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The Creolophins: A Family of Linear Triquinanes from *Creolophus cirrhatus* (Basidiomycete)

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Complicatic acid and five novel linear triquinanes were isolated from mycelial cultures of *Creolophus cirrhatus*. The creolophins A, C, D, and E represent a novel type of highly oxidized triquinane sesquiterpenoids. Whereas those compounds with a secondary alcohol moiety in ring A are stable, the exomethylene ketone creolophin E (**5**) partly dimerized during workup to form the decacyclic 1,4-dioxepin-6-one neocreolophin (**6**). Compounds **5** and **6** display cytotoxic activities against several tumor cell lines.

Culture filtrates of the tooth fungus *Creolophus cirrhatus* (German: Dorniger Stachelseitling) were found to exhibit both antibacterial and cytotoxic activity. Here, we report the isolation and characterization of five novel highly oxidized linear triquinanes, one of which inhibits the growth of various microorganisms and human cancer cell lines at low micromolar concentrations.

Creolophus cirrhatus was grown in BAF medium[1] at ambient temperature until the glucose was consumed (24 d). The mycelia were removed by filtration, and the culture fluid was extracted with ethyl acetate. Removal of the solvent, fractionation, and purification by silica gel column chromatography and RP-HPLC furnished complicatic acid,[2,3] a 4.5:1 mixture of creolophin A (**1**) and creolophin B (**2**) as well as creolophin C (**3**) and D (**4**) as pure compounds. Creolophin C (yellowish crystals, $C_{14}H_{16}O_3$, m.p. 101–104 °C) is the least polar compound of the first series, and it could be identified as an α,β-unsaturated ketone on the basis of IR ($\tilde{\nu}$ = 1698 cm^{-1}) and UV [λ_{max} (MeOH) = 230 nm, log ε = 3.93; 330 nm, log ε = 1.98] spectroscopy. The ^{13}C NMR spectrum shows the carbonyl group at δ = 207.8 ppm, the α carbon (C_q) at 142.1, and the β carbon (CH) at δ = 158.6 ppm. Moreover, an *exo* methylene group (CH_2, 114.7, C_q 156.7 ppm) and a secondary alcohol [ν(O–H) 3433 cm^{-1}, broad; C_α δ = 73.7 ppm, H_α = 4.64 ppm] are present (Tables 1 and 2). With the aid of 2D NMR spectroscopic methods such as COSY, HSQC, and HMBC, the linear triquinane core of **3** could be elucidated (Figure 1).

In contrast to the well-known hirsutane-type sesquiterpenes,[4] the creolophins A, C, and D contain only 14 carbon atoms. Their parent ring system can thus be termed norhirsutane. The relative configuration of the six stereogenic centers of **3** could be established by NOESY and NOEDS measurements. Contacts between 2-H and 9-H with 5-H and 6-H revealed a chair-like *cis–trans–cis* arrangement of the three five-membered rings (Figure 2). The absolute configuration was tentatively assigned by comparison with hirsutanes such as hypnophilin or complicatic acid.[4,5]

Creolophin D (**4**, colorless oil, $C_{14}H_{16}O_4$) does not contain an α,β-unsaturated ketone as judged by NMR and UV spectroscopy. Instead, carbon atoms 10 and 11 are members of a second epoxide ring. In creolophin A (**1**, colorless crystals, $C_{14}H_{16}O_5$, m.p. 148–150 °C), which could be obtained in pure form after a second HPLC chromatography, the same additional epoxide ring is found. In addition, the methine proton 2-H is substituted by an angular hydroxy group. Whereas the configuration of the norhirsutane skeleton is identical in all cases, the relative configuration of the C-ring epoxide was determined on the basis of the ^3J coupling constant between 10-H and 9-H as well as by comparison of the NOESY distances between 10-H, 9-H, and *endo*-8-H with molecular models. Creolophin B (**2**, $C_{15}H_{20}O_5$), which could not be isolated as a pure compound, differs from all other creolophins, as it contains the complete hirsutane skeleton. One of the geminal methyl groups at C-11 is oxidized to a carboxylic acid and, except for the additional hydroxy group in 10-position, the compound is identical to hirsutic acid C.[6] Decarboxylative loss of the additional carbon atom may convert creolophin B to a norhirsutane, although it is unclear whether **2** is the biogenetic precursor of the other creolophins.

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Table 1. ^{1}H NMR chemical shifts (ppm, $CDCl_3$) of the creolophins.

Atom No.	Creolophin A[a]	Creolophin B[a,b]	Creolophin C	Creolophin D	Creolophin E
2-H	–	2.23	2.56	2.48	–
5-H	4.48	4.59	4.64	4.54	–
6-H	3.44	3.32	3.54	3.47	3.48
8a-H	2.29	2.30	2.05	2.42	2.60
8b-H	2.01	2.30	2.01	1.87	2.17
9-H	2.66	2.62	3.32	2.92	2.80
10-H	3.83	4.02	7.25	3.69	3.78
12-H_3	1.45	1.28	1.75	1.44	1.52
13-H_3	1.03	1.00	0.96	1.11	1.21
14a-H	5.34	5.09	5.42	5.36	6.30
14b-H	5.13	4.95	5.35	5.30	5.52

[a] Solvent CD_3CN. [b] Norhirsutane carbon numbering.

Table 2. ^{13}C NMR chemical shifts (ppm, $CDCl_3$) of the creolophins.

Atom No.	Creolophin A[a]	Creolophin B[a,b]	Creolophin C	Creolophin D	Creolophin E
C-1	209.1	33.2	207.8	207.6	207.6
C-2	85.6	48.2	54.3	54.9	84.6
C-3	54.7	48.6	48.3	49.2	51.5
C-4	156.3	160.2	156.7	157.7	147.8
C-5	75.8	74.3	73.7	73.6	196.0
C-6	64.7	64.1	63.7	63.6	60.3
C-7	73.9	75.5	74.8	74.7	74.0
C-8	25.7	22.6	27.1	25.1	25.0
C-9	46.9	44.3	39.8	35.9	45.4
C-10	64.9	75.5	158.6	64.5	63.6
C-11	65.3	58.5	142.1	65.8	64.7
C-12	11.0	19.7	9.9	10.6	10.7
C-13	14.9	15.0	15.7	15.7	14.6
C-14	114.7	110.3	114.7	114.8	123.2

[a] Solvent CD_3CN. [b] Norhirsutane carbon numbering, $\delta(CO_2H)$ = 178.4 ppm.

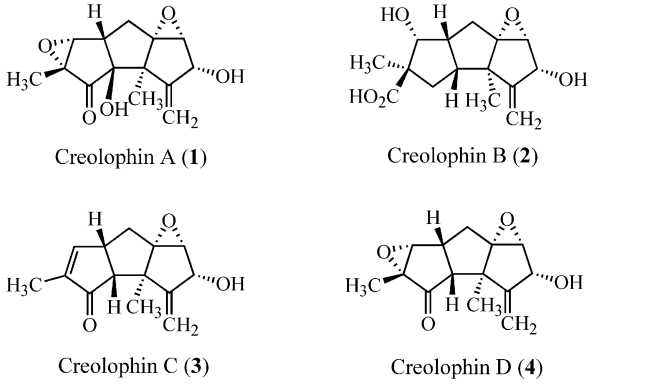


Figure 1. Structures of creolophins A–D.

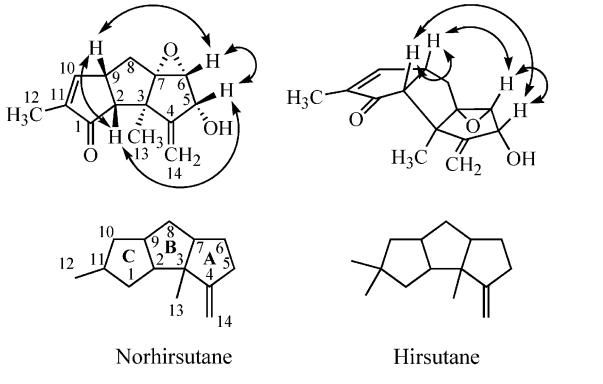


Figure 2. Typical NOE contacts in creolophin C, and the norhirsutane ring system.

For the production of creolophin E (Figure 3), *Creolophus cirrhatus* was grown in YMG medium[7] until the glucose was consumed (13 d). The mycelia were removed by filtration, and the culture fluid was extracted with ethyl acetate. Removal of the solvent, fractionation, and purification by silica gel column chromatography and RP-HPLC furnished creolophin E (**5**, $C_{14}H_{14}O_5$) as a colorless oil. The ^{13}C NMR spectrum showed the presence of two carbonyl groups, one of which is conjugated with an *exo* methylene group (CO 207.6 ppm, CO_Δ 196.0 ppm, C_q 147.8 ppm, CH_2 123.2 ppm), which could be confirmed by IR ($\tilde{\nu}$ = 1747, 1733, 1641 cm^{-1}) and UV [λ_{max} (MeOH) = 224 nm, log ε = 3.32; 322 nm, log ε = 1.62] spectroscopy. Two-dimensional NMR measurements indicated that the substitution pattern of rings B and C is identical to that of creolophin A, whereas the allylic alcohol moiety in ring A is oxidized to the enone. Creolophin E inhibits the growth of various cancer cell lines. For example, its IC_{50} against Jurkat cells

(ATCC TIB-152) amounts to 0.75 μg mL^{-1} or 2.9 μM. Details on its biological activity will, however, be reported in a separate publication. Along with creolophin E, a compound of similar polarity and double molecular weight was isolated from the culture fluid as a colorless oil. Structure elucidation by NMR spectroscopy revealed this compound (**6**) to possess a unique decacyclic framework comprising an unprecedented 1,4-dioxepin-6-one as the bridging element between two similar norhirsutane units.

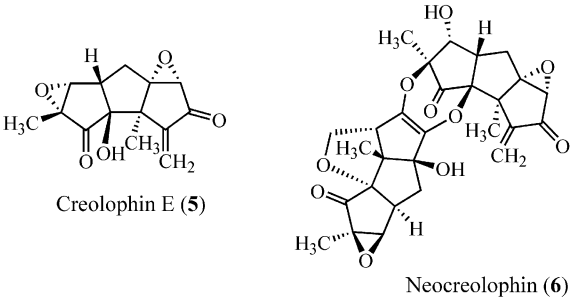
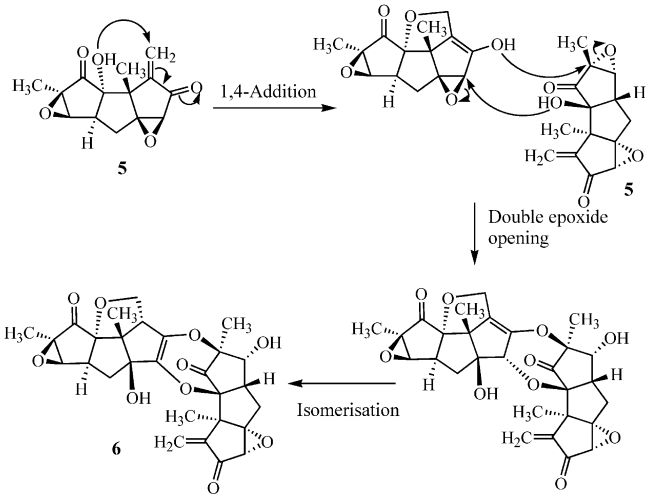


Figure 3. Structures of creolophin E and neocreolophin.

The regiochemistry of the enediol diether moiety had to be determined by using weak peripheral NOE contacts as the bridging region is "HMBC silent". As for the creolophins A to E, the absolute configuration of compound **6** was tentatively assigned on the basis of the hirsutanes. Fortunately, the $CDCl_3$ adduct of **6** crystallized upon evaporation of the NMR sample as white needles. Anomalous X-ray dispersion on the 24 chlorine atoms in the unit cell unequivocally proved this assignment to be correct (Figure 4).

Compound **6** shows bactericidal and cytotoxic properties similar to creolophin E, although its isolation from cultures of the fungus proved cumbersome and unreliable. It turned out that **6** was not directly produced by *Creolophus cirrhatus* but was rather formed from creolophin E upon warming during isolation and purification. Therefore, artifact **6** was given the name neocreolophin. The unusual dimerization of **5** could be followed by NMR spectroscopy in neutral and basic solution with **6** being the major but not the sole product formed. The initial step of this process might be the intramolecular 1,4-addition of the angular hydroxy group to the enone and the subsequent opening of the 10,11-epoxide ring in a second molecule of **5** by the formed enol or enolate. Opening of the 10,11-epoxide in the first molecule by the 2-OH group of the second triquinane unit forms the second interresidual ether bond. Isomerization of the enol ether double bond to the 5,6-position could then furnish neocreolophin (Scheme 1).



Scheme 1. Possible mechanism for the formation of neocreolophin from creolophin E.

Experimental Section

Detailed procedures for fermentation, isolation, and purification of the described compounds as well as biological data will be published in a separate paper. NMR spectra were recorded with a Bruker Avance II 400 instrument with the use of standard pulse sequences for gs-COSY, gs-HSQC, gs-HMBC, gs-NOESY, and

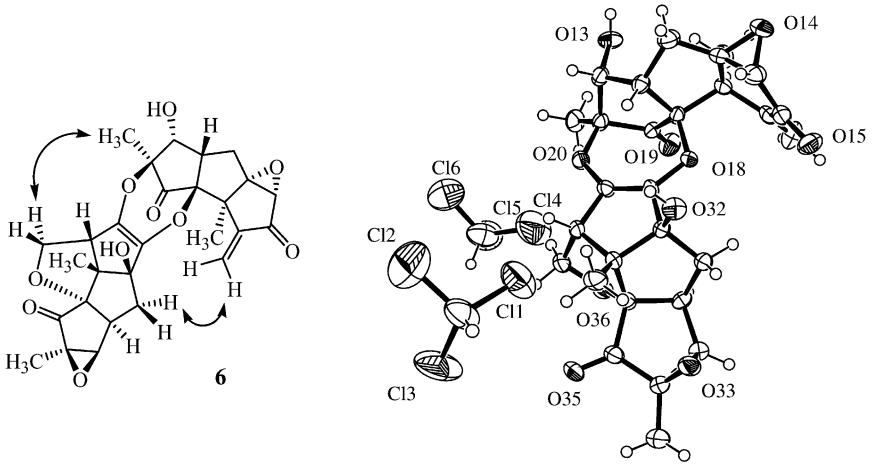


Figure 4. NOE contacts in **6** and the crystal structure of **6**·2$CDCl_3$ (ORTEP, ellipsoids drawn at 50% probability).

transient NOE experiments. Chemical shifts were referenced to the residual solvent signal ($CDCl_3$: δ_H = 7.24 ppm, δ_C = 77.0 ppm; CD_3CN: δ_H = 1.94 ppm, δ_C = 1.24 ppm). ESI-MS spectra were measured from solutions of the analyte in acetonitrile or methanol with a Waters Q-TOF-Ultima 3, HRMS spectra were measured with the same apparatus equipped with a LockSpray interface (Trialkylamines or NaI/CsI as external reference). FD-MS spectra were recorded with a Finnigan MAT 95 at a desorption voltage of 5 kV and a heater current ramp of 10 mA min^{-1}. IR and UV spectra were measured with a Bruker IFS48 FTIR spectrometer and a Perkin–Elmer Lambda-16 spectrophotometer, respectively. Optical rotations were measured with a Perkin–Elmer 241 polarimeter at 546 nm and 578 nm and were extrapolated to 589 nm. Melting points were determined with a Dr. Tottoli apparatus and are uncorrected.

Creolophin A (1): Colorless crystals, m.p. 148–150 °C (dec.). $[\alpha]_D^{25}$ = +181.6 (c = 0.94, CD_3CN). ^{1}H NMR, COSY, HSQC, HMBC (400 MHz, CD_3CN): δ = 1.03 (s, 3 H, 13-H_3), 1.45 (s, 3 H, 12-H_3), 2.01 (dd, J = 12.7, 8.8 Hz, 1 H, 8-H_b), 2.29 (dd, J = 12.7, 8.8 Hz, 1 H, 8-H_a), 2.66 (dt, J_t = 8.8, J_d = 2.5 Hz, 1 H, 9-H), 3.44 (d, J = 1.8 Hz, 1 H, 6-H), 3.83 (d, J = 2.5 Hz, 1 H, 10-H), 4.48 (pseudo-q, J = 2 Hz, 1 H, 5-H), 5.13 (d, J = 2.3 Hz, 1 H, 14-H_b), 5.34 (J = 2.3 Hz, 1 H, 14-H_a) ppm. Significant NOE-contacts (NOEDS, NOESY): 12-H_3/10-H, 10-H/9-H, 9-H/6-H, 13-H_3/8-H_a, 13-H_3/14-H_b, 14-H_a/5-H, 5-H/6-H, 6-H/9-H. FD-MS: m/z (%) = 264.2 (100) $[M]^+$. ESI-HRMS: calcd. for $C_{14}H_{16}NaO_5$ $[M + Na]^+$ 287.0895; found 287.0902.

Creolophin A + B (1 + 2, 4.5:1 mixture): Colorless crystals. $[\alpha]_D^{25}$ = +199.1 (c = 1.13, CD_3CN). IR (KBr): $\tilde{\nu}$ = 3408 (s, br), 2975, 2932, 1745 (s), 1631, 1439, 1375, 1114, 1075, 1024, 918 cm^{-1}. ESI-MS: m/z (%) = 583.3 (17) [2 **2** + Na]$^+$, 567.3 (9) [**1** + **2** + Na]$^+$, 551.2 (23) [2 **1** + Na]$^+$, 303.1 (41) [**2** + Na]$^+$, 287.1 (100) [**1** + Na]$^+$. No UV absorption maximum between 200 and 300 nm (MeOH).

Characteristic data of creolophin B (**2**): ^{1}H NMR, COSY, HSQC, HMBC (400 MHz, CD_3CN): δ = 1.00 (s, 3 H, 13-H_3), 1.28 (s, 3 H, 12-H_3), 1.48 (dd, J = 12.5, 9.8 Hz, 1 H, 1-H_b), 1.94 (dd, J = 12.5, 8.6 Hz, 1 H, 1-H_a), 2.20–2.30 (m, 3 H, 2-H, 8-H_2), 2.61 (mc, 1 H, 9-H), 3.32 (d, J = 1.6 Hz, 1 H, 6-H), 4.02 (d, J = 5.1 Hz, 1 H, 10-H), 4.59 (pseudo-q, J = 2 Hz, 1 H, 5-H), 4.95 (d, J = 2.5 Hz, 1 H, 14-H_b), 5.09 (J = 2.0 Hz, 1 H, 14-H_a) ppm. Significant NOE contacts (NOEDS, NOESY): 12-H_3/1-H_b, 13-H_3/1-H_b, 9-H/10-H, 1-H_a/9-H. ESI-HRMS: calcd. for $C_{15}H_{20}NaO_5$ $[M + Na]^+$ 303.1208; found 303.1203.

Creolophin C (3): Yellowish crystals, m.p. 101–104 °C. $[\alpha]_D^{25}$ = +190.5 (c = 0.85, $CHCl_3$). ^{1}H NMR, COSY, HSQC, HMBC (400 MHz, $CDCl_3$): δ = 0.96 (s, 3 H, 13-H_3), 1.75 (dd, J = 2.0, 1.4 Hz, 3 H, 12-H_3), 2.01 (dd, J = 13.1, 9.2 Hz, 1 H, 8-H_b), 2.05 (dd, J = 13.1, 8.5 Hz, 1 H, 8-H_a), 2.56 (d, J = 7.0 Hz, 1 H, 2-H), 3.32 (mc, 1 H, 9-H), 3.54 (d, J = 2.2 Hz, 1 H, 6-H), 4.64 (br. s, 1 H, 5-H), 5.35 (dd, J = 2.4, 0.8 Hz, 1 H, 14-H_b), 5.42 (d, J = 2.4 Hz, 1 H, 14-H_a), 7.25 (dq, J_d = 2.8, J_q = 1.4 Hz, 1 H, 10-H) ppm. Significant NOE contacts (NOEDS, NOESY): 12-H_3/13-H_3, 12-H_3/10-H, 9-H/10-H, 9-H/2-H, 9-H/8-H_a, 5-H/6-H, 5-H/2-H, 5-H/14-H_a, 5-H/9-H, 13-H_3/14-H_b. IR (KBr): $\tilde{\nu}$ = 3433 (s, br), 2968, 2923, 1698 (s), 1631, 1441, 1329, 1111, 1088, 1052, 1013, 924, 889 cm^{-1}. ESI-MS: m/z (%) = 255.1 (100) $[M + Na]^+$. ESI-HRMS: calcd. for $C_{14}H_{16}NaO_3$ $[M + Na]^+$ 255.0997; found 255.1003.

Creolophin D (4): Colorless oil. $[\alpha]_D^{25}$ = +106.1 (c = 1.30, $CHCl_3$). ^{1}H NMR, COSY, HSQC, HMBC (400 MHz, $CDCl_3$): δ = 1.11 (s, 3 H, 13-H_3), 1.44 (s, 3 H, 12-H_3), 1.87 (dd, J = 12.9, 8.8 Hz, 1 H, 8-H_b), 2.42 (dd, J = 12.9, 8.8 Hz, 1 H, 8-H_a), 2.48 (d, J = 11.1 Hz, 1 H, 2-H), 2.92 (ddt, J_d = 11.1, 2.3, J_t = 8.8 Hz, 1 H, 9-H), 3.47 (d, J = 2.3 Hz, 1 H, 6-H), 3.69 (d, J = 2.3 Hz, 1 H, 10-H), 4.54 (br. s, 1 H, 5-H), 5.30 (dd, J = 2.2, 0.7 Hz, 1 H, 14-H_b), 5.36 (J = 2.2 Hz, 1 H, 14-H_a) ppm. Significant NOE contacts (NOEDS, NOESY): 12-H_3/10-H, 2-H/9-H, 2-H/5-H, 13-H_3/14-H_b, 13-H_3/8-H_a, 14-H_a/5-H, 5-H/6-H, 6-H/8-H_b, 6-H/9-H, 9-H/10-H, 8-H_b/9-H, 8-H_a/10-H. IR (KBr): $\tilde{\nu}$ = 3435 (s, br), 2947, 2930, 1738 (s), 1439, 1110, 1089, 1055, 1020, 895, 829 cm^{-1}. ESI-MS: m/z (%) = 271.1 (100) $[M + Na]^+$, 519.2 (9) $[2M + Na]^+$. ESI-HRMS: calcd. for $C_{14}H_{16}NaO_4$ $[M + Na]^+$ 271.0946; found 271.0947.

Creolophin E (5): Yellowish oil. $[\alpha]_D^{25}$ = +67.4 (c = 0.38, $CDCl_3$). ^{1}H NMR, COSY, HSQC, HMBC (400 MHz, $CDCl_3$): δ = 1.21 (s, 3 H, 13-H_3), 1.52 (s, 3 H, 12-H_3), 2.17 (dd, J = 13.3, 8.9 Hz, 1 H, 8-H_b), 2.60 (ddd, J = 13.3, 8.9, 0.8 Hz, 1 H, 8-H_a), 2.80 (ddt, J_t = 8.9, J_d = 2.4, 0.8 Hz, 1 H, 9-H), 3.47 (br. s, 1 H, 6-H), 3.78 (d, J = 2.4 Hz, 1 H, 10-H), 5.52 (d, J = 0.6 Hz, 1 H, 14-H_b), 6.30 (s, 1 H, 14-H_a) ppm. IR (KBr): $\tilde{\nu}$ = 3452 (s, br), 2978, 2937, 1746 (s), 1734 (s), 1734 (s), 1641, 1454, 1418, 1376, 1285, 1264, 1076, 1009, 969, 920, 854 cm^{-1}. APCI-MS: m/z (%) = 263.0 (100) $[M + H]^+$. ESI-HRMS: calcd. for $C_{14}H_{15}O_5$ $[M + H]^+$ 263.0919; found 263.0930.

Neocreolophin (6): Colorless oil. ^{1}H NMR, COSY, HSQC, HMBC (400 MHz, $CDCl_3$): δ = 1.02 (s, 3 H, 13′-H_3), 1.28 (s, 3 H, 13-H_3), 1.42 (s, 3 H, 12′-H_3), 1.45 (s, 3 H, 12-H_3), 1.96 (dd, J = 13.4, 8.2 Hz, 1 H, 8′-H_b), 2.03 (dd, J = 13.4, 9.8 Hz, 1 H, 8-H_b), 2.26 (d-pseudo-t, J_t = 9, J_d = 2.2 Hz, 1 H, 9′-H), 2.45 (dd, J = 13.4, 9.1 Hz, 1 H, 8′-H_a), 2.69 (d, J = 4.3 Hz, 1 H, 4′-H), 2.85 (dd, J = 13.4, 8.5 Hz, 1 H, 8-H_a), 3.14 (d-pseudo-t, J_t = 9, J_d = 6.0 Hz, 1 H, 9-H), 3.50 (s, 1 H, 6′-H), 3.54 (d, J = 2.2 Hz, 1 H, 10′-H), 3.81 (d, J = 9.1 Hz, 1 H, 14′-H_b), 4.07 (br. dd, J = 6.0, 3.7 Hz, 1 H, 10-H), 4.13 (dd, J = 9.1, 4.3 Hz, 1 H, 14′-H_a), 5.67 (s, 1 H, 14-H_b), 6.34 (s, 1 H, 14-H_a) ppm. Significant NOE contacts (NOEDS, NOESY): 15-H_3/14′-H_b, 14-H_a/8′-H_a, 13-H_3/8′-H_a, 6-H/8-H_b, 13-H_3/8-H_a, 8-H_a/10-H, 8-H_b/9-H, 10-H/9-H, 13′-H_3/4′-H, 13′-H_3/14′-H_a, 9′-H/8′-H_a, 9′-H/10′-H, 10′H/12′-H_3. ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ = 10.6 (C-12′), 13.8 (C-13′), 14.1 (C-13), 15.0 (C-12), 21.8 (C-8), 39.2 (C-8′), 43.1 (C-9′), 45.0 (C-9), 49.5 (C-3), 55.1 (C-4′), 58.0 (C-3′), 60.1 (C-6), 64.7 (C-10′), 65.2 (C-11′), 70.2 (C-14′), 70.5 (C-10), 74.2 (C-7), 89.71 (C-2), 89.75 (C-7′), 91.3 (C-11), 98.9 (C-2′), 123.8 (C-14), 126.7 (C-6′), 131.1 (C-5′), 146.5 (C-4), 196.8 (C-5), 203.6 (C-1), 208.6 (C-1′) ppm. IR (KBr): $\tilde{\nu}$ = 3435 (s, br), 2972, 2937, 1736 (s), 1687, 1639, 1262, 1223, 1202, 1123, 1092, 1053, 978 cm^{-1}. ESI-MS: m/z (%) = 1627.5 (5) [3M + Na + CH_3OH]$^+$, 1595.5 (10) [3M + Na]$^+$, 1103.4 (45) [2M + Na + CH_3OH]$^+$, 1071.3 (100) [2M + Na]$^+$, 579.2 (5) [M + Na + CH_3OH]$^+$, 547.1 (34) [M + Na]$^+$. ESI-HRMS: calcd. for $C_{28}H_{28}NaO_{10}$ [M + Na]$^+$ 547.1580; found 547.1576. Neocreolophin·2$CDCl_3$: Colorless crystals, m.p. 237–238 °C (dec.). $[\alpha]_D^{25}$ = +71.5 (c = 0.51, $CHCl_3$).

Crystal Data for 6·2$CDCl_3$ (neocreolophin·2$CDCl_3$): Formula $C_{28}H_{28}O_{10}$·2$CDCl_3$, orthorhombic, space group $P2_12_12_1$, a = 30.036(2) Å, b = 12.9766(7) Å, c = 8.7794(5) Å, V = 3421.8(4) Å^3, Z = 4, D = 1.482 g cm^{-3}, T = 193 K, R = 0.0704, Rw = 0.2013. CCDC-646198 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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