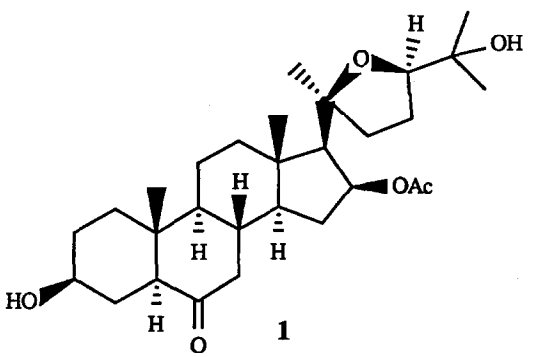
Abstract: The title compound which was isolated as its 3β-sophoroside from the defensive secretion of *Chrysomela varians* (Coleoptera: Chrysomelidae) has been synthesized from diosgenin in 8 steps.

Chrysomelid beetles belonging to the subtribe Chrysolinina generally produce cardiac glycosides in their defensive glands[1]. However, several species of Chrysolinina exclusively feeding on *Hypericum* plants produce characteristic polyoxygenated steroid glycosides. Till now, fifteen of these compounds have been isolated and their structure determined by spectroscopic methods[2-4]. They are characterized by a cholestane or a stigmastane skeleton having an unusual oxidation pattern, at C-3, C-6, C-16, C-20, C-25 and C-24 or C-28. Among these compounds, (20S,24R)-20,24-epoxy-3β,16β,25-trihydroxy-6-oxo-5α-cholestane 16-acetate- 3-*O*-β-sophoroside is so far unique in possessing a tetrahydrofurane ring in the side chain[3]. We have now undertaken the hemisynthesis of the steroidal moiety (**1**) of this compound to prove unambiguously its structure and its configuration at C-20 and C-24, and to obtain a sufficient amount of material in order to evaluate its biological activities.



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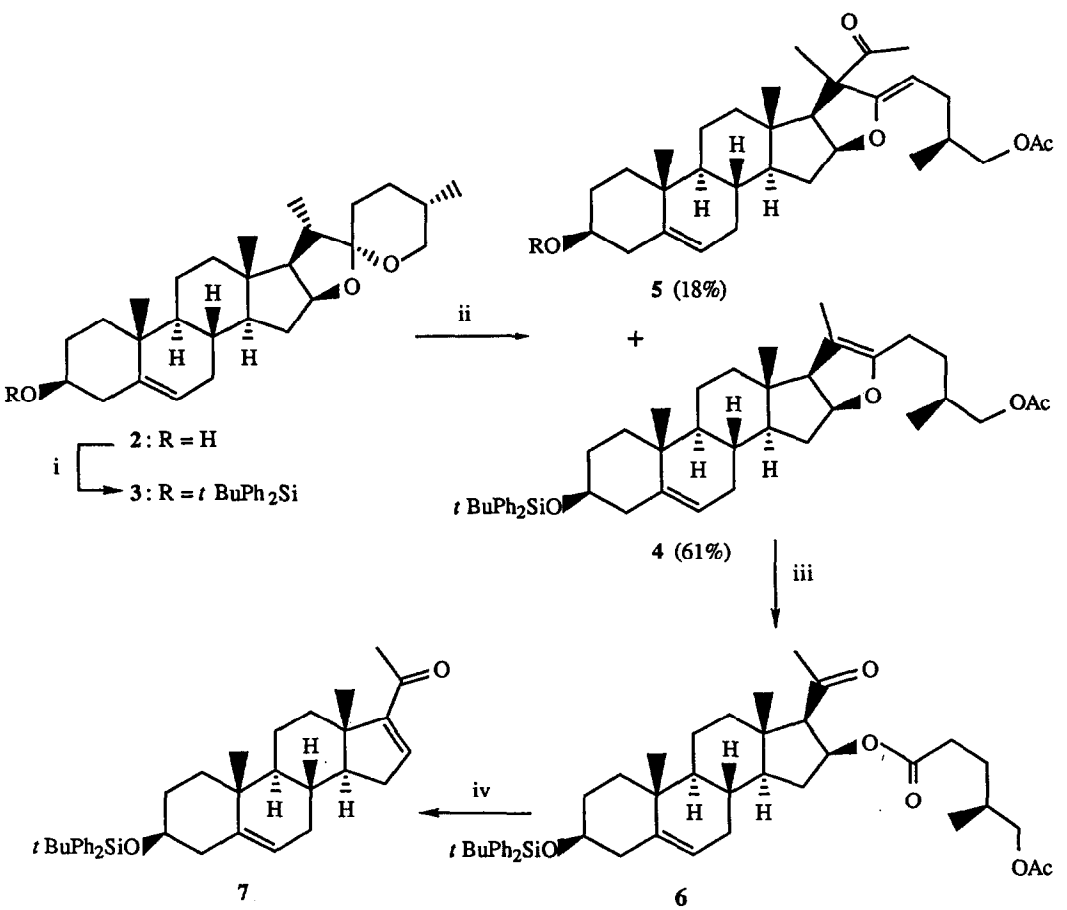
The key steps of the hemisynthesis are i) the generation of ketoester **6** by degradation of the side chain of diosgenin **2**; ii) a Grignard reaction between **6** and 4-methylpent-3-enylmagnesium bromide to afford the (20S)-alcohol **8**; iii) the stereoselective formation[5] of the (20S,24R)-tetrahydrofurane derivative **14** by

oxidation of **13** with *tert*-butyl hydroperoxide in the presence of $VO(AcAc)_2$; and iv) the introduction of the 6-oxo functionality by hydroboration-oxidation of the Δ^5 double bond of **14**.

Our synthesis began with the preparation of ketoester **6** as follows (scheme 1). Diosgenin was first protected as its *tert*-butyldiphenylsilylether **3**, and the latter was submitted to a side chain degradation using the conditions recently described by Micovic et al.[6] (acetic anhydride, pyridine, ammonium chloride, 150°C). This led cleanly to enol ether **4**, which was obtained in 61% yield after chromatography on silica gel. A minor compound (18%) was also isolated from the reaction mixture and characterized as **5** on the basis of its spectral properties (see Experimental). It arises most probably from an electrophilic attack of CH_3CO^+ on the 20(22) double bond of **4**, followed by proton loss from C-23. Treatment of **4** with CrO_3 in acetic acid[7] afforded the crude ketoester **6** in 78% yield. However, during its purification by silica gel or Florisil chromatography, a substantial amount of the conjugated ketone **7** was always obtained. The latter is formed by elimination of the C-16 ester group of **6**, a transformation already well-documented in the literature[8].

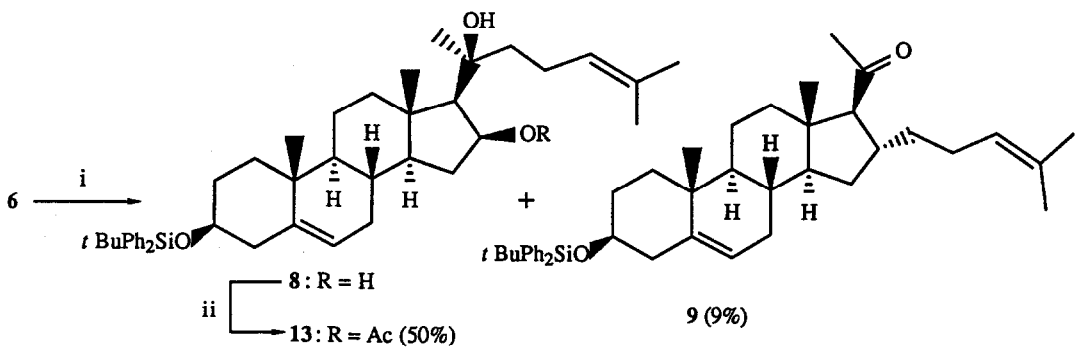


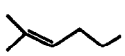
Scheme 1. i) *t* $BuPh_2SiCl$, imidazole, DMF, r.t., 24 h; ii) Ac_2O, Py, NH_4Cl, 150°C, 8 h; iii) CrO_3, AcOH, 0°C →r.t., 30 min; iv) SiO_2 or Florisil chromatography, or trace of acid or base.

Thus, after ordinary flash chromatography on silica gel, the yields of **6** and **7** were respectively 44 and 15%, whereas purification by vacuum liquid chromatography afforded **6** in 52% yield.

The next step (scheme 2) was the stereoselective introduction of the 2-methylpent-2-enyl side chain at C-20 of **6**. To this aim, 5-bromo-2-methylpent-2-ene was synthesized in 80% yield as described previously[9].

Grignard reactions on 20-oxosteroids are known to be stereoselective and to favour the (20S)-hydroxy epimer over the (20R)-epimer. For example, (20S)- and (20R)-20-hydroxycholesterol were obtained in a 1.6:1 ratio by reaction of pregnenolone acetate with 4-methylpentylmagnesium bromide[10]. The latter was also reacted on a compound closely related to ketoester **6** (3-Ac instead of 3-*t* $BuPh_2Si$)[11]. In this case, however, the reaction was conducted in refluxing benzene for 14 h using a large excess (20 eq) of Grignard reagent, leading to only 16% of the expected 20-hydroxy derivative (unspecified configuration at C-20)[11]. We found that treatment of **6** with 6 eq of 4-methylpent-3-enylmagnesium bromide at room temperature for 1 h afforded the expected alcohol **8**, isolated as its C-16 acetyl derivative **13** in 50% yield, after flash chromatography (scheme 2).



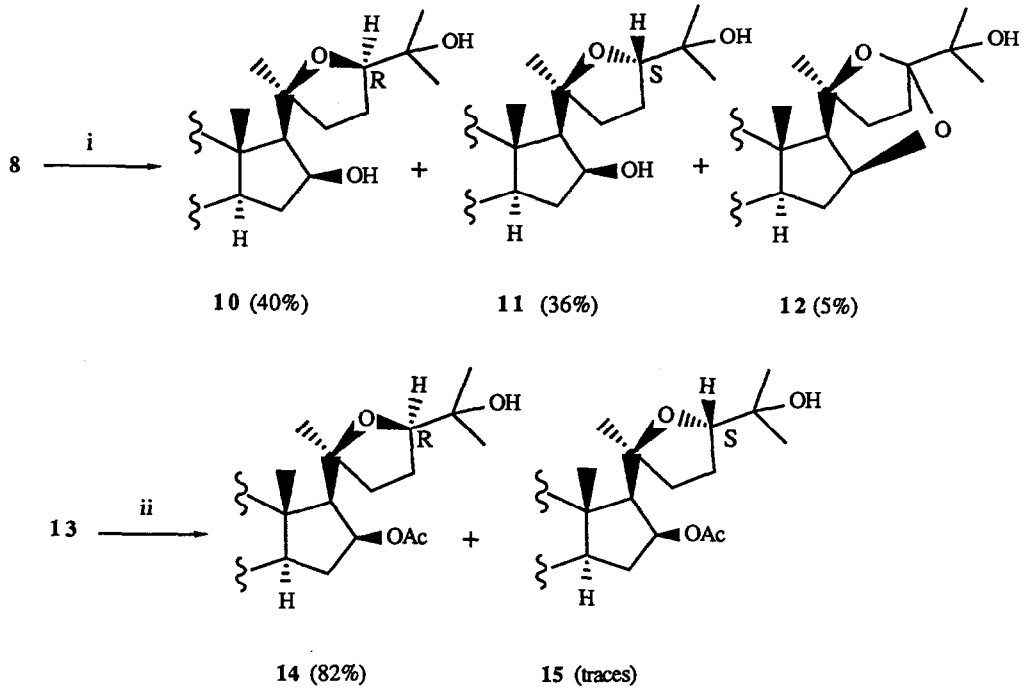
Scheme 2. i)  , Et_2O, O°C, then, r.t., 1 h; ii) Ac_2O, Py, r.t., 72h.

It was accompanied by 9% of a compound identified as **9**, on the basis of its spectral properties. The latter is probably formed by elimination of the C-16 ester group (**6**→**7**), and subsequent 1,4-addition of the Grignard reagent upon the α face of the unsaturated ketone moiety of **7**[12]. The yield of **8** could not be improved despite several modifications of the experimental procedure (lower temperature, varying the addition rate of ketoester **6** to the Grignard reagent, inverted addition). The 20S stereochemistry of **8** was supported not only by the expected stereochemical course of the reaction[10], but also by the chemical shift[10] of the 21-CH_3 group in ^1H NMR (δ 1.30). In our case, the 20R-epimer could not be detected in the reaction mixture. This highly stereoselective reaction could result from the presence in compound **6** of a bulky ester substituent at C-16 β.

A key step of our synthesis was the stereoselective introduction of the 20,24-tetrahydrofurane moiety in the side chain. It is known that allylic and homoallylic alcohols treated with *tert*-butyl hydroperoxide in the presence of catalytic amounts of $VO(AcAc)_2$ afford stereoselectively (9:1 ratio) the epoxide which is *syn* with respect to the hydroxyl function[13]. Moreover, this reaction can also be applied to dihomoallylic alcohols with the same stereoselectivity, but in this case, the resulting epoxyalcohol is not isolated and cyclizes directly by a

SN_2 reaction into a tetrahydrofurane ring under the influence of the vanadium catalyst[14,15]. Thus, we submitted diol **8** to these experimental conditions (scheme 3) but were disappointed to obtain, after flash chromatography, a mixture of the two diastereomeric tetrahydrofuranes **10** (40%) and **11** (36%) together with a minor compound (5%), tentatively identified as **12**. The stereochemistry of **10** and **11** was ascertained by comparison of their ^1H NMR spectra with that of **14** (*vide infra*). This lack of stereoselectivity could be attributed to the presence in **8** of a free hydroxyl group at C-16β, able to coordinate with the vanadium catalyst and thus to promote an epoxidation of the Δ^{24} double bond which competes with that directed by the C-20 hydroxyl group. To test this hypothesis, monoacetate **13** was submitted to the above-mentioned epoxidation conditions (scheme 3). In this case, we indeed obtained tetrahydrofurane **14** (yield 82%), whose *R* configuration at C-24 is based on the known stereochemical course of the $VO(AcAc)_2$ catalyzed oxidation reaction and subsequent cyclization[13,14,15], as discussed above, accompanied by traces of its C-24 epimer **15**.

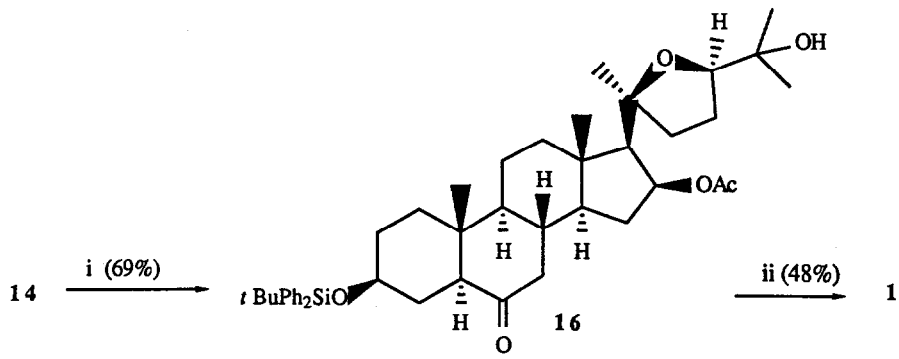
To complete our synthesis, there remained only to introduce the 6-oxo group on the steroid skeleton by hydroboration-oxidation of the Δ^5 double bond of **14**. This seemingly straightforward transformation was



Scheme 3. i) TBHP, $VO(AcAc)_2$, CH_2Cl_2, r.t., 4 h; ii) id, 24 h.

unexpectedly difficult to perform. After several experiments with model compounds *(vide infra)*, the best yields of 6-oxo derivative **16** (69%) were obtained by treatment of **14** with 10M BH_3.DMS (24 eq) in

CH_2Cl_2, at room temperature for 24 h, followed by oxidation with PCC adsorbed on silica gel in CH_2Cl_2 under ultrasounds. Deprotection of **16** with tetra *n*-butyl ammonium fluoride afforded the target compound **1** (scheme 4), the spectral properties of which were in complete agreement with those of the steroidal moiety of the natural sophoroside[3].

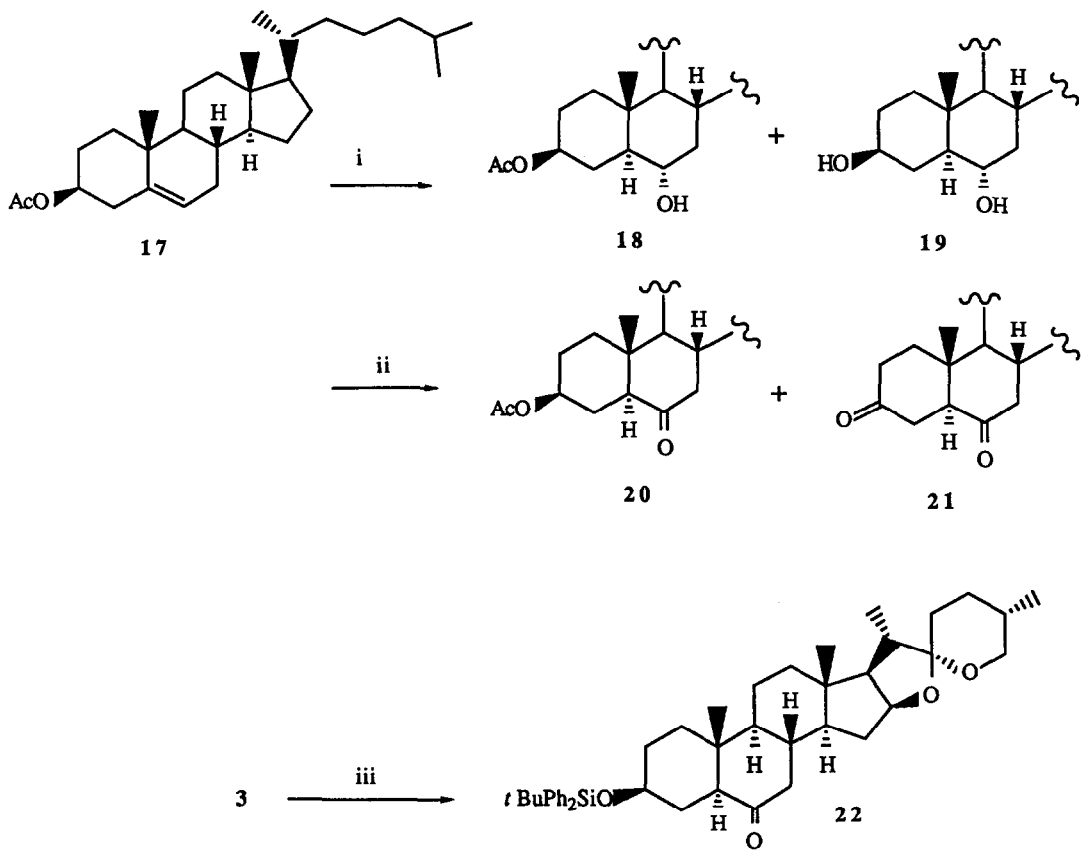


Scheme 4. i) BH_3.DMS (24 eq), CH_2Cl_2, r.t., 24 h, then PCC/SiO_2, CH_2Cl_2, ultrasounds, 2h; ii) *n* Bu_4NF, THF, 72 h..

The problems we encountered with the hydroboration-oxidation procedure deserve some comments. We first planned to synthesize **1** starting with diosgenin acetate. However, when we submitted a model compound, namely 3β-acetoxycholest-5-ene (**17**), to treatment with 10M BH_3.DMS (20 eq)[16] at room temperature for 3 h, followed by the usual oxidation with H_2O_2/2N NaOH[17], we obtained a mixture of 3β-acetoxy-6α-hydroxy-5α-cholestane (**18**) and 3β, 6α-dihydroxy-5α-cholestane (**19**) in a ratio of 3:7 (scheme 5). This result was first attributed to the hydrolysis of the acetate group under the basic conditions used in the borane oxidation step. Thus, the hydroboration-oxidation was repeated by replacing the 2N NaOH solution successively by $NaBO_3$[18] (ratio **18/19**: 5:5), by NaOAc[19] (ratio **18/19**: 6:4) or by a phosphate buffer, pH 7.0[20] (ratio **18/19**: 6:4). These results showed that even under neutral conditions a high proportion of diol **19** was still obtained. This prompted us to try the direct formation of the 6-oxo derivative by oxidation of the intermediate borane by PCC, as recently described by Parish et al[21]. These authors report that treatment of **17** with 1M BH_3.THF (3.15 eq) at 2°C for 1 h, followed by PCC oxidation for 3 h in refluxing CH_2Cl_2 containing molecular sieves, leads cleanly to 3β-acetoxy-6-oxo-5α-cholestane (**20**) in 72% yield.

However, in our hands, these conditions led only to the recovery of the starting material. When an excess of BH_3.THF was used at room temperature, we obtained after PCC oxidation and chromatography the desired monoketone **20** (26%) and the 3,6-dione **21** (6%). Replacement of 1M BH_3.THF by 10M BH_3.DMS (18 eq) and using buffered PCC in the oxidation step afforded 25% of **21** and 6% of **20**. Thus, taking into account the reported stability of esters towards PCC[22], it seemed likely that the formation of the 3,6-dione **21** may be attributed to a reduction of the C-3 acetate group of **17** by BH_3, followed by PCC oxidation of the resulting alcohol. Ester groups are reported to be much more slowly reduced by BH_3 than carbon-carbon double bonds[23], but the presence of an unsaturation in the vicinity of the ester group increases the rate of

reduction of the latter[24]. This could explain the results reported above for 3β-acetoxycholest-5-ene (**17**). Since the hydroboration of the trisubstituted Δ^5 double bond of steroids is slow, a competition between this reaction and acetate reduction becomes possible. Consequently, the *tert*-$BuPh_2Si$ group was chosen as protective group for the OH group at C-3. Indeed, in a model experiment, 3-*tert*-butyldiphenylsilyldiosgenin **3** was treated with 1M BH_3.THF (9 eq) at room temperature for 24 h, followed by PCC oxidation in refluxing CH_2Cl_2 for 1 h, affording the expected 6-oxo derivative **22** in 70% yield (scheme 5).



Scheme 5. i) BH_3.DMS (20 eq), r.t., 3 h, then see text; ii) BH_3.THF (excess), r.t., 24 h, then PCC, CH_2Cl_2, reflux, 3 h; iii) BH_3.THF (9 eq), r.t., 24 h; PCC, CH_2Cl_2, reflux, 1 h.

EXPERIMENTAL

^{1}H NMR spectra (250MHz) were recorded on a BRUKER WM 250 spectrometer and are reported in ppm from internal TMS on the δ scale ($CDCl_3$). Data are reported as follows: chemical shift [multiplicity (s: singlet, d: doublet, bd: broad doublet, t: triplet, q: quartet, m: multiplet), coupling constant in Hertz]. Infrared spectra were taken with a BRUKER IFS 25 instrument. Mass spectra were recorded on a VG Micromass 7070 spectrometer. Thin layer chromatography analyses were performed on POLYGRAM silica gel SILG/UV$_{254}$ precoated plates (0.25mm). Column chromatography was performed over MACHEREY-NAGEL silica gel (0.04-0.063 mm). During work up, organic solutions were dried with $MgSO_4$.

Preparation of 3.

To a magnetically stirred solution of diosgenin **2** (2.34 g, 5.65 mmol) and imidazole (2.47 g, 36.28 mmol) in dry DMF (85 ml) was added a solution of *tert*-butyldiphenylsilyl chloride (4.40 g, 16.0 mmol) in dry DMF (5 ml). The reaction mixture was stirred for 24 h at room temperature. After extraction of the product with hexane (5x50 ml), and concentration in vacuo, silica gel flash chromatography (hexane/acetone 95:5) led to white needles (F: 165-167°C) of **3** (3.60 g, 5.52 mmol, 98%) : EIMS m/z 652 ($M^{+\cdot}$), 595 ($M^{+\cdot}$-C_4H_9), 518 ($M^{+\cdot}$-C_4H_9-C_6H_5), 199; IR (KBr) 1078 and 982 cm^{-1} (Si-O) ; ^{1}H NMR δ 0.76 (s, 3H, H_3C-18), 0.77 (d: 7.8 Hz, 3H, H_3C-27), 0.95 (d: 6.9 Hz, 3H, H_3C-21), 0.99 (s, 3H, H_3C-19), 1.05 (s, 9H, *ter* -Bu), 3.35 (m, 2H, H_2C-26), 3.48 (m, 1H, HC-3), 4.38 (m, 1H, HC-16), 5.11 (bd: 5.1 Hz, 1H, HC-6), 7.37 (m, 6H, H-Ar), 7.67 (m, 4H, H-Ar).

Preparation of enol ether 4.

Compound **3** (4.17 g, 6.40 mmol), NH_4Cl (0.68 g, 12.7 mmol) and py (1.0 g, 12.78 mmol) were stirred for 8 h at 150°C in Ac_2O (30 ml). The mixture was extracted with hexane (3x75 ml), washed and dried. Purification of the crude product by flash chromatography (hexane/acetone 95:5 to 90:10) gave enol ether **4** (2.70 g, 3.89 mmol, 61%) and ketone **5** (F: 72-73°C) (0.84 g, 1.14 mmol, 18%).

4: EIMS m/z 694 ($M^{+\cdot}$), 637 ($M^{+\cdot}$-C_4H_9), 199; IR (NaCl) 1732 (C=O), 1694 cm^{-1} (C=C); ^{1}H NMR δ 0.66 (s, 3H, H_3C-18), 0.93 (d: 6.7 Hz, 3H, H_3C-27), 1.0 (s, 3H, H_3C-19), 1.06 (s, 9H, *tert*-Bu), 1.56 (s, 3H, H_3C-21), 2.04 (s, 3H, OAc), 2.43 (d: 10.1 Hz, 1H, HC-17), 3.53 (m, 1H, HC-3), 3.96, 3.86 (AB of ABX, J_{AB} 10.7 Hz, J_{AX} 6.0 Hz, J_{BX} 6.6 Hz, 2H, H_2C-26), 4.70 (m, 1H, HC-16), 5.12 (bd: 5.2 Hz, 1H, HC-6), 7.38 (m, 6H, H-Ar), 7.67 (m, 4H, H-Ar).

5: EIMS m/z 736 ($M^{+\cdot}$), 693 ($M^{+\cdot}$-C_2H_3O), 679 ($M^{+\cdot}$-C_4H_9), 636 ($M^{+\cdot}$-C_4H_9-C_2H_3O), 199; IR (KBr) 1738 cm^{-1} (C=O); ^{1}H NMR δ 0.86 (s, 3H, H_3C-18), 0.92 (d: 6.7 Hz, 3H, H_3C-27), 0.98 (s, 3H, H_3C-19), 1.05 (s, 9H, *tert*-Bu), 1.40 (s, 3H, H_3C-21), 2.04 (s, 3H, OAc), 2.18 (s, 3H, $COCH_3$), 2.41 (d: 6.5 Hz, 1H, HC-17), 3.53 (m, 1H, HC-3), 3.98, 3.85 (AB of ABX, J_{AB} 10.7 Hz, J_{AX} 5.9 Hz, J_{BX} 6.7 Hz, 2H, H_2C-26), 4.22 (t: 7.2 Hz, 1H, HC-23), 4.51 (m, 1H, HC-16), 5.10 (bd: 4.7 Hz, 1H, HC-6), 7.37 (m, 6H, H-Ar), 7.67 (m, 4H, H-Ar).

Preparation of ketoester 6.

To a magnetically stirred solution of **4** (2.16 g, 3.11 mmol) in AcOH precooled to 0°C was added dropwise a solution of CrO_3 (0.50 g, 5.0 mmol) in 90% aqueous AcOH (10 ml). When 90% of the solution had been added, cooling was discontinued and the remaining portion added. After stirring for 0.5 h at room temperature, the mixture was treated slowly with a saturated solution of $NaHCO_3$ until neutral pH was

reached. The resulting solution was extracted with Et_2O (5x100 ml) and the combined extracts washed with aqueous $NaHCO_3$, with H_2O, dried and concentrated to dryness (temperature less than 60°C), yielding the crude ketoester **6** (1.75 g, 2.40 mmol, 78%), that was purified by silica gel vacuum liquid chromatography (hexane/acetone 8:2) to give white crystals of **6** (F: 108-109°C) (1.17 g, 1.62 mmol, 52%). Standard flash chromatography (hexane/acetone 90:10 to 85:15) of a portion (1.30 g) of this material on silica gel led to the isolation, besides **6**, of unsaturated ketone **7** (0.20 g, 0.37 mmol, 15%).

6: EIMS m/z 724 ($M^{+\cdot}$), 667 ($M^{+\cdot}$-C_4H_9), 494 ($M^{+\cdot}$-$C_8H_{13}O_4$-C_4H_9), 199; IR (KBr) 1734 (C=O), 1712 (C=O), 1232, 1184 cm^{-1} ; ^1H NMR δ 0.92 (d: 6.6 Hz, 3H, H_3C-27), 1.00 (s, 3H, H_3C-19), 1.03 (s, 3H, H_3C-18), 1.05 (s, 9H, *tert*-Bu), 2.04 (s, 3H) and 2.05 (s, 3H) (H_3C-21 and OAc), 3.52 (m, 1H, HC-3), 3.89 (d: 6.0 Hz, 2H, H_2C-26), 5.10 (bd: 4.9 Hz, 1H, HC-6), 5.49 (dt: 7.7, 4.3 Hz, 1H, HC-16), 7.37 (m, 6H, H-Ar), 7.67 (m, 4H, H-Ar).

7: EIMS m/z 550 ($M^{+\cdot}$), 493 ($M^{+\cdot}$-C_4H_9), 199; IR (NaCl) 1652 cm^{-1} ; ^1H NMR δ 0.89 (s, 3H, H_3C-18), 1.02 (s, 3H, H_3C-19), 1.06 (s, 9H, *tert*-Bu), 2.23 (s, 3H, H_3C-21), 3.52 (m, 1H, HC-3), 5.13 (bd: 5.3 Hz, 1H, HC-6), 6.67 (t: 1.8 Hz, 1H, HC-16), 7.36 (m, 6H, H-Ar), 7.66 (m, 4H, H-Ar).

Preparation of monoacetate 13

A solution of freshly distilled 5-bromo-2-methylpent-2-ene (0.96 g, 5.89 mmol) in dry Et_2O (5 ml) was added dropwise to Mg turnings (0.20 g, 8.33 mmol) in dry Et_2O (5 ml) under N_2. After stirring for 0.5 h at room temperature, the mixture was gently refluxed (2-3 hrs) on a waterbath, till complete disappearance of the Mg. To this solution was added dropwise ketoester **6** (0.71 g, 0.98 mmol) in dry Et_2O (12 ml) at 0°C. The mixture was stirred for 1 h at room temperature, then treated with aqueous NH_4Cl and extracted with Et_2O (3x50 ml). Acetylation of the crude product (Ac_2O, py, r.t., 72 h) afforded, after flash chromatography (hexane/acetone 95:5), monoacetate **13** (340 mg, 0.49 mmol, 50%) and compound **9** (56 mg, 0.09 mmol, 9%). A portion of the unacetylated material was purified by flash chromatography (hexane/acetone 90:10 to 85:15), yielding crystals (F: 124-126°C) of diol **8**.

13: amorphous solid; EIMS m/z 696 ($M^{+\cdot}$), 639 ($M^{+\cdot}$-C_4H_9), 621 ($M^{+\cdot}$-C_4H_9-H_2O), 579 ($M^{+\cdot}$-C_4H_9-$C_2H_4O_2$), 561 ($M^{+\cdot}$-C_4H_9-$C_2H_4O_2$ -H_2O), 199; IR (NaCl) 3418 (OH), 1732 cm^{-1} (C=O) ; ^1H NMR δ 1.0 (s, 3H, H_3C-19), 1.05 (s, 3H, *tert*-Bu), 1.10 (s, 3H, H_3C-18), 1.28 (s, 3H, H_3C-21), 1.58 (s, 3H, H_3C-26), 1.66 (s, 3H, H_3C-27), 2.07 (s, 3H, OAc), 2.96 (s, 1H, OH), 3.53 (m, 1H, HC-3), 5.09 (m, 2H, HC-6, HC-24), 5.34 (m, 1H, HC-16), 7.38 (m, 6H, H-Ar), 7.66 (m, 4H, H-Ar).

9: oil; EIMS m/z 636 ($M^{+\cdot}$), 579 ($M^{+\cdot}$-C_4H_9), 496 ($M^{+\cdot}$-C_4H_9-C_6H_{11}), 199; IR (NaCl) 1704 cm^{-1} (C=O) ; ^1H NMR δ 0.63 (s, 3H, H_3C-18), 0.97 (s, 3H, H_3C-19), 1.06 (s, 9H ,*tert*-Bu), 1.66 (s, 6H, $(CH_3)_2C$=), 2.09 (s, 3H, H_3CCO), 3.54 (m, 1H, HC-3), 5.07 (m, 2H, HC-16, HC=), 7.38 (m, 6H, H-Ar), 7.67 (m, 4H, H-Ar).

8: EIMS m/z 654 ($M^{+\cdot}$), 597 ($M^{+\cdot}$-C_4H_9), 579 ($M^{+\cdot}$-C_4H_9-H_2O), 571 ($M^{+\cdot}$-C_6H_{11}), 199; IR (KBr) 3206 cm^{-1} (OH) ; ^1H NMR δ 1.02 (s, 3H, H_3C-19), 1.07 (s, 9H, *tert* Bu), 1.14 (s, 3H, H_3C-18), 1.30 (s, 3H, H_3C-21), 1.62 (s, 3H, H_3C-26), 1.69 (s, 3H, H_3C-27), 3.53 (m, 1H, HC-3), 4.60 (m, 1H, HC-16), 5.14 (m, 2H, HC-6, HC-24), 7.39 (m, 6H, H-Ar), 7.69 (m, 4H, H-Ar).

TBHP oxidation of diol 8.

To a solution of **8** (22.2 mg, $3.39.10^{-2}$ mmol) in dry CH_2Cl_2 (3 ml) was added dropwise a freshly dried[13] solution of TBHP (16 µl, $3.70.10^{-2}$ mmol) in the presence of catalytic amounts of $VO(AcAc)_2$ (0.5 mg, $2.8.10^{-3}$ mmol) and the mixture was stirred for 4 h at room temperature. Removal of the solvent and purification of the crude mixture by silica gel flash chromatography (hexane/acetone 95:5 to 85:15) gave three

compounds: **10** (9.1 mg, $1.36.10^{-2}$ mmol, 40%), **11** (8.2 mg, $1.22.10^{-2}$ mmol, 36%) and **12** (1.2 mg, $1.74.10^{-3}$ mmol, 5%).

10: oil; EIMS m/z 670 ($M^{+}\cdot$), 613 ($M^{+}\cdot$-C_4H_9), 199, 143 ($C_8H_{15}O_2^{+}$); IR (NaCl) 3382 cm^{-1} (OH) ; ^1H NMR δ 1.0 (s, 3H, H_3C-18 or H_3C-19), 1.05 (s, 12H, *tert* -Bu and H_3C-19 or H_3C-18), 1.11 (s, 3H, H_3C-26), 1.20 (s, 3H, H_3C-21), 1.34 (s, 3H, H_3C-27), 3.52 (m, 1H, HC-3), 3.85 (dd: 6.0, 10.0 Hz, 1H, HC-24), 4.49 (m, 1H, HC-16), 5.12 (bd: 5.2 Hz, 1H, HC-6), 7.36 (m, 6H, H-Ar), 7.68 (m, 4H, H-Ar).

11: oil; EIMS m/z 670 ($M^{+}\cdot$), 613 ($M^{+}\cdot$-C_4H_9), 199, 143 ($C_8H_{15}O_2^{+}$) ; IR (NaCl) 3382 cm^{-1} (OH) ; ^1H NMR δ 1.0 (s, 3H, H_3C-19), 1.05 (s, 9H, *tert*-Bu), 1.08 (s, 3H, H_3C-18), 1.13 (s, 3H, H_3C-26), 1.23 (s, 3H, H_3C-21), 1.31 (s, 3H, H_3C-27), 3.53 (m, 1H, HC-3), 3.81 (t: 7.3 Hz, 1H, HC-24), 4.53 (m, 1H, HC-16), 5.17 (bd: 4.9 Hz, 1H, HC-6), 7.37 (m, 6H, H-Ar), 7.67 (m, 4H, H-Ar).

12: oil; EIMS m/z 668 ($M^{+}\cdot$), 611 ($M^{+}\cdot$-C_4H_9), 593 ($M^{+}\cdot$-C_4H_9-H_2O), 199; IR (NaCl) 3445 cm^{-1} (OH) ; ^1H NMR δ 1.0 (s, 3H) and 1.02 (s, 3H) (H_3C-18 and H_3C-19), 1.05 (s, 9H, *tert*-Bu), 1.17 (s, 3H, H_3C-26), 1.26 (s, 3H, H_3C-21), 1.39 (s, 3H, H_3C-27), 3.53 (m, 1H, HC-3), 4.36 (m, 1H, HC-16), 5.10 (bd: 5.1 Hz, 1H, HC-6), 7.37 (m, 6H, H-Ar), 7.67 (m, 4H, H-Ar).

TBHP oxidation of monoacetate 13.

To a solution of **13** (25.0 mg, $3.59.10^{-2}$ mmol) in dry CH_2Cl_2 (3 ml) was added dropwise a freshly dried[13] solution of TBHP (25 µl, $5.78.10^{-2}$ mmol) in the presence of catalytic amounts of $VO(AcAc)_2$ (0.5 mg, $2.80.10^{-3}$ mmol). The mixture was stirred for 24 h at room temperature. Removal of the solvent and purification of the crude mixture by silica gel flash chromatography (hexane/acetone 95:5) afforded **14** (F: 55-56°C) (21.0 mg, $2.95.10^{-2}$ mmol, 82%) as major product and its C-24 epimer **15** as traces.

14: EIMS m/z 712 ($M^{+}\cdot$), 655 ($M^{+}\cdot$-C_4H_9), 199, 143 ($C_8H_{15}O_2^{+}$) ; IR (NaCl) 3520 (OH), 1738 (C=O), 1244 cm^{-1}; ^1H NMR δ 0.99 (s, 3H, H_3C-18), 1.03 (s, 3H, H_3C-19), 1.05 (s, 9H, *tert*-Bu), 1.11 (s, 3H, H_3C-26), 1.20 (s, 3H, H_3C-21), 1.28 (s, 3H, H_3C-27), 2.02 (s, 3H, OAc), 3.53 (m, 1H, HC-3), 3.64 (dd: 6.6, 8.2 Hz, 1H, HC-24), 5.10 (bd: 5.0 Hz, 1H, HC-6), 5.46 (m, 1H, HC-16), 7.38 (m, 6H, H-Ar), 7.68 (m, 4H, H-Ar).

Hydroboration-oxidation (PCC) of 14.

Compound **14** (68.0 mg, $9.56.10^{-2}$ mmol) in CH_2Cl_2 (2 ml) was treated with 10M BH_3.DMS complex (75 µl, 75.10^{-2} mmol, 24 eq) under a N_2 atmosphere at room temperature for 24 h. After removal of the solvent and of DMS under reduced pressure, the resulting borane in CH_2Cl_2 was added to a well stirred suspension of silica gel (0.04-0.063 mm)-supported PCC[25] (160.0 mg: 1/1) in CH_2Cl_2 and the mixture sonicated for 2h. Then, the mixture was diluted with Et_2O (10 ml) and filtered through a short column of Celite. Purification of the crude mixture by silica gel flash chromatography (hexane/acetone 9:1) afforded ketone **16** (F: 67-68°C) (48.0 mg, $6.59.10^{-2}$ mmol, 69%).

16: EIMS m/z 728 ($M^{+}\cdot$), 671 ($M^{+}\cdot$-C_4H_9), 611 ($M^{+}\cdot$-C_4H_9-$C_2H_4O_2$), 199, 143 ($C_8H_{15}O_2^{+}$); IR (NaCl) 1732 and 1716 cm^{-1} (C=O); ^1H NMR δ 0.75 (s, 3H, H_3C-19), 1.04 (s, 12H, H_3C-18 and *tert*-Bu), 1.11 (s, 3H, H_3C-26), 1.20 (s, 3H, H_3C-21), 1.27 (s, 3H, H_3C-27), 2.02 (s, 3H, OAc), 3.52 (m, 1H, HC-3), 3.65 (dd: 6.5, 8.3 Hz, 1H, HC-24), 5.46 (m, 1H, HC-16), 7.37 (m, 6H, H-Ar), 7.65 (m, 4H, H-Ar).

Hydroboration-oxidation (PCC) of 3.

Compound **3** (46.0 mg, $7.06.10^{-2}$ mmol) in THF (1 ml) was treated with 1M BH_3.THF complex (210 µl, $20.0.10^{-2}$ mmol, 9 eq) under a N_2 atmosphere at room temperature for 24 h. The resulting borane was added dropwise to a well stirred suspension of PCC (232.0 mg) in CH_2Cl_2 (5 ml) and the mixture refluxed for 1h. Dilution with Et_2O (10 ml), filtration through a short column of Florisil and removal of the solvent under reduced pressure afforded the 6-oxosteroid **22** (33.0 mg, $4.94.10^{-2}$ mmol, 70%).

22: EIMS m/z 668 ($M^{+\cdot}$), 611 ($M^{+\cdot}$-C_4H_9), 199; IR (NaCl) 1712 cm^{-1} (C=O) ; ^1H NMR δ 0.74 (s, 3H) and 0.75 (s, 3H) (H_3C-18 and H_3C-19), 0.78 (d: 6.3 Hz, 3H, H_3C-27), 0.95 (d: 6.8 Hz, 3H, H_3C-21), 1.04 (s, 9H, *tert*-Bu), 3.36 (m, 2H, H_2C-26), 3.47 (m, 1H, HC-3), 4.38 (m, 1H, HC-16), 7.33 (m, 6H, H-Ar), 7.67 (m, 4H, H-Ar).

Deprotection of 16: compound 1.

To a solution of **16** (78.0 mg, $10.7.10^{-2}$ mmol) in THF (10 ml) was added a 1M solution of *n*-Bu_4NF (210 µl, $21.0.10^{-2}$ mmol) and the mixture was stirred for 3 days at room temperature. Purification of the crude mixture by silical gel flash chromatography (hexane/acetone 8:2) afforded compound **1** (F: 148-150°C) (25.0 mg, $5.1.10^{-2}$ mmol, 48%).

1: Calc. for $C_{29}H_{46}O_6$: C 70.96%; H 9.46%; found: C 70.45%; H 10.0%. EIMS m/z 475 ($M^{+\cdot}$-CH_3), 431 ($M^{+\cdot}$-C_3H_7O), 371 ($M^{+\cdot}$-C_3H_7O-$C_2H_4O_2$), 353 ($M^{+\cdot}$-C_3H_7O-$C_2H_4O_2$-H_2O), 329 ($M^{+\cdot}$-$C_8H_{15}O_2$-H_2O), 143 ($C_8H_{15}O_2^+$); IR (KBr) 3500 (OH), 1735, 1712 (C=O), 1245 cm^{-1} ; ^1H NMR δ 0.77 (s, 3H, H_3C-19), 1.04 (s, 3H, H_3C-18), 1.13 (s, 3H, H_3C-26), 1.21 (s, 3H, H_3C-21), 1.30 (s, 3H, H_3C-27), 2.03 (s, 3H, OAc), 3.66 (dd: 8.4, 6.5 Hz, 1H, HC-24), 5.49 (m, 1H, HC-16).

Hydroboration-oxidation (H_2O_2) of 17

3β-Acetoxycholest-5-ene **17** (100.0 mg, $2.24.10^{-4}$ mol) in THF (3 ml) was treated with 10M BH_3.DMS complex (150 µl, $15.0.10^{-4}$ mol) under a N_2 atmosphere at room temperature. After 3 h, H_2O was added and the mixture oxidized at 0 °C by adding either one of the following reagents: 0.5 ml 2N NaOH/0.5 ml H_2O_2; 100 mg $NaBO_3$.4 H_2O/H_2O_2; 0.5 ml 3N NaOAc /0.5 ml H_2O_2; 2.0 ml KH_2PO_4 + $NaHPO_4$/0.5 ml H_2O_2.

After 15 min the mixture was extracted with Et_2O and the solvent was removed under reduced pressure. Purification by silica gel flash chromatography (hexane/acetone 9/1 to 7/3) gave compounds **18** and **19** in a ratio presented in text.

18: EIMS m/z 446 ($M^{+\cdot}$), 386 ($M^{+\cdot}$-$C_2H_4O_2$) ; IR (NaCl) 3418 (OH), 1734 (C=O), 1246 cm^{-1} ; ^1H NMR δ 0.65 (s, 3H, H_3C-18), 0.83 (s, 3H, H_3C-19), 0.87 (d: 6.0 Hz, 3H, H_3C-21), 0.90 (d: 6.0 Hz, 6H, H_3C-26, H_3C-27), 2.02 (s, 3H, OAc), 3.38 (dt: 4.0, 10.0 Hz, HC-6), 4.67 (m, 1H, HC-3);

19: EIMS m/z 404 ($M^{+\cdot}$) ; IR (NaCl) 3264 cm^{-1} (OH); ^1H NMR δ 0.65 (s, 3H, H_3C-18), 0.81 (s, 3H, H_3C-19), 0.87 (d: 6.0 Hz, 3H, H_3C-21), 0.90 (d: 6.0 Hz, 6H, H_3C-26, H_3C-27), 3.46 (dt: 4.0, 10.0 Hz, 1H, HC-6), 3.57 (m, 1H, HC-3).

Hydroboration-oxidation (PCC) of 17

3β-Acetoxycholest-5-ene **17** (100.0 mg, $2.24.10^{-4}$ mol) in THF (3 ml) was treated with 10M BH_3.DMS complex (150 µl, $15.0.10^{-4}$ mol) under a N_2 atmosphere at room temperature. After 3 h the solvent was removed under vacuum. The resulting borane in CH_2Cl_2 (6 ml) was added to a suspension of PCC (0.7 g, $3.26.10^{-3}$ mol) and NaOAc (53.0 mg, $6.50.10^{-4}$ mol) in CH_2Cl_2 (15 ml) and the heterogeneous

mixture refluxed for 0.5 h. After dilution with Et_2O (15 ml) and filtration through a short column of Florisil, purification of the crude mixture by silica gel flash chromatography (hexane/acetone 95:5) gave monoketone **20** (5.6 mg, 13.9 mmol, 6%) and diketone **21** (24.7 mg, 55.0 mmol, 25%).

20: EIMS m/z 444 ($M^{+\cdot}$); IR (NaCl) 1734 and 1714 (C=O), 1240 cm^{-1}; ^1H NMR δ 0.66 (s, 3H, H_3C-18), 0.77 (s, 3H, H_3C-19), 0.86 (d: 6.6 Hz, 3H, H_3C-26), 0.87 (d: 6.6 Hz, 3H, H_3C-27), 0.91 (d: 6.5 Hz, 3H, H_3C-21), 2.02 (s, 3H, OAc), 2.28 (m, 1H, HC-5), 4,67 (m, 1H, HC-3);

21: EIMS m/z 400 ($M^{+\cdot}$) ; IR (NaCl) 1712 cm^{-1} (C=O); ^1H NMR δ 0.69 (s, 3H, H_3C-18), 0.87 (d: 6.6 Hz, 6H, H_3C-26, H_3C-27), 0.94 (d: 6.5 Hz, 3H, H_3C-21), 0.96 (s, 3H, H_3C-19), 2.59 (m, 1H, HC-5).

Preparation of dimethylcyclopropylcarbinol[26]

Anhydrous Et_2O (25 ml) and Mg turnings (1.55 g, $6.4.10^{-2}$ mol) were placed in a 3-necked flask, fitted with a mechanical stirrer, a dropping funnel and a condenser, and a stream of N_2 was passed through. The flask was cooled in an ice bath and an ethereal solution of CH_3I (9.65 g, $6.8.10^{-2}$ mol) added dropwise. Stirring was prolonged until the Mg was dissolved and methylcyclopropylketone (5.0 g, $6.0.10^{-2}$ mol) added. After stirring for 3 h at room temperature, a solution of H_2SO_4/H_2O (1/25) was added dropwise, the organic layer separated, washed with H_2O and dried. Removal of the solvent yielded dimethylcyclopropylcarbinol as a clear liquid (5.35 g, $5.35.10^{-2}$ mol, 90%): EIMS m/z 85 ($M^{+\cdot}$-CH_3), 59 ($C_3H_7O^+$), 41 ($C_3H_5^+$) ; ^1H NMR δ 0.33 (m, 4H, H_2C-4, H_2C-5), 0.85 (m, 1H, HC-3), 1.16 (s, 6H, H_3C-1, H_3C-2'), 3.55 (bs, 1H, OH).

Preparation of 5-bromo-2-methylpent-2-ene[9]

To a solution of dimethylcyclopropylcarbinol (8.0 g, $8.0.10^{-2}$ mol) in anhydrous Et_2O (200 ml), $MgBr_2.Et_2O$ (20.0 g, $8.0.10^{-2}$ mol) was added. After stirring for 8 h at reflux, the reaction mixture was diluted with H_2O (100 ml) and extracted with Et_2O (3x200 ml). Removal of the solvent and vacuum distillation afforded 5-bromo-2-methylpent-2-ene (11.5 g, $7.12.10^{-2}$ mol, 89%): EIMS m/z 162-164 (1:1, $M^{+\cdot}$) ; ^1H NMR δ 1.63 (s, 3H, H_3C-1), 1.71 (d: 0.9 Hz, 3H, H_3C-2'), 2.55 (q: 7.2 Hz, 2H, H_2C-4), 3.33 (t: 7.2 Hz, 2H, H_2C-5), 5.13 (tt: 7.2, 1,4 Hz, 1H, HC-3).

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