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5,6-DIHYDRO-α-PYRONES AND TWO BICYCLIC TETRAHYDRO-α-PYRONE DERIVATIVES FROM *CRYPTOCARYA LATIFOLIA*

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Key Word Index—*Cryptocarya latifolia*; Lauraceae; bark; 6-substituted-5,6-dihydro-α-pyrones; bicyclic derivatives of tetrahydro-α-pyrone; cryptocaryolone.

Abstract—Two new 6-substituted-5,6-dihydro-α-pyrones have been isolated from the bark *Cryptocarya latifolia*. In addition two new, closely related dioxabicyclo [3,3,1]nonan-2-one derivatives, have been obtained in lower concentration from the same plant source.

INTRODUCTION

We have previously reported [1] on a novel 6-substituted 5,6-dihydro-α-pyrone, cryptofolione (**1**), isolated from two *Cryptocarya* species indigenous to South Africa. Further investigation into the constituents of *C. latifolia* has revealed the presence of additional 5,6-dihydro-α-pyrone derivatives (**2**–**5**). Interest in this work stems not only from the fact that the bark extract of *Cryptocarya* species is widely used for magical and medicinal purposes, but also because it is being used on an increasing scale to replace extractives from the more traditional *Ocotea bullata* [2], which also belongs to the Lauraceae.

RESULTS AND DISCUSSION

Over the past seven years, an increasing number of α-pyrones have been isolated from a variety of sources and a few of these will be mentioned here. McLaughlin *et al.* [3] reported the isolation of goniopypyrone (**6**) and 8-acetylgoniotriol (**7**) from *Goniothalamus giganteus* (Annonaceae); both of these compounds are cytotoxic to human tumour cells. From *Syncolostemon rotundifolius* (Lamiaceae), Davies-Coleman and Rivett [4] reported the compound, synrotolide (**8**), and the same authors also report [5] the stereochemistry of boronolide (**9**), first isolated by Polonsky [6]. Boronolide occurs in the leaves of *Tetradenia barberae* (Lamiaceae). Related α-pyrones have also been identified very recently by Davies-Coleman [7] from *S. densiflorus*. A striking feature of these α-pyrone derivatives is the almost-invariable presence of one or more acetate groups in the side-chain. This same phenomenon is evident in the compounds now isolated by us.

The structures of the α-pyrones presented in this paper were established by employing the normal spectral techniques (COSY, HETCOR) at 200 MHz. Where any doubt existed with regard to specific features in the molecules, more advanced gradient techniques, such as DQFCOSY [8], HSQC [9] and HMBC at 500 MHz were applied in order to give an unambiguous result.

It was possible to establish all relevant $^1H/^1H$ correlations and all relevant $^{13}C/^1H$ long-range (up to three bonds away) correlations for **2** using the techniques mentioned above. For example, the correlation between the two H-5 protons (δ 2.42, 2.29) to the carbonyl group at C-2 (δ 163.70), which is four bonds away, was clearly discernible. The critical H-6 proton (δ 4.47) exhibited a very clear connectivity to C-2 (δ 163.70), C-4 (δ 144.46), C-2^1 (δ 67.75), C-1^1 (δ 39.14) and C-5 (δ 29.17). This proton, in turn, showed $^1H/^1H$ connectivties to H-5a (δ 2.42), H-5b (δ 2.29), H-1^{1}a (δ 2.14), and H-1^{1}b (δ 1.93). The structure of **3** was readily established by analogy with **2**, since it simply has a side-chain which is two carbon atoms longer.

The structure of **4** (named cryptocaryolone), with molecular formula $C_{12}H_{20}O_5$, was much more elusive. From the ^1H and ^{13}C NMR spectra, it was clear that the α,β-unsaturated system found in **2** and **3** was absent. The ^1H NMR spectrum at 200 MHz in chloroform-*d* showed a serious overlap of peaks in the CH(OH) region. However, the ^{13}C NMR peaks clearly represented one methyl, five methylene, five methine and one quaternary carbon (ester group). From the COSY spectrum, it was evident that none of the five methine hydrogens were coupled with one another. From the HETCOR spectrum, it was evident that the two hydroxyl protons gave rise to the broad resonance at δ 3.67–4.11.

Far better resolution was obtained for the ^1H NMR spectrum of **4** by replacing chloroform-*d* with benzene-d_6;

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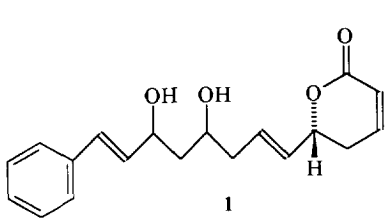

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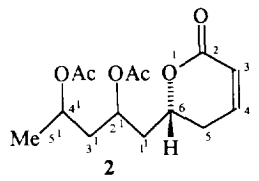

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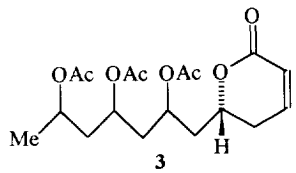

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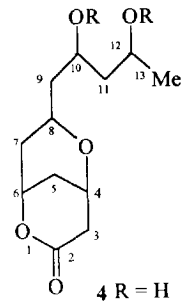

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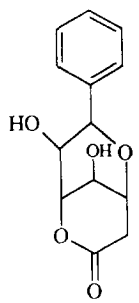
5 R = Ac



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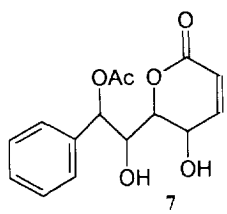

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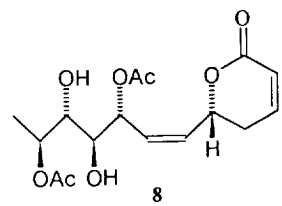

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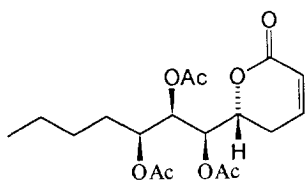

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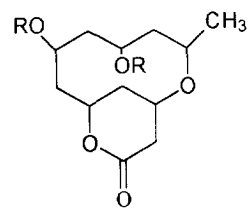


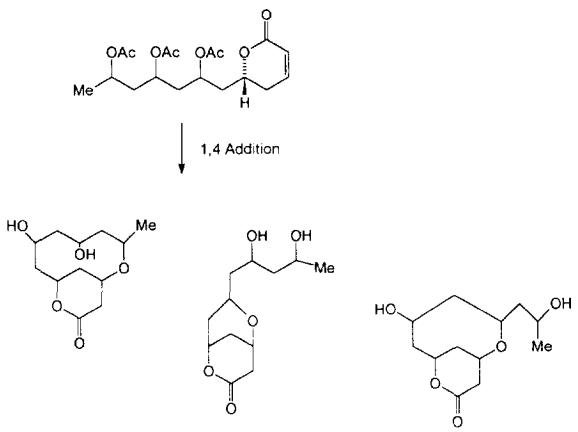
10

various pulse sequences were employed at 500 MHz. These correlations persuade us that structure **4** is indeed correct, rather than the alternative structure **10**, which features a 10-membered ring. Our decision to choose **4** is based on a very definite correlation evident from the gradient HMBC spectrum. In this sequence, C-4 (δ 66.0) has a definite cross-peak to H-8 (δ 3.62). Clearly such a correlation would not be possible for structure **10**. Careful scrutiny of the spectra also did not reveal a cross-peak between H-12 (δ 4.0) and C-4 (δ 66.0), which would have been anticipated in the alternative 10-membered ring. This conclusion is further strengthened by reference to McLaughlin's work [3] on the analogous structure for goniopypyrone.

From the foregoing discussion, it is obvious that we believe that **3** is a likely precursor for **4**. Michael addition of one of the three available hydroxyl (acetyl) groups would result in a 6-, 8-, or 10-membered ring (Scheme 1). It was also established beyond doubt that acetylation of **4** affords a compound identical to the naturally occurring acetate, **5**.

Determination of the structure of **5** was greatly facilitated by the knowledge that benzene-d_6 was an ideal solvent for maximum resolution of the NMR peaks of such compounds. In the ^{1}H NMR spectrum, the appearance and chemical shifts of H-4, H-8 and H-6 is similar to that found in **4** but the signals for H-12 and H-10 are further downfield at δ 5.11 and δ 5.21, respectively. This obviously reflects the paramagnetic influence of the acetyl group attached to these two carbon atoms. In the HETCOR spectrum, the diastereotopic nature of the geminal protons attached to C-5, C-3, C-7, C-9 and C-11 is neatly illustrated. The delayed HETCOR (12 Hz) indicated unambiguously the interrelationship of the ring atoms through a positive correlation of the C-2 carbonyl groups (δ 168.8) with H-6, H-4 and H-3.

It is relevant to point out that the compounds described in this paper are all new. However, Nakata and



Scheme 1. Possible cyclic products from 1,4-addition.

coworkers [10] have synthesized a series of δ-lactones of 5,7-dihydroxy-2,3-unsaturated acids which are similar to **2** and **3**, but have a terminal $C_{15}H_{31}$ side-chain instead of the methyl group reported here [11].

EXPERIMENTAL

General. ^{1}H and ^{13}C NMR spectra were at 200 or 500 MHz, solvents as indicated in the text, with TMS as int. standard. CC was carried out on silica gel 60.

Plant material. Mature trunks (10–15 cm in diameter) of *Cryptocarya latifolia* Sond. were collected in March 1993 in the Karkloof forest (district of Pietermaritzburg, Kwazulu/Natal). Plant material was autheticated by R.S.-S. and a voucher specimen (No. 6095) is lodged in the C.P.F. Herbarium (Natal Parks Board, Pietermaritzburg, Kwazulu/Natal).

Extraction and isolation. Milled bark (2 kg) was extracted with EtOH (Soxhlet) and thereafter concd under vacuum to remove EtOH. H_2O was added and the soln extracted sequentially with C_6H_6, $CHCl_3$ and EtOH. The C_6H_6 extract (19.2 g) was purified by MPLC using petrol–EtOAc (3:1) as eluent. A fr. containing a mixt. of **2** and **3** was again sepd by MPLC using petrol–EtOAc (3:1). A fr. containing a mixt. of **2** and **3** was then sepd by MPLC using petrol–EtOAc–$CHCl_3$ (6:4:1). The individual frs were obtained in pure form after final purification by centrafugal TLC using 4 mm plates and eluting with petrol–EtOAc–$CHCl_3$ (30:20:7). This step afforded **2** (279 mg) and **3** (160 mg) as light yellow oils.

(2′,4′-*diacetoxy*)-6-*Pentyl*-5,6-*dihydro*-2-H-*pyran*-2-*one* (**2**). Yellow oil. $[\alpha]_D^{22}$ + 55.8° ($CHCl_3$; *c* 1.06). IR ν_{max} cm^{-1}: 2950, 1733, 1435, 1375, 1245, 1040, 960, 820. ^{1}H NMR (500 MHz, C_6D_6): δ1.24 (3H, *d*, *J* = 6.26 Hz, Me). 1.77 (1H, *ddd*, *J* = 14.34, 5.80 Hz, H-3^{1}a), 1.99 (1H, *ddd*, *J* = 14.49, 5.80 Hz, H-3^{1}b). 1.93 (1H, *m*, H-1^{1}a). 2.14 (1H, *ddd*, *J* = 15.26, 6.41 Hz, H-1^{1}b), 2.02 (3H, *s*, OAc), 2.05 (3H, *s*, OAc), 2.29 (1H, *dddd*, *J* = 18.31, 11.59, 2.60 Hz, H-5a), 2.42 (1H, *dddd*, *J* = 18.31, 5.95, 1.07 Hz, H-5b), 4.47 (1H, *dddd*, *J* = 11.58, 6.41, 3.97 Hz, H-6), 4.96 (1H, *m*, H-4^1), 5.08 (1H, *dddd*, *J* = H-2^1), 5.99 (1H, *ddd*, *J* = 9.77, 2.74, 1.07 Hz, H-3), 6.85 (1H, *ddd*, *J* = 9.76, 5.79, 2.44 Hz, H-4). ^{13}C NMR (C_6D_6): δ20.1 (Me), 21.09 and 21.2 (OAc), 29.2 (C-5). 39.1 (C-1^1), 40.4 (C-3^1), 67.7 (C-4^1), 67.8 (C-2^1), 74.9 (C-6), 121.3 (C-3), 144.5 (C-4), 163.7 (lactone C=O), 170.5, 170.49 (3 × OAc). CI-MS (CH_4) *m/z* (rel. int.): 285 $[M + H]^+$ (15), 265 (0.04), 253 (4), 226 (16), 225 (100), 193 (4), 165 (23). HR-MS: $[M]^+$ 284.1250; calcd. for $C_{14}H_{20}O_6$ $[M]^+$ 284.1260.

(2′,4′,6′-*triacetoxy*)-6-*Heptyl*-5,6-*dihydro*-2-H-*pyran*-2-*one* (**3**). Yellow oil. $[\alpha]_D^{25}$ + 43.8° ($CHCl_3$; *c* 0.63). IR ν_{max} cm^{-1}: 2950, 1730, 1435, 1370, 1245, 1040, 960, 820. ^{1}H NMR (200 MHz, $CDCl_3$): δ1.23 (3H, *d*, *J* = 6.24 Hz, Me) 1.77, 1.99, 2.15 (6H, overlapping *m*, H-3^1, H-5^1, H-1^1) 2.03 (3H, *s*, OCOMe), 2.07 (6H, *s*, OCOMe), 2.40 (2H, *m*, H-5), 4.49 (1H, *dddd*, *J* = 11.60, 6.41, 4.01 Hz, H-6), 4.83–5.13 (3H, *m*, H-2^1, H-4^1, H-6^1), 6.01 (1H, *ddd*, *J* = 9.76, 2.50 1.16 Hz, H-3), 6.89 (1H, *ddd*, *J* = 9.80, 5.72, 2.80 Hz, H-4). ^{13}C NMR ($CDCl_3$): 20.0 (Me), 21.1, 21.2, 21.3 (OAc), 29.1 (C-5), 39.0 (C-1^1, C-5^1), 40.2 (C-3^1), 67.6 (C-4^1), 67.8 (C-2^1), 68.1 (C-6^1), 74.9 (C-6), 121.2 (C-3), 144.9 (C-4), 163.8 (lactone C=O), 170.4, 170.5, 170.6 (3 × OAc). CI-MS (CH_4) *m/z* (rel. int.): 371 $[M + H]^+$ (4), 312 (12), 311 (100), 251 (6), 191 (10). HR-MS: $[M]^+$ 370.1627; calcd. for $C_{18}H_{26}O_8$ $[M]^+$ 370.1625.

Cryptocaryolone (**4**). From the $CHCl_3$ extract (see above), a brown powder (5.25 g) was obtained and this was fractionated repeatedly by MPLC using EtOAc–CH_2Cl_2–petrol–MeOH (5:2:7:1) and finally centrifugal TLC (EtOAc–CH_2Cl_2–petrol–MeOH, 9:2:2:1) to give **4** as a yellow oil (60 mg). $[\alpha]_D^{24}$ − 128° ($CHCl_3$; *c* 0.04). IR ν_{max} cm^{-1}: 2940, 1733, 1435, 1045, 960. ^{1}H NMR (500 MHz, C_6D_6): δ0.84 (1H, *ddd*, *J* = 14.01, 11.61, 2.20 Hz, H-7a), 1.40 (1H, *m*, H-7b), 0.90 (1H, *m*, H-9a), 1.33 (1H, *ddd*, *J* = 14.28, 9.2 Hz, H-9b), 0.91 (1H, *m*, H-5a), 1.05 (1H, *ddd*, *J* = 13.73, 2.06 Hz, H-5b), 1.12 (1H, *ddd*, *J* = 14.01, 2.47 Hz, H-11a) and 1.47 (1H, *ddd*, *J* = 14.01, 10.16 Hz, H-11b), 2.03 (1H, *dd*, *J* = 19.09, 5.35 Hz, H-3a), 2.40 (1H, *dm*, *J* = 19.09 Hz, H-3b), 3.37 (1H, *m*, H-4), 3.62 (1H, *m*, H-8), 3.66 (1H, *m*, H-10), 4.0 (1H, *ddq*, *J* = 6.18 Hz, H-12), 4.05 (1H, *m*, H-6). ^{13}C NMR (C_6D_6): δ24.2 (C-13), 29.1 (C-5), 36.4 (C-3), 37.2 (C-7), 43.2 (C-9), 45.7 (C-11), 66.0 (C-4), 66.6 (C-8), 68.2 (C-12), 71.9 (C-6), 72.3 (C-10), 168.0 (C=O). CI-MS (CH_4) *m/z* (rel. int.): 245 $[M + H]^+$ (53), 191 (17), 183 (25), 165 (22), 157 (37), 155 (18), 141 (100), 139 (19). HRMS: $[M]^+$ 244.1291; calcd. For $C_{12}H_{20}O_5$ $[M]^+$ 244.1309.

Cryptocaryolone diacetate (**5**). This compound was also present in the $CHCl_3$ extract and was purified by a similar procedure to that used for **4**. After final purification by centrifugal TLC (petrol–EtOAc–$CHCl_3$, 5:7:3) this afforded 111 mg of a yellow oil. $[\alpha]_D^{23}$ − 145° ($CHCl_3$; *c* 0.27). IR ν_{max} cm^{-1}: 2945, 1740, 1430, 1240, 1045, 965, 820. ^{1}H NMR (200 MHz, C_6D_6): δ0.99 (1H, *ddd*, *J* = 11.61, 2.1 Hz, H-7a), 1.61 (1H, *m*, H-7b) 1.14 (3H, *d*, Me), 1.02 (1H, *m*, H-5a), 1.22 (1H, *m*, H-5b), 1.38 (1H, *m*, H-9a), 1.71 (1H, *m*, H-9b), 1.50 (1H, *m*, H-11a), 1.95 (1H, *m*, H-11b), 1.71 and 1.73 (6H, *s*, 2 × OAc), 2.19 (1H, *dd*, *J* = 19.02, 5.31 Hz, H-3a), 2.67 (1H, *br d*, *J* = 19.01 Hz, H-3b), 3.63 (1H, *m*, H-4), 3.82 (1H, *m*, H-8), 4.20 (1H, *m*, H-6), 5.11 (1H, *m*, *J* = 6.36 Hz, H-12), 5.21 (1H, *m*, H-10). ^{13}C NMR (C_6D_6): δ20.6 (Me), 21.2, 21.4 (2 ×) COMe,

29.8 (C-5), 36.8 (C-3), 37.5 (C-7), 40.6 (C-9), 40.9 (C-11), 63.8 (C-8), 66.5 (C-4), 68.4 (C-12), 68.8 (C-10), 72.8 (C-6), 168.9, 170.5 (2 × OCOMe). CI-MS (CH_4) *m/z* (rel. int.): 329 $[M + H]^+$ (0.2),.297 (2), 269 (100), 237 (4), 209 (12) 169 (2). HRMS: $[M - MeCO_2H]^+$ 268.1301; calcd. for $C_{14}H_{20}O_5$ $[M - 60]^+$ 268.1311.

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REFERENCES

1. Drewes, S. E., Sehlapelo, B. M. and Scott-Shaw, R. (1994) *Phytochemistry* **37**, 847.
2. Cunningham, A. B. (1988) in *An Investigation of the Herbal Medicine Trade in Natal/Kwazulu*, p. 70. Institute of Natural Resources Report, No. 29, Pietermaritzburg.
3. Fang, X., Anderson, J. E., Chang, C., Fanwick, P. E. and McLaughlin, J. (1990) *J. Chem. Soc., Perkin Trans I* 1655.
4. Davies-Coleman, M. T., English, R. B. and Rivett, D. E. A. (1987) *Phytochemistry* **26**, 1497.
5. Davies-Coleman, M. T. and Rivett, D. E. A. (1987) *Phytochemistry* **26**, 3047.
6. Franca, N. C. and Polonsky, J. (1971) *C. R. Acad. Sci. Paris* **273**, 439.
7. Davies-Coleman, M. T. and Rivett, D. E. A. (1994) *Phytochemistry* **35**, 1590.
8. Piantini, U., Sorenson, O. W. and Ernst, R. R. (1982) *J. Am. Chem. Soc.* **104**, 6800.
9. Hull, W. E. (1987) in *Two-Dimensional NMR Spectroscopy* (Croasmun, W. R. and Carlson, R. M. K., eds), pp. 222–224. VCH, Weinheim.
10. Nakata, T., Noriaki, H., Koichi, N. and Oishi, T. (1987) *Chem. Pharm. Bull.* **35**, 4355.
11. Nakata, T., Nagao, S. and Oishi, T. (1985) *Tetrahedron Letters* **26**, 75.