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ABSOLUTE CONFIGURATION OF α-PYRONES FROM *CRYPTOCARYA LATIFOLIA* AND *SYNCOLOSTEMON DENSIFLORUS*

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Key Word Index—*Cryptocarya latifolia*; Lauraceae; *Syncolostemon densiflorus*; Lamiaceae; 6-substituted 5,6-dihydro-α-pyrones; triacetate; diacetate; syndenolide.

Abstract—The stereochemical structures of two α-pyrones previously isolated from *Cryptocarya latifolia* have been shown to be 6*R*-[2*R*,4*S*,6*S*-(triacetoxy)-heptyl]-5,6-dihydro-2*H*-pyran-2-one and 6*R*-[2*S*,4*S*-(diacetoxy)-pentyl]-5,6-dihydro-2*H*-pyran-2-one. Syndenolide from *Syncolostemon densiflorus* is 6*R*-[5*S*-(acetoxy)-1*R*,2*R*,3*S*-(trihydroxy)-heptyl]-5,6-dihydro-2*H*-pyran-2-one.

INTRODUCTION

The isolation and structural determination, without stereochemistry, of the triacetate (**1**) and the diacetate (**2**) from *Cryptocarya latifolia* has been reported recently [1]. We now assign the absolute stereochemistry to all chiral centres in these compounds. In addition, the unknown stereochemistry at C-5′ in syndenolide (**3**) from *Syncolostemon densiflorus* [2] has also been determined.

RESULTS AND DISCUSSION

The positive n → π* Cotton effect observed at λ_{max} 256 nm ($\Delta\varepsilon = +2.5$ and $+2.8$) indicates a (6*R*)-configuration in both **1** and **2** [3]. The (2′*R*,4′*S*,6′*S*)-configuration of the acetoxy groups in the side-chain of **1** was shown as follows.

Saponification followed by acetonide formation [4] of **1** gave, as expected, a mixture of two acetonides (**4**) and (**5**), which were separated by HPLC. The chirality of the secondary hydroxyl groups in **4** and **5** was determined using Mosher's method by conversion to their (*R*)- and (*S*)-MTPA esters [5] and application of the MTPA determination rule [6]. The positive and negative $\Delta\delta_H$-values observed for the signals of the protons in the left and right segments (Figs 1 and 2) indicated a (2′*R*,6′*S*)-stereochemistry in **1**.

The stereochemistry of the remaining centre at C-4′ followed from the *syn*-diol relationships of the two acetal oxygen atoms in **4** and **5**, as determined from their ^{13}C NMR spectra [7]. The proton and ^{13}C signals were first assigned unambiguously from COSY, HMQC and HMBC experiments. The acetonide rings in both compounds possessed chair conformations with the alkyl substituents equatorial and the one methyl group axial (δ 20) and the other equatorial (δ

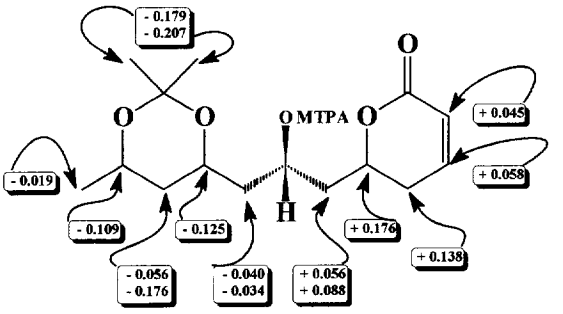


Fig. 1. MTPA ester of compound **4** ($\Delta\delta_H$ values in ppm).

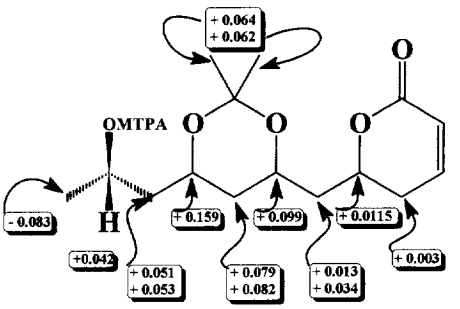
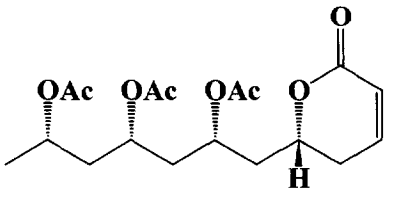


Fig. 2. MTPA ester of compound **5** ($\Delta\delta_H$ values in ppm).

* Author to whom correspondence should be addressed.



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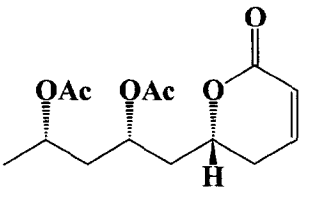

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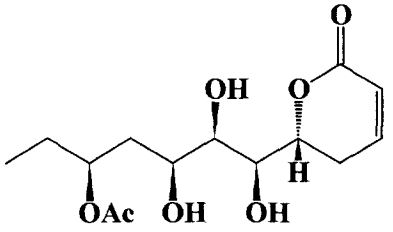

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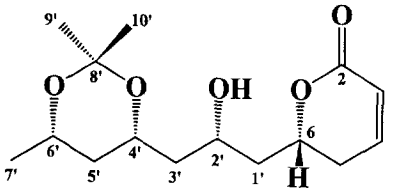

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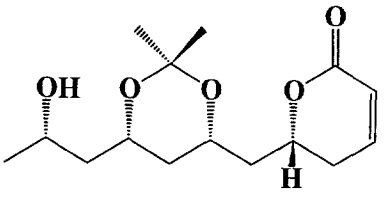

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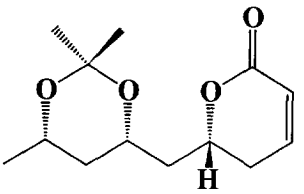

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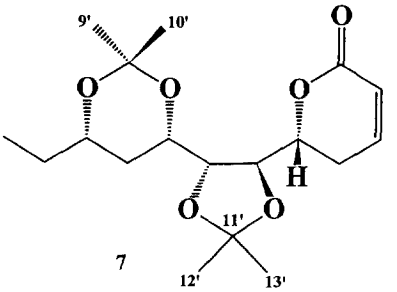

7

30). The *syn*-stereochemistry of H-4′ and H-6′ in **4** was confirmed by NOE difference experiments. Irradiation of H-6′ gave significant enhancement of the axial acetonide C-10′ methyl signal. The expected enhancement of H-4′ was not observed, because the chemical shifts of H-4′ and H-6′ are too close together and both signals collapsed on irradiation of H-6′. Irradiation of the equatorial C-9′ methyl signal gave no enhancements but irradiation of the axial C-10′ methyl signal resulted in enhancements of the H-4′, H-6′ and one of the H-5′ (δ 1.25) signals.

The acetonide (**6**) prepared from the diacetate (**2**) also possesses a chair conformation with the one methyl group axial (δ 19.9) and the other equatorial (δ 30.2). Accordingly, the acetoxy groups in **2** are *syn*. Because it is not possible to correlate the stereochemistry of the C-2′ methine hydrogen with that at C-6 by NMR due to the intervening rotating C-1′ methylene group, the absolute stereochemistry at C-2′ and C-4′ remains unknown. However, because of the proven stereochemistry of the triacetate (**1**) at these positions in the heptyl side-chain, the diacetate (**2**) probably also possesses a 2′*S*,4′*S*-configuration.

The unknown stereochemistry at C-5′ in syndenolide (**3**) followed from a detailed NMR analysis of its diacetonide (**7**). An acetone solution of saponified syndenolide was slowly filtered through a column of Amberlyst-15 to give a mixture of products which was separated by HPLC. The molecular formula of the main product (**7**) was established as $C_{18}H_{28}O_6$ from high-resolution mass spectrometry. The ^{13}C and DEPT-135 NMR spectra showed that the compound

contained three quaternary carbon atoms corresponding with two acetonide rings (δ 98.8 and 110.6) and a carbonyl carbon (δ 162.9) in the α-pyrone ring. A DEPT-135 experiment indicated the presence of four methyl groups resonating at δ30.0, 27.7, 26.7 and 19.8. This observation is best explained by the presence of a six-membered acetonide ring in the chair conformation with one methyl equatorial (δ 30.0) and one axial (δ 19.8), as well as a puckered five-membered acetonide ring with equivalent methyl groups, as in structure (**7**).

The positions of the acetonide rings and the absolute stereochemistry of **7** was supported by NOE enhancement experiments. Irradiation of H-5′ resulted in an enhancement of the axial C-10′ methyl signal and of the overlapping H-2′ and H-3′ signal, proving that the 1,3-dioxolane ring bridging C-3′ and C-5′ was in a chair conformation with the H-3′ and H-5′ protons on the same side of the ring and, hence, axial. Irradiation of H-1′ resulted in enhancements of the C-5 methylene protons, H-2′ and H-3′, and a weak enhancement of the methyl signal (δ 1.43) belonging to the *anti* acetonide ring. Irradiation of both H-2′ and H-3′ resulted in strong enhancements of H-6, H-1′ and the C-10′ axial methyl protons, as well as weak enhancements of the C-5 methylene and H-5′ proton signals. These results confirmed the stereochemistry that had been assigned previously [2] to C-6, C-1′, C-2′ and C-3′, and also that the 1,3-dioxolane ring was in a chair conformation. Hence, the 3′,5′ and 1′,2′-diols in saponified **3** are in *syn*- and *anti*-arrangements, respectively. Syndenolide is therefore 6*R*-[5*S*-(acetoxy)-1*R*,2*R*,3*S*-(trihydroxy)-heptyl]-5,6-dihydro-2*H*-pyran-2-one.

EXPERIMENTAL

Acetonides **4** *and* **5**. A soln of **1** (0.20 g) in MeOH (2 ml) and 0.22 M NaOH (17 ml) was left overnight, the MeOH removed by evapn under red. pres., the soln acidified with 2 M HCl (3 ml) and then heated for 2 min at 100° to complete lactonisation of the free acid. The cooled soln was satd by the addition of NaCl (5 g) to facilitate extraction of the extremely water-sol. product with Et_2O in an efficient extraction apparatus for 10 hr. A soln of the product (132 mg) in dry Me_2CO (2 ml) was left on a column (1.8 × 14 cm) of Amberlyst 15 [previously left to stand for 1 hr in dry Me_2CO and eluted with Me_2CO (120 ml)] for 20 min and then slowly eluted with dry Me_2CO. The product was chromatographed on alumina with benzene to afford an oil (70 mg), shown by silica gel TLC in EtOAc to consist of two closely moving spots. These spots were sepd by semiprep. HPLC on a normal-phase column (EtOAc) to give the acetonides (**4**) and (**5**) as oils (20 and 25 mg, respectively).

Compound **4**. $[\alpha]_D^{30}$ +83° ($CHCl_3$; 1.8). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (3H, *d*, $J_{6',7'}$ = 6.1 Hz, H-7′), 1.25 (1H, *m*, H-5′), 1.38 (3H, *s*, H-9′), 1.45 (1H, *m*, H-5′), 1.47 (3H, *s*, H-10′), 1.60 (1H, *m*, H-3′), 1.65 (1H, *m*, H-3′), 1.76 (1H, *m*, H-1′), 2.0 (1H, *m*, H-1′), 2.44 (2H, *m*, $J_{4,5}$ = 4.4 Hz, $J_{3,5}$ = 1.8 Hz, H-5), 3.65 (1H, *s*, OH), 4.0 (1H, *m*, $J_{6',7'}$ = 6.1 Hz, H-6′), 4.09 (1H, *m*, H-2′), 4.14 (1H, *m*, H-4′), 4.66 (1H, *m*, H-6), 6.01 (1H, *d*, $J_{3,4}$ = 9.8 Hz, H-3), 6.88 (1H, *dt*, $J_{3,4}$ = 9.8 Hz, $J_{4,5}$ = 4.4 Hz, H-4). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4 (C-2), 145.2 (C-4), 121.3 (C-3), 98.7 (C-8′), 75.5 (C-6), 70.4 (C-4′), 68.1 (C-2′), 65.0 (C-6′), 42.7 (C-3′), 41.8 (C-1′), 38.8 (C-5′), 30.2 (C-9′e), 29.3 (C-5), 22.0 (C-7′), 20.0 (C-10′a). HREIMS: $[M]^+$ 284.1633. $C_{15}H_{24}O_5$ requires 284.1624.

Compound **5**. $[\alpha]_D^{30}$ +58.5° ($CHCl_3$; *c* 1.1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (3H, *d*, $J_{6',7'}$ = 6.2 Hz, H-7′), 1.28 (1H, *m*, H-3′), 1.35 (3H, *s*, H-9′), 1.45 (3H, *s*, H-10′), 1.54 (1H, *m*, H-3′), 1.54 (1H, *m*, H-5′) 1.60 (1H, *m*, H-5′), 1.75 (1H, *m*, H-1′), 2.05 (1H, *m*, H-1′), 2.39 (2H, *m*, $J_{3,5}$ = 1.3 Hz, $J_{4,5a}$ = 4.5 Hz, $J_{4,5e}$ = 5.9 Hz, H-5), 3.22 (1H, *s*, OH), 3.97 (1H, *m*, $J_{6',7'}$ = 6.2 Hz, H-6′), 4.12 (1H, *m*, H-4′), 4.17 (1H, *m*, H-2′), 4.59 (1H, *m*, H-6), 6.01 (1H, *dd*, $J_{3,4}$ = 9.7 Hz, $J_{3,5}$ = 1.3 Hz, H-3), 6.88 (1H, *ddd*, $J_{3,4}$ = 9.7 Hz, $J_{4,5a}$ = 2.6 Hz, $J_{4,5e}$ = 5.9 Hz, H-4), ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3 (C-2), 145.2 (C-4), 121.3 (C-3), 98.7 (C-8′), 74.5 (C-6), 70.1 (C-4′), 67.7 (C-6′), 64.9 (C-2′), 44.7 (C-5′), 40.7 (C-1′), 36.7 (C-3′), 30.1 (C-9′e), 29.3 (C-5), 23.4 (C-7′), 20.0 (C-10′a). HREIMS: $[M]^+$ 284.1641. $C_{15}H_{24}O_5$ requires 284.1624.

(S)- *and* (R)- *MPTA esters of acetonides* **4** *and* **5**. The following prepn is representative. A soln of **4** (8 mg) and DMAP (9 mg) in CH_2Cl_2 (1 ml) was added to a soln of (*R*)-MPTA (25 mg) and DCC (55 mg) in CH_2Cl_2 (0.2 ml). The mixt. was shaken periodically and, after 30 min, was dild with H_2O and EtOAc (10 ml). The EtOAc layer was washed with 0.2 M HCl, H_2O, aq. $NaHCO_3$ and H_2O, then dried and evapd. The residue was chromatographed on silica gel in benzene–hexane–EtOAc. The fr. eluted with EtOAc–hexane (1:2) afforded needles (9 mg) of the (*R*)-MPTA ester.

Acetonide (**6**) *of saponified diacetate*. Diacetate (0.11 g) was saponified and converted to the acetonide as described above and the product obtained purified by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.16 (3H, *d*, $J_{4',5'}$ = 6.1 Hz, H-5′), 1.2 (1H, *m*, H-3′), 1.37 (3H, *s*, H-8′), 1.43 (3H, *s*, H-7′), 1.50 (1H, *m*, H-3′), 1.75 (1H, *m*, H-1′), 2.04 (1H, *m*, H-1′), 2.39 (2H, *m*, H-5), 3.98 (1H, *m*, $J_{4',5'}$ = 6.1 Hz, H-4′), 4.13 (1H, *m*, H-2′), 4.60 (1H, *m*, H-6), 6.02 (1H, *d*, $J_{3,4}$ = 9.8 Hz, H-3), 6.87 (1H, *m*, $J_{3,4}$ = 9.8 Hz, H-4). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4 (C-2), 145.2 (C-4), 121.3 (C-3), 98.5 (C-6′), 74.6 (C-6), 64.9 and 65.0 (C-2′ and C-4′), 42.4 (C-1′), 38.2 (C-3′), 30.2 (C-8′), 29.3 (C-5), 22.1 (C-5′), 19.9 (C-7′), HREIMS: M^+ 240.1354. $C_{13}H_{20}O_4$ requires 240.1361.

Acetonide (**7**) *of saponified syndenolide*. A soln of syndenolide (28.3 mg) in MeOH (0.5 ml) and 0.2 M NaOH (1.5 ml) was left overnight and the MeOH then evapd. The soln was acidified with HCl, heated for 2 min, cooled, satd with NaCl and extracted continuously with Et_2O for 36 hr. The product obtained

(18.9 mg) was converted to the acetonide to afford an oil (6.9 mg) whose ^{1}H NMR spectrum suggested that two α-pyrone products were present in 3:1 ratio. Semi-prep. HPLC on a normal-phase column (hexane–EtOAc, 1:1) afforded the major product, acetonide (**7**) (2.8 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (3H, *t*, $J_{6',7'}$ = 7.5 Hz, H-7′), 1.38 (3H, *s*, H-9′), 1.40 (3H, *s*, H-13′), 1.41 (3H, *s*, H-10′), 1.43 (3H, *s*, H-12′), 1.5 (2H, *m*, H-4′), 1.5 (2H, *m*, H-6′), 2.57 (2H, *m*, H-5), 3.72 (1H, *m*, H-5′), 4.00 (1H, *m*, H-2′), 4.00 (1H, *m*, H-3′), 4.28 (1H, *dd*, $J_{6,1'}$ = 7.3 Hz, $J_{1',2'}$ = 6.6 Hz, H-1′), 4.42 (1H, *td*, $J_{5,6}$ = 7.3 Hz, $J_{6,1'}$ = 7.3 Hz, H-6), 6.02 (1H, *dt*, $J_{3,4}$ = 9.8 Hz, $J_{3,5}$ = 1.7 Hz, H-3), 6.90 (1H, *m*, H-4). ^{13}C NMR (100 MHz, $CDCl_3$, $CDCl_3$): δ 162.9 (C-2), 144.9 (C-4), 121.3 (C-3), 110.6 (C-11′), 98.8 (C-8′), 81.7 (C-2′), 78.8 (C-6), 75.9 (C-1′), 70.3 (C-5′), 68.5 (C-3′), 32.2 (C-4′), 30.0 (C-9′), 29.2 (C-6′), 27.7 (C-13′), 26.7 (C-12′), 26.0 (C-5), 19.8 (C-9′), 9.3 (C-7′). HREIMS: $[M]^+$ 340.1873. $C_{18}H_{28}O_6$ requires 340.1886.

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