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HETEROCYCLIC STEROIDS—III†

THE SYNTHETIC UTILITY OF A 2-FURYL STEROID

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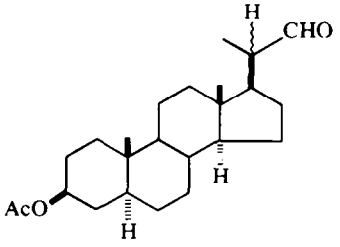
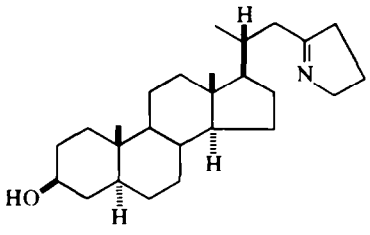
Abstract—Preparation and reactions of the 2-furyl steroid **4** is described. In acidic medium, a product, **8**, arising from furan ring opening with the introduction of functional groups in 23, 25 and 26 carbon atoms, is observed. In slightly different experimental conditions, **4** yields a product **10** of a new molecular rearrangement, involving the 3 oxo-cyclopentene-5 hydroxy unit in the steroid side chain.

In previous papers we described the new synthesis and the remarkable utility of the aldehyde **1**; this aldehyde was easily obtained, as a C_{20} diastereoisomer mixture, from 3β-acetoxy-5α-pregnan-20-one with almost quantitative yield and showed a wide synthetic versatility: it is a key intermediate able to afford a considerable variety of aza-,[1] thia-[2] (**2** and **3**) and oxasteroids of potential interest as regards the physiological properties.



1



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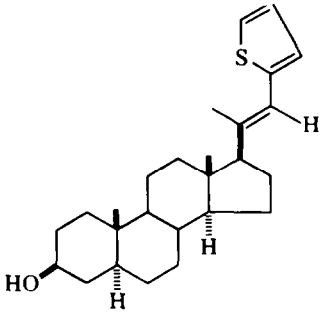

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In this paper we describe the preparation of a 2-furyl steroid and its application in the synthetic field.

By reaction of **1** with 2-furyl lithium in dry Et_2O at −20°C, we obtained the furylcarbinol **4**, $C_{26}H_{40}O_3$, as C_{20} and C_{22} diastereoisomer mixture;‡ IR spectrum: 1605 cm^{-1} (furan ring); ^{1}H-NMR spectrum: 7.30 δ (1H, m, C_{26}-H), 6.28 δ (1H, m, C_{25}-H), 6.19 δ (1H, m, C_{24}-H). Acetylation of **4** yielded the diacetoxy derivative **5**, $C_{30}H_{44}O_5$, and **4**, reacted with MeOH in acidic medium, furnished two products, **6** and **8**, in nearly 1:1 ratio (Scheme 1). **6**, $C_{27}H_{42}O_3$, resulted to be the 22-methoxy derivative,§ as the analytical and spectroscopic data proved; the ^{1}H-NMR spectrum, besides the typical signals due to the 2-furyl group, showed between 3.20 and 3.35 δ singlets relative to $-OCH_3$; the mass spectrum, besides the molecular ion at *m/e* 414 in agreement with the presence of one $-OCH_3$ only, showed the base peak at *m/e* 111 (21–22 bond fission), sure sign of the introduction of the $-OCH_3$ group in C_{22}. Furthermore, **6** yielded a monoacetoxy derivative **7**, $C_{29}H_{44}O_4$; ^{1}H-NMR spectrum: 2.0 δ (3H, s, $-OCOCH_3$). **8**, arising from the opening of the furan ring, resulted to be the most interesting product; the ring fission allowed the introduction of some functional groups simultaneously at C-23, C-25 and C-26 carbon atoms of the side chain. The proposed structure was confirmed by the analytical and spectroscopic data. The infrared spectrum showed a band at 1708 cm^{-1} (ketone C=O), while was absent any signal due to double bond. The mass spectrum presented the molecular ion at *m/e* 478, in agreement with the proposed formula, $C_{29}H_{50}O_5$. ^{1}H-NMR spectrum: 4.30 δ (1H, d, C_{26}-H; J = 5.0 Hz), 3.80 δ (1H, m, C_{25}-H), 3.45 δ (9H, s, 3-OCH_3), nearly 2.78 δ (4H, broad m, C_{22}-H_2 and C_{24}-H_2).[||] **8** afforded a monoacetoxy derivative **9**, $C_{31}H_{52}O_6$, whose ^{1}H-NMR is reported in Fig. 1.

By irradiation of the multiplet at 2.63 δ, relative to C_{24}-H_2, the complex pattern at 3.86 δ simplified into a doublet, A part of an AB system, relative to C_{26}-H and C_{25}-H protons ($J_{25,26}$ = 5.0 Hz).[3]

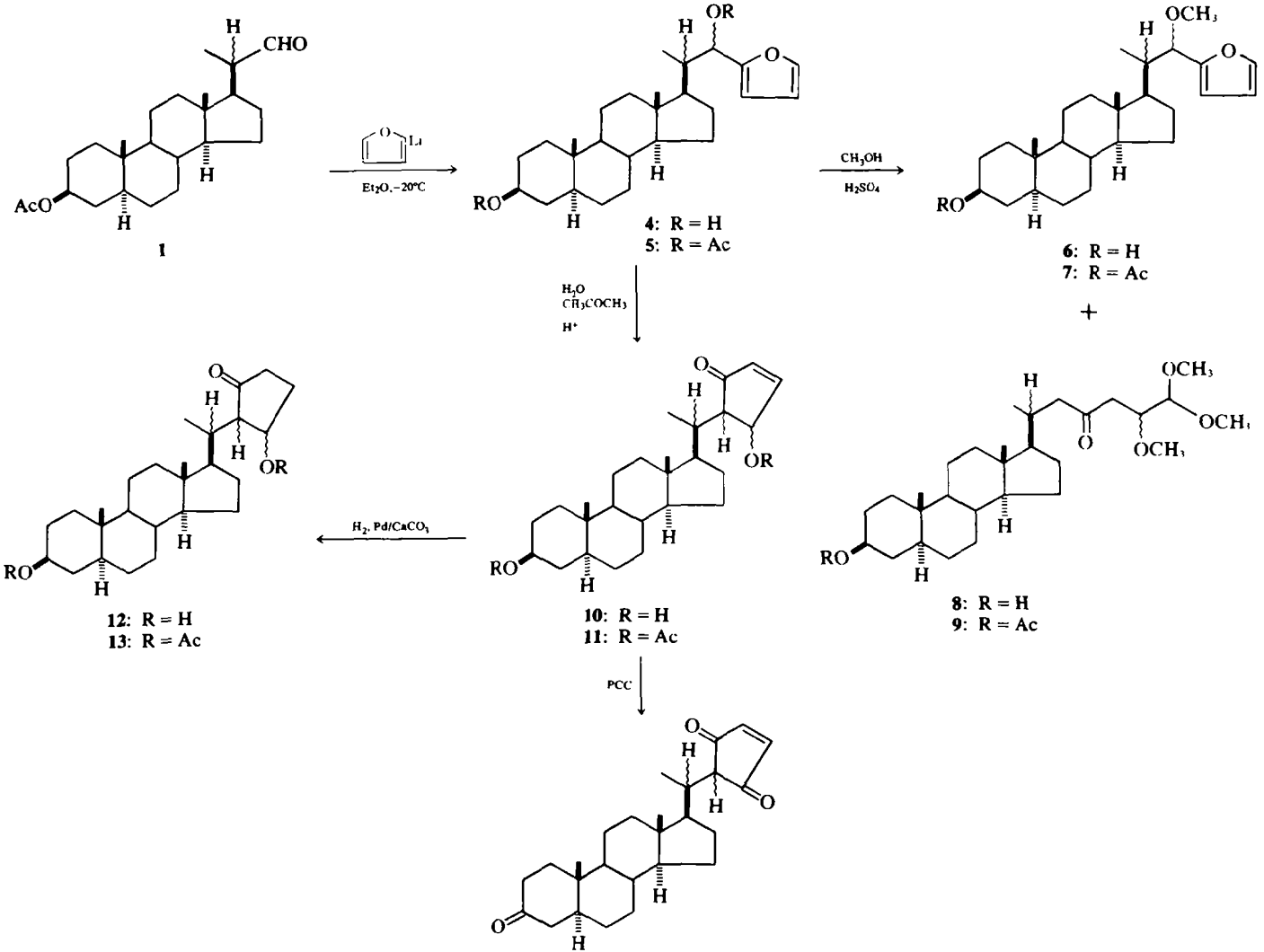
The most interesting reaction was given by **4** under slightly different experimental conditions (the acid-catalyzed hydrolysis was carried out in a more protic solvent, an acetone–water mixture, instead of methanol). In these mild conditions **4** yielded directly **10** (90%), $C_{26}H_{40}O_3$, which possessed the 3-oxo-cyclopentene, 5-hydroxy unit in the side chain; this product was interesting, since several biological active natural compounds have this moiety as a major structural feature.[4] Furthermore, **10** proved to be the first example of a direct molecular rearrangement in acidic medium of a 2-

†The investigation was supported by the Italian C.N.R.

‡We failed to separate the diastereoisomers, since they showed nearly the same R_f on TLC.

§**6** was a mixture of C_{20} and C_{22} diastereoisomers with nearly identical R_f on TLC.

||The spectrum, made in C_6D_6, showed clearly two singlets at 3.38 δ ($-OCH_3$) and 3.20 δ (2 $-OCH_3$).


CHO
AcO
1
Et2O, -20°C
OR
RO
4: R = H
5: R = Ac
CH3OH
H2SO4
OCH3
6: R = H
7: R = Ac
+
H2O
CH3COCH3
H+
OCH3
OCH3
OCH3
8: R = H
9: R = Ac
H2, Pd/CaCO3
10: R = H
11: R = Ac
12: R = H
13: R = Ac
PCC
14

Scheme 1.

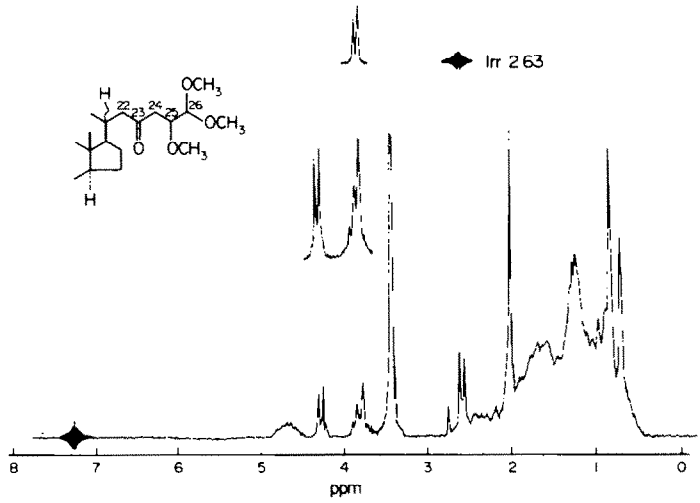
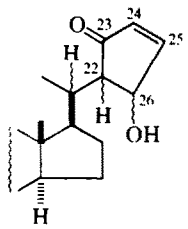


Fig. 1. ^{1}H-NMR of **9**.

furylcarbinol to 3-oxo-5-hydroxy-cyclopentene. The structure of **10** was confirmed by the analytical and spectroscopic data. IR spectrum: 1710 cm^{-1} (α-β unsatd ketone C=O in a five membered-ring),[5] 1595 cm^{-1} (conjugated double bond).[6] UV spectrum: λ_{max} 203 nm; log ϵ = 3.8 (3-oxo-cyclopentene).[7] Mass spectrum: 414 (M^+) in agreement with the proposed formula, $C_{26}H_{40}O_3$. ^{1}H-NMR spectrum: 7.60 δ (1H, q, C_{25}-H; $J_{26,25}$ = 2.4 Hz, $J_{25,24}$ = 6.0 Hz) 6.19 δ (1H, q, C_{24}-H; $J_{26,24}$ = 1.0 Hz, $J_{25,24}$ = 6.0 Hz), 4.81 δ (1H, m, C_{26}-H), 2.57 δ (1H, m, C_{22}-H). The experiments of spin decoupling confirmed the signals assignment and showed clearly the presence of the oxo-cyclopentene group in **10**.



10

Irradiation at 7.60 δ caused the quartet at 6.19 δ to become a doublet ($J_{24,26}$ = 1.0 Hz); by irradiation at 6.19 δ the quartet at 7.60 δ simplified into a doublet ($J_{25,26}$ = 2.4 Hz), and by irradiation at 4.81 δ, the C_{25}-H and C_{24}-H protons gave a clean AB system ($J_{24,25}$ = 6.0 Hz), while a multiplet at 2.57 δ (C_{22}-H) turned into a doublet ($J_{22,21}$ = 2.6 Hz).†

The acetylation of **10** gave a diacetoxy derivative **11**, $C_{30}H_{44}O_5$, in agreement with the presence of two secondary alcoholic functions. From **10**, by catalytic reduction with H_2 and 5% Pd/$CaCO_3$, we obtained a dihydroderivative **12**,‡ $C_{26}H_{42}O_3$, whose infrared spectrum showed a clear band at 1745 cm^{-1} (typical of oxo-cyclopentane), while in ^{1}H-NMR spectrum the signals due to the olefinic protons were absent. Through acetylation, **12** afforded a dihydro-diacetoxy derivative **13**, $C_{30}H_{46}O_5$. At last, a mild oxidation of **10** with pyridinium chlorochromate (PCC),[8] gave the triketo derivative **14**,§ $C_{26}H_{36}O_3$. IR spectrum: 1705 cm^{-1} (broad, ketone groups at C_3, C_{23} and C_{26}). ^{1}H-NMR spectrum: the olefinic protons presented as an AB system; doublet at 7.20 δ (J = 6.0 Hz) and doublet at 7.12 δ (J = 6.0 Hz).¶

Experiments to elucidate the rearrangement mechanism are in hand.

EXPERIMENTAL

M.ps were determined on a Kofler block and are uncorrected. ^{1}H-NMR spectra were taken with a Perkin-Elmer R 32 spectrometer, using usually $CDCl_3$ soln with TMS as an internal standard. IR spectra were taken with a Perkin-Elmer 257 Infracord spectrometer. UV spectra were taken with a Beckmann DU spectrometer. Commercial Merck silica gel (140–230 mesh) and Woelm alumina were used for column chromatography. Merck precoated silica gel plates were used in TLC. The chromatograms were detected by spraying with 5 N H_2SO_4 and heating at 110°C for 10 min. Mass spectra were obtained with an AEI MS-12 spectrometer at 70 eV, by using direct insertion at source temperature of 150°C.

2-Furyl steroid **4** *and its diacetate* **5**

25 ml of 1.8 N n-BuLi soln were added to 3.2 ml of furan, diluted with 50 ml of anhyd Et_2O at −20°C under N_2. The mixture was refluxed for 4 h, then, again at −20°C, 1 g of **1**, dissolved in the least amount of anhyd Et_2O, was added and the mixture was stirred at room temp. for 16 h. Then 60 ml of a cold soln, satd with NH_4Cl, were added and a vigorous stirring was kept for 1 hr. The organic layer was separated and the aqueous phase was extracted 3 times with AcOEt. The neutral extracts were dried over anhyd Na_2SO_4 and the removal of the solvent yielded 1.9 g of crude product that was chromatographed on Al_2O_3 B III. The elution with C_6H_6–Et_2O 4:1 gave 970 mg of **4**, $C_{26}H_{40}O_3$, needles from n-hexane, m.p. 195°C (dec.) Elemental analysis: Found C, 78.09; H, 10.15. Calc. for $C_{26}H_{40}O_3$: C, 77.95; H, 10.06%. IR ($CHCl_3$, ν_{max} cm^{-1}): 3670 and 3520 (free and bond -OH), 1605 (furan ring). ^{1}H-NMR (CD_3OD–$CDCl_3$ 1:1, δ): besides the signals due to the furan ring, 4.86 (1H, q, C_{22}-H), 3.55 (1H, broad m, C_3-H). MS, *m/e*: 400 (M^+) in agreement with proposed formula. 50 mg of **4** were treated with 2 ml of pyridine and 2 ml of Ac_2O for 16 hr at room temp. The usual isolation procedure yielded 60 mg of crude product that was purified by chromatography on Al_2O_3 B III. The elution with benzene gave 48 mg of **5**, $C_{30}H_{44}O_5$, prisms from MeOH, m.p. 125–29°C. Elemental analysis: Found: C, 74.30; H, 9.21. Calc. for $C_{30}H_{44}O_5$: C, 74.34; H, 9.15%. IR ($CHCl_3$, ν_{max}

†The broad signal at 4.81 δ (C_{26}-H) sharpens in all experiments of double resonance.

‡**10** and **12** give two spots on TLC with nearly the same R_f, and we failed to separate them.

§**14** was pure by TLC.

¶The spectroscopic data of **14** did not show any sign of ketoenol equilibrium, as reported in analogue compounds.[9]

cm^{-1}): 1727 (broad, acetate C=O), 1603 (furan ring). MS, *m/e*: 484 (M^+), in agreement with the proposed formula.

6 and 8, the corresponding 3β-acetoxy derivatives 7 and 9

A mixture of 105 mg of **4**, 10 ml of MeOH and 2 drops of conc. H_2SO_4 was stirred at 50°C for 1 hr. Then it was poured into water and the usual work up yielded 113 mg of crude product that was chromatographed on Al_2O_3 B III. The elution with C_6H_6–Et_2O 4:1 gave 50 mg of **6** and with C_6H_6–Et_2O 2:1 47 mg of **8**. **6**, $C_{27}H_{42}O_3$, plates from MeOH/H_2O, m.p. 95–100°C. Elemental analysis: Found: C, 78.06; H, 10.30. Calc. for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21%. IR ($CHCl_3$, ν_{max} cm^{-1}): 3665 and 3590 (free and bond –OH), 1600 (furan ring). ^{1}H-NMR ($CDCl_3$, δ): 7.40 (1H, m, C_{26}-H), 6.36 (1H, m, C_{25}-H), 6.22 (1H, m, C_{24}-H), 4.32 (1H, broad m, C_{22}-H), 3.60 (1H, broad m, C_3-H), 3.35–3.20 (3H, 3 singlets of relative intensity 1:1:2 due to $-OCH_3$ group). MS, *m/e*: 414 (M^+), in agreement with the proposed formula. As regards **8**, $C_{29}H_{50}O_5$, IR, ^{1}H-NMR and MS data, see the initial section. Elemental analysis: Found: C, 72.85; H, 10.60. Calc. for $C_{29}H_{50}O_5$: C, 72.76; H, 10.53%. The corresponding 3β-acetoxy derivatives **7** and **9** were prepared quantitatively according the already described procedure. **7**, $C_{29}H_{44}O_4$, needles from MeOH/H_2O, m.p. 143–48°C. Elemental analysis: Found: C, 76.39; H, 9.84. Calc. for $C_{29}H_{44}O_4$: C, 76.27; H, 9.71%. IR ($CHCl_3$, ν_{max} cm^{-1}): 1720 (acetate C=O), 1600 (furan ring). ^{1}H-NMR ($CDCl_3$, δ): 7.32 (1H, m, C_{26}-H), 6.30 (1H, m, C_{25}-H), 6.19 (1H, m, C_{24}-H), 4.7 (1H, broad m, C_3-H), 4.3 (1H, broad m, C_{22}-H), 3.32–3.20 (3H, 3 singlets of relative intensity 1:1:2 due to $-OCH_3$ group), 2.00 (3H, s, $-OCOCH_3$ in C_3). MS, *m/e*: 456 (M^+), in agreement with the proposed formula. **9**, $C_{31}H_{52}O_6$, plates from MeOH/H_2O, m.p. 65–70°C. Elemental analysis: Found: C, 71.63; H, 9.99. Calc. for $C_{31}H_{52}O_6$: C, 71.50; H, 10.07%. IR ($CHCl_3$, ν_{max} cm $^{-1}$): 1714 (ketone and acetate C=O). For ^{1}H-NMR data, see the initial section. MS, *m/e*: 520 (M^+), in agreement with the proposed formula.

10 and its diacetate 11

A mixture of 100 mg of **4**, 25 ml of CH_3COCH_3 (previously distilled over $KMnO_4$), 20 ml of distilled water and 5 drops of conc. H_2SO_4 were stirred at 50°C for 30 hr. Then it was poured into H_2O and the precipitate was extracted with AcOEt. The combined neutral organic extracts were dried over anhyd Na_2SO_4 and the removal of the solvent yielded 113 mg of crude product that was chromatographed on SiO_2. The elution with C_6H_6–Et_2O 1:1 gave 90 mg of **10**, $C_{26}H_{40}O_3$, needles from $CHCl_3$/n-hexane, m.p. 170°C (dec.). Elemental analysis: Found: C, 77.84; H, 9.99. Calc. for $C_{26}H_{40}O_3$: C, 77.95; H, 10.06%. For IR, ^{1}H-NMR, UV and MS data, see Discussion. The diacetate **11**, $C_{30}H_{44}O_5$, was prepared in the usual way; plates from $CHCl_3$/MeOH, m.p. 95–100°C. Elemental analysis: Found: C, 74.20; H, 9.07. Calc. for $C_{30}H_{44}O_5$: C, 74.34; H, 9.15%. IR ($CHCl_3$, ν_{max} cm^{-1}): 1724 (broad, ketone and acetate C=O), 1606 ($\alpha-\beta$ unsatd double bond). ^{1}H-NMR (CCl_4, δ): 7.40 (1H, q, C_{25}-H), 6.21 (1H, q, C_{24}-H), 5.80 (1H, m, C_{26}-H), 4.55 (1H, broad m, C_3-H), 2.58 (1H, m, C_{22}-H), 2.05 and 2.00 (3H, two singlets of relative intensity 1:1 due to $-OCOCH_3$ group in C_{26}), 1.9 (3H, s, $-OCOCH_3$ in C_3). MS, *m/e*: 484 (M^+), in agreement with the proposed formula.

12 and its diacetate 13

70 mg of **10**, dissolved in the least amount of MeOH, were added to a suspension of 60 mg of 5% Pd/$CaCO_3$ in 5 ml of MeOH and stirred under H_2 for 16 hr at room temp. Then the catalyst was filtered off and, after the removal of the solvent, 68 mg of crude product was obtained and was chromatographed on SiO_2. The elution with C_6H_6–Et_2O 1:1 gave 44 mg of pure **12**, $C_{26}H_{42}O_3$, prisms from MeOH/$CHCl_3$, m.p. 210–15°C (dec.). Elemental analysis: Found: C, 77.41; H, 10.15. Calc. for $C_{26}H_{42}O_3$: C, 77.56; H, 10.51%. For IR data see Discussion. ^{1}H-NMR (CD_3OD–$CDCl_3$ 1:1, δ): 4.4 (1H, broad m, C_{26}-H), 3.6 (1H, broad m, C_3-H). MS, *m/e*: 402 (M^+), in agreement with the proposed formula.

The diacetate **13**, $C_{30}H_{46}O_5$, was obtained in the usual way; plates from MeOH/H_2O, m.p. 120–24°C. Elemental analysis: Found: C, 73.90; H, 9.60. Calc. for $C_{30}H_{46}O_5$: C, 74.04; H, 9.53%. IR ($CHCl_3$, ν_{max} cm^{-1}): 1728 (strong, ketone and acetate C=O). ^{1}H-NMR ($CDCl_3$, δ): 5.4 (1H, broad m, C_{26}-H), 4.7 (1H, broad m, C_3-H) 2.05 and 1.99 (6H, 2s, $-OCOCH_3$ in C_{26} and in C_3). MS, *m/e*: 486 (M^+), in agreement with the proposed formula.

The oxidation product 14

73 mg of **10**, dissolved in the least amount of anhyd CH_2Cl_2, were added to a suspension of 950 mg of PCC in 5 ml of anhyd CH_2Cl_2 and stirred for 2 hr at room temp. Then the mixture was diluted with AcOEt and washed with H_2O satd with NaCl. After the removal of the solvent, we obtained 83 mg of crude product that was chromatographed on SiO_2. The elution with C_6H_6–Et_2O 95:5 yielded 41 mg of **14**, $C_{26}H_{36}O_3$, plates from n-hexane, m.p. 240–44°C. Elemental analysis: Found: C, 78.90; H, 9.08. Calc. for $C_{26}H_{36}O_3$: C, 78.75; H, 9.15%. For IR and ^{1}H-NMR data, see the initial section. MS, *m/e*: 396 (M^+), in agreement with the proposed formula.

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