Bisabolanes from the Red Alga *Laurencia scoparia*

Danilo Davyt,[†] Rafael Fernandez,[†] Leopoldo Suescun,[‡] Alvaro W. Mombrú,[‡] Jenny Saldaña,[§] Laura Domínguez,[§] Mutue T. Fujii,[#] and Eduardo Manta*[,†]

Facultad de Química, Universidad de la República, Avenida Gral. Flores 2124, Montevideo, Uruguay, and Instituto de Botânica, Avenida Miguel Estéfano 3687, 04301-902 São Paulo, Brazil

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Three novel halogenated β-bisabolene sesquiterpenoids (**1**−**3**), together with two know triquinane alcohol sesquiterpenes (**6** and **7**), were isolated from the red alga *Laurencia scoparia* and their structures elucidated by spectroscopic methods. Single-crystal X-ray crystallography allowed us to confirm the structure of **1** as well as to determine the absolute configuration of all stereocenters. To the best of our knowledge, the isolation of β-bisabolenes from the genus *Laurencia* has no precedent in the literature. Compound **1** showed weak in vitro anthelmintic activity against parasitant stage (L4) *Nippostrongilus brasiliensis*.

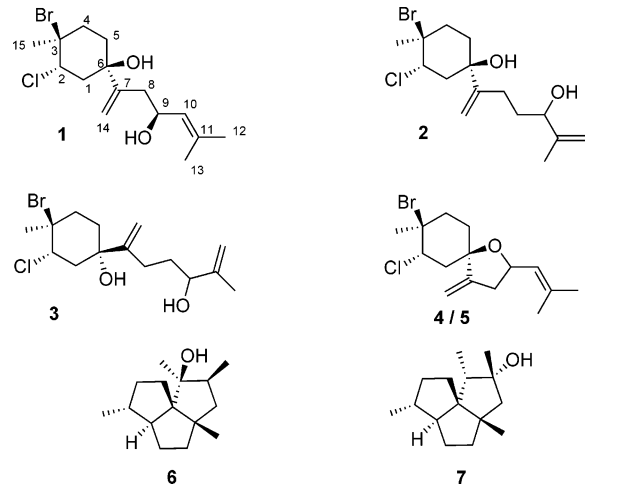
The red algae of the genus *Laurencia* are known as a rich source of secondary metabolites, predominantly sesquiterpenes, diterpenes, and acetylenes.[1] In the course of our ongoing investigations toward the isolation and biological evaluation of compounds from marine organisms of the South American coasts, we have studied *L. scoparia* J. Agardh specimens from Brazil and reported several sesquiterpenes with chamigrane or rearranged chamigrane structures.[2] In this paper we wish to describe the isolation and structural elucidation of three new bisabolane-type compounds from the dichloromethane extracts of *L. scoparia* (**1**−**3**, Chart 1), together with two reported triquinanes previously isolated from *L. majuscula* (**6** and **7**, Scheme 1).[3]

Compound **1** was obtained as an optically active white powder. HREIMS measurements and analysis of the NMR data presented below indicated a molecular formula of $C_{15}H_{24}BrClO_2$. EIMS showed an $[M - H_2O]^+$ ion cluster at 332/334/336 with intensities in a 3:4:1 ratio, revealing the presence of one bromine and one chlorine atom. The IR spectrum exhibited a strong absorption at 3199 cm^{-1}, indicating the presence of hydroxyl groups. 1D and DEPT ^{13}C NMR experiments showed the presence of 15 carbon atoms, corresponding to four quaternary, three methine, five methylene, and three methyl carbons. Of these, two were bonded to oxygen, with resonances at δ_C 73.8 (C) and 71.0 (CH), two were halogenated carbons, resonating at δ_C 68.7 (C) and 67.9 (CH), and four were olefinic, displaying signals at δ_C 152.6 (C), 136.4 (C), 127.4 (CH), and 112.9 (CH_2).

The basic skeleton of **1** was established using mass spectroscopy and NMR, including COSY, HMQC, and HMBC experiments, as a bisabolane sesquiterpene having a terminal trisubstituted double bond (δ_H 5.24, 1H, bd, δ_H 1.71 and 1.73, 3H each, d; δ_C 127.4, CH and 136.4, C). Several correlations observed in the HMQC experiment matched those observed for the bromo-chlorocyclohexyl moiety found in obtusene-type chamigrenes, indicating the presence of a similar cyclic fragment in **1**. Obtusene and obtusol are chamigrenes of this structural lineage previously isolated in this extract of *L. scoparia*.[2,5]

The HMBC NMR spectrum of compound **1** showed long-range correlation between the broad singlets typical of an exocyclic methylene group at δ_H 5.08 and δ_H 4.97, with an oxygenated quaternary carbon at δ_C 73.8 (C-6), suggesting that the tertiary hydroxyl group was located on the cyclohexyl moiety. In addition,

Chart 1. Structure and Numbering of Compounds Isolated from *L. scoparia*[4]



the position of the allylic alcohol group in the side chain was established by means of COSY and HMBC correlations (δ_H 4.48, ddd; δ_C 71.0 d).

The X-ray crystallographic analysis of compound **1** was nontrivial. Since rapid decomposition was observed upon irradiation, several single crystals were required in order to determine the structure and absolute configuration of all chiral centers in the molecule. Protection of the crystals from air by embedding them in a droplet of wax reduced the decomposition rate, allowing for short periods of data collection. A complete data set suitable for determining both the structure and the absolute configuration of the entire molecule was obtained by combining results from two different crystals.[6] An ORTEP diagram depicting the solid state conformation and the absolute stereochemistry of **1** (2*S*,3*S*,6*R*,9*S*) is shown in Figure 1. Refinement of the Flack parameter led to a value of 0.01(3), corroborating the reliability of this absolute configuration.[7] The X-ray structure also reveals that the oxygen at C-6 is axial and bridged by a hydrogen bond with the allylic alcohol at C-9.

Compound **2** was obtained as a colorless oil. A molecular formula of $C_{15}H_{20}BrClO$ was deduced from the HREIMS data and analysis of the NMR spectra. The LREIMS of the compound showed $[M - 2H_2O]^+$ peaks at *m*/*z* 314/316/318, with relative intensities 3:4:1, suggesting again the presence of one bromine and one chlorine atom. The elemental composition of peaks at *m*/*z* 314 was further confirmed by analysis of the HREIMS data.

* To whom correspondence should be addressed. Phone: (5982) 9241805. Fax: (5982) 9241906. E-mail: emanta@fq.edu.uy.
[†] Cátedra de Química Farmacéutica, Universidad de la República.
[‡] Cátedra de Cristalografía, Universidad de la República.
[§] Cátedra de Farmacología, Universidad de la República.
[#] Instituto de Botânica, Seção de Ficologia.

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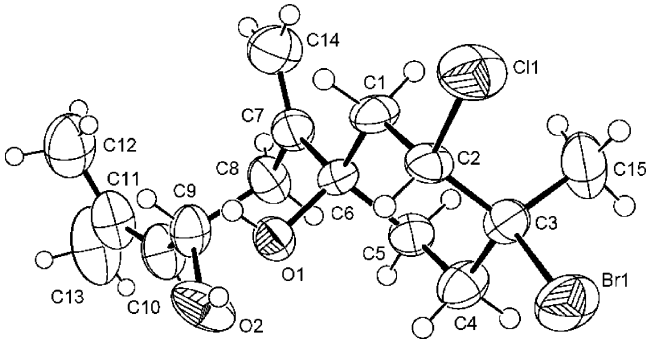

Figure 1. ORTEP representation of compound **1**, together with the X-ray labeling scheme. Thermal ellipsoids are represented at the 30% probability level. Hydrogen atoms are represented as spheres of arbitrary radius.

Table 1. ^{13}C NMR Spectral Data for Compounds **1**−**5** ($CDCl_3$)[a]

C	**1**	**2**	**3**	**4**−**5**[b]
1	45.4 (CH_2)	45.9 CH_2)	40.1 (CH_2)	46.00−43.43 (CH_2)
2	67.9 (CH)	67.4 (CH)	66.7 (CH)	67.4−67.5 (CH
3	68.7 (C)	68.2 (C)	67.5 (C)	68.15−68.17 (C)
4	40.4 (CH_2)	44.3 $(CH)_2$	39.9 (CH_2)	40.97−41.09 (CH_2)
5	25.7 (CH_2)	34.0 (CH_2)	28.6 (CH_2)	35.98−33.23 (CH_2)
6	73.8 (C)	75.3 (C)	85.6 (C)	83.15 (C)
7	152.6 (C)	154.1 (C)	149.4 (C)	154.84 (C)
8	39.4 (CH_2)	27.0 (CH_2)	25.2 (CH_2)	33.24 (CH_2)
9	71.0 (CH)	34.6 (CH_2)	32.9 (CH_2)	73.29−73.39 (CH)
10	127.4 (CH)	75.8 (CH)	75.0 (CH)	125.46 (CH)
11	136.4 (C)	147.8 (C)	147.7 (C)	137.4−137.5 (C)
12	18.6 (CH_3)	111.5 (CH_2)	111.4 (CH_2)	18.73−18.79 (CH_3)
13	26.1 (CH_3)	18.2 (CH_3)	14.6 (CH_3)	26.23 (CH_3)
14	112.9 (CH_2)	109.9 (CH_2)	113.1 (CH_2)	105.11−105.05 (CH_2)
15	23.7 (CH_3)	23.7 (CH_3)	24.0 (CH_3)	23.67−23.71 (CH_3)

[a] Carbon types were determined by DEPT. [b] **4**−**5** corresponds to an isomeric mixture (see text).

The ^{1}H and ^{13}C NMR spectra of **2** were very similar to those of compound **1** (Tables 1 and 2), except for the spectral regions of the fragment C-9 through C-13. A terminal double bond between C-11 and C-12 was confirmed by the ^{13}C signals of C-11 (δ_C147.8, C) and C-12 (δ_C 111.5, CH_2) and the olefinic ^{1}H signals for H-12 (δ_H 4.89, s) and H-12′ (δ_H 4.99, s). Furthermore, the ^{1}H NMR spectrum revealed signals from one vinylic methyl group at δ_H 1.76 (s), which was assigned to C-13 and confirmed by HMBC correlations (see Figure 2), and one allylic hydroxyl group (δ_H 4.12, dd). The main difference between compounds **1** and **2** was the position of the allylic alcohol in the side chain moiety. In compound **2** this alcohol is on the C-10 carbon, an assignment that was unambiguously corroborated by means of COSY and HMBC correlations (Figure 2).

Compound **3** was also isolated as a colorless oil, and its chromatographic mobility resembled that of compounds **1** and **2**. The LREIMS and IR spectra were almost identical with those recorded for **1**. Comparison of the NMR data of **3** with those of **1** and **2** suggested that this metabolite was also a bisabolene with the same allylic side chain as **2**. The most significant difference between compound **3** and **2** was the chemical shift of the C-6 oxygenated quaternary carbon. The signal for this carbon was shifted downfield from δ_C 73.8 in **2** to δ_C 85.6 in **3**, implying that the tertiary hydroxyl group attached to C-6 in compound **3** was in an equatorial configuration. COSY and HMBC correlation data confirmed that alcohol **3** was a stereoisomer of **2**, with the hydroxyl group at C-6 residing in an equatorial position of the six-membered ring.

The only problem left to solve was the determination of the absolute configuration at C-10 in both compounds **2** and **3**. Unfortunately, the low available amounts of compounds **2** and **3** precluded a derivatization reaction that could have led to an unambiguous determination of the absolute configuration at the C-10 carbon in either case.[8,9]

The allylic−homoallylic system present in the side chain of compound **1** was found to be very reactive. When nonstabilized deuterochloroform was used to obtain its NMR spectra, decomposition into an unresolvable mixture was observed during the course of the experiment. As understanding this decomposition mechanism could provide important clues regarding the formation of other metabolites from bisabolane **1**, we decided to determine the structure of the compounds in the mixture. TLC analysis indicated that the components of the mixture were less polar than compound **1**, and its IR data revealed the absence of hydroxyl group absorptions. Since all attempts to separate these decomposition products by means of semipreparative HPLC were unsuccessful, their structures were determined simultaneously by direct analysis of the mixture.

The LREIMS of the mixture displayed the same fragment ions observed for compound **1**, showing peaks at *m*/*z* 332/334/336 $[M]^+$, with intensities in a 3:4:1 ratio, indicating the presence of one bromine and one chlorine atom as well as the same base peak at *m*/*z* 85. The ^{1}H and ^{13}C NMR spectra of the mixture were then compared with those of compound **1**. Resonances attributable to the bromo-chloro cyclohexyl moiety, corresponding to carbons C-1 to C-5, were split into pairs of narrowly separated signals, indicating that they arose from a mixture of two closely related molecules, compounds **4** and **5**, present in a 2:1 ratio. A similar situation was observed for most of the carbon signals in the C-9 to C-13 region. However, the ^{13}C NMR spectrum of the mixture displays an isolated signal at δ_C 83.2 (C), which can be unambiguously assigned to C-6, the quaternary carbon attached to oxygen. This signal, together with a pair of resonances at δ_C 73.29 (C) and δ_C 73.39 (C), assigned to the C-9 oxymethine carbons in compounds **4** and **5**, suggests that the oxygen atom is involved in an ether linkage and that both molecules are oxa-bicyclic stereoisomers. Detailed analysis of the 1D ^{1}H and ^{13}C NMR spectra of the mixture, as well as its COSY, HMBC, and HMQC spectra, allowed the assignment of the ^{1}H and ^{13}C resonances shown in Tables 1 and 2.

On the basis of the aforementioned evidence, the structures of compounds **4** and **5** were established as shown in Scheme 1. Their formation from bisabolene **1** can be easily rationalized by means of an acid-catalyzed stepwise mechanism. First, protonation of the hydroxyl group at C-9 followed by water loss leads to an allylic carbocation. Subsequent nucleophilic attack by the tertiary hydroxyl group on C-6 from either face of the carbocation yields the ether linkage. On the basis of this mechanistic rationale, a mixture of C-9 epimeric oxa-byciclic compounds **4** and **5** should be obtained, in agreement with what was determined experimentally.

Compounds **6** and **7** were purified in successive chromatographic separations. Both were isolated as colorless oils. Analysis of their spectroscopic properties indicated that they were identical to sesquiterpene triquinanes previously reported in the literature.[3,5] It is interesting that these triquinanes and two uncommon chamigranes were isolated from Australian *L. majuscula* and Brazilian *L. scoparia*, two species for which comparative studies were not possible until now.

As part of an ongoing project to discover potential new anthelmintic drugs, compounds **1**−**3**, **6**, and **7** were tested in vitro using a *Nippostrongylus brasiliensis* model.[10] Compounds **2**, **3**, **6**, and **7** were not active, and compound **1** showed moderate antiparasitic activity, with an EC_{50} of 0.11 mM.

To the best of our knowledge, compounds **1**−**3** represent the first examples of *β*-bisabolene sesquiterpenes ever found in red algae of the genus *Laurencia*. Consequently, these compounds could be of significant interest in future biogenetic and taxonomic studies.

Experimental Section

General Experimental Procedures. Melting points were determined on a Gallenkamp capillary melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 141 polarimeter

Table 2. ^{1}H NMR Spectral Data for Compounds **1**−**5** ($CDCl_3$)[a]

H	1	2	3	4−5[c]
1	2.03 (dd 13.5, 12.2)	2.01 (dd 13.0, 13.0)	1.84 (m)	1.95 (m)−1.77 (m)
1′	2.19 (ddd 13.5, 4.5, 3.0)	2.11 (m)	2.47 (ddd 13.8, 4.7, 3.0)	2.13 (m)−2.19 (m)
2	4.80 (dd 12.2, 4.5)	4.78 (dd 12.1, 4.6)	4.67 (dd 12.4, 4.7)	4.67 (m)
4	2.26 (m)	2.35 (ddd 13.6, 13.6, 2.5)	2.35 (m)	2.36(m)
4′	2.77 (ddd 13.4, 13.4, 4.6)	2.81 (ddd 13.6, 13.6, 4.5)	2.74 (ddd 14.0, 14.0, 3.4)	2.69 (m)
5	1.58 (dd 13.4, 3.0)	1.54 (ddd 14.3, 4.6, 2.5)	1.72 (ddd 14.0, 14.0, 4.0)	1.52 (m)−1.50 (m)
5′	1.63 (m)	1.75 (m)	2.07 (ddd 14.0, 7.0, 3.4)	1.68 (m)- 1.62 (m)
8	2.41 (dd 14.1, 9.0)	2.17 (m)	2.37 (m)	2.65 (m)
8′	2.29 (m)	2.17 (m)	2.15 (m)	2.35 (m)
9	4.48 (ddd 8.8, 8.8, 3.5)	1.75 (m)	1.82 (m)	4.57 (m)
9′		1.75 (m)	1.82 (m)	
10	5.24 (bd 8.8)	4.12 (dd 5.5, 1.3)	4.21 (dd 9.1, 3.8)	5.23 (m)
12	1.71 (d 1.1)	4.89 (s)	4.91 (s)	1.72 (s)−1.73 (s)
12′		4.99 (s)	5.00 (s)	
13	1.73 (d 1.1)	1.76 (s)	1.77 (s)	1.77 (s)
14	5.08 (s)	5.15 (s)	5.20 (s)	4.99 (s)
14′	4.97 (s)	4.93 (s)	5.10 (s)	4.79 (s)
15	1.85 (s)	1.85 (s)	1.85 (s)	1.89 (s)
OH			9.11 (s)[b]	

[a] Multiplicities and coupling constants in Hz are in parentheses. [b] Exchangeable in D_2O. [c] **4**−**5** corresponds to an isomeric mixture (see text).

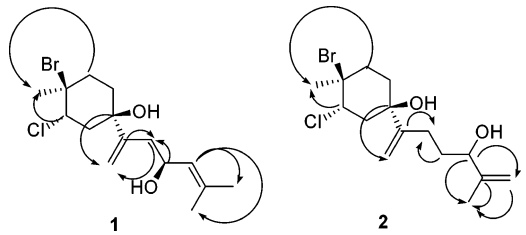

Figure 2. Relevant HMBC connectivities observed for compounds **1** and **2**.

equipped with a sodium lamp (589 nm) using a 1.0 mL cell. IR spectra were recorded on a Shimadzu DR-8031 FT IR. X-ray data were collected on a Rigaku AFC7S diffractometer at room temperature with Mo Kα radiation using the MSC/AFC Diffractometer Control Software.[11] NMR spectra were recorded on a Bruker AVANCE DPX 400 instrument operating at ^{1}H and ^{13}C frequencies of 400.13 and 100.62 MHz, respectively. Chemical shifts are related to TMS as internal standard. Low-resolution mass spectra (EIMS) were obtained on a Shimadzu QP 1100-EX GCMS instrument. MPLC column chromatography was carried out with silica gel 60 for flash chromatography (40 μm average particle diameter, J. T. Baker). HPLC chromatography was carried out on a Shimadzu LC-8A system equipped with a SPD-M6A photodiode array detector and a MetaChem Intersil (10 μ, 250 × 20 mm). Chromatographic separations were monitored by TLC performed on 0.25 mm silica gel plastic sheets (Polygram SIL G/UV 254, Macherey-Nagel). Spots were visualized using UV light (254 nm), iodine vapor, or 50% phosphomolybdic acid in EtOH.

Plant Material. *L. scoparia* was collected in September 2000 at Praia Brava, coast of Ubatuba, State of Sao Paulo, Brazil. The specimens were identified taxonomically, and a voucher specimen was deposited at the Herbarium of the Botanical Institute, Brazil (SP 336317 and 336318).

Extraction and Isolation. The extract preparation and fractionation were conducted as previously described.[2]

(2*S*,3*S*,6*R*,9*S*)-3-Bromo-2-chloro-2,3-dihydro-6,9-dihydroxy-*β*-bisabolene[(1*R*,3*S*,4*S*)-4-bromo-3-chloro-1-((*S*)-4-hydroxy-6-methylhepta-1,5-dien-2-yl)-4-methylcyclohexanol] (1): colorless crystals (70 mg, 0.004%); mp 96 °C (hexanes/EtOAc); $[\alpha]_D^{25}$ +6.4 (*c* 0.50, $CHCl_3$); IR (KBr pellet) ν_{max} (cm^{-1}) 3179, 2963, 2924, 2370, 1717, 1647, 1456,1437; ^{1}H NMR, see Table 2; ^{13}C NMR, see Table 1; LREIMS (70 eV) *m*/*z* (rel int) 336/334/332 $[M - H_2O]^+$ (0.5/3.6/2.5), 319 (1), 316 (2), 314 (2), 299 (4), 297 (4), 253 (12), 217 (22), 199 (10), 197 (20), 169 (20), 133 (32), 91 (32), 85 (100); HREIMS *m*/*z* 332.0434 $[M - H_2O]^+$ (calcd for $C_{15}H_{20}{}^{81}Br^{35}ClO$ 332.0366). Crystal data: $C_{15}H_{24}BrClO_2$, orthorhombic, $P2_12_12_1$, a = 11.2509(18) Å, b = 22.566(5) Å, c = 6.8262(12) Å, V = 1733.1(6) Å^3, Z = 4, ρ = 1.348 Mg/m^3, 2491 collected reflections (4.04° < 2θ < 55.00°). The structure was solved by direct methods, and all atoms were freely refined, using the SHELXS97 and SHELXL97 programs, respectively.[12,13] The final residuals were $R(F)$ = 0.064 and weighted $R(F^2)$ = 0.1650 for the 1274 observed reflections.

(2*S,3*S**,6*R**)-3-Bromo-2-chloro-2,3-dihydro-6,10-dihydroxy-*β*-bisabolene[(1*R**,3*S**,4*S**)-4-bromo-3-chloro-1-(5-hydroxy-6-methylhepta-1,6-dien-2-yl)-4-methylcyclohexanol] (2):** colorless oil (30 mg, 0.002%); $[\alpha]_D^{25}$ +14.4 (*c* 0.15, $CHCl_3$); IR (film) ν_{max} (cm^{-1}) 3399, 2968, 2936, 2870, 1647, 1456; ^{1}H NMR, see Table 2; ^{13}C NMR, see Table 1; LREIMS (70 eV) *m*/*z* (rel int) 318/316/314 $[M - 2H_2O]^+$ (0.5/2.2/1.6), 301 (2), 299 (2), 253 (14), 235(5), 217 (21), 199 (27), 198 (27), 183 (40), 149 (100), 105 (73), 91 (76), 85 (22); HREIMS *m*/*z* 314.0383 $[M - 2H_2O]^+$ (calcd for $C_{15}H_{20}{}^{79}Br^{35}Cl$ 314.0437).

(2*S,3*S**,6*S**)-3-Bromo-2-chloro-2,3-dihydro-6,10-dihydroxy-*β*-bisabolene[(1*S**,3*S**,4*S**)-4-bromo-3-chloro-1-(5-hydroxy-6-methylhepta-1,6-dien-2-yl)-4-methylcyclohexanol] (3):** colorless oil (15 mg, 0.001%); $[\alpha]_D^{25}$ +5.3 (*c* 0.10, $CHCl_3$); IR (film) ν_{max} (cm^{-1}) 3399, 2936, 2870, 1716, 1647, 1456; ^{1}H NMR, see Table 2; ^{13}C NMR, see Table 1; LREIMS (70 eV) *m*/*z* (int rel) 318/316/314 $[M - 2H_2O]^+$ (0.2/0.7/0.5), 299 (2), 253 (7), 235(2), 217 (12), 199 (7), 198 (3), 197 (13), 149(2), 105 (9), 85 (100).

Compounds 4−**5:** colorless oil (5 mg); IR (film) ν_{max} (cm^{-1}) 2932, 1663,1427, 1379, 1081; ^{1}H NMR, see Table 2; ^{13}C NMR, see Table 1; LREIMS (70 eV) *m*/*z* (rel int) 336/334/332 $[M]^+$ (1.7/6.8/5.2), 319 (2), 299 (5), 297 (5), 253 (18), 249(15), 217 (25), 197 (35), 169 (28), 133 (43), 85 (100).

Anthelmintic in Vitro Assay. The effect of compounds on the parasitant stage (L4) of *N. brasiliensis* was evaluated as previously described.[2,10]

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of compounds **1**−**5** and X-ray crystallographic data of compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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