Pergamon

Tetrahedron Letters 39 (1998) 1469–1472

TETRAHEDRON
LETTERS

An Unusual Erythrolide Containing a Bicyclo [9.2.1.] Tetradecane Skeleton

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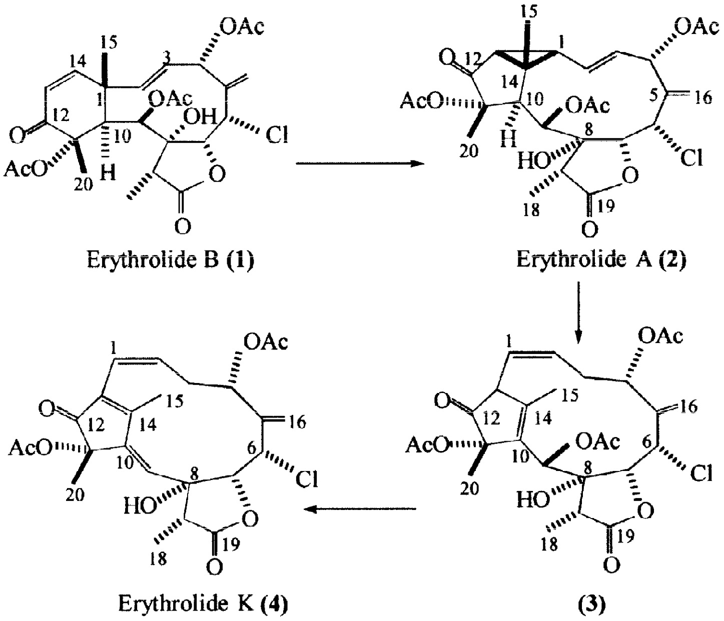
Received 24 October 1997; revised 1 December 1997; accepted 2 December 1997

Abstract: Erythrolide K (4), isolated from *Erythropodium caribaeorum* possesses an unusual bicyclo [9.2.1.] tetradecane skeleton. The structure was deduced by 2D NMR and confirmed by X-ray analysis. It was synthesised in two steps from erythrolide A (2), the first involving a thermal [1,5] sigmatropic hydrogen shift to give the intermediate (3). © 1998 Elsevier Science Ltd. All rights reserved.

Previous investigations[1,2,3] of the Caribbean gorgonian octocoral *Erythropodium caribaeorum* have yielded the briarein diterpenes erythrolides A-J. We report here the structure of an unusual diterpene erythrolide K (4) from a sample of *E. caribaeorum* collected at Eastern Reef, Buccoo, Tobago, along with its two-step synthesis from Erythrolide A (2).

Erythrolide K (4) was obtained as colourless crystals, mp 220° (dec.), $C_{24}H_{27}ClO_8$ (hreims), $[\alpha]_D$ -50.0° (c 0.40, $CHCl_3$), ir ($CHCl_3$) 3450, 1785, 1745, 1705 cm^{-1} and uv (MeOH) 208 nm (log ε 3.92), 214 nm (log ε 3.91), 296nm (log ε 3.67). The latter absorptions suggested an extended conjugated system.



Erythrolide B (1)

Erythrolide A (2)

Erythrolide K (4)

(3)

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PII: S0040-4039(97)10838-3

Table 1: ^{13}C- and ^{1}H- NMR Data for Compounds (3) and (4)

	(3)^a		(4)	
Position	δ_C	δ_H	δ_C	δ_H
1	125.4	5.78 (t, 10.5)	122.7	6.32 (d, 10.5)
2	133.9	5.96 (m)	134.9	5.98 (dt, 10.5, 5.3)
3	33.3	2.64 (m) 2.36 (bs)	34.9	2.16 (m) 3.12 (dd, 14.9,10.5)
4	70.8	5.04 (bs)	71.0	5.48 (bd, 10.9)
5	143.5	-	142.8	-
6	63.5	5.08 (bs)	58.3	4.60 (d, 8.9)
7	79.6	5.48 (m)	81.1	5.22 (d,8.9)
8	-^{b}	-	78.7	-
9	75.9	5.36 (bs)	122.3	5.49 (bs)
10	134.8	-	144.3	-
11	87.3	-	82.6	-
12	208.0	-	195.0	-
13	52.9	3.60 (dt,10.5,1.0)	144.3	-
14	144.4	-	160.0	-
15	17.2	2.20 (3H, bs)	21.1	2.43 (3H, d, 1.3)
16	120.7	5.59 (bs) 5.90 (d, 2.0)	120.1	5.40 (s) 5.44 (d, 2.2)
17	43.1	2.54 (bs)	49.2	3.03 (dq, 7.0, 1.5)
18	10.1	1.37 (3H, bd)	7.8	1.38 (3H, d, 7.0)
19	177.0	-	174.6	-
20	23.6	1.79 (3H, s)	23.9	1.53 (3H, s)
Acetates	171.2	-	169.6	-
	20.8	2.06 (3H, s)	20.8	2.16 (3H, s)
	168.6	-	167.5	-
	21.7	1.98 (3H, s)	20.6	2.08 (3H, s)
	169.1	-		
	20.5	2.12 (3H, s)		
8 - OH		2.86 (s)		3.14 (d, 1.8)

Chemical shifts were measured at 125 MHz (^{13}C) and 500 MHz (^{1}H) for $CDCl_3$ solutions with TMS as internal standard. Coupling constants (Hz) are in parentheses. ^{a}Spectra recorded at 52°C. ^{b}Not observed due to broadening or hidden under solvent peak.

The ^{1}H and ^{13}C assignments for erythrolide K (4) are shown in Table 1. A combination of COSY, HMQC and HMBC data revealed the structure (4). The direct connectivities from C-1 to C-14 and through to C-17 as well as the relationship of the latter to C-18 and C-19 were easily traced.

The stereochemical assignments were carried out with the aid of vicinal coupling constants and selected NOE experiments. The *cis* geometry of the C_1 - C_2 double bond was indicated by a 10.5 Hz coupling constant between H-1 and H-2 and a large enhancement of the H-1 signal (15.0%) when the H-2 signal was irradiated.

Large enhancements involving the H_3-15 and H-4, H-7 and H-17 as well as H-7 with H-4 and H-17 indicated that all these protons were on the same face of the molecule and pointing towards the center of the macrocyclic ring. When the C8-OH proton was irradiated, H-6 (5.6%) and H-9 (11.3%) were enhanced indicating the close spatial proximity of these hydrogens to the C8-OH group. A coupling constant of 8.9 Hz between H-6 and H-7 supported these stereochemical conclusions which were confirmed by the X-ray crystal structure (Figure 1).[4]

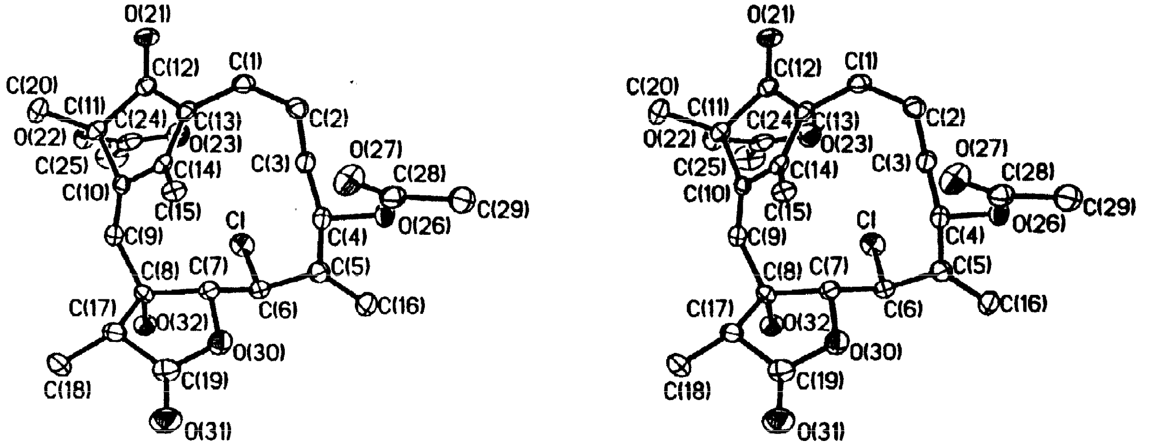

Figure 1: ORTEP Drawing of Erythrolide K (4).

In considering the relationship between erythrolides A (2) and K (4) it occurred to us that a [1,5] sigmatropic hydrogen shift across the vinyl cyclopropane moiety of erythrolide A (2) would lead to the erythrolide K (4) skeleton. Accordingly, erythrolide A (2) was refluxed in toluene for 15h. The product (colourless gum) obtained in quantitative yield, proved to be compound (3), which indeed would have arisen from sigmatropic migration of H-10 to C-3 with concomitant opening of the cyclopropane ring.

The molecular formula of compound (3) was established as $C_{26}H_{31}ClO_{10}$ (hreims), $[\alpha]_D$ -160° (c 0.60, $CHCl_3$) and ir ($CHCl_3$) 3480,1775 and 1740 cm^{-1}. The uv (MeOH) showed only end absorption 208nm (log ε 3.94). The ^{1}H- and ^{13}C- NMR indicated three -OAc groups and COSY data revealed the relationship of H-13 (δ 3.63, dt 10.5, 1.0 Hz) to H-1 (δ 5.78, t 10.5 Hz) and H-2 (δ 5.96, m). HMBC measurements related H-13 to C-1, C-2, C-12 and C-14. The ^{1}H-NMR spectrum of this compound obtained at 25°C in $CDCl_3$ contained broadened signals indicating slow conformational interconversions. The signals sharpened significantly when the spectrum was run at 52° in $CDCl_3$ or in C_6D_6 at 45°. The ^{1}H and ^{13}C data for compound (3) are shown in Table 1.

The conversion of the intermediate (3) to erythrolide K (4) by loss of acetic acid was achieved by refluxing it (45 min.) in a methanol suspension of silica gel (Merck 60).

Fenical et al.[1] have shown that erythrolide B (1) is converted to erythrolide A (2) via a photochemically induced di - π - methane rearrangement. With the results of our work, the full pathway from 1 → 2 → 4 has now been elucidated.

ACKNOWLEDGEMENTS

This study was supported by the Canadian International Development Agency / University of the West Indies Institutional Strengthening Project (Sustainable Development grant #13) and, at the University of Toronto, by grants from the Natural Sciences and Engineering Research Council of Canada.

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4. Colourless crystal, orthorhombic, $P2_1\,2_1\,2_1$, $a = 9.733(1)$, $b = 14.533(1)$, $c = 16.385(2)$ Å, $V = 2317.6(4)$ Å^3, $D_c = 1.373$ Mg m^{-3} for $Z = 4$. A total of 3651 reflections ($5.0<2\theta<54.0^\circ$) were measured with graphite monochromated MoKα radiation using the ω-scan technique; 3454 unique reflections (R_{int} = 1.49%). The structure was solved by direct methods and refined by full-matrix least squares on F^2 (only very large negative intensities were suppressed) using SHELXTL/PC[5]. No absorption correction was applied. All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were included in calculated positions and are treated as riding atoms except for the hydroxyl, H32, which was refined with an isotropic thermal parameter. $R_1 = 0.0327$, $wR_2 = 0.0813$ for 3016 reflections with $F>4\sigma(F)$ and $R_1 = 0.0391$, $wR_2 = 0.0839$ (all data). The weighting scheme was $w=1/[\sigma^2(F_o^2)+(0.0515P)^2]$ where $P = (F_o^2+ 2F_c^2)/3$. Minimum and maximum peaks in the final ΔF map -0.183 and 0.218eÅ^{-3}. The methyl hydrogen atoms bonded to C(15) are disordered equally over two sites by a rotation of 60° about the C(14)-C(15) bond. Atomic coordinates bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.
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