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HALOGENATED METABOLITES--INCLUDING FAVORSKY REARRANGEMENT PRODUCTS-- FROM THE RED SEAWEED BONNEMAISONIA NOOTKANA

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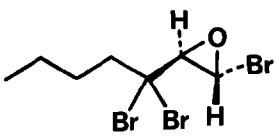
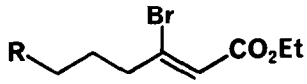
From our continuing interest in the chemistry of members of the family of red algae Bonnemaisoniaceae[1], we have confirmed the structures of 8 new halogenated secondary metabolites from Bonnemaisonia nootkana (Esp.) Silva. While a variety of halo-2-heptanones have been isolated from B. hamifera[2], B. nootkana contains, instead, trans-1,3,3-tribromo-1-heptene oxide (1), tetrabromo-2-heptanol and tetrabromo-2-nonanol (5a,b), 1,1,3,3-tetrabromo-2-nonanone (4) and, more importantly, Z-3-bromo-2-heptenoic acid and Z-3-bromo-2-nonenoic acid (2a,b), and 3,3-dibromo-n-butyl- and 3,3-dibromo-n-hexylacrylic acids (3a,b). The presence of these acids was confirmed by biomimetic synthesis via Favorsky rearrangement of the appropriately brominated methyl ketone precursors.

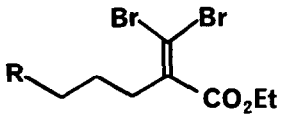
The $CHCl_3$/EtOH extract of fresh B. nootkana (collected at Carmel,California) yielded purified 1 and several fractions containing complex mixtures upon chromatography on Si gel (1-10% Et_2O/PE). Compound 1, $[\alpha]_D^{20}$ +78.6° (c 6, $CHCl_3$), M^+-Br = $C_7H_{11}OBr_2$ by high res. MS, contains a n-butyl moiety and an oxygen as a bromoepoxide: 220 MHz NMR, $CDCl_3$ (bz-d_6) δ 0.95 [3H, t, J = 7(0.79)], 1.43 [2H, q, t, J = 7,7(1.14)], 1.80 [2H, d, d, t, J = 7,7,7 (1.75)], 2.42 [1H, m (2.32)], 2.62 [1H, m (2.50)], 3.88 [1H, d, J = 3(3.33)], and 5.34 [1H, d, J = 3(4.51)]; 20 MHz CMR [bz-d_6 ($CDCl_3$)]; C-1 δ 60.2 (56); C-2, 63.5 (59.4); C-3, 68.2 (64.2); C-4, 45.8 (41.8); C-5, 30.0 (25.8); C-6, 22.1 (18.0); C-7, 13.9 (9.8). The location of the epoxide functionality was confirmed by treatment of 1 with



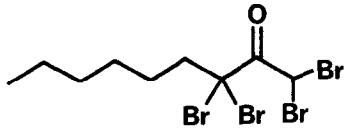
1 (26% crude extract)
[0.21% wet wt.]



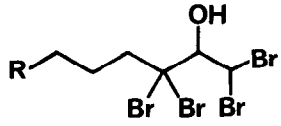
2a R=CH_3 (1%)
2b R=$CH_2CH_2CH_3$ (0.9%)



3a R=CH_3 (0.4%)
3b R=$CH_2CH_2CH_3$ (0.2%)



4 (0.5%)



5a R=CH_3 (1.0%)
5b R=$CH_2CH_2CH_3$ (2.5%)

LAH/Et_2O to yield E-3-bromo-2-hepten-1-ol (6) and by reaction with 2 equivalents n-buLi/THF, -78°, to give 7-bromo-6-undecen-5-ol (7). The structures of 6 and 7 could be assigned after examination of their respective spectral data and that obtained from various oxidation products. From the coupling constant of J = 3 Hz[4] and the large difference ($\Delta\delta$ = .28) in chemical shift changes of the two epoxide protons in the solvents $CDCl_3$ and bz-d_6, the epoxide was assigned trans. Synthesis of (±) 1: bromination of 2-heptanone (HBr/Br_2)[3] to give 1,1,3,3-tetrabromo-2-heptanone (8), followed by xs. $NaBH_4$/MeOH, yielded material (15%-GC) with identical MS and GC retention time to that of the natural compound.

The ethyl esters 2a,b and 3a,b, which are fortuitously generated from the acids during storage in EtOH[1b], were initially assigned from their MS fragmentations and isotope compositions (M^+-Br, M^+-OEt). Following modified procedures of Rappe[3,5], the corresponding normal and branched acids were synthesized via Favorsky rearrangements. Base treatment (Na_2CO_3, H_2O/MeOH, 3:1, rt., 20 hrs) of synthetic 1,1,3-tribromo-2-hepta- and 2-nonanone yielded, as the sole isolable products, the linear acids (~20% yields). In contrast, base treatment (as above,

reflux 24 hrs) of 8 and synthetic 4 yielded exclusively the 3,3-dibromo branched acids (50% isol. yields). The ethyl esters of these acids were prepared (EtOH, H_2SO_4), and their MS and GC characteristics were found to be identical to those isolated from B. nootkana (2a,b; 3a,b). A comparison of the MS spectra from 3a,b with those from ethyl-E- and Z-2,3-dibromo-2-heptenoate and 2-nonenoate (prepared via halogenation and esterification of the commercial acetylenic acids) verified that the branched systems are produced in the synthesis of 3a and 3b.

Stereochemical assignments of 2a,b as the Z isomers are proposed, based upon chemical shift data. Comparisons of the C-2 olefin protons of synthetic compounds were made with Rappe's values[5] and with 6 (obtained from 1) and its oxidation and esterification products (all in CCl_4). The ester obtained from 6 has an identical MS to that of 2a, but its GC retention time (3% SP-2401) is much shorter. In addition, the chemical shifts of the C-4 protons of the various E and Z isomers reveal, as expected, significant deshielding of these protons in the E isomers at the higher oxidation levels.

	ester		acid		aldehyde		alcohol	
	C-2	C-4	C-2	C-4	C-2	C-4	C-2	C-4
δ (2a,Z)-	6.22	2.58	6.31	2.65	--	--	5.89	2.48
δ (6,E)-	6.30	3.10	6.40	3.13	6.50	3.00	6.05	2.48

Only one Favorsky precursor, the C-9 ketone 4, was detected. Its presence was confirmed by comparing the GC retention time and mass spectrum with synthetic 4[3]. Another nine-carbon metabolite, the tetrabromo alcohol 5b, was detected, as well as its C-7 counterpart. The structure of 5b was assigned from the following data: 220 MHz NMR ($CDCl_3$) δ 0.87 (3H, J = 6), 1.23 (6H, m), 1.70 (2H, m), 2.36 (2H, m), 3.27 (1H, bd, J = 9, D_2O exchangeable), 4.39 (1H, bd, J = 9), and 6.55 (1H, d, J = 0.25); 20 MHz CMR ($CDCl_3$) δ 45.4 (d, C-1), 83.5 (d, C-2), 77.7 (s, C-3), 46.6 (t, C-4), 31.5 (t, C-5), 28.5 (t, C-6), 27.3 (t, C-7), 22.5 (t, C-8), and 14.0 (q, C-9); IR (CCl_4) ν_{O-H} = 3322 cm^{-1} (sharp); low resol. MS (50 ev) M^+-HBr, 376 (0.4%, Br_3) followed by α-cleavage: a) 205 (6.4%, Br), b) 175 (2.6%, Br). Reduction of synthetic 8 and 4 with LAH/Et_2O or $NaBH_4$/DME gave 5a and 5b, respectively, identical (MS, GC) to the natural products. Finally, there are two halogenated metabolites in very minor amounts that we believe to be 1,1,1,3-tetrabromo-2-hepta- and -2-nonanol, based on MS and GC

evidence, but we have yet to definitively prove these structures.

All of the genera of the Bonnemaisoniaceae examined chemically thus far--Asparagopsis[1b], Bonnemaisonia[1c], Delisea[6], and Ptilonia[6]--appear to produce halogenated secondary metabolites via regio- and stereospecific biological Favorsky rearrangements. In B. nootkana this is exemplified in both the C-7 and C-9 series. The competing biological reduction reaction appears to be favored, however, as is evidenced by the preponderant amount of the optically-active epoxide 1.

Acknowledgements

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