Pergamon

Tetrahedron Letters, Vol. 38, No. 47, pp. 8261-8264, 1997
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0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10162-9

Stereochemical Features of Sesquiterpene Metabolites as a Distinctive Trait of Red Seaweeds in the Genus *Laurencia*

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Abstract: Red seaweeds in the genus *Laurencia* may be classified into four lineages according to the stereochemical features of their metabolites, i.e. the known obtusane (like obtusol (+)-**1**), isoobtusane (like isoobtusol (+)-**2**) and rogiolane (like rogiolol (-)-**3**) and - structurally revised and renamed here - cartilagineane chamigrene sesquiterpenes (like cartilagineol **10**), in a vision that encompasses also biogenetic descendants, like cuparane sesquiterpenes, and fits ideas of historical contingency.
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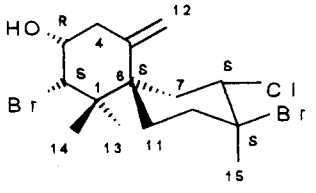
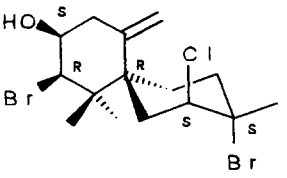
With few exceptions,[2-5] the natural product chemistry of red seaweeds in the genus *Laurencia* is characterized by fragmentary observations that parallel a confusion at the taxonomic level of species. We suggest here that the stereochemical features of sesquiterpene metabolites may reflect phylogeny and therefore may be taken as an additional distinguishing trait for seaweeds in the genus *Laurencia*.

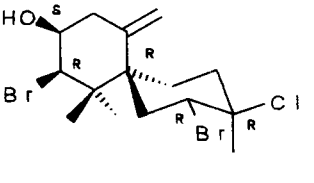
So far three stereochemical types of polyhalogenated chamigrene sesquiterpenes have been described, all



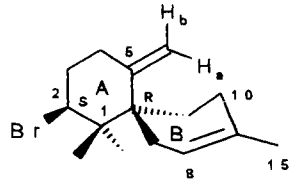
(+)-1



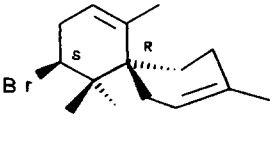
(+)-2



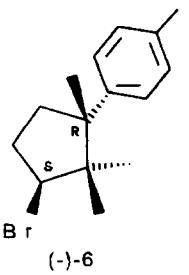
(-)-3



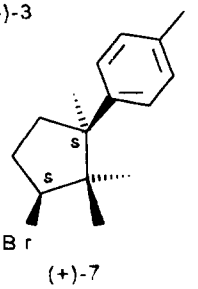
(+)-4



(+)-5



(-)-6

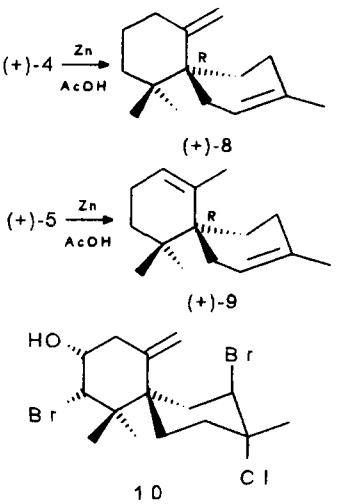


(+)-7

derived from *Laurencia* spp. or opisthobranch molluscs that feed on them. They are obtusane (like obtusol (+)-**1**),[3]

isoobtusane (like isooobtusol (+)-**2**),[3] and rogiolane sesquiterpenes (like rogiolol (-)-**3**).[4] We first wish to show that a relationship exists between the stereochemical features of these sesquiterpenes and those in other classes from the same sources. Thus, *Laurencia* sp. (753M, which may be considered of the vague species *obtusa*) taken along the coast of Gökceada Island in the Aegean Sea, was air-dried (244 g) and extracted with CH_2Cl_2/MeOH 2:1. Head fractions from gradient-elution FC with *n*-hexane/EtOAc were subjected to Si-60 TLC and RP18 HPLC to give chamigrenes (+)-**4**[6] (10 mg) and (+)-**5**[7,8] (8 mg), as well as *ent*-α-bromocuparene (-)-**6**[9,10] (7 mg) and α-isobromocuparene (+)-**7**[12] (3 mg), while from intermediate-polarity fractions rogiolol (-)-**3**[4] was isolated (22 mg).

Structures (+)-**4** and (+)-**5** represent relative configurations {for (+)-**4** from strong NOE's for (i) 7-H_β with both 12-H_a and 14-H_3, (ii) 13-H_3 with 2-H, 7-H_α and 11-H_α, and (iii) 2-H with 11-H_β, while similar evidence exists for (+)-**5**}, absolute configurations {from chemical correlations with (+)-**8**[3,13] and (+)-**9**[7a,14,15]} and preferred conformations {from NMR data and molecular mechanics calculations, which disfavour both an inverted-chair conformation for ring A and an inverted half-chair conformation for ring B, while 2*R*,6*R* or 2*S*,6*S* diastereomers would be expected to exist as two conformers of equal weight}. Cuparenes[2] (-)-**6** and (+)-**7** have the same 2*S*-configuration as (+)-**4** and (+)-**5**. Thus, this seaweed is characterized by both chamigrenes belonging to the 6*R* series ((-)-**3**, (+)-**4** and (+)-**5**) and cuparenes that share with them the 2*S* configuration.

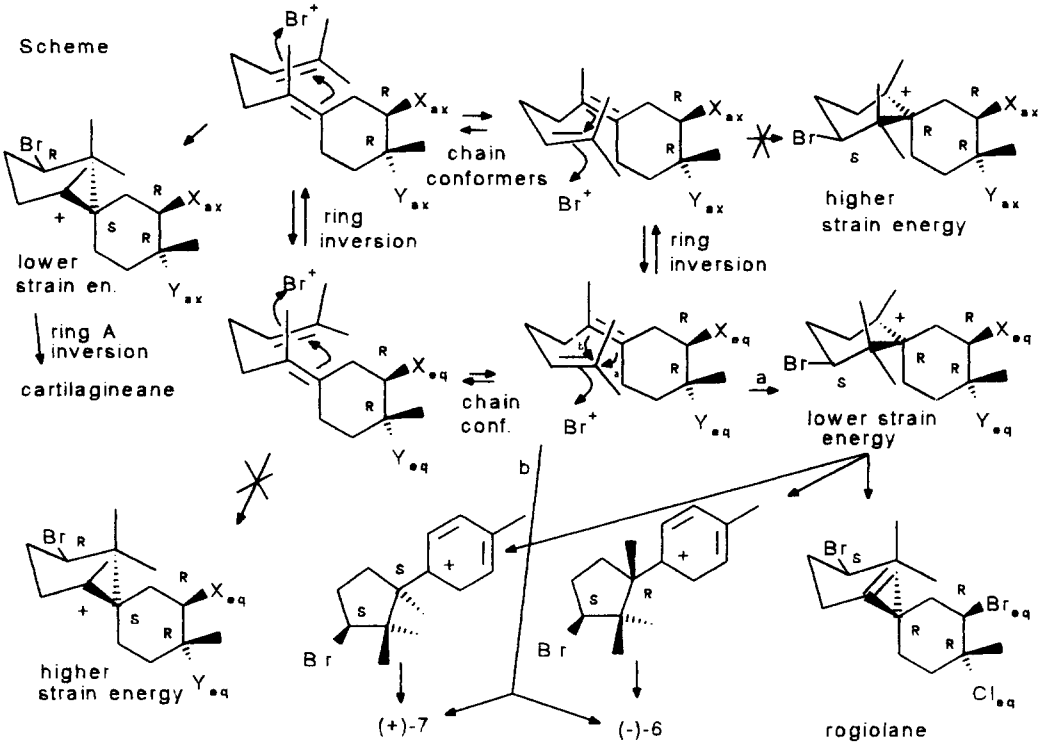


Second, we wish to bring the attention to literature data[17] that may reveal the existence of a fourth stereochemical type of chamigrene. Thus, a new cytotoxic chamigrene isolated from *Laurencia cartilaginea* of Hawaii,[17] *allo*-isoobtusol, was judged to be a diastereomer of isoobtusol ((+)-**2**). However, by attributing axial Me-15 to the latter {from a ^{13}C resonance, δ_C 25.7 ppm,[17] that actually relates to the C-5 methylene triplet[3,4]}, *allo*-isoobtusol was represented[17] with a structural drawing ((+)-**2**) that pertains to isoobtusol.[3,4] Using our numbering, δ_H 1.75 s (Me-15) and δ_C 57.1 d (C-8) for *allo*-isoobtusol[17] indicate[3,4,18] that the positions for the two halogen atoms on ring B must be reversed with respect to the original attribution.[17] Thus, there are two possible structures for *allo*-isoobtusol:[17] either it is a regioisomer of isoobtusol ((+)-**2**) with the halogens at ring B interchanged, or it is the enantiomeric form **10** of it. We strongly favour the latter since the optical rotation for *allo*-isoobtusol[17] is opposite to that of isoobtusol (+)-**2**,[3] while the exchange of halogen atoms at C-8/C-9 is irrelevant as to the sign and value of optical rotation.[4] In this view, *allo*-isoobtusol is better renamed cartilagineol.[19]

As delineated here, cartilagineane is the fourth series of stereochemically defined chamigrenes, which adds to the obtusane,[3] isoobtusane[3] and rogiolane[4] series. Elaborating previous schemes,[5] though neglecting any formal halogen interchange at C-8/C-9 which is immaterial to our main reasoning, we suggest (Scheme) that Br$^+$-induced cyclization of an *E*-γ-bisabolene having 8*R*,9*R* configuration at the cyclohexane ring, from which the chamigrane ring B is formed, may lead to compounds with the stereochemical features of either rogiolane (6*R*) and cuparane (10*S*) (path a) or cartilagineane (6*S*) sesquiterpenes, according to the initial conformation of the chain. Alternatively, and probably more reasonably, (10*S*)-cuparenes may arise along path b. A similar scheme might be constructed from 8*S*,9*S* *E*-γ-bisabolene leading to analogues with the stereochemical features of obtusane (6*S*), isoobtusane (6*R*) and (10*R*)-cuparane sesquiterpenes. As far as rogiolane and cartilagineane sesquiterpenes are

concerned, the routes to chamigrenes with different stereochemical features (Scheme) must involve transition states of higher energy. This mainly arises from strong steric repulsions of the *gem*-dimethyl substituents at C-1 with protons on ring B. Higher strain energies are expected for the carbocation intermediates either by the examination of molecular models or by molecular mechanics calculations.

The stereochemical features of the sesquiterpenoids described here must be closely related to the organization of the functional genes coding for the relevant enzymes in their producers and may therefore have phylogenetic significance by identifying four lineages of *Laurencia*. This should be taken into account in a much waited



taxonomic revision of this algal genus. To this regard, there is no evidence for more than one stereochemical type of chamigrene, or related, sesquiterpene from a morphologically homogeneous collection of *Laurencia*; as to the challenging question whether this situation may be expected to change as analysis of these seaweeds is more refined - in the perspective that clavulanic acid and clavam metabolites of antipodal skeleton were found in an actinomycete[20] - one should not forget that the concept of species is rather loose in prokaryotes. In any event, our observations fit ideas of historical contingency.[21]

We thank the Mr A. Sterni for running the mass spectra, and MURST (Progetti 40%) and CNR (including the Progetto Strategico 96-05073), Roma, for financial support.

References and Notes

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6. Data of (+)-**4**: Colourless oil. $[\alpha]_D^{20}$ (*c* = 0.11, $CHCl_3$) +84. ^1H NMR in C_6D_6 (here and in the following taken at 299.94 MHz, δ_H in ppm with respect to internal Me_4Si, *J* in Hz) δ_H 4.30 (dd, $J_{2,3\beta}$ 5.6, $J_{2,3\alpha}$ 11.3, 2-H), 1.98 (m, 3-H_2); 1.89 (tdd, $J_{4\beta,12} \approx J_{4\beta,3\beta}$ 1.8, $J_{4\beta,3\alpha}$ 11.0, $J_{4\beta,4\alpha}$ 13.0, 4-H_β);1.76 (ddd, $J_{4\alpha,3\beta}$ 2.0, $J_{4\alpha,3\alpha}$ 4.8, $J_{4\alpha,4\beta}$ 13.0, 4-H_α); 1.84 (dd, $J_{7\beta,8}$ 5.1, $J_{7\beta,7\alpha}$ 18.1, 7-H_β), 2.01 (br.dd, $J_{7\alpha,8}$ 2.7, $J_{7\beta,7\alpha}$ 18.1, 7-H_α); 5.20 (br.dd, $J_{8,7\alpha}$ 2.7, $J_{8,7\beta}$ 5.1, 8-H); 2.00 (m, 10-H_2); 1.32 (tdd, $J_{11\beta,10\beta} \approx J_{11\beta,7\beta}$ 3.3, $J_{11\beta,10\alpha}$ 5.7, $J_{11\beta,11\alpha}$ 13.1, 11-H_β); 1.22 (ddd, $J_{11\alpha,10\alpha}$ 6.5, $J_{11\alpha,10\beta}$ 10.5, $J_{11\beta,11\alpha}$ 13.1, 11-H_α); 4.60 (d, $J_{12a,12b}$ 1.8, 12-H_a); 4.81 (t,$J_{12b,12a} \approx J_{12b,4\beta}$ 1.8, 12-H_b); 1.02 (s, 13-H_3); 0.97 (s, 14-H_3), 1.56 (br.s, 15-H_3). ^{13}C NMR in C_6D_6 (here and in the following taken at 75.43 MHz, δ_C in ppm with respect to internal Me_4Si) δ 43.46(s, C-1), 66.54 (d, C-2), 36.68 (t, C-3), 33.70 (t, C-4), 146.60 (s, C-5), 47.84 (s, C-6), 31.23 (t, C-7), 120.90 (d, C-8), 133.14 (s, C-9), 28.38 (t, C-10), 26.32 (t, C-11), 113.33 (t, C-12), 24.65 (q, C-13), 18.37 (q, C-14), 24.05 (q, C-15). EI-MS *m z* (%) 282, 284 (M^+, 15/15), 267, 269 ([M - CH_3]$^+$, 12/12), 253, 257 ([M - C_2H_5]$^+$, 5/5), 203 ([M - Br]$^+$, 57), 147 (24), 135 (28), 105 (77), 81 (56), 69 (98), 41 (100).
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8. Data of (+)-**5**: Colourless oil. $[\alpha]_D^{20}$ (*c* = 0.91, $CHCl_3$) +75 (for (-)-**5** lit[7a] -81) . ^1H NMR in C_6D_6, δ_H 4.58 (dd, $J_{2,3\beta}$ 7.8, $J_{2,3\alpha}$ 9.7, 2-H); 2.51 (qddd, $J_{3\beta,12}$ 1.5, $J_{3\beta,4}$ 3.8, $J_{3\beta,2}$ 7.8, $J_{3\beta,3\alpha}$ 17.8, 3-H_β); 2.57 (qddd, $J_{3\alpha,12}$ 1.5, $J_{3\alpha,4}$ 3.5, $J_{3\alpha,2}$ 9.7, $J_{3\alpha,3\beta}$ 17.8, 3-H_α); 4.94 (qt, $J_{4,12}$ 1.5, $J_{4,3\alpha} \approx J_{4,3\beta}$ 3.5, 4-H); 2.04 (br.dd, $J_{7\beta,8}$ 5.0, $J_{7\beta,7\alpha}$ 18.1, 7-H_β), 1.68 (brdd, $J_{7\alpha,8}$ 3.7, $J_{7\beta,7\alpha}$ 18.1, 7-H_α); 5.33 (m, 8-H); 1.71(m, 10-H_2); 1.23 (tdd, $J_{11\beta,10\beta} \approx J_{11\beta,7\beta}$ 2.3, $J_{11\beta,10\alpha}$ 5.0, $J_{11\beta,11\alpha}$ 12.7, 11-H_β); 1.50 (ddd, $J_{11\alpha,10\alpha}$ 5.9, $J_{11\alpha,10\beta}$ 11.5, $J_{11\beta,11\alpha}$ 12.7, 11-H_α); 1.57 (br.s, 12-H_3); 1.05 (s, 13-H_3); 0.94 (s, 14-H_3), 1.57 (br.s, 15-H_3). ^{13}C NMR in C_6D_6, δ_C 42.45 (s, C-1), 63.65 (d, C-2), 37.54 (t, C-3),122.54 (d, C-4), 134.41 (s, C-5), 44.60 (s, C-6), 30.68 (t, C-7), 123.26 (d, C-8), 134.41 (s, C-9), 29.49 (t, C-10), 31.71 (t, C-11), 24.18 (q, C-12), 25.68 (q, C-13), 17.78 (q, C-14), 24.21 (q, C-15). EI-MS *m z* (%) 282, 284 (M^+, 5/5), 214, 216 ([M - C_5H_8]$^+$, 45/45), 203 ([M - Br]$^+$, 10), 147 (17), 135 (100).
9. Data for (-)-**6**: Colourless oil; $[\alpha]_D^{20}$ (*c* 0.50, $CHCl_3$) -19.0 (lit[10,11] -23.7).
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12. Data of (+)-**7**:colourless oil.; $[\alpha]_D^{20}$ (*c* = 0.18, $CHCl_3$) +88 (lit[11] +91).
13. Data of (+)-**8**: $[\alpha]^{20}$ (*c* = 0.10, $CHCl_3$) +29 (for (-)-**8**, lit[14] -52.7), +36, +45, +70 and +115 at λ 589, 577, 546, 435 and 365 nm, respectively.
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15. Data of (+)-**9**: $[\alpha]^{20}$ (*c* = 0.13, $CHCl_3$) +20 (for (-)-**9**, lit[16] -14.5), +26, +38, and +45 at λ 589, 546, 435 and 365 nm, respectively.
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19. Other inconsistencies in the work at ref. 17 have to cleared away. Thus, elatol {for (+)-elatol see Sims, J. J.; Lin, G. H. Y.;Wing, R. A. *Tetrahedron Lett.* **1974**, 3487-3490; for (-)-elatol see Rinehart, K.L. Third International Symposium on Marine Natural Products, IUPAC, Brussels, **1980**} was represented[17] by a diastereomer of it, while rogiolol ((-)-**3**)[4b] was represented by a structure {**8** in ref 17, taken from Coll, J.C.; Wright, A.D. *Aust. J. Chem.* **1989**, *42*, 1591-1603} that was revised to (-)-**3**.[4b]
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(*Received in UK* 14 *August* 1997; *revised* 16 *September* 1997; *accepted* 19 *September* 1997)