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RUBRENOLIDE AND RUBRYNOLIDE: AN ALKENE–ALKYNE PAIR FROM *NECTANDRA RUBRA**

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Key Word Index—*Nectandra rubra*; Lauraceae; rubrenolide; rubrynolide; (2*S*,4*R*)-2-[(2′*S*)-2′,3′-dihydroxypropyl]-4-(dec-9″-enyl)-γ-lactone; (2*S*,4*R*)-2-[(2′*S*)-2′,3′-dihydroxypropyl]-4-(dec-9″-ynyl)-γ-lactone.

Abstract—Structures are proposed for rubrenolide, (2*S*,4*R*)-2-[(2′*S*)-2′,3′-dihydroxypropyl]-4-(dec-9″-enyl)-γ-lactone, and rubrynolide, (2*S*,4*R*)-2-[(2′*S*)-2′,3′-dihydroxypropyl]-4-(dec-9″-ynyl)-γ-lactone, isolated from *Nectandra rubra* (Lauraceae).

INTRODUCTION

In a preliminary communication [2] constitutions were proposed for rubrenolide (**1a**) and rubrynolide (**1b**), which may represent variants upon the biosynthetic routes to fatty acids [3]. In the present paper we wish to report the complete sequence of arguments which led to the constitutions and the absolute configurations of these structurally unique natural products isolated from the trunk wood of the Amazonian tree *Nectandra rubra* (Mez) C. K. Allen [4].

Constitutions of rubrenolide and rubrynolide

Rubrenolide, $C_{17}H_{30}O_4$, and rubrynolide, $C_{17}H_{28}O_4$, differed only in their degree of unsaturation, as indicated by their IR and NMR spectra. The IR spectrum of rubrenolide showed features characteristic of a long chain monoalkene with bands at 1635, 990 and 910 cm^{-1} attributable to a terminal vinyl group, whereas rubrynolide showed highly characteristic bands at 3280 and 2100 cm^{-1} associated with a terminal monoalkyne. The NMR spectra of rubrenolide (**1a**) and rubrynolide (**1b**) were identical except for those features associated with the allyl (^1H τ 7.97, 5.04, 4.19; ^{13}C δ 33.7, 138.7, 113.9) or propargyl (^1H τ 7.82, 8.06; ^{13}C δ 18.2, 84.5, 67.9) groups, respectively. Catalytic reduction transformed both rubrenolide and rubrynolide to the same derivative, dihydrorubrenolide (**1c**), $C_{17}H_{32}O_4$, which possessed a terminal methyl group (^1H-NMR τ 9.4).

The IR spectra of **1a**, **1b** and **1c** showed bands at 1745 and 1180 cm^{-1} typical of a lactone function which would account for the remaining two hydrogen deficiencies in dihydrorubrenolide. Indeed, rubrenolide was soluble in dilute aqueous NaOH and could be recovered on acidification by extraction with ether (see below). Having accounted for two of the oxygens, the remaining two were shown to be present as one primary and one secondary hydroxyl group (ν_{OH} 3450 cm^{-1}) by reaction of rubrenolide with trichloroacetyl isocyanate (TAI) [5]. After the addition of TAI to a deuteriochloroform solution of rubrenolide in an NMR tube, sharp one proton singlets appeared (τ 1.19 and 1.26) due to the two NH groups of the carbamate ester formed. The signal at 6.27 in the NMR spectrum of rubrenolide moved downfield by 1.48 ppm, and the AB part of an ABX system centred in the spectrum of rubrenolide at τ 6.37 and 6.52 shifted downfield to give a similar pattern centred at τ 5.44 and 5.71. The two hydroxyl groups were shown to be vicinal by periodate oxidation of dihydrorubrenolide which gave formaldehyde and an aldehyde (**2a**), $C_{16}H_{28}O_3$, both characterised as the 2,4-dinitrophenylhydrazones. Intramolecular hydrogen bonding made a direct deduction of the lactone ring size in rubrenolide (ν_{CO} 1745 cm^{-1}) rather uncertain, but the carbonyl frequencies associated with the lactone in the diacetyl (**1d**, **1e**, **1f**: ν_{CO} 1775 cm^{-1}), bistrimethylsilyl (**1g**, **1h**: ν_{CO} 1760 cm^{-1}), dimethyl (**1l**: ν_{CO} 1760 cm^{-1}) and acetonide (**1i**, **1j**, **1k**: ν_{CO} 1770 cm^{-1}) derivatives located the lactone function in a 5-membered ring.

In order to determine the nature of the rubrenolide–rubrynolide C_{17}-skeleton, rubrenolide was converted to the saturated hydrocarbon $C_{17}H_{36}$ via the sequence **1a** → **3a** → **4a** → **4b**. The alkane obtained was identified by direct IR, NMR, GLC and GC–MS comparison with an authentic sample of 4-methylhexadecane, prepared via Grignard synthesis from pentan-2-one and dodecylmagnesium bromide, followed by dehydration of the resulting 4-methylhexadecan-4-ol with phosphoric acid and catalytic reduction of the alkene. The MS of the synthetic and degradatively obtained alkanes were virtually identical. The branching point in the hydrocarbon chain is clearly at C-4. Characteristic peaks [6] of enhanced intensity relative to those in the spectrum of the straight chain isomer appeared at *m/e* 225 (M-Me), 197 (M-C_3H_7) and 71 (M-$C_{12}H_{25}$).

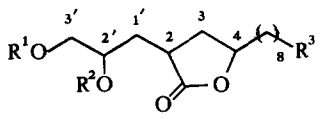
Oxidation of rubrenolide with chromic oxide in refluxing aqueous acetic acid gave a mixture of dicarboxylic acids which was esterified by treatment with diazomethane. The methyl ester mixture was analysed by

* Part 42 in the series 'The Chemistry of Brazilian Lauraceae'. For Part 41 see ref. [1]. Based on the Doctorate thesis presented by N.C.F. to Universidade de São Paulo (1971). Sponsored by Fundação de Amparo à Pesquisa do Estado de São Paulo and by Instituto Nacional de Pesquisas da Amazônia, CNPq, Manaus.

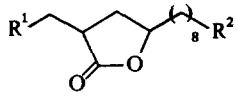
GC–MS and shown to be a mixture of dimethyl azelate (**5a** ~40%) and dimethyl sebacate (**5b**, ~60%). At this stage two possible constitutions, **1a** or **6**, could be considered for rubrenolide. The 1,2-diol system or the vinyl group could occupy either terminal of the C_{16}-chain, but the C_1 branch must correspond to the carboxy group of the γ-lactone. Both of these structures could give rise to azelaic and sebacic acid on vigorous oxidation. On mild oxidation with chromic oxide in aqueous acetic acid at room temperature, however, rubrenolide gave a vinylic acid, $C_{16}H_{26}O_4$ (**2c**, ν_{max} 1645, 990, 910, 1760 and 1695 cm^{-1}). The NMR spectrum of this acid showed two signals at τ 7.05 (1H, *dd*, *J* 17.5 and 3.5 Hz) and 7.49 (1H, *dd*, *J* 17.5 and 8.5 Hz), absent from the analogous spectrum of rubrenolide. These signals were assigned to a methylene group (geminal coupling constant 17.5 Hz) flanked on one side by an oxidatively generated carboxyl group and on the other by a methine. The formation of this product required the constitution of rubrenolide to be represented by the formula **1a**.

Structure of rubrenolide and rubrynolide

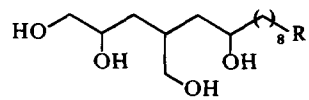
The constitutions of rubrenolide (**1a**), rubrynolide (**1b**) and dihydrorubrenolide (**1c**) are compatible with the detailed interpretation of their IR and NMR spectra, as well as the high resolution examination of their MS fragmentation patterns (Scheme 1). Peaks which are common to all three compounds appear at *m/e* 159, 116 and



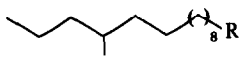
(**1a**) $R^1 = R^2 = H$, $R^3 = CH{=}CH_2$
(**1b**) $R^1 = R^2 = H$, $R^3 = C{\equiv}CH$
(**1c**) $R^1 = R^2 = H$, $R^3 = CH_2Me$
(**1d**) $R^1 = R^2 = Ac$, $R^3 = CH{=}CH_2$
(**1e**) $R^1 = R^2 = Ac$, $R^3 = C{\equiv}CH$
(**1f**) $R^1 = R^2 = Ac$, $R^3 = CH_2Me$
(**1g**) $R^1 = R^2 = SiMe_3$, $R^3 = CH{=}CH_2$
(**1h**) $R^1 = R^2 = SiMe_3$, $R^3 = C{\equiv}CH$
(**1i**) R^1-$R^2 = CMe_2$, $R^3 = CH{=}CH_2$
(**1j**) R^1-$R^2 = CMe_2$, $R^3 = C{\equiv}CH$
(**1k**) R^1-$R^2 = CMe_2$, $R^3 = CH_2Me$
(**1l**) $R^1 = R^2 = Me$, $R^3 = CH{=}CH_2$
(**1m**) $R^1 = Me$, $R^2 = H$, $R^3 = CH{=}CH_2$



(**2a**) $R^1 = CHO$, $R^2 = CH_2Me$
(**2b**) $R^1 = CH_2OH$, $R^2 = CH_2Me$
(**2c**) $R^1 = CO_2H$, $R^2 = CH{=}CH_2$
(**2d**) $R^1 = CO_2Me$, $R^2 = CH{=}CH_2$
(**2e**) $R^1 = CO_2Me$, $R^2 = CH_2Me$

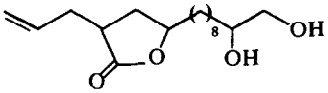


(**3a**) R = $CH{=}CH_2$
(**3b**) R = $C{\equiv}CH$

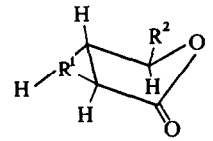


(**4a**) R = $CH{=}CH_2$
(**4b**) R = CH_2Me

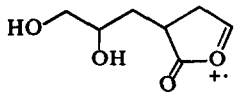
$MeO_2C{-}(CH_2)_n{-}CO_2Me$
(**5a**) $n = 7$
(**5b**) $n = 8$



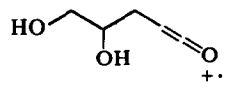
(**6**)



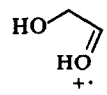
(**9a**) = (**1a**) $R^1 = C_3H_7O_2$, $R^2 = C_{10}H_{19}$
(**9b**) = (**1b**) $R^1 = C_3H_7O_2$, $R^2 = C_{10}H_{17}$



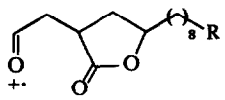
m/e 159



m/e 116



m/e 61



m/e ex **1a** 267
ex **1b** 265
ex **1c** 269

Scheme 1. Constitution of principal MS fragment ions of rubrenolide (**1a**, R = $VH{=}CH_2$), rubrynolide (**1b**, R = $C{\equiv}CH$) and dihydrorubrenolide (**1c**, R = CH_2CH_3)

61. Other fragment ions have masses whose differences are due to differential constitution of the R-substituents of **1a**, **1b** and **1c**. The NMR spectrum of dihydrorubrenolide (**1c**) is more informative than that of rubrenolide (**1a**) or rubrynolide (**1b**) due to the absence of signals from either allylic or propargylic methylene protons. In the 220 MHz spectrum of dihydrorubrenolide (**1c**), seven distinct one proton multiplets are observed between τ 5–8, in addition to a broad methylene signal with a peak at τ 8.70 and a terminal methyl triplet (J 6.5 Hz) at τ 9.14. Double resonance experiments at 100 MHz revealed that the methine H-4 (τ 5.54) was spin coupled (J 5.5 Hz) with H-3α (τ 7.45) and the methine of the secondary alcohol (τ 6.28) was spin coupled (J 10 Hz) with one of the protons of the methylene at C-2 (τ 8.02), in agreement with the assignments given. Two one proton signals, those due to H-3β and the other proton at C-2, were obscured by the broad methylene band which extended down to τ 8.2. The position and exact nature of the resonance due to H-3β was of particular interest with regard to the configuration and conformation of the lactone ring. This seemed an ideal problem for solution by the LIS method with a suitable derivative. Indeed, addition of Eu(dpm)$_3$ [7] to the monoalcohol **2b**, prepared by borohydride reduction of **2a**, gave NMR spectra in which the chemical shift of H-3β was assignable by extrapolation to O% complexing agent. The signal was expected to appear as a double double doublet, since H-3β is coupled to H-3α (J_{gem} 12.5 Hz), H-2 and H-4, but the signal observed was an apparent quartet of approximate intensity ratio 1:3:3:1 and of width 36 Hz. This suggested that the vicinal coupling constants $J_{2,3\beta}$ and $J_{3\beta,4}$ were of the same order (11–12 Hz) as the geminal coupling constant.

Further derivatives which proved useful for NMR study were the methyl esters **2d** and **2e** derived from the acid **2c**. The 220 MHz NMR spectrum of the ester **2e** clearly showed signals due to H-3α and H-3β at τ 7.42 and 8.40, respectively. H-3α appeared as a *ddd* (J 12.5, 8.5 and 5.5 Hz) partly obscured by the double doublet (J 17.5 and 8.5 Hz) due to one of the protons of C-2 at τ 7.51; and H-3β appeared as an approximately symmetrical 1:3:3:1 quartet of width 35 Hz. 'Spin tickling' at τ 5.61, corresponding to H-4, caused the collapse of both of these multiplets, whereas all other signals in the spectrum remained apparently unchanged.

The complete assignment of all proton resonances and coupling constants associated with the γ-lactone showed rubrenolide to possess the 2,4-*trans* configuration. Comparison with analogous data given by some model *cis* (**7**) and *trans* (**8**) 2,4-disubstituted γ-butyrolactones (Table 1), specially synthesized for this purpose [8], yielded unequivocal proof of this fact.

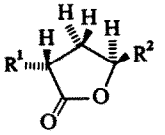
Rubrenolide and its derivatives were all optically active. ORD curves were determined on rubrenolide (**1a**), rubrynolide (**1b**) and the two tetra-ols **3a** and **3b** obtained by respective aluminium hydride reduction. The curves for rubrenolide and rubrynolide were very similar, showing a positive Cotton effect and a peak maximum (ϕ + 1700) at 226 nm. The two tetra-ols gave plain positive curves of very low amplitude. Application of the modified Hudson Lactone Rule [9] therefore enabled the assignment of the *R*-configuration to the chiral centre at C-4. C-2 must, consequently, possess the *S*-configuration. This allows both substituents of the lactone ring to be in *quasi*-equatorial position (**9**).

A priori it could be imagined that hydrolysis of the lactone moiety in rubrenolide and relactonization with the alternative γ-hydroxyl of the 2′,3′-dihydroxypropyl group should be a facile reaction. In spite of several trials, such a reaction was not observed, rubrenolide being recovered as the sole lactonic product in all experiments. This may indicate that C-2′ of the 2′,3′-dihydroxypropyl group does not exist in the *R*-configuration which would allow both substituents of the hypothetical lactone again to occupy *quasi*-equatorial configurations. In order to understand lack of formation, this alternative lactone must be less stable, and it can be implied that C-2′ exists in the *S*-configuration. Indeed, as expected, when Horeau's method [10] was applied to rubrenolide, or more precisely to its monomethyl ether **1m** in order to avoid esterification of the primary hydroxyl, d-α-phenylbutyric acid was obtained in 31.3% optical yield.

Table 1. Comparison of vicinal coupling constants (Hz) and of geminal proton chemical shift differences (ppm) of synthetic *trans* (**7**) and *cis* (**8**) disubstituted γ-butyrolactones [8] with rubrenolide (**1a**), rubrynolide (**1b**) and derivatives (**1c**, **2**)

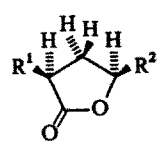
Lactone	$J_{2,3\alpha}$	$J_{2,3\beta}$	$J_{3\alpha,4}$	$J_{3\beta,4}$	$\Delta\tau_{3\beta-3\alpha}$
7	7.0–8.1*	9.0–9.7*	6.8–7.8*	5.5–7.0*	0.00–0.18†
8	8.1–8.5*	12·8–12.9*	5.7–6.0*	10·8*	0.68–1.26‡
1a	8.5		5.5		0.96
1b	8.5		5.5		0.97
1c	8.5		5.5		0.95
2b	9.0	~11	5.5	~11	0.97
2d	8.5		5.5		0.96
2e	8.5	~11	5.5	~11	0.98

* Range of values for compounds **a–d**
† Range of values for compounds **a–h**
‡ Range of values for compounds **b–h**



(**7**)

a $R^1 = R^2 =$ *t*-Bu
b $R^1 = R^2 =$ Ph
c $R^1 =$ Ph, $R^2 =$ Me
d $R^1 =$ Me, $R^2 =$ Ph
e $R^1 = R^2 =$ Me
f $R^1 = R^2 =$ Et
g $R^1 =$ Et, $R^2 =$ Me
h $R^1 =$ *n*-Bu, $R^2 =$ Me



(**8**)

EXPERIMENTAL

Isolation of the constituents of Nectandra rubra. Trunk wood was collected in the Ducke Forest Reserve, Instituto Nacional de Pesquisas da Amazônia, Manaus. The C_6H_6 extract (210 g) of a ground sample (5.4 kg) was washed with boiling petrol. The insoluble part (107 g) was suspended in hot MeOH and filtered. The filtrate was evaporated. The residue (74 g) was crystallized from $CHCl_3$–CCl_4 to colourless crystals (40 g), mp 91–93°, $[\alpha]_D^{22°}$ + 22° ($CHCl_3$), one TLC spot. The crystals (3.45 g) in 95% EtOH (30 ml) were added to a 5% soln of $AgNO_3$ in 95% EtOH (150 ml). The milky precipitate which formed almost immediately was separated by filtration in the dark and washed with 95% EtOH. The precipitate was transferred to a flask and stirred with Et_2O (80 ml). An aq. soln of 10% NaCN (100 ml) was slowly added to this suspension, with stirring, until both phases became clear. The Et_2O phase was then separated and the aq. soln extracted with more Et_2O (3 × 30 ml). The combined Et_2O extracts were washed, dried and evaporated to give crude **1b** (1.4 g), which was crystallized from Et_2O–$CHCl_3$ to give *rubrynolide* (**1b**, 1.2 g) as colourless needles, mp 88° (Found: C, 68.82; H, 9.50. $C_{17}H_{28}O_4$ requires: C, 68.89; H, 9.52%). $[\alpha]_D^{22°}$ + 21° ($CHCl_3$). ν_{max}^{KBr} cm^{-1}: 3450, 3300, 1745, 1460, 1200, 1185, 1018, 980, 875, 850, 725, 715. MS *m/e* (rel. int.): 296 (< 1, M), 265 (42), 116, (29), 95 (50),.81 (92), 67 (100), 61 (24), 55 (92), 41 (85). ^{1}H-NMR (220 MHz, $CDCl_3$–D_2O) τ: 7.05 (*m*, H-2), 7.43 (*ddd*, *J* 12.5, 8.5, 5.5 Hz, H-3α), *ca* 8.4 (*m*, H-3β), 5.55 (*m*, H-4); 8.00 (*ddd*, *J* 14.5, 10, 5 Hz, H-1'), *ca* 8.2 (*m*, H-1'), 6.25 (*m*, H-2'), 6.36 (*dd*, *J* 11.5, 3.5 Hz, H-3'), 6.51 (*dd*, *J* 11.5, 6.5 Hz, H-3'); 8.70 (*br*, H-1'' to H-7''), 7.82 (*dt*, *J* 7, 2.5 Hz, H-8''), 8.06 (*t*, *J* 2.5 Hz, H-10''). ^{13}C-NMR ($CDCl_3$) δ: 38.7 (C-2), 35.5★ (C-3), 70.2 (C-4), 33.7★ (C-1'), 79.6 (C-2'), 66.5 (C-3'), 35.2★ (C-1''), 24.9 (C-2''); 28.7, 28.5, 28.2, 27.1 (respectively 1, 1, 1 and 2C, C-3'' to C-7''); 18.2 (C-8''), 84.5 (C-9''), 67.9 (C-10''), 180.2 (CO). Values marked ★ represent interchangeable assignments. ORD (*c* 5.0 mg/ml, MeOH): $[\phi]_{500}$ + 204, $[\phi]_{400}$ + 354, $[\phi]_{300}$ + 685, $[\phi]_{250}$ + 1246, $[\phi]_{227}^{PK}$ + 1632, $[\phi]_{218}$ + 1495. The filtrate and washings were evaporated to one third of the initial vol. H_2O (100 ml) was added and the aq. soln was then extracted with Et_2O (4 × 50 ml). The Et_2O extract gave crude **1a** (1.7 g). Crystallization from Et_2O–$CHCl_3$ gave *rubrenolide* (**1a**, 1.4 g) as colourless needles, mp 100° (Found: C, 68.52: H. 10.18. $C_{17}H_{30}O_4$ requires: C, 68.42; H, 10.13%). $[\alpha]_D^{22°}$ + 21 ($CHCl_3$). ν_{max}^{KBr} cm^{-1}: 3450, 1745, 1635, 1460, 1200, 1185, 1018, 990, 980, 925, 910, 875, 850, 725, 715. MS *m/e* (rel. int.): 298 (25, M), 267 (46), 159 (20), 116 (32), 95 (44), 81 (55), 67 (65), 61 (20), 55 (100), 41 (80). ^{1}H-NMR (220 MHz, $CDCl_3$–D_2O) τ: 7.05 (*m*, H-2), 7.44 (*ddd*, *J* 12.5, 8.5, 5.5 Hz, H-3α), *ca* 8.4 (*m*, H-3β), 5.57 (*m*, H-4); 8.00 (*m*, H-1'), *ca* 8.2 (*m*, H-1'), 6.27 (*m*, H-2'), 6.37 (*dd*, *J* 11.5, 3.5 Hz, H-3'), 6.52 (*dd*, *J* 11.5, 6.5 Hz, H-3'); 8.70 (*br*, 14 H-1'' to H-7''), 7.97 (*m*, 2H-8''), 5.04 (*m*, H-9''), 4.19 (*m*, 2H-10''). ^{13}C-NMR ($CDCl_3$) δ: 38.8 (C-2), 35.7★ (C-3), 70.2 (C-4); 33.7★ (C-1'), 79.7 (C-2'), 66.5 (C-3'); 35.2★ (C-1''), 25.0 (C-2''); 28.7 and 29.2 (respectively 2C and 3C, C-3'' to C-7''); 33.7 (C-8''), 138.9 (C-9''), 113.9 (C-10''); 180.2 (CO).★ Interchangeable assignments. ORD (*c* 5.0 mg/ml, MeOH); $[\phi]_{500}$ + 224, $[\phi]_{400}$ + 352, $[\phi]_{300}$ + 640, $[\phi]_{250}$ + 1175, $[\phi]_{227}^{PK}$ + 1755, $[\phi]_{218}$ + 1420.

Catalytic hydrogenation of **1a** *and* **1b**. Rubrenolide (100 mg) in abs. EtOH (4 ml) was hydrogenated over 10% Pd/C (30 mg) (1 hr). The catalyst was removed by filtration. Evaporation of the filtrate gave a residue (95 mg) which crystallized from $CHCl_3$ as colourless needles of *dihydrorubrenolide* (**1c**), mp 106–107° (Found: C, 68.08; H, 10.67. $C_{17}H_{32}O_4$ requires: C, 67.96; H, 10.74%). $[\alpha]_D^{20}$ + 22° ($CHCl_3$). Appl. of a modified Hudson method [11]: $[\alpha]_D^{20°}$ + 45.1° (EtOH), $[\alpha]_D^{20°}$ + 3.9° (EtOH + KOH conc). ν_{max}^{KBr} cm^{-1}: 3450, 1745, 1460, 1210, 1185, 880, 855, 720. MS *m/e* (rel. int.): 300 (4, M), 282 (8), 269 (100), 159 (70), 130 (49), 116 (49), 85 (54), 69 (54), 61 (18), 55 (75), 44 (70), 41 (78). ^{1}H-NMR (220 MHz, CD_3OD–D_2O) τ: 7.06 (*m*, H-2), 7.45 (*ddd*, *J* 12.5, 8.5, 5.5 Hz, H-3α), *ca* 8.4 (*m*, H-3β), 5.54 (*m*, H-4); 8.02 (*ddd*, *J* 14.5, 10, 5 Hz, H-1'), *ca* 8.2 (*m*, H-1'), 6.28 (*m*, H-2'), 6.38 (*dd*, *J* 11.5, 3.5 Hz, H-3'), 6.51 (*dd*, *J* 11.5, 6.5 Hz, H-3'); 8.70 (*br*, 18 H-1'' to H-9''), 9.14 (*t*, *J* 6.5 Hz, 3H-10''). Rubrynolide (60 mg) was hydrogenated in the same way as rubrenolide. The product obtained (57 mg) crystallized from $CHCl_3$ as colourless needles, mp 106–107°, $[\alpha]_D^{20°}$ + 22° ($CHCl_3$). NMR, IR, MS and ORD of tetrahydrorubrynolide were identical with those of dihydrorubrenolide (**1c**).

Alkaline hydrolysis of **1c**. Dihydrorubrenolide (40 mg) was added to a 5% aq. soln of NaOH (10 ml) and warmed on a water bath (5 min). The soln was left overnight at room temp. and then acidified with 2 M HCl. Extraction of the aq. soln with $CHCl_3$ (4 × 5 ml) gave on evaporation a solid residue (38 mg). Crystallization from $CHCl_3$ gave colourless needles, mp 106–107°. IR, NMR and MS of this material were identical with the analogous spectra of the original dihydrorubrenolide. R_f values on TLC (3 solvent systems) were identical. However: $[\alpha]_D^{22°}$ + 11° ($CHCl_3$) and ORD curve of generally reduced amplitude.

Acetylation of **1a**, **1b** *and* **1c**. The compounds (100 mg) were added to solns of Ac_2O (1 ml) and dry C_5H_5N (1 ml). The mixtures were left overnight at room temp. and then worked up in the usual way. Chromatography of the products on Si gel (C_6H_6–$CHCl_3$) provided the *diacetates* as colourless oils. **1d**, ν_{max}^{film} cm^{-1}: 1770, 1745, 1645, 1450, 1370, 1220, 1185, 990, 910, 720. **1e**, ν_{max}^{film} cm^{-1}: 1770, 1745, 1450, 1370, 1220, 1185, 720. **1f** (Found: M, 384.2508. $C_{21}H_{36}O_6$ requires: M, 384.2511). ν_{max}^{film} cm^{-1}: 1775, 1745, 1455, 1370, 1220, 1180, 720. MS *m/e* (rel. int.): 384 (0.8, M), 269 (67), 201 (76), 43 (100). ^{1}H-NMR (100 MHz, $CDCl_3$) τ: 5.6 (*m*, H-4); 4.87 (*m*, H-2'), 5.74 (*dd*, *J* 12, 3.5 Hz, H-3'), 5.99 (*dd*, *J* 12, 6 Hz, H-3'), 7.93 (*s*, OAc), 7.96 (*s*, OAc); 7.1–7.8 (*m*, H-2, H-3α), 8.1–8.5 (*m*, H-3β, 2H-1'); 8.75 (*br s*, 18 H-1'' to H-9''), 9.13 (*t*, *J* 6.5 Hz, 3H-10'').

Trimethylsilylation of **1a** *and* **1b**. Hexamethyldisilazane (0.3 ml) and trimethylsilyl chloride (0.15 ml) were added to solns of the compounds (6 mg) in dry C_5H_5N (1 ml). The mixtures were left for 10 min and then evaporated. The residues were extracted with C_6H_{14} (2 × 10 ml) and the combined extractions were filtered and evaporated to give the *bistrimethylsilyl ethers* (8 mg) as colourless oils. **1g**, $\nu_{max}^{CHCl_3}$ cm^{-1}; 1760, 1640, 1450, 1350, 1240, 1200, 1100, 995, 910, 840. MS *m/e* (rel. int.): 442 (2, M), 339 (63), 203 (10), 186 (11), 147 (24), 73 (100). **1h**, $\nu_{max}^{CHCl_3}$ cm^{-1}: 2100, 1760, 1450, 1350, 1240, 1200, 1100, 840. MS *m/e* (rel. int.): 440 (0.3, M), 337 (65), 201 (5), 186 (6), 147 (22), 73 (100).

Acetonide formation of **1a**, **1b** *and* **1c**. A soln of the compounds (150 mg) in dry Me_2CO (70 ml) was boiled under reflux with dry $CuSO_4$ (2 g) (36 hr). Inorganic salt was removed by filtration and the solns evaporated. Crude oils obtained were purified by chromatography on Si gel. $CHCl_3$ eluting the acetonides (130 mg). **1i**, colourless oil, ν_{max}^{film} cm^{-1}: 1770, 1645, 1460, 1370, 1180, 835. **1j**, low melting solid, ν_{max}^{film} cm^{-1}: 2105, 1770, 1460, 1370, 1180, 835. **1k**, colourless plates, mp 47–48° (C_6H_{14}, 0°) (Found: C, 70.31; H, 10.51; $C_{20}H_{36}O_4$ requires: C, 70.55, H, 10.66%), $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770, 1460, 1373, 830. MS *m/e* (rel. int.): 340 (0.3, M), 325 (100), 283 (27), 116 (17), 101 (13), 43 (50). ^{1}H-NMR (220 MHz, $CDCl_3$) τ: 7.07 (*m*, H-2), 7.40 (*m*, H-3α), 5.54 (*m*, H-4); 7.76 (*m*, H-1'), 6.34 (*m*, H-2'), 5.81 (*m*, 2H-3'); 8.1–8.5 (*m*, H-3β, H-1', 2H-1''), 8.72 (*br s*, 16 H-2'' to H-9''), 9.10 (*t*, *J* 6.5 Hz, 3H-10''), 8.56 (*s*, Me), 8.63 (*s*, Me).

Methylation of **1a**. Rubrenolide (500 mg) was added to a suspension of BaO (2 g) in DMSO (2.5 ml) and DMF (2.5 ml) and the soln. was cooled to 0°. Me_2SO_4 (2.0 ml) was added dropwise and the mixture was stirred at room temp. (16 hr). NH_4OH (2 ml) was then added and the soln was stirred for a further 30 min to decompose the excess DMSO. The soln was diluted with H_2O (50 ml), acidified with 2M HCl and extracted with $CHCl_3$ (4 × 10 ml). Evaporation gave a colourless oil (492 mg) which showed three spots on TLC. Chromatography of the crude product on Si gel (EtOAc) provided a *dimethyl ether* (**1l**, 200 mg), a *monomethyl ether* (**1m**, 250 mg) and recovered starting material (**1a**, 40 mg). **1l**, colourless oil (Found: M, 326.2449. $C_{19}H_{34}O_4$ requires: M, 326.2457). ν_{max}^{film} cm^{-1}: 1760, 1645, 1460, 1175, 990, 910, 720. MS *m/e* (rel. int.): 327 (13), 326 (8, M), 281 (46), 89 (14), 81 (54), 71 (60), 67 (59), 55 (53), 45 (86), 41 (100). ^{1}H-NMR (100 MHz, $CDCl_3$) τ: 7.16 (*m*, H-2), 7.52 (*ddd*, *J* 12, 8.5, 5.5 Hz, H-3α), 5.56 (*m*, H-4); 6.6 (*m*, H-2', 2H-3'), 6.61 (*s*, OMe), 6.66 (*s*, OMe); 7.96 (*m*, 3H), 8.2–8.5 (*m*, 4H), 8.71 (*br s*, 12H), 4.19 (*m*, H-9''), 5.04 (*m*, 2H-10''). **1m**, colourless needles, mp 38–39°

(C_6H_{14}) (Found: M, 312.2309. $C_{18}H_{32}O_4$ requires: M, 312.2300). ν_{max}^{KBr} cm^{-1}: 3500, 1748, 1645, 1465, 1115, 1055, 990, 910, 720. MS *m/e* (rel. int.): 313 (2.5), 312 (4, M), 267 (8), 249 (5), 173 (13), 128 (19), 75 (16), 67 (58), 55 (80), 45 (80), 41 (100). ^{1}H-NMR (100 MHz, $CDCl_3$) τ: 7.11 (*m*, H-2), 7.46 (*ddd*, *J* 12, 8.5, 5.5 Hz, H-3α), 5.62 (*m*, H-4); 8.01 (*ddd*, *J* 14.5, 10, 5.5 Hz, H-1'); 6.21 (*m*, H-2'), 6.91 (*d*, *J* 3.5 Hz, OH-2'), 6.6 (*m*, 2H-3'), 6.63 (*s*, OMe-3'); 8.2–8.5 (*m*, H-3β, H-1', 2H), 8.71 (*br s*, 12H), 7.97 (*m*, 2H-8''), 4.19 (*m*, H-9''), 5.04 (*m*, 2H-10''). Acc. to Horeau's method [9], α-phenylbutyric anhydride (120 mg) was added to **1m** (60 mg) in dry C_5H_5N (3 ml). The soln was left overnight at room temp. H_2O (0.15 ml) was added and, after 30 min, the opt. rot. was determined (22°): α_1 + 1.090°. Et_3N (0.30 ml) was then added and the opt. rot. determined again: α_2 + 0.250°. α_1–1.1α_2 + 0.815. Optical yield: 0.815 × 100/2.6 = 31.3%.

Periodate oxidation of **1c**. Sodium metaperiodate (2.0 g) in water (60 ml) was added to dihydrorubrenolide (1.0 g) in *n*-pentanol (30 ml). The heterogeneous mixture was stirred vigorously overnight at room temp. H_2O (150 ml) was then added and the soln was extracted with Et_2O (3 × 50 ml). Careful evaporation of the combined extractions gave a colourless solid (900 mg) and a distillate smelling of *formaldehyde*. The distillate was treated with 2,4-dinitrophenylhydrazone and gave an orange precipitate of *formaldehyde* 2,4-*dinitrophenylhydrazone*, mp 168°. Crystallization of the solid from Et_2O gave the *aldehyde* **2a**, colourless plates, mp 50–53° (Found: M, 268.2038. $C_{16}H_{28}O_3$ requires: M, 268.2038). ν_{max}^{KBr} cm^{-1}: 2700, 1760, 1720, 1460, 1370, 1180, 720. MS *m/e* (rel. int.) 269 (13), 268 (3, M), 251 (33), 240 (11), 225 (17), 159 (70), 127 (48), 116 (58), 55 (90), 43 (100), 41 (87). ^{1}H-NMR (100 MHz, $CDCl_3$) τ: 0.22 (*s*, CHO), 5.59 (*m*, H-4), 6.8–7.6 (*m*, 4H), 8.1–8.4 (*m*, 3H), 8.74 (*br s*, 16H), 9.13 (*t*, *J* 6.5 Hz, 3H-10''). Treatment of **2a** (215 mg) with 2,4-dinitrophenylhydrazine in acidified EtOH soln gave a yellow oil. Crystallization from EtOH gave the 2,4-*dinitrophenylhydrazone* as an orange microcrystalline solid, mp 85–88° (Found: C, 58.63; H, 6.81; N, 12.89. $C_{22}H_{32}O_6N_4$ requires: C, 58.91; H, 7.19; N, 12.49%). ν_{max}^{KBr} cm^{-1}: 3300, 1770, 1620, 1590, 1520, 1330, 920, 830, 775, 725. MS *m/e* (rel. int.): 448 (23, M), 431 (11), 413 (30), 266 (30), 183 (15), 165 (15), 164 (18), 81 (45), 69 (60), 67 (45), 55 (90), 43 (100), 41 (90). ^{1}H-NMR (100 MHz $CDCl_3$) τ: −1.14 (*s*, NH), 0.97 (*d*, *J* 2.5 Hz, ArH), 1.73 (*dd J* 9, 2.5 Hz, ArH), 2.14 (*d*, *J* 9 Hz, ArH), 2.27 (*t*, *J* 4.5 Hz, CH=N), 5.51 (*m*, H-4), 6.8–7.6 (*m*, 4H), 8.1–8.4 (*m*, 3H), 8.75 (*br s*, 16H), 9.13 (*t*, *J* 6.5 Hz, 3H-10'').

Sodium borohydride reduction of **2a**. $NaBH_4$ (400 mg) was added slowly in portions to a soln of the aldehyde **2a** (400 mg) in MeOH (5 ml). The soln was stirred at room temp. (1 hr), diluted with H_2O (100 ml), acidified with 2 M HCl and extracted with $CHCl_3$ (4 × 30 ml). Evap. gave a solid (370 mg) which was purified by chromatography on Si gel to give a colourless solid (170 mg). Crystallization from Et_2O gave the *alcohol* (**2b**, 170 mg) as colourless plates mp 65–66° (Found: C, 71.20; H, 11.13. $C_{16}H_{30}O_3$ requires: C, 71.06; H, 11.18%). ν_{max}^{KBr} cm^{-1}: 3350, 1760, 1460, 1220, 1180, 1060, 720. MS *m/e* (rel. int.): 271 (8, M + 1), 252 (3), 240 (10), 226 (12), 208 (18), 129 (100), 55 (80), 43 (60), 41 (60). ^{1}H-NMR (220 MHz, $CDCl_3$) τ: 7.11 (*m*, H-2), 7.43 (*ddd*, *J* 12.5, 9.0, 5.5 Hz, H-3α), *ca* 8.4 (*m*, H-3β), 5.50 (*m*, H-4); 7.89 (*m*, H-1'), *ca* 8.2 (*m*, H-1'), 6.16 (*m*, 2H-2'), 8.72 (*br*, H-1'' to H-9''), 9.12 (*t*, *J* 6.5 Hz, 3H-10'').

Lithium aluminium hydride reduction of **1a** *and* **1b**. A soln of rubrenolide (965 mg) in dry THF (20 ml) was slowly added to a slurry of $LiAlH_4$ (300 mg) in dry THF (30 ml). The mixture was stirred at room temp. (2 hr) and the excess $LiAlH_4$ was then destroyed by addition of EtOAc (20 ml). H_2O (50 ml) and satd aq. Na_2SO_4 (50 ml) were then added and, after filtration, the organic phase was separated and the aq. soln extracted with Et_2O (3 × 30 ml). The combined organic phase provided a wax-like solid (880 mg) which showed several spots on TLC. Chromatography on Si gel ($CHCl_3$–MeOH 9:1) gave the *tetra-ol* **3a** (500 mg) as a low mp waxy solid, ν_{max}^{film} cm^{-1}: 3350, 1645, 1460, 1030, 990, 910, 720. Ms *m/e* (rel. int.): 303 (0.6, M + 1), 285 (2), 267 (1.5), 253 (26), 127 (70), 81 (92), 69 (52), 67 (62), 61 (22), 55 (100), 43 (44), 41 (96). ^{1}H-NMR (100 MHz, $CDCl_3$) τ: 4.19 (*m*, CH=); 5.03 (*m*, $=CH_2$); 5.58 (*br*, 4OH, disap. with D_2O), 6.35 (*m*, 2C<u>H</u>OH), 6.5 (*m*, 2C<u>H</u>$_2$OH), 7.99 (*m*, C<u>H</u>$_2$—CH=), 8.71 (*br s*, 19H). ORD (*c* 5.0 mg/ml, MeOH): $[\phi]_{50}$ + 100, $[\phi]_{400}$ + 100, $[\phi]_{300}$ + 130, $[\phi]_{250}$ + 200, $[\phi]_{227}$ + 240. Reduction of rubrynolide with $LiAlH_4$ under similar conditions gave the *tetra-ol* **3b**, ν_{max}^{film} cm^{-1}: 3350, 2100, 1460, 1030, 720. MS *m/e* (rel. int.): 301 (<0.5, M + 1), 283 (0.7), 265 (0.5), 251 (25), 127 (83), 81 (100), 67 (90), 61 (30), 55 (90), 41 (90). ^{1}H-NMR (100 MHz, $CDCl_3$) τ: 5.4 (*m*, 4OH disap. with D_2O), 6.35 (*m*, 2C<u>H</u>OH), 6.5 (*m*, 2C<u>H</u>$_2$OH), 7.83 (*dt*, *J* 2.5, 7 Hz, 2C<u>H</u>$_2$—C≡), 8.07 (*t*, *J* 2.5 Hz, ≡C<u>H</u>), 8.70 (*br s*, 19H). ORD (*c* 5.0 mg/ml, MeOH): $[\phi]_{500}$ + 100, $[\phi]_{400}$ + 100, $[\phi]_{300}$ + 120, $[\phi]_{250}$ + 180, $[\phi]_{277}$ + 210.

Lithium aluminium hydride reduction of the mesylate of **3a**. MsCl (3 ml, redist. bp 154°) was added to a soln of the tetra-ol **3a** (340 mg) in dry C_5H_5N (20 ml) at 0°. The mixture was left overnight at room temp. and then diluted with H_2O (100 ml). The aq. soln was extracted with Et_2O (3 × 40 ml) and the combined extract was washed with satd aq. $NaHCO_3$ (40 ml) and H_2O (30 ml) before drying over $MgSO_4$. Evaporation of the solvent gave the crude *mesylate* (460 mg) as a yellow oil. This was dissolved in dry Et_2O (50 ml) and added to a soln of $LiAlH_4$ (250 mg) in dry Et_2O (50 ml). The mixture was boiled under reflux (24 hr), H_2O (50 ml) was cautiously added, followed by 10M NaOH (50 ml) and more H_2O (50 ml). The aq. soln was then extracted with Et_2O (3 × 40 ml). Evaporation provided an oil (200 mg) which was chromatographed on Si gel. C_6H_{14} eluted an *alkene* (**4a**, 125 mg) as colourless oil. $\nu_{max}^{cm^{-1}}$ 1645, 1465, 1380, 990, 910, 720. The alkene (120 mg) was dissolved in EtOH (8 ml) and hydrogenated over Pd/C (50 mg) (5 hr) at room temp. The catalyst was removed by filtration and the solvent evaporated to give an oil. This was purified by chromatography on Si gel with *n*-pentane. The *alkane* **4b** (70 mg) was obtained as a colourless oil. ν_{max}^{film} cm^{-1}: 1460, 1375, 720. MS *m/e* (rel. int.): 240 (0.5, M), 197 (13), 71 (94), 57 (90), 43 (100), 41 (33). ^{1}H-NMR (100 MHz, $CDCl_3$) τ: 8.74 (*br s*, 13CH_2, 1CH), 9.13 (*m*, 3Me). The alkane was shown by GLC to be identical with a synthetic sample of 4-methylthexadecane under the following two sets of conditions (1) Column 6' × 1/4", 2.5% OV1, temp. programmed 100–250° at 3°/min and (2) Column 50 × 0.1 mm wall coated capillary Apiezon L isothermal at 200°.

Vigorous chromic oxide oxidation of **1a**. Rubrenolide (200 mg) in glacial AcOH (2.5 ml) was added to a soln of CrO_3 (1.2 g) in AcOH (4 ml) and H_2O (1 ml). The soln was boiled under reflux overnight and then diluted with H_2O (30 ml). Extraction of the aq. soln with Et_2O and evaporation of the extract gave a solid (100 mg). This (30 mg) was dissolved in Et_2O (2 ml) and methylated by addition of CH_2N_2 soln. Evaporation of the resultant soln gave a colourless oil (32 mg). GLC on a 1% OV1 column, programmed 100–200°, proved this to be a mixture of two components. These were separated and identified by GC–MS as *dimethyl azelate* (**5a**, *ca* 40%) and *dimethyl sebacate* (**5b**, *ca* 60%).

Mild chromic oxide oxidation of **1a**. Rubrenolide (300 mg) in AcOH (2 ml) was added to a soln of CrO_3 (800 mg) in AcOH (8 ml) and H_2O (2 ml). The soln was left to stand overnight at room temp., diluted with H_2O (20 ml) and then extracted with Et_2O (4 × 10 ml). Evaporation gave a solid (200 mg) which crystallized from Et_2O to give the *acid* **2c** as colourless plates, mp 95–98°. ν_{max}^{KBr} cm^{-1}: 3500–2500, 1760, 1695, 1645, 1280, 1210, 1180, 990, 910, 720, MS *m/e* (rel. int.): 282 (1, M), 264 (15), 246 (25), 165 (25), 125 (42), 109 (27), 81 (73), 67 (70), 55 (87), 41 (100). ^{1}H-NMR (100 MHz, $CDCl_3$) τ: *ca* 7.0 (*m*, H-2), *ca* 7.4 (*m*, H-3α), *ca* 8.4 (*m*, H-3β), 5.59 (*m*, H-4); 7.05 (*dd*, *J* 17.5, 3.5 Hz, H-1'), 7.49 (*dd*, *J* 17.5, 8.5 Hz, H-1'); 8.71 (*br*, 14H), 7.95 (*m*, 2H-8''), 5.02 (*m*, H-9''), 4.19 (*m*, 2H-10''). The acid (50 mg) was dissolved in Et_2O (5 ml) and excess CH_2N_2 soln in Et_2O was added. The soln was left to stand overnight at room temp. and was then evaporated to give the *ester* **2d** as a low melting crystalline solid (Found: M, 296.1979. $C_{17}H_{28}O_4$ requires: M, 296.1987). ν_{max}^{film} cm^{-1}: 1770, 1735, 1645, 1460, 1435, 1370, 1170, 990, 910, 720. MS *m/e* (rel. int.): 297 (6), 296 (2, M), 278 (8), 265 (9), 246 (26), 157 (58), 129 (35), 74 (25), 55 (88), 41 (100). ^{1}H-NMR (100 MHz, $CDCl_3$) τ: *ca* 7.0 (*m*, H-2), 7.42 (*ddd*, *J* 12.5, 8.5, 5.5 Hz, H-3α), 8.4 (*m*-3β),

5.59 (*m*, H-4); 7.08 (*dd*, *J* 17.5, 4 Hz, H-1'), 7.54 (*dd*, *J* 17.5, 9.5 Hz, H-1'), 8.70 (*br*, 14H), 7.94 (*m*, H-8''), 5.00 (*m*, H-9''), 4.16 (2H-10'').

Catalytic hydrogenation of **2d**. The ester **2d** (50 mg) in EtOH (4 ml) was hydrogenated over Pd–C (20 mg) at room temp. (5 hr). The catalyst was removed by filtration and the soln evaporated to give a solid (48 mg). Crystallization from Et_2O gave the *ester* **2c** as colourless plates, mp 46–47° (Found: M, 298.2146. $C_{17}H_{30}O_4$ requires: M, 298.2144). ν_{max}^{film} cm^{-1}: 1770, 1735, 1460, 1435, 1410, 1370, 1345, 1320, 1260, 1170, 995, 885, 825, 720. MS *m/e* (rel. int.): 299 (3), 298 (4, M), 280 (11), 267 (11), 157 (100), 132 (50), 125 (37), 74 (33), 57 (35), 43 (64), 41 (73). ^{1}H-NMR (220 MHz, $CDCl_3$) τ: 6.97 (*m*, H-2), 7.42 (*ddd*, *J* 12.5, 8.5, 5.5 Hz, H-3α), 8.40 (*ddd*, *J* 12.5, *ca* 11, *ca* 11, Hz, H-3β), 5.61 (*m*, H-4); 7.08 (*dd*, *J* 17.5, 4.0 Hz, H-1'), 7.51 (*dd*, *J* 17.5, 9.5 Hz, H-1'), 8.70 (*br*, 18 H), 9.14 (*t*, *J* 6.5 Hz, 3H-10'').

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