# *Notes*

## New Tetracyclic Sesterterpenes from *Cydonia vulgaris*

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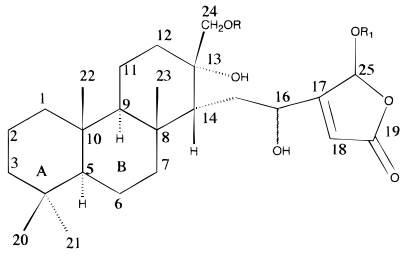
The $CHCl_3$−MeOH extract of *Cydonia vulgaris* Pers. (Rosaceae) was shown to contain four new sesterterpene esters, namely 24,25-*O*-diacetylvulgaroside (**1**), 25-*O*-acetylvulgaroside (**2**), 24-*O*-acetyl-25-*O*-cinnamoylvulgaroside (**3**), and 25-*O*-cinnamoylvulgaroside (**4**). The structure elucidation of these compounds was accomplished using homonuclear and heteronuclear 2D-NMR experiments and FABMS.

The aerial parts of *Cydonia vulgaris* Pers. (Rosaceae), a small tree widely cultivated in Italy and commonly known as "melo cotogno," have been used in folk medicine for the treatment of various skin diseases.[1] In this paper, the isolation of four novel sesterterpene esters from this material is described. The basic aglycon skeleton of the isolated compounds **1**−**4** resembles that of luffolide, a sesterterpene previously reported from a marine sponge (*Luffariella* species),[2] except for the stereochemistry at C-13 and C-14. Vulgarosides **1**−**4** were evaluated in vitro for potential antiviral activity against the human retrovirus HIV-1 and were found to be inactive.



| | | |
|---|---|---|
| **1** | R=Ac | $R_1$=Ac |
| **2** | R=H | $R_1$=Ac |
| **3** | R=Ac | $R_1$=Cinn |
| **4** | R=H | $R_1$=Cinn |

Ac=Acetyl; Cinn=trans-cinnamoyl

The $CHCl_3$−MeOH (9:1) extract of the aerial parts of *C. vulgaris* afforded four new sesterterpenes (**1**−**4**) by Si gel and Sephadex LH-20 column chromatography and reversed-phase HPLC. The molecular formula for **1** was determined from $^{13}$C-NMR and DEPT-$^{13}$C-NMR data and FABMS analysis as $C_{29}H_{44}O_8$.

The presence of a $\beta$-substituted-$\gamma$-acetoxybutenolide moiety in **1** was established by interpretation of the $^{13}$C-NMR spectrum, which displayed resonances for two carbonyl groups [$\delta$ 172.7 (−*C*OMe) and 172.0 (C-19)], one hemiacetal [$\delta$ 94.6 (C-25)] group, and two sp$^2$ [$\delta$ 118.6 (C-18), 170.3 (C-17)] carbons, in addition to the signal of an *Me*CO− group [$\delta$ 21.0]. $^1$H-NMR resonances at $\delta$ 6.20 (1H, s, H-18), 7.02 (1H, s, H-25), and 2.07 (3H,s, *Me*CO−) confirmed the above assignment (Table 1). $^1$H−$^1$H COSY measurements showing coupling between H-14, $\delta$ 1.67 (1H, dd, $J$ = 3.5, 5.0 Hz); H-15a, $\delta$ 2.32 (1H, ddd, $J$ = 11.0, 8.0, 3.5 Hz); H-15b, $\delta$ 1.98 (1H, ddd, $J$ = 11.0, 5.0, 1.5 Hz); and H-16, $\delta$ 4.99 (1H, dd, $J$ = 8.0, 1.5 Hz) established the connectivities C14−C15−C16. The linkage at C16−C17 was deduced by long-range $^{13}$C−$^1$H correlations in a COLOC experiment: the signal at 70.8 ppm (C-16) correlated to $\delta$ 6.20 (H-18) and at 170.3 ppm (C-17) to $\delta$ 2.23 (H-15). The same COLOC experiment showed the correlations C13−H14, C13−H15, C14−H24 (Tables 1 and 2). This allowed us to position the quaternary carbon C13 (80.0 ppm), which is oxygen-linked and bears an acetoxymethylene group (C-14). An allylic coupling in the $^1$H-NMR spectrum of **1** between H16 and H18, confirmed by $^1$H−$^1$H COSY and selective decoupling experiments (Table 1) along with $^{13}$C−$^1$H couplings via $^3J$ correlating C16 with H18 and C18 with H16 in the COLOC experiment, confirmed the C16 hydroxylation.

The remaining part of the molecule, as inferred by the molecular formula and inspection of the $^{13}$C-NMR and DEPT-$^{13}$C-NMR spectra, had to be composed of only sp$^3$ hybridized carbon atoms (four methyls, seven methylenes, two methines, and three quaternary carbons) and must be tricyclic. Furthermore, because all methyls were singlets in the $^1$H-NMR spectrum of **1**, they should be linked to quaternary carbon atoms.

2D-COSY $^1$H−$^1$H experiment provided evidence for

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**Table 1.** NMR Data for Compound **1** (500 MHz in $CD_3OD$)[a]

| Position | DEPT | δ C | δH (*J* in Hz) |
|---|---|---|---|
| 1 | $CH_2$ | 40.0 | 1.60 ddd, *J* = 11.0, 2.0, 4.0; 0.85 ddd, *J* = 11.0, 8.5, 5.0 |
| 2 | $CH_2$ | 18.8 | 1.58 br m, 1.40 br m |
| 3 | $CH_2$ | 42.1 | 1.36 ddd, *J* = 11.0, 4.0, 3.0; 1.13 ddd, *J* = 11.0, 9.0, 5.5 |
| 4 | C | 34.4 | |
| 5 | CH | 58.1 | 0.85 dd, *J* = 12.0, 2.0 |
| 6 | $CH_2$ | 19.4 | 1.40 br m, 1.58[b] |
| 7 | $CH_2$ | 43.0 | 1.16 ax dt, *J* = 12.0, 2.5; 1.58[b] |
| 8 | C | 38.6 | |
| 9 | CH | 62.4 | 0.99 dd, *J* = 11.0, 3.0 |
| 10 | C | 37.9 | |
| 11 | $CH_2$ | 19.9 | 1.26 br m, 1.76 br m |
| 12 | $CH_2$ | 35.7 | 2.16 ddd, *J* = 13.0, 3.5, 2.0; 1.33 ddd, *J* = 13.0, 9.5, 5.0 |
| 13 | C | 80.0 | |
| 14 | CH | 63.7 | 1.67 dd, *J* = 3.5, 5.0 |
| 15 | $CH_2$ | 29.2 | 2.32 ddd, *J* = 11.0, 8.0, 3.5; 1.98 ddd, *J* = 11.0, 1.5, 5.0 |
| 16 | CH | 70.8 | 4.99 ddd, *J* = 8.0, 1.5, 1.0 |
| 17 | C | 170.3 | |
| 18 | CH | 118.6 | 6.20 br s |
| 19 | C | 172.0 | |
| 20 | $CH_3$ | 21.6 | 0.91 s |
| 21 | $CH_3$ | 33.7 | 0.89 s |
| 22 | $CH_3$ | 16.6 | 0.93 s |
| 23 | $CH_3$ | 16.6 | 0.93 s |
| 24 | $CH_2$ | 64.3 | 4.08 d, *J* = 12.0; 4.48 d, *J* = 12.0 |
| 25 | CH | 94.6 | 7.02 s |
| $CH_3CO$- | | 172.7; 21.0 | 2.00 s |
| $CH_3CO$- | | 171.7; 20.4 | 2.07 s |

[a] All assignments were confirmed by COSY and HETCOR experiments. [b] These represent overlapped signals.

**Table 2.** Observed Long-Range Carbon−Proton Correlations (COLOC) of Compounds **1** and **3**

| | proton | | | proton | |
|---|---|---|---|---|---|
| carbon | **1** | **3** | carbon | **1** | **3** |
| 1 | 3, 22 | 22 | 19 | 18, 25 | 18, 25 |
| 2 | | | 20 | 3, 21 | 3, 21 |
| 3 | 21, 5 | 20, 21 | 21 | 5, 20 | 5, 20 |
| 4 | 6 | 2, 6 | 22 | 9, 5 | 9, 5 |
| 5 | 6, 22, 21 | 6, 22, 21 | 23 | 14, 7 | 14, 7, 9 |
| 6 | | | 24 | 14, 12 | 14, 12 |
| 7 | 5, 23 | 5, 23, 9 | 25 | 18 | 18 |
| 8 | 6, 7 | 6, 23 | $CH_3CO$ | 25 | |
| 9 | 7, 23 | 7, 23 | 1′ | | 8′, 3′, 5′ |
| 10 | 6, 11, 22 | 6, 11, 22, 9 | 2′ | | 7′ |
| 11 | | | 3′ | | |
| 12 | 9, 14 | 9, 11 | 4′ | | 6′, 2′ |
| 13 | 11, 14, 15 | 11, 14, 15 | 5′ | | |
| 14 | 16, 23, 24 | 16, 23, 15, 24 | 6′ | | 7′, 2′ |
| 15 | | | 7′ | | 8′ |
| 16 | 14, 18 | 14, 18 | 8′ | | 7′ |
| 17 | 18, 15 | 18, 15 | 9′ | | 8′, 7′, 25 |
| 18 | 16, 25 | 16, 25 | | | |

the presence in the molecule of segments C1−C3, C5−C7, C9−C12.

The elucidation of the whole basic carbon skeleton from the above subunits was achieved on the basis of a series of $^1J$ (HETCOR) and *J* long-range (COLOC) 2D $^{13}C-^1H$ correlations, which also allowed the assignment of the resonances in the $^{13}C$-NMR spectrum to the pertinent carbons (Tables 1 and 2). The relative stereochemistry at C-5, C-8, C-9, and C-10 was established by taking into account the *J* values for H-9 and H-5 (see Table 1), and their axial orientation was indicated by a 2D-ROESY experiment showing ROE cross peaks among protons spatially related (particularly those correlating H-9 with H-5 and $H_3$-22 and $H_3$-23 with $H_{ax}6$). These

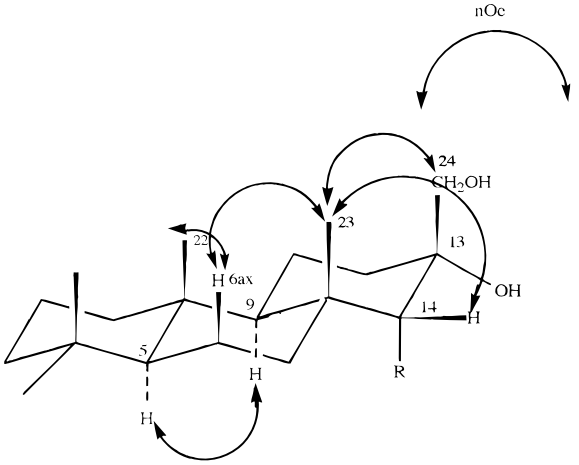


**Figure 1.**

data pointed to a *trans-anti-trans* nature for the perhydrophenanthrene moiety of the molecule as depicted in Figure 1. This conclusion was confirmed by the chemical shifts of the carbon atoms of rings A and B, which matched well with those of related sesterterpenes recently described in the literature.[3] NOE effects observed in the ROESY spectrum between H-14 and Me-23 and Me-23 and $H_2$-24 allowed us to ascertain the relative stereochemistry at C-13 and C-14. Attempts were made to establish the stereochemistry of the −OH group at C16 in compound **1** by preparation of the 16-OH *p*-bromobenzoyl derivative for evaluation of sign and intensity of CD curve.[4] Regrettably, these efforts did not prove fruitful due to degradation of the compound. Thus, compound **1** was established as 24,25-*O*-diacetylvulgaroside.

The FABMS of **2** gave a molecular ion at *m*/*z* 477 [M − H]$^-$. The $^1$H-NMR spectrum of **2** is very similar to that of **1**, suggesting the same skeleton. The main difference was the absence of a singlet at δ 2.07 attributed in **1** to *Me*CO. Another difference was observed in the chemical shift of $H_2$-24 (H 24a, d, δ 3.34, *J* = 12 Hz; H 24b, d, δ 4.10, *J* = 12.0 Hz), which was found upfield to those shifts observed in **1** (H 24a, d, δ 4.08, *J* = 12.0 Hz; H 24b, d, δ 4.48, *J* = 12.0 Hz) (Table 1), which suggested that **2** was not esterified at position 24.[5] The $^{13}$C-NMR chemical shift of C-13 and C-24 in **2** (Table 3) was indicative of the absence of C-24 substitution with respect to **1**. Therefore, compound **2** was established as 25-*O*-acetylvulgaroside.

The FABMS of **3** gave a molecular ion at *m*/*z* 607 [M − H]$^-$, which was 130 mass units higher than that of **2** and was compatible with an additional cinnamoyl moiety. An analysis of its NMR spectral data (see Table 3 and Experimental Section) indicated that **3** possessed the same basic structure as **1** but was esterified with an acetyl and a cinnamoyl moiety. The $^1$H-NMR spectrum of **3** showed the signals due to a cinnamoyl group: δ 6.67 (1H, d, *J* = 16.2 Hz, 8′-H) and 7.82 (1H, d, *J* = 16.2 Hz, 7′-H) were characteristic for the −CH═CH− *trans* group, and signals at δ 7.63 (3H, m, 3′,4′,5′-H), 7.42 (2H,dd *J* = 7.5, 1.5 Hz, 2′,6′-H) required an aromatic ring.[6] The $^{13}$C-NMR spectrum of **3** showed, with respect to **2**, nine further signals ascribable to a *trans*-cinnamic acid. The position of attachment of the cinnamoyl and acetyl units was determined by 2D $^1H-^{13}C$ heterocorrelations (*J* long-range, COLOC) (Table 2). Two clear long-range carbon-proton shift correlations

**Table 3.** $^{13}C$ NMR Data for Compounds **2**−**4** (500 MHz in $CD_3OD$)

| Position | DEPT | 2 | 3 | 4 |
|---|---|---|---|---|
| 1 | $CH_2$ | 41.0 | 41.0 | 41.0 |
| 2 | $CH_2$ | 18.8 | 18.8 | 18.8 |
| 3 | $CH_2$ | 42.1 | 42.1 | 42.1 |
| 4 | C | 34.4 | 34.4 | 34.4 |
| 5 | CH | 58.1 | 58.1 | 58.1 |
| 6 | $CH_2$ | 19.4 | 19.4 | 19.4 |
| 7 | $CH_2$ | 43.0 | 43.0 | 43.0 |
| 8 | C | 38.6 | 38.6 | 38.6 |
| 9 | CH | 62.3 | 62.3 | 62.3 |
| 10 | C | 37.8 | 37.8 | 37.8 |
| 11 | $CH_2$ | 19.9 | 19.9 | 19.9 |
| 12 | $CH_2$ | 35.0 | 35.7 | 35.3 |
| 13 | C | 82.9 | 80.7 | 83.0 |
| 14 | CH | 62.5 | 62.7 | 62.6 |
| 15 | $CH_2$ | 29.2 | 29.2 | 30.0 |
| 16 | CH | 70.8 | 70.8 | 70.1 |
| 17 | C | 170.3 | 170.3 | 171.2 |
| 18 | CH | 118.6 | 118.6 | 120.0 |
| 19 | C | 172.0 | 172.1 | 173.5 |
| 20 | $CH_3$ | 21.6 | 21.6 | 21.6 |
| 21 | $CH_3$ | 33.8 | 33.8 | 33.8 |
| 22 | $CH_3$ | 16.6 | 16.6 | 16.7 |
| 23 | $CH_3$ | 16.6 | 16.6 | 17.0 |
| 24 | $CH_2$ | 62.0 | 64.3 | 61.6 |
| 25 | CH | 94.6 | 94.6 | 95.4 |
| $CH_3CO$− | $CH_3$ | 21.0 | 21.10 | |
| $CH_3CO$− | C | 173.0 | 172.7 | |
| 1′ | C | | 135.7 | 135.7 |
| 2′, 6′ | CH | | 129.7 | 129.7 |
| 3′, 5′ | CH | | 130.0 | 130.0 |
| 4′ | CH | | 131.0 | 131.0 |
| 7′ | CH | | 145.5 | 145.5 |
| 8′ | CH | | 119.0 | 119.0 |
| 9′ | C | | 168.0 | 168.0 |

between the carbonyl carbon at 167.95 and 7′-H of the cinnamoyl acid residue ($\delta$ 7.82) and 25-H ($\delta$ 7.05) showed that the cinnamoyl residue is linked to C-25 and the acetyl residue to C-24. Therefore, **3** is 24-*O*-acetyl-25-*O*-cinnamoylvulgaroside.

The FABMS spectrum of **4** showed a molecular ion at *m*/*z* 565 $[M - H]^-$. The $^1H$-NMR spectrum of **4** is very similar to that of **3**. The main differences were the absence of one acetyl unit and the chemical shift of $H_2$-24 (see Experimental Section), which was shifted upfield about 0.7 ppm compared with compound **3**, suggesting that **4** was not esterified at position 24. Therefore, compound **4** was assigned as 25-*O*-cinnamoylvulgaroside.

As a part of our screening of natural compounds as potential anti-HIV agents, we tested the in vitro anti-HIV activity of compounds **1**−**4**, by methods previously described[7] and found them to be inactive at the highest nontoxic concentration of 2.5 $\mu$g/mL (data not shown).

## Experimental Section

**General Experimental Procedures.** For NMR, Bruker WH-250 Spectrospin or Bruker AMX-500 spectrometers equipped with a Bruker X-32 computer using the UXNMR software package were used. Two-dimensional homonuclear proton chemical shift correlation (COSY) experiments were measured by employing the conventional pulse sequence. The HETCOR experiments were performed with HXCORR pulse sequence optimized for $^1J_{CH}$ coupling of 135 Hz.[8] In the case of COLOC experiments, delays were adjusted to an average CH coupling of 8 Hz. NOE measurements were performed using 2D ROESY experiments.[8] Optical rotations were measured on a Perkin-Elmer 243-B polarimeter in $CHCl_3$ solution at 20−22 °C, using a sodium lamp operating at 589 nm. FABMS measurements were obtained on a VG-ZAB instrument equipped with a FAB source. HPLC separation was performed on a Waters Model 6000A pump equipped with a U6K injector and E401 refractive index detector.

**Plant Material.** The aerial parts of *Cydonia vulgaris* Pers. were collected in April 1991, in Benevento, southern Italy, and were identified by V. De Feo, Universitá degli Studi di Salerno. A voucher sample (No. 5h) is deposited at the herbarium of the Dipartimento di Chimica delle Sostanze Naturali, Universitá degli Studi di Napoli.

**Extraction and Isolation.** The air-dried plant (300 g) was defatted with petroleum ether and successively extracted with $CHCl_3$ and $CHCl_3$−MeOH (9:1), yielding, respectively, 7.0, 14.0, and 8.0 g of extracts. The $CHCl_3$−MeOH (9:1) extract (4 g) was chromatographed on a Sephadex LH-20 column (100 × 5 cm). The column was eluted with MeOH, and fractions (8 mL each) were checked by TLC [Si gel plates, $CHCl_3$−MeOH−$H_2O$ (40:9:1 and 7:3:0.3)]. Combined fractions 18−25 (800 mg) containing the crude sesterterpenoid mixture were further purified by Si gel column (60 g) using $CHCl_3$ with increasing volumes of MeOH as elution solvent (10 mL each).

Fractions 120−126 (1200 mg), 140−150 (50 mg), and 154−162 (60 mg) containing sesterterpene esters were submitted to HPLC on a C-18 $\mu$-Bondapak column (30 cm × 7.8 mm i.d. flow rate 2.5 mL/min) to give **1** (26 mg) and **2** (8 mg) from fractions 120−126 (MeOH−$H_2O$, 75:25), **1** (6 mg) and **3** (20 mg) from fractions 140−150 (MeOH−$H_2O$, 8:2), and **4** (10 mg) from fractions 154−162 (MeOH−$H_2O$, 8:2).

**Compound 1**: $[\alpha]^{25}_D + 30$ (*c* 1, $CHCl_3$); FABMS *m*/*z* 519 $[M - H]^-$; $^1H$- and $^{13}C$-NMR data, see Table 1.

**Compound 2**: $[\alpha]^{25}_D +63$ (*c* 1, $CHCl_3$); FABMS *m*/*z* 477 $[M - H]^-$; $^{13}C$-NMR data, see Table 3; $^1H$ NMR $\delta$ 0.89 (3H, s, Me-21), 0.91 (3H, s, Me-20), 0.93 (6H, s, Me-22 and Me-23), 1.67 (1H, dd, $J$ = 3.0, 5.0 Hz, H-14), 1.96 (1H, ddd, $J$ = 11.0, 2.0, 5.0 Hz, H-15a), 2.32 (1H, ddd, $J$ = 11.00, 8.0, 3.0 Hz, H-15b), 2.00 ($CH_3$C0), 3.34 (1H, d, $J$ = 12 Hz, H-24a), 4.10 (1H, d, $J$ = 12 Hz, H-24b), 4.94 (1H, dd, $J$ = 8, 2.0 Hz, H-16), 6.15 (1H, s, H-18), 7.00 (1H, s, H-25); the remaining signals are superimposable with those of compound **1**.

**Compound 3**: $[\alpha]^{25}_D +17$ (*c* 1, $CHCl_3$); FABMS *m*/*z* 607 $[M - H]^-$; $^{13}C$ NMR, see Table 3; $^1H$ NMR $\delta$ 0.89 (3H, s, Me-21), 0.91 (3H, s, Me-20), 0.93 (6H, s, Me-22 and Me-23), 1.69 (1H, dd, $J$ = 3.0, 5.0 Hz, H-14), 1.98 (1H, ddd, $J$ = 11.0, 2.0, 5.0 Hz, H-15a), 2.33 (1H, ddd, $J$ = 11.0, 8.0, 3.0 Hz, H-15b), 2.02 ($CH_3$CO), 4.08 (1H, d, $J$ = 12.0 Hz, H-24a)), 4.48 (1H, d, $J$ = 12.0 Hz, H-24b), 4.99 (1H, dd, $J$ = 8.0, 2.0 Hz, H-16), 6.18 (1H, s, H-18), 7.05 (1H, s, H-25), 6.67 (1H, d, $J$ = 16.0 Hz, H-8′), 7.42 (2H, dd, $J$ = 7.5, 1.5 Hz, H-2′ and 6′), 7.63 (3H, m, H-3′,4′,5′), 7.82 (1H,d, $J$ = 16.00 Hz, H-7′).

**Compound 4**: $[\alpha]^{25}_D +17$ (*c* 1, $CHCl_3$); FABMS *m*/*z* 677 $[M - H]^-$; $^{13}C$ NMR, see Table 3; $^1H$ NMR $\delta$ 0.89 (3H, s, Me-21), 0.91 (3H, s, Me-20), 0.93 (6H, s, Me-22 and Me-23), 1.69 (1H, dd, $J$ = 3.0, 5.0 Hz, H-14), 1.98 (1H, ddd, $J$ = 11.0, 2.0, 5.0 Hz, H-15a), 2.33 (1H, ddd, $J$ = 11.0, 8.0, 3.0 Hz, H-15b), 3.26 (1H, d, $J$ = 12 Hz, H-24a), 4.00 (1H, d, $J$ = 12 Hz, H-24b), 5.02 (1H, dd, $J$

= 8, 2.0 Hz, H-16), 6.20 (1H, s, H-18), 7.00 (1H, s, H-25), 6.67 (1H,d, $J$ = 16 Hz, H-8′), 7.42 (2H, dd, $J$ = 7.5, 1.5 Hz, H-2′ and 6′), 7.63 (3H, m, H-3′,4′,5′), 7.81 (1H, d, $J$ = 16 Hz, H-7′). The remaining signals are superimposable with those of compound **3**.

**Antiviral Assay.** The anti-HIV-1 activities of compounds were assessed in C8166 cells (a normal T-cell transformed by co-cultivation with leukemia lymphocytes harboring HTLV-1) infected with HIV-1.[7] The cells were cultured in RPMI 1640 with 10% calf serum. Aliquots of $4 \times 10^4$ cells per microtiter plate well were mixed with 5-fold dilutions of compound prior to addition of 10 $CCID_{50}$ units of virus and incubated for 5−7 days. Formation of syncytia was examined from 2 days post-infection. Cell culture supernatant was collected at 5−7 days and gp120 antigen production was measured by ELISA. Viability of infected cells and cytotoxicity to uninfected cell controls were tested by the MTT-Formazan method.[7]

## References and Notes

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