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REGULAR AND IRREGULAR SESQUITERPENES CONTAINING A HALOGENATED HYDROPYRAN FROM *LAURENCIA CAESPITOSA*

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Key Word Index—*Laurencia caespitosa*; Rhodomelaceae; halogenated sesquiterpenes; laucapyranoids; 6-hydroxycaespitol; caespitane; caespitol; isocaespitol.

Abstract—The red seaweed *Laurencia caespitosa* is an unusually rich source of secondary metabolites. Five novel regular and irregular halogenated sesquiterpenes were isolated and characterized from this alga. The laucapyranoids A, B and C form a new class of rearranged terpenoids. The structures of laucapyranoids A and B were established by 1D and 2D NMR experiments, the latter being confirmed by X-ray crystallography. The identity of the unstable laucapyranoid C was established by reconstruction of its hydrodebrominated derivatives, whose structures were determined by spectroscopic data and X-ray analysis. The structures of the regular sesquiterpenoids 6-hydroxycaespitol and caespitane were elucidated from spectroscopic data and confirmed by X-ray analysis in the case of caespitane. Finally, the exciton chirality method was applied to the determination of the absolute configuration of caespitol and isocaespitol. The circular dichroism allylic benzoate approach circumvented the problems associated with the Bijvoet X-ray diffraction method in a previous study of these sesquiterpenes.

INTRODUCTION

Secondary metabolites from marine organisms are increasingly playing a major role in the chemistry of natural products. Research in this area has produced a host of compounds with unique structural features, such as the presence of one or more halogen atoms, as well as promising biological activity. Examples include the punaglandins, from the octocoral *Telesto riisei* [1], various polyhalogenated sesquiterpenes [2] and venustatriol [3] from the red alga *Laurencia*, and the pseudopterosins from the deep water Caribbean gorgonian *Pseudopterogorgia elisabethae* [4], which show potential as antitumour or antimicrobial agents. The brevetoxins [5–7] the neurotoxins responsible for red tide poisoning, and amphikuemin [8] which mediates the symbiotic relationship between the sea anemone and the anemone fish, are prime examples of the role of marine natural products in mediating interspecific communication.

We have focused our attention on the natural products chemistry of the prolific red alga *Laurencia* (Rhodomelaceae), which is widely distributed in the Canary Islands. One such species, *L. caespitosa* Lamx, was found to be an unusually rich source of bromochlorinated sesquiterpenes with a bisabolane skeleton containing a tetrahydropyranyl ring system [9–11]. These metabolites not only possess unique structural features, such as the presence of a C_{15} skeleton and one or more halogen atoms, but some of these compounds have been found to display moderate antimicrobial activity [2]. On the other hand, comparative biochemical studies of the previously reported deodactol [12, 13], an antineoplastic sesquiterpenoid from the digestive glands of the marine opisthobranch *Aplysia dactylomela*, have shown that this compound is, in fact, an algal metabolite and has been actually isolated from *L. caespitosa*. In addition, previous studies of this alga in our laboratory have afforded C_{12}terpenoids with an unprecedented sesquiterpenoid degraded skeleton [14–16].

We report here the isolation and structure elucidation of laucapyranoids A (**1**), B (**2**) and C (**3**), which constitute a new class of irregular rearranged terpenoids, and the novel regular sesquiterpenes 6-hydroxycaespitol (**4**) and caespitane (**5**). In addition, experiments defining the absolute configurations of caespitol (**6**) and isocaespitol (**7**), previously isolated from *L. caespitosa*, are described.

RESULTS AND DISCUSSION

Both collections of *L. caespitosa* at Punta del Hidalgo, Tenerife and from the island La Graciosa contained identical compounds but in slightly different ratios. Extraction of the air-dried algae with acetone and diethyl ether, followed by chromatography on silica gel afforded the novel sesquiterpenes.

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Laucapyranoid A (**1**) was isolated as a crystalline solid from the acetone extract. Electron impact mass spectrometry of this compound showed a molecular ion at m/z 414, with the characteristic isotope pattern consistent with the presence of two bromine atoms and one chlorine atom. High resolution EI mass spectrometry confirmed this and established a molecular formula of $C_{15}H_{23}Br_2ClO$. The ^{1}H NMR spectrum of compound **1** was similar to that of caespitol (**6**) [9]: two methines α to a bromine atom (δ 4.05 and 4.38) and four methyl groups (δ 1.27, 1.37, 1.72 and 1.73). However, the 8-H resonance was missing and the methyl group at C-14 was further deshielded (δ 1.7). The absence of either a hydroxyl or a carbonyl band in the IR spectrum suggested that the oxygen was involved in an ether linkage. This was supported by the presence of an absorption at 1635 cm^{-1} attributed to the C=C stretching band of a vinyl ether. ^{13}C NMR spectroscopy confirmed this assignment and revealed two olefinic resonances at δ 104.7 and 143.9, corresponding to C-8 and C-7, respectively. The coupling constant $J_{10\text{-}9\text{ax}} = 8.7$ Hz established the bromine on the pyranose ring at the equatorial position. A COSY map of laucapyranoid A showed the familiar $CH_{ax}CH_2CH_{ax}$ cross peaks correlating the protons at C-6, C-1 and C-2. This data, together with the coupling constant $J_{2\text{-}1\text{ax}} = 12.2$ Hz, indicated the presence of a bromochlorinated cyclohexane ring with substitutions identical to caespitol. Structure **1** was, therefore, established for laucapyranoid A.

Laucapyranoid B (**2**) was isolated as a crystalline solid from a mixture containing laucapyranoids B and C in *ca* a 1 : 1 ratio. While the mixture of both compounds was very sensitive to air and moisture, the isolated crystalline laucapyranoid B was found to be stable. A molecular ion at m/z 431.9710 established a molecular formula of $C_{15}H_{23}Br_2ClO_2$ for laucapyranoid B. Its ^{1}H NMR spectrum showed signals for all the heteroatom-methine protons (δ 4.00 and 4.37) found in caespitol (**6**), but lacked one for 8-H. Moreover, only three methyl groups were present (δ 1.31, 1.44 and 1.66). A hydroxyl group and a vinyl ether moiety were evident from the IR bands at 3580, 3400 and 1640 cm^{-1}. Both ^{1}H and ^{13}C NMR spectra established the vinyl ether to be exocyclic with ^{1}H NMR resonances for 14-H's at δ 4.60 and 4.64, and ^{13}C NMR signals at δ 97.3 and 159.5, corresponding to C-14 and C-7, respectively. The structure assignment of laucapyranoid B, including absolute configuration, was determined by the single crystal X-ray diffraction method. A computer-generated perspective drawing of the final X-ray model of laucapyranoid B is shown in Fig. 1. This analysis confirmed the presence of a 2-methylenetetrahydropyranyl moiety and established a rearranged bisabolane skeleton for this compound.

Laucapyranoid C (**3**) was extremely unstable and on standing rapidly decomposed to the hydrodebrominated terpenes **8** and **9**. Acetylation of a mixture of laucapyranoids B and C afforded the monoacetate **10** and the terpenes **2** and **8**, which could not be acetylated. The more polar terpene **8** was isolated as a crystalline solid. High resolution EI mass spectrometry gave a peak at m/z 323.0412, arising from α-cleavage to the methyl ketone, and established a molecular formula of $C_{15}H_{24}BrClO_3$. The IR spectrum showed the presence of a hydroxyl moiety (3540 and 3400 cm^{-1}) and a carbonyl (1700 cm^{-1}) group. ^{1}H NMR spectrum confirmed this with a D_2O exchangeable resonance at δ 4.19 and a signal at δ 2.29, attributed to a methyl group adjacent to a carbonyl moiety. A ketone was evident in the ^{13}C NMR spectrum of terpene **8**: δ 210.9 (C-7). In addition, the ^{1}H NMR spectrum suggested that the cyclohexane ring portion of the molecule had remained intact: δ 1.68 and 4.29, corresponding to 15-H and 2-H, respectively. X-ray crystallography determined the structure and absolute stereochemistry of compound **8** as shown in Fig. 2.

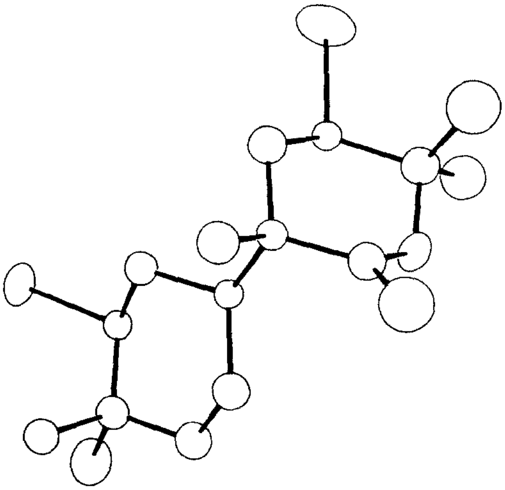


Fig. 1. ORTEP drawing of laucapyranoid B (**2**).

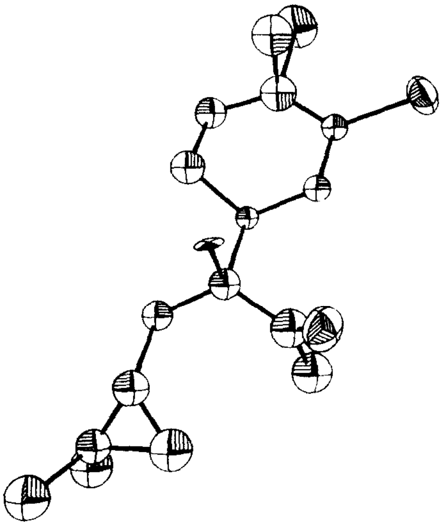


Fig. 2. ORTEP drawing of compound **8**.

The FAB mass spectrum of the hydrodebrominated derivative **10** showed a molecular ion at m/z 410.0661 and established a molecular formula of $C_{17}H_{26}BrClO_4$. α-Cleavage to the C=O bond, as well as the IR bands at 1730 and 1710 cm^{-1}, suggested this compound contained an acetyl group and an isolated carbonyl. The ^{13}C NMR spectrum supported this assignment with resonances at δ 170.2 and 212.8. The ^{1}H NMR spectrum showed the presence of four methyl groups (δ 1.11, 1.22, 1.65 and 2.23), a methine α to a bromine (δ 4.31) and a methine α to an acetyl group (δ 4.94). These spectroscopic data, together with the ^{13}C NMR signals at δ 78.7 and 84.1, corresponding to the quaternary carbons C-10 and C-11, respectively, indicated the existence of a pentasubstituted tetrahydrofuran ring. Further support was given by the COSY spectrum of compound **10**, which showed cross peaks correlating the AB doublet of doublets at δ 1.81 and 2.85, corresponding to the protons at C-9, with 10-H at δ 4.94. In addition, the COSY map, together with the coupling constant $J_{2\text{-}1ax} = 12.1$ Hz, established that the cyclohexane ring, as in the case of terpene **8** (*vide supra*), had substitutions identical to those of caespitol. The relative stereochemistry of compound **10** was unambiguously assigned by X-ray crystallographic analysis (Fig. 3). The absolute stereochemistry of compound **10** was established as 2*S*, 3*S*, 6*S*, 8*S*, 10*S* by the anomalous dispersion technique.

The structure of laucapyranoid C (**3**) was determined based on the identity of its hydrodebrominated derivatives **8** and **10**. The ready decomposition of laucapyranoid C to a mixture of compounds **8** and **9** can be rationalized in terms of initial hydration of the unstable natural compound and subsequent bromide elimination with inversion at C-10 to give the isolated epoxide **8**. Further cyclization of the latter gives the tetrahydrofuranyl derivative **9**. The proposed structure **3**, including absolute configuration, for laucapyranoid C is consistent with the transformations outlined in Scheme 1.

6-Hydroxycaespitol (**4**) was obtained upon chromatography with petrol–EtOAc (5:2). This compound showed IR bands at 3400 and 3300 cm^{-1}, which suggested the presence of an intermolecularly hydrogen bonded hydroxyl group. The ^{1}H NMR spectrum of compound **4** resembled that of caespitol (**6**) [9]. However, it showed additional hydroxyl groups at δ 2.98 and 5.31, both D_2O exchangeable. A close similarity between the two compounds was evident in the ^{13}C NMR spectrum: two tertiary carbons α to a bromine atom (δ 52.5 and 59.3), one tertiary carbon having a hydroxyl group (δ 72.3), three quaternary carbons bearing an oxygen atom (δ 65.9, 77.1 and 79.5), one quaternary carbon α to a chlorine moiety (δ 70.8), four methylene groups (δ 28.8, 35.7, 37.3 and 38.2), and four methyl groups (δ 22.0, 23.6, 24.0 and 31.0). High resolution EI mass spectrometry further supported this assignment with a molecular ion at m/z 449.9815 ($C_{15}H_{25}Br_2ClO_3$) displaying the characteristic quartet indicative of the presence of two bromine atoms and one chlorine atom. Moreover, the mass spectral fragmentation pattern was essentially identical to that of caespitol, suggesting similar halogen substitutions in both compounds. The coupling constants $J_{2\text{-}1ax} = 12.0$ Hz and $J_{10\text{-}9ax} = 12.5$ Hz were consistent with both bromine atoms in equatorial positions. Single crystal X-ray diffraction confirmed its structure, including absolute configuration, as depicted in **4**. A stereoview of a single molecule is shown in Fig. 4.

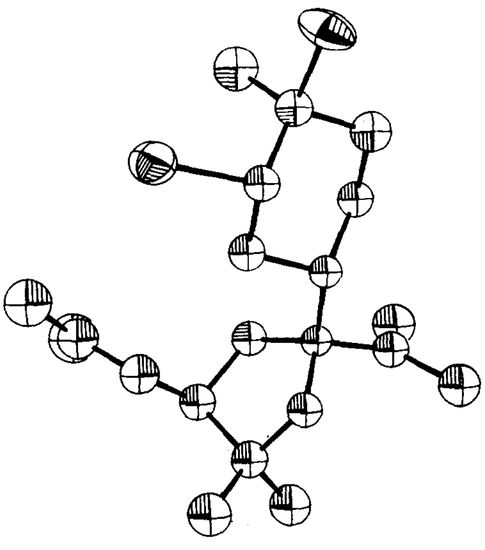
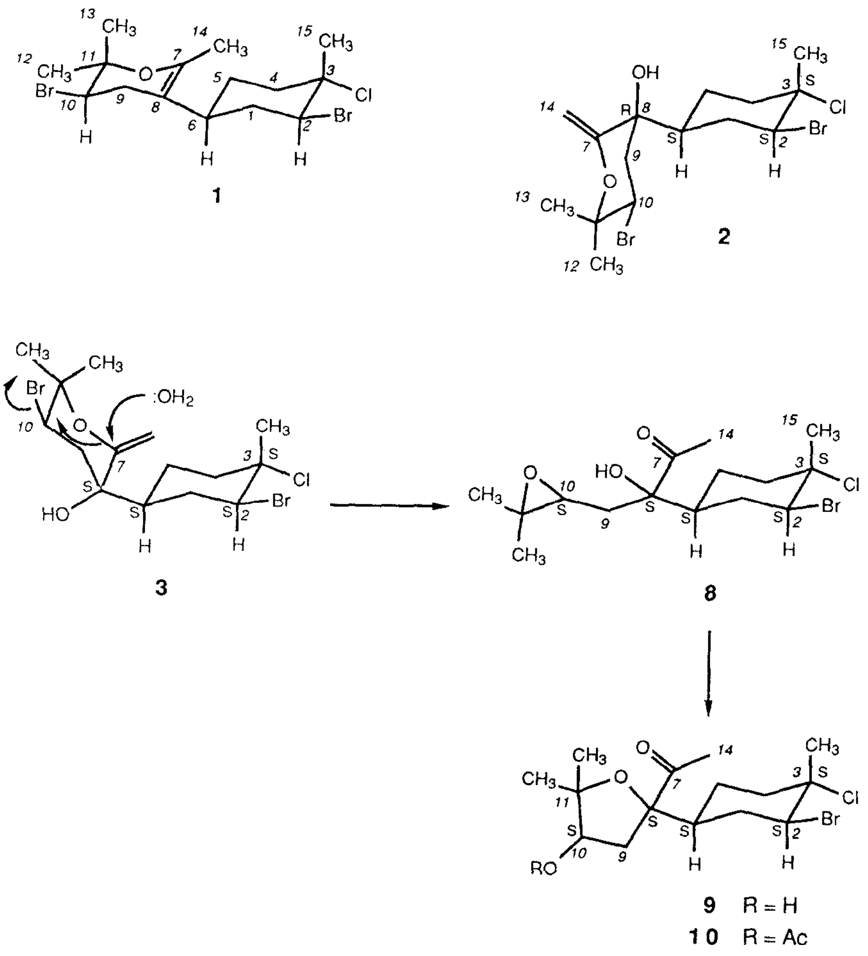


Fig. 3. ORTEP drawing of compound **10**.

Chromatography of the acetone extract with non-polar eluants afforded caespitane (**5**). High resolution EI mass spectrometry gave a molecular ion at m/z 417.9926, again displaying the isotope peak intensity pattern characteristic of the presence of two bromine atoms and one chlorine atom, and established a molecular formula of $C_{15}H_{25}Br_2ClO$. The ^{1}H NMR spectrum of caespitane was similar to that of caespitol (**6**) [9], except for the absence of the 8-H resonance, corresponding to the methine α to a hydroxyl group in compound **6**. This was further confirmed by the lack of a broad hydroxyl stretch band in the IR spectrum of compound **5**. Difference NOE experiments indicated that the relative stereochemistry of caespitane was identical to that of caespitol. A strong NOE was observed for 9_{ax}-H when H-14 was irradiated, suggesting that the methyl group at C-7 was located at an axial position. Likewise, irradiation of H-13 and H-12 resulted in NOE enhancements of 9_{ax}-H and 10-H, respectively, and suggested that the bromine atom on the pyranose ring was attached at the equatorial position in C-10. This was further supported by the large coupling constant $J_{10\text{-}9ax} = 12.4$ Hz. Finally, the *trans*-diequatorial dihalide conformation of the cyclohexane ring was deduced from the coupling constant $J_{2\text{-}1ax} = 12.2$ Hz of the resonance at δ 4.32 attributed to the axial 2-H. These spectroscopic data, therefore, identified caespitane as compound **5**.

Although X-ray crystallography was instrumental in the structure elucidation of these novel sesquiterpenes, the absolute configuration of caespitol (**6**) and isocaespitol (**7**) compounds previously isolated from *L. caespitosa* [9] which show moderate antimicrobial activity, could not be unambiguously determined by this method. Crystals of caespitol, despite belonging to a chiral crystallographic space group, unfortunately failed to show a measurable rotation at the sodium D line. Thus, although the relative configuration of isocaespitol had been previously determined by X-ray crystallography [10] and confirmed by racemic synthesis [17], an unequivocal absolute configuration assignment of this compound was not made since the crystallographic differences between Friedel pairs were small. We have now established the absolute configurations of caespitol and isocaespitol by application of the exciton chirality method. These results are relevant in view of the fact that some groups are already engaged in the stereoselective total synthesis of this type of cytotoxic molecules [2, 12]. Furthermore, these studies are indispensable to the elucidation of the metabolic pathways of these marine metabolites.

The circular dichroic exciton chirality method, a powerful chiroptical approach that complements the Bijvoet X-ray diffraction method, has proven to be an excellent tool for determination of absolute configurations [18, 19]. The allylic benzoate method, based on



Scheme 1.

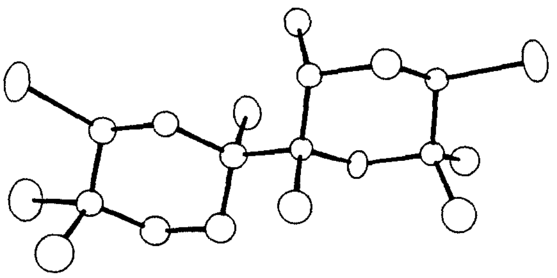
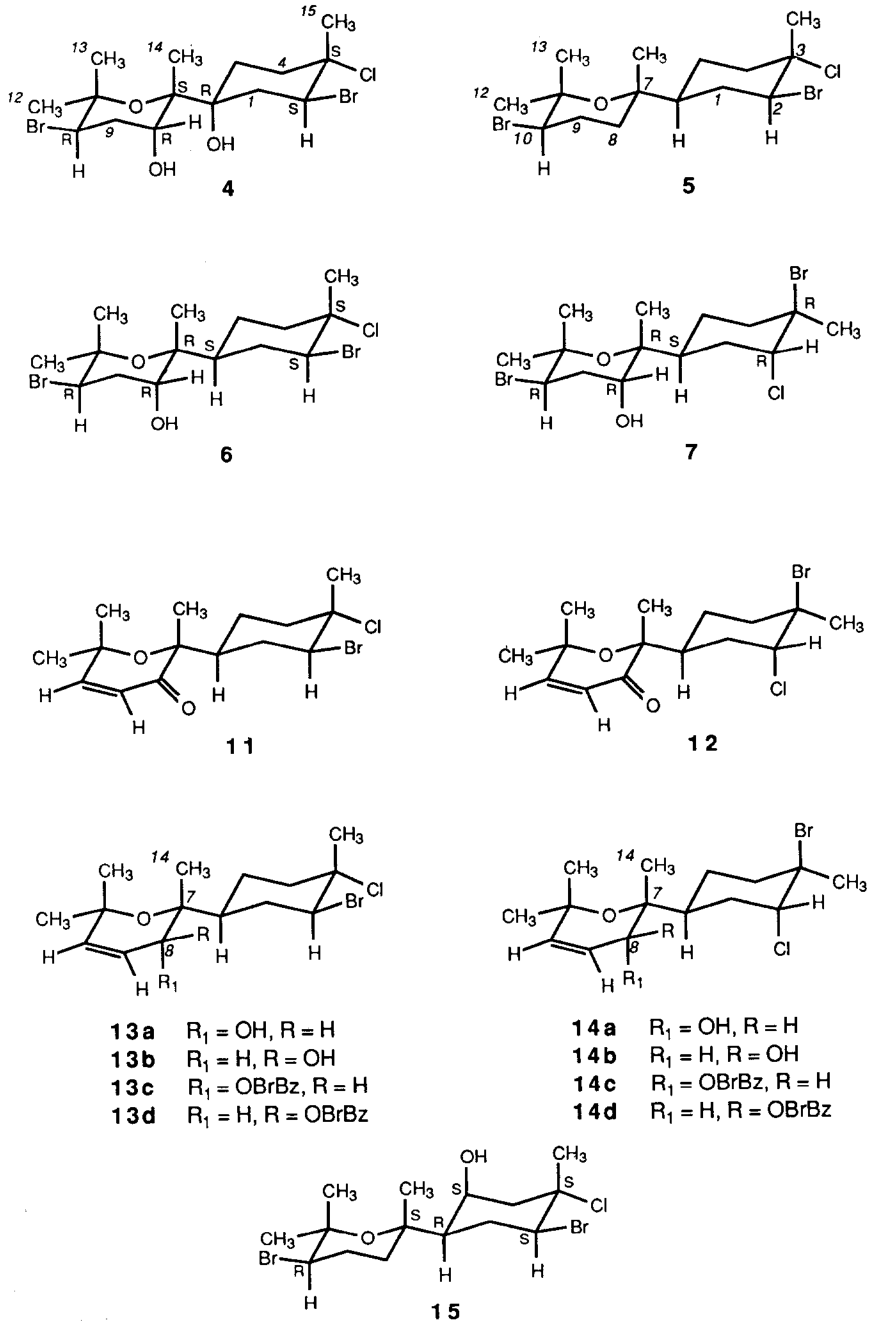


Fig. 4. ORTEP drawing of 6-hydroxycaespitol (4).

coupling between the double bond and benzoate chromophores, has been applied to many natural products containing exocyclic [20], endocyclic [18, 21], and acyclic olefins [22]. In order to apply this chirooptical method, the sesquiterpenes had to be suitably derivatized. In the case of compounds **6** and **7**, this was accomplished by oxidation of the halogenated terpenoids with Jones reagent [23] to the corresponding unstable ketones, which on standing were converted to the unsaturated ketones **11** and **12**, respectively. Reduction with diisobutylaluminum hydride [24] gave both α (**13a**, **14a**) and β(**13b**, **14b**) allylic alcohols, the α-isomer being the major product. Subsequent bromobenzoylation [25] and purification by HPLC afforded the *p*-bromobenzoate derivatives **13c**, **13d**, **14c** and **14d**. The stereochemistry at C-8 of these compounds was determined by NOE difference experiments. Irradiation of the H-14 protons gave rise to 8.7 and 10.9% enhancements of the 8-H signals in α-benzoates **13c** and **14c**, respectively. A similar experiment with the β-benzoate **14d** gave no such enhancement.

Circular dichroic studies [26] of the bromobenzoylated sesquiterpenes showed a negative Cotton effect at 237 nm ($\Delta\varepsilon = -14.9$) [27] for the α-caespitenol bromobenzoate (**13c**), while the β-isomer (**13d**) showed a positive Cotton effect at 238 nm ($\Delta\varepsilon = +6.9$). The corresponding isocaespitenol derivatives displayed similar Cotton effects: $\Delta\varepsilon = -12.8$ at 237 nm for **14c** and $\Delta\varepsilon = +3.0$ at 238 nm for **14d**. Since the signs of the CD Cotton effects represent the chirality between the double bond and the allylic C–O bond [19], this leads to absolute configurations **6** and **7** for caespitol and isocaespitol, respectively. Comparison between caespitol and deodactol, a compound whose absolute stereochemistry was firmly established by X-ray crystallographic techniques [12] as drawn in **15**, showed that all these compounds belong to the same stereochemical series.



Scheme 2.

EXPERIMENTAL

General. All reagents were of the best grade commercially available. Mps: uncorr. Silica gel chromatography was performed on silica gel 60 (32–63 mesh) obtained from ICN Biomedicals. Sephadex LH-20 (25–100 μm particle size) obtained from Pharmacia was used for gel filtration chromatography. HPLC was carried out on a semi prep. silica gel column (5 μm) attached to a Dupont pump and monitored at 254 nm with a Schoeffel SF 770 detector. Preparative and analytical TLC were performed on commercially prepared silica gel glass plates. ^{1}H NMR spectra: 250 and 200 MHz. ^{13}C NMR spectra: 50 MHz. Homonuclear ^{1}H connectivities were determined from double resonance and COSY experiments. Correlation spectroscopy utilized the $(\pi/2 - \Delta - t_1 - \pi/2 - \Delta - t_2)_n$ pulse sequence [27]. Difference NOE experiments used a selective 180° irradiation of a given resonance followed after a delay by a 90° observed pulse. The spectrum was acquired simultaneously with one in which the selective pulse was further downfield. The two spectra were computer substracted to observe the enhancements. Samples for NOE experiments were degassed by bubbling He through the solutions. Low and high resolution mass spectra were determined in either EI (70 eV, 200°) or FAB mode, with a VG MM ZAB-2F spectrometer. Xe provided the primary beam of fast atoms for the FAB spectra, and glycerol–oxalic acid was used as matrix. Low resolution MS spect data: DCI-NH_3. Optical rotations were determined for solns in $CHCl_3$. CD data were recorded on a JASCO J-500 spectropolarimeter interfaced with a JASCO DP500N Data Processor and an IBM-PC.

Collection, extraction and chromatographic separation. Laurencia caespitosa was collected in shallow water at low tide in Punta del Hidalgo, Tenerife, and in the Island of La Graciosa, from May to July, 1983 and 1984. The air-dried alga (1.2 kg) was extracted with cold Me_2CO and solvent was evapd *in vacuo* to afford 32 g of crude extract. Subsequent extractions with Et_2O (3 l) and $CHCl_3$ (3 l) yielded an additional 15.2 g. No significant differences were observed between the latter two extracts.

The Me_2CO extract (32 g) was chromatographed on a silica gel column eluted isocratically with petrol. After an initial 500 ml of void volume, fraction A (500 ml) was collected and solvent evapd *in vacuo* to afford 1.13 g of a solid. Subsequent elution with petrol–EtOAc (9:1, 500 ml), petrol–EtOAc (5:2, 1 l), and petrol–EtOAc (1:1, 2l) to gave three fractions (B–D) containing 5.2, 13.8 and 1.3 g of residue, respectively.

Fraction A (1.13 g) was rechromatographed on a silica gel column with *n*-hexane (50 ml) to afford after solvent evaporation 47 mg of crystalline caespitane (**5**). On further elution with *n*-hexane (100 ml), a colourless oil (320 mg) was collected and was further purified by flash chromatography on silica gel (*n*-hexane). Final purification on prep. TLC (*n*-hexane–EtOAc, 19:1, x3) gave laucapyranoid A (**1**, 18 mg) and furocaespitane [14] (58 mg). By similar chromatographic techniques (*vide supra*) fraction C (13.8 g) afforded 6-hydroxycaespitol (**4**, 230 mg), caespitol (**6**, 4.3 g) and isocaespitol (**7**, 3.4 g).

The Et_2O and $CHCl_3$ extracts (15.2 g) were chromatographed on Sephadex LH-20 using CH_2Cl_2–MeOH (1:1) as eluant. Fractions of 500 ml were collected and pooled together as monitored by TLC analysis (*n*-hexane–EtOAc, 4:1). An air and moisture sensitive fraction (2.8 g) was obtained and was flash chromatographed on silica gel using a *n*-hexane–Et_2O gradient elution. Final purification on Partisil with *n*-hexane–Et_2O (1:1) afforded laucapyranoid B (**2**, 220 mg) as a crystalline solid, and a mixture of laucapyranoids B and C (**2** and **3**, 315 mg) as a very unstable non-crystalline residue. An aliquot (200 mg) of this mixture was treated with Ac_2O–pyridine (1:1) at room temp. overnight. After evapn of the solvent *in vacuo*, the mixture was purified by normal phase flash chromatography (*n*-hexane–Et_2O gradient elution), followed by prep. TLC (*n*-hexane–EtOAc, 7:3) to give the monoacetate **10** (42 mg), the hydrodebrominated terpene **8** (23 mg), and laucapyranoid B (**2**, 15 mg). The dry weight yields were: **1** (0.0015%), **2** (0.02%), **4** (0.02%), **5** (0.0004%), **6** (0.36%), **7** (0.28%), **8** (0.002%), and **10** (0.035%).

Laucapyranoid A (**1**). Mp 118–120°; $[\alpha]_D + 0.5°$ ($CHCl_3$; *c* 0.87); IR ν_{max}^{KBr} cm^{-1}: 1635, 1380, 1220, 1100, 1060, 1020, 980, 963 and 880; ^1H NMR (200 MHz, $CDCl_3$): δ1.27 (*s*, 3H, H-13), 1.37 (*s*, 3H, H-12), 1.56 (*m*, 1H, H-5_{eq}), 1.63 (*m*, 1H, H-6), 1.72 and 1.73 (2*s*, 3H each, H-14 and H-15), 1.72 and 2.47 (*m*, 1H each, H-1's), 1.75 (*m*, 1H, H-5_{ax}), 1.95 (*dd*, 1H, J = 8.7 and 14.5 Hz, H-9_{ax}), 2.03 (*m*, 1H, H-4_{ax}), 2.39 (*m*, 1H, H-4_{eq}), 2.52 (*dd*, 1H, J = 5.8 and 14.5 Hz, H-9_{eq}), 4.05 (*dd*, 1H, J = 5.8 and 8.7 Hz, H-10), 4.38 (*dd*, 1H, J = 4.8 and 12.2 Hz, H-2); ^{13}C NMR (50 MHz, $CDCl_3$): δ16.5 (C-14), 20.6 (C-13), 24.0 (C-15), 26.9 (C-12), 27.4 (C-5), 30.5 (C-9), 40.0 (C-1), 40.3 (C-6), 42.8 (C-4), 54.1 (C-10), 62.6 (C-2), 71.1 (C-3), 75.3 (C-11), 104.7 (C-8), 143.9 (C-7); EIMS *m/z* (rel. int.): 418, 416, 414, 412 $[M]^+$ (3, 12, 18, 8), 337, 335, 333 $[M-Br]^+$ (19, 75, 58), 300, 298 $[M-Br-Cl]^+$ (3, 3), 299, 297 $[M-Br-HCl]^+$ (4, 4) 295, 293, 291 $[M-Br-C_3H_6]^+$ (1, 6, 5), 255, 253 $[M-Br-HBr]^+$ (2, 5), 232, 230 (19, 19), 217 (7), 199 (3), 175 (13), 151 (14), 119 (13), 109, 107 (13, 13), 95 (16), 93 (36), 91 (21), 81 (14), 79 (16), 69 (22), 55 (24), 43 (100); High resolution EIMS: *m/z* 415.9770 (415.9765, calc. for $C_{15}H_{23}{}^{81}Br_2{}^{35}ClO$).

Laucapyranoid B (**2**). Mp 97–98°; $[\alpha]_D + 11.0°$ ($CHCl_3$; *c* 1.12); IR ν_{max}^{KBr} cm^{-1}: 3580, 3400, 3150, 1640, 1450, 1380, 1250, 1100, 985, 950 and 880; ^1H NMR (200 MHz, $CDCl_3$): δ1.31 (*s*, 3H, H-13), 1.44 (*s*, 3H, H-12), 1.66 (*s*, 3H, H-15), 2.36 (*ddd*, 1H, J = 3.4, 3.4 and 13.6 Hz, H-4_{eq}), 2.54 (*dd*, 1H, J = 4.2 and 13.3 Hz, H-9_{eq}), 4.00 (*dd*, 1H, J = 4.2 and 13.3 Hz, H-10), 4.37 (*dd*, 1H, J = 4.6 and 12.4 Hz, H-2), 4.60 and 4.64 (each *s*, 1H, H-14's); ^{13}C NMR (50 MHz, $CDCl_3$): δ18.9 (C-13), 23.3 (C-5), 24.0 (C-15), 28.2 (C-12), 29.9 (C-9), 35.0 (C-1), 40.8 (C-6), 42.3 (C-4), 51.2 (C-10), 63.4 (C-2), 71.8 (C-3), 74.8 (C-11), 80.3 (C-8), 97.3 (C-14), 159.5 (C-7); EIMS *m/z* (rel. int.): 353, 351, 349 $[M-Br]^+$ (1, 3, 2), 316, 314 $[M-Br-Cl]^+$ (1, 1), 315, 313 $[M-Br-HCl]^+$ (4, 4), 234 $[M-2Br-HCl]^+$ (4), 222 (100), 220 (100), 139 (19), 136 (11), 123 (70); High resolution FABS: *m/z* 431.9710 (431.9714, calc. for $C_{15}H_{23}{}^{81}Br_2{}^{35}ClO_2$).

Compound **8**. Mp 112–114°; $[\alpha]_D + 14.1°$ ($CHCl_3$; *c* 0.69); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3540, 3400, 1700, 1380, 1355, 1130 and 1040; ^1H NMR (200 MHz, $CDCl_3$): δ1.26 (*s*, 6H, H-12 and H-13), 1.68 (*s*, 3H, H-15), 2.29 (*s*, 3H, H-14), 2.48 (*ddd*, 1H, J = 3.3, 3.3 and 13.5 Hz, H-4_{eq}), 2.70 (*dd*, 1H, J = 2.7 and 8.6 Hz, H-10), 4.19 (*s*, 1H, OH), 4.29 (*dd*, 1H, J = 4.7 and 12.3 Hz, H-2); ^{13}C NMR (50 MHz, $CDCl_3$): δ19.1 (C-12), 23.0 (C-5), 23.9 (C-15), 24.8 (C-13), 31.1 (C-14), 35.5 (C-9), 35.7 (C-1), 42.3 (C-4), 44.8 (C-6), 58.2 (C-11), 59.3 (C-10), 62.1 (C-2), 71.1 (C-3), 81.5 (C-8), 210.9 (C-7); EIMS *m/z* (rel. int.): 327, 325, 323 $[M-MeCO]^+$ (1, 4, 3), 241, 239, 237 $[M-C_7H_{13}O_2]^+$ (3, 12, 10), 213 (1), 211 (4), 209 (8), 207 (5), 175, 173 (5, 5), 159 (6), 157 (16), 129 (28), 123 (20), 111 (9), 95 (80); High resolution EIMS: *m/z* 323.0412 (323.0414, calc. for $C_{13}H_{21}{}^{79}Br{}^{35}ClO_2$).

Compound **10**. Mp 98–100°; $[\alpha]_D - 12.3°$ ($CHCl_3$; *c* 0.95); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730, 1710, 1460, 1370, 1250, 1150, 1107, 1060 and 1035; ^1H NMR (200 MHz, $CDCl_3$): δ1.10 (*m*, 1H, H-6), 1.11 and 1.22 (2*s*, 3H each, H-12 and H-13), 1.44 (*m*, 1H, H-5_{eq}), 1.65 (*s*, 3H, H-15), 1.70 (*m*, 1H, H-5_{ax}), 1.75 (*m*, 1H, H-1_{ax}), 1.81 (*dd*, 1H, J = 3.1 and 14.8 Hz, H-9), 1.99 (*ddd*, 1H, J = 4.3, 13.7 and 13.8 Hz, H-4_{ax}), 2.10 (*s*, 3H, Ac-Me), 2.23 (*s*, 3H, H-14), 2.30 (*ddd*, 1H, J = 3.4, 3.4 and 13.7 Hz, H-4_{eq}), 2.43 (*m*, 1H, H-1_{eq}), 2.85 (*dd*, 1H, J = 6.7 and 14.8 Hz, H-9), 4.31 (*dd*, 1H, J = 4.2 and 12.1 Hz, H-2), 4.94 (*dd*, 1H, J = 3.1 and 6.7 Hz, H-10); ^{13}C NMR (50 MHz, $CDCl_3$): δ21.1 (C-13), 22.8 (C-12), 24.1 (C-15), 24.5 (C-5), 26.2 (C-14), 34.6 (C-9), 25.6 (Ac-Me), 36.2 (C-1), 42.5 (C-4), 44.0 (C-6), 62.7 (C-2), 71.2 (C-3), 78.7 (C-10), 84.1 (C-11), 90.8 (C-8), 170.2 (Ac-C =O), 212.8 (C-7); EIMS *m/z* (rel. int.): 369, 367, 365 $[M-MeCO]^+$ (< 1, 1, 1), 309, 307, 305 $[M-MeCO-AcOH]^+$ (17, 68, 52), 271, 269 $[M-MeCO-AcOH-Cl]^+$ (3, 3), 192 (9), 191 (9), 140 (8), 123 (29), 105 (5), 97 (14), 43 $[MeCO]^+$ (100); High resolution FABMS: *m/z* 410.0661 (410.0684, calc. for $C_{17}H_{26}{}^{81}Br{}^{35}ClO_4$).

6-Hydroxycaespitol (**4**). Mp 152–153°; $[\alpha]_D + 11.7°$ ($CHCl_3$: *c* 0.29); IR ν_{max}^{KBr} cm^{-1}: 3400, 3300, 1380, 1210, 1120, 1100, 1060, 1020, 960, 845 and 830; ^1H NMR (200 MHz, $CDCl_3$): δ1.18 (*s*, 3H, H-14), 1.36 (*s*, 3H, H-13), 1.40 (*s*, 3H, H-12), 1.65 (*s*, 3H, H-15), 2.98 (*br s*, 1H, D_2O-exchangeable, OH), 3.70 (*br s*, 1H, H-8), 4.43 (*dd*, 1H, J = 5.0 and 12.0 Hz, H-2), 4.69 (*dd*, 1H, J = 5.0 and 12.5 Hz, H-10), 5.31 (*br s*, 1H, D_2O exchangeable, OH); ^{13}C NMR (50 MHz, $CDCl_3$): δ22.0 (C-14), 23.6 (C-15), 24.0 (C-13), 28.8 (C-5), 31.0 (C-12), 35.7 (C-1), 37.3 (C-9), 38.2 (C-4), 52.5 (C-10), 59.3 (C-2), 65.9 (C-6), 70.8 (C-3), 72.3 (C-8), 77.1 (C-11), 79.5 (C-7); EIMS *m/z* (rel. int.): 273, 271, 269 $[M-C_6H_{10}OBr]^+$ (< 1, 2, 1), 255, 253, 251 $[M-C_6H_{10}OBr-H_2O]^+$ (< 1, 1, 1), 235, 233 $[M-C_6H_{10}OBr-HCl]^+$ (3, 3), 223, 221 $[C_8H_{11}OBr]^+$ (10, 10), 206, 204 $[M-C_6H_{10}OBr-H_2O-Cl]^+$ (12, 12), 179, 177 (3, 3), 149 (10), 137 (14), 125 (35), 123 (21), 109 (14), 55 (23), 43 (100); High resolution EIMS: *m/z* 449.9815 (449.9820, calc. for $C_{15}H_{25}{}^{81}Br_2{}^{35}ClO$).

Caespitane (**5**). Mp 82–84°; $[\alpha]_D + 39.8°$ ($CHCl_3$; *c* 0.89); IR ν_{max}^{KBr} cm^{-1}: 1410, 1384, 1370, 1235, 1125, 1105 and 1025; ^{1}H NMR (200 MHz, $CDCl_3$): δ1.19 (*s*, 3H, H-14), 1.27 (*s*, 3H, H-13), 1.39 (*s*, 3H, H-12), 1.67 (*s*, 3H, H-15), 2.04 (*dddd*, 1H, $J = 3.5$, 12.4, 13.5 and 13.5 Hz, H-9_{ax}), 3.82 (*dd*, 1H, $J = 4.3$ and 12.4 Hz, H-10), 4.32 (*dd*, 1H, $J = 4.5$ and 12.4 Hz, H-2); ^{13}C NMR (50 MHz, $CDCl_3$): δ22.9 (C-14), 23.4 (C-13), 23.7 (C-5), 24.1 (C-15), 28.3 (C-8), 31.2 (C-12), 36.1 (C-1), 35.3 (C-9), 42.8 (C-4), 51.1 (C-6), 58.3 (C-10), 64.0 (C-2), 71.8 (C-3), 75.2 (C-11), 77.2 (C-7); EIMS: *m/z* (rel. int.) 405, 403, 401, 399 $[M-Me]^+$ (< 1, 2, 3, 1), 362, 360, 358, 356 $[M-C_3H_6O]^+$ (< 1, 3, 3, < 1), 302, 300 $[M-Br-Cl]^+$ (1, 1), 252, 250 (9, 8), 207, 205 (73, 75), 171 (4), 149, 147 (5, 5), 135 (26), 125 (62), 119 (14), 107 (48), 105 (12), 95 (12), 93 (3), 55 (37), 53 (29), 43 (100); High resolution EIMS: *m/z* 417.9926 (417.9922, calc. for $C_{15}H_{25}{}^{81}Br_2{}^{35}ClO$).

Caespitol (**6**). Spectroscopic data were reported previously [9].

Oxidation of caespitol (**6**). To a soln of **6** (6.7 mg, 15.5 μmol) in Me_2CO (1 ml) Jones reagent (25 ml, 8N) was added, and the mixture was stirred for 30 min at room temp. Subsequently, the reaction was quenched with *i*-PrOH (2 drops). The pptd green salt was filtered and the filtrate neutralized with satd aq. $NaHCO_3$. The filtrate was then concd *in vacuo* and purified on a microflash silica gel column (0.55 i.d. × 2.0 cm) with CH_2Cl_2. The eluate was concentrated to dryness and on standing at room temp. overnight afforded 4.1 mg (11.7 μmol) of **11**. Yield 76%; R_f 0.30 (*n*-hexane–EtOAc, 9:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ1.32 (*s*, 3H, H-14), 1.36 and 1.41 (2*s*, 3H each, H-12 and H-13), 1.66 (*s*, 3H, H-15), 4.34 (*dd*, 1H, $J = 4.5$ and 12.3 Hz, H-2), 5.89 (*d*, 1H, $J = 10.6$ Hz, H-10), 6.63 (*d*, 1H, $J = 10.6$ Hz, H-9).

Reduction of compound **11**. An aliquot of DIBAL in *n*-hexane (1 M, 40 μmol) was added dropwise to a soln of compound **11** (4.1 mg, 11.7 μmol) in 1 ml dry THF. After 1 hr stirring at room temp under N_2, the reaction was quenched with excess MeOH. The pptd salt was removed by filtration and washed with MeOH. The combined filtrate was purified on a silica gel column (0.55 i.d. × 7.0 cm, *n*-hexane → *n*-hexane–EtOAc, 1:1 to give alcohols **13a** and **13b** (3.2 mg, 9.1 μmol), yield 78%. Compound **13a**, R_f 0.19 (*n*-hexane–EtOAc, 90:10); ^{1}H NMR (250 MHz, $CDCl_3$): δ1.05 (*s*, 3H, H-14), 1.22 (*s*, 6H, H-12 and H-13), 1.69 (*s*, 3H, H-15), 3.55 (*dd*, 1H, $J = 6.2$ and 10.5 Hz, H-8), 4.39 (*dd*, 1H, $J = 4.5$ and 12.3 Hz, H-2), 5.80 (*d*, 1H, $J = 10.2$ Hz, H-10), 5.95 (*dd*, 1H, $J = 6.2$ and 10.2 Hz, H-9). Compound **13b**, R_f 0.11 (*n*-hexane–EtOAc, 9:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ1.12 and 1.14 (2*s*, 3H each, H-12 and H-13), 1.22 (*s*, 3H, H-14), 1.69 (*s*, 3H, H-15), 4.12 (*ddd*, 1H, $J = 1.9$, 2.2 and 8.4 Hz, H-8), 4.36 (*dd*, 1H, $J = 4.5$ and 12.6 Hz, H-2), 5.56 (*dd*, 1H, $J = 1.9$ and 10.3 Hz, H-10, 5.69 (*dd*, 1H, $J = 2.2$ and 10.3 Hz, H-9).

Benzoylation of caespitenols **13a** and **13b**. 4-Bromobenzoyl chloride (4.4 mg, 20 μmol) and silver triflate (5.1 mg, 20 μmol) were added to a soln of caespitenols **13a** and **13b** (1.4 mg, 4.0 μmol) in dry CH_2Cl_2 (1 ml) and dry pyridine (100 μl). The suspension was stirred for 1 hr at room temp. under N_2 and the excess reagent destroyed with MeOH (2 drops). The pptd silver salt was filtered and washed with MeOH. Concentration of the filtrate *in vacuo* and subsequent purification by HPLC (silica, 1.0 i.d. × 25 cm, *n*-hexane–EtOAc, 39:1, 2 ml/min, 254 nm) afforded the benzoates **13c** (0.8 mg, 1.5 μmol) and **13d** (0.5 mg, 0.9 μmol). Yield of **13c**, 38%; $R_t = 25.0$ min; ^{1}H NMR (250 MHz, $CDCl_3$): δ1.16 (*s*, 3H, H-14), 1.26 and 1.27 (2*s*, 3H each, H-12 and H-13), 1.61 (*s*, 3H, H-15), 4.15 (*dd*, 1H, $J = 4.4$ and 12.5 Hz, H-2), 4.95 (*d*, 1H, $J = 6.0$ Hz, H-8), 5.94 (*d*, 1H, $J = 10.1$ Hz, H-10), 6.05 (*dd*, 1H, $J = 6.0$ and 10.1 Hz, H-9), 7.60 (*d*, 2H, $J = 8.5$ Hz, benzoate-3,5-H's), 7.88 (*d*, 2H, $J = 8.5$ Hz, benzoate-2, 6-H's); UV λ_{max}^{MeCN} nm 245; CD: $\Delta\varepsilon_{237} - 14.9$ (MeCN; *c* 38.0 μM)*; DCIMS (NH_3) *m/z* (rel. int.): 556, 554, 552, 550 $[M+NH_4]^+$ (1, 3, 6, 6), 539, 537, 535, 533 $[M+H]^+$ (1, 2, 3, 2), 457, 455, 453 $[MH-HBr]^+$ (1, 2, 2), 421, 419 $[MH-Br-Cl]^+$ (5, 5), 337, 335, 333 $[MH-BrBzOH]^+$ (30, 100, 80). Yield of **13d**, 24%; $R_t = 17.0$ min; ^{1}H NMR (250 MHz, $CDCl_3$): δ1.21 (*s*, 3H, H-14), 1.28 and 1.30 (2*s*, 3H each, H-12 and H-13), 1.66 (*s*, 3H, H-15), 4.30 (*dd*, 1H, $J = 4.6$ and 12.6 Hz, H-2), 5.55 (*dd*, 1H, $J = 1.8$ and 2.2 Hz, H-8), 5.57 (*dd*, 1H, $J = 1.8$ and 10.2 Hz, H-10), 5.81 (*dd*, 1H, $J = 2.2$ and 10.2 Hz, H-9), 7.59 (*d*, 2H, $J = 8.4$ Hz, benzoate-3,5-H's), 7.85 (*d*, 2H, $J = 8.4$ Hz, benzoate-2,6-H's); UV λ_{max}^{MeCN} nm 245; CD: $\Delta\varepsilon_{238} + 6.9$ (MeCN; *c* 47.7 μM)*; DCIMS (NH_3) *m/z* (rel. int.): 556, 554, 552, 550 $[M+NH_4]^+$ (< 1, 1, 2, 1), 539, 537, 535, 533 $[M+H]^+$ (< 1, 1, 2, 1), 457, 455, 453 $[MH-HBr]^+$ (1, 3, 3), 421, 419 $[MH-Br-Cl]^+$ (10, 8), 337, 335, 333 $[MH-BrBzOH]^+$ (25, 100, 80).

Isocaespitol (**7**). Spectroscopic data has been previously described [10].

Oxidation of isocaespitol (**7**). Isocaespitol (4.0 mg, 9.3 μmol) was oxidized with Jones reagent to give 2.8 mg (8.0 μmol) of compound **12** as described for **6** (*vide supra*). Yield 87%; R_f 0.36 (*n*-hexane–EtOAc, 9:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ1.31 (*s*, 3H, H-14), 1.39 and 1.41 (2*s*, 3H each, H-12 and H-13), 1.90 (*s*, 3H, H-15), 4.52 (*br s*, 1H, H-2), 5.91 (*d*, 1H, $J = 10.6$, H-10), 6.83 (*d*, 1H, $J = 10.6$ Hz, H-9).

Reduction of compound **12**. The procedure was similar to the reduction of **11** (*vide supra*). Compound **12** (2.8 mg, 8.0 μmol) was reduced with DIBAL to the unsaturated alcohols **14a** and **14b** (2.1 mg, 6.0 μmol), the latter being the major product. Yield 75%. Compound **14a**, R_f 0.24 (*n*-hexane–EtOAc, 9:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ1.11 (*s*, 3H, H-14), 1.24 (*s*, 6H, H-12 and H-13), 1.93 (*s*, 3H, H-15), 3.54 (*dd*, 1H, $J = 6.2$ and 10.3 Hz, H-8), 4.50 (*br s*, 1H, H-2), 5.80 (*d*, 1H, $J = 10.1$ Hz, H-10), 5.95 (*dd*, 1H, $J = 6.2$ and 10.1 Hz, H-9).

Benzoylation of **14a** *and* **14b**. Without purification these alcohols were benzoylated as described for caespitenol (*vide supra*). The resulting benzoates (1.3 mg, 2.43 μmol, 66%) were purified by HPLC (silica, 1.0 i.d. × 25 cm, *n*-hexane–EtOAc, 98:2, 2 ml/min, 254 nm). Compound **14c**, $R_t = 21.3$ min, ^{1}H NMR (250 MHz, $CDCl_3$): δ1.20 (*s*, 3H, H-14), 1.28 (*s*, 6H, H-12 and H-13), 1.85 (*s*, 3H, H-15), 4.36 (*br s*, 1H, H-2), 4.99 (*d*, 1H, $J = 5.6$ Hz, H-8), 5.96 (*d*, 1H, $J = 10.0$ Hz, H-10), 6.02 (*dd*, 1H, $J = 5.6$ and 10.0 Hz, H-9), 7.52 (*d*, 2H, $J = 8.6$ Hz, benzoate-3,5-H's), 7.90 (*d*, 2H, $J = 8.6$ Hz, benzoate-2,6-H's); UV λ_{max}^{MeCN} nm: 245; CD: $\Delta\varepsilon_{237} - 12.8$ (MeCN; *c* 42.5 μM); DCIMS (NH_3) *m/z* (rel. int.): 556, 554, 552, 550 $[M+NH_4]^+$ (15, 57, 80, 38), 539, 537, 535, 533 $[M+H]^+$ (16, 58, 100, 53), 457, 455, 453 $[MH-HBr]^+$ (21, 27, 8), 421, 419 $[MH-Br-Cl]^+$ (85, 83), 337, 335, 333 $[MH-BrBzOH]^+$ (18, 70, 38). Compound **14d**, $R_t = 15.7$ min; ^{1}H NMR (250 MHz, $CDCl_3$): δ1.23 (*s*, 3H, H-14), 1.30 (*s*, 6H, H-12 and H-13), 1.88 (*s*, 3H, H-15), 4.49 (*br m*, 1H, H-2), 5.51 (*dd*, 1H, $J = 1.7$ and 2.4 Hz, H-8), 5.65 (*dd*, 1H, $J = 2.4$ and 10.2 Hz, H-10), 5.84 (*dd*, 1H, $J = 1.7$ and 10.2 Hz, H-9), 7.58 (*d*, 2H, $J = 8.6$ Hz, benzoate-3,5-H's), 7.86 (*d*, 2H, $J = 8.6$ Hz, benzoate-2,6-H's): UV λ_{max}^{MeCN} nm: 247; CD: $\Delta\varepsilon_{238} + 3.0$ (MeCN; *c* 27.4 μM); DCIMS (NH_3) *m/z* (rel. int.): 556, 554, 552, 550 $[M+NH_4]^+$ (5, 25, 46, 21), 539, 537, 535, 533 $[M+H]^+$ (10, 42, 85, 28), 457, 455, 453 $[MH-HBr]^+$ (31, 37, 9), 421, 419 $[MH-Br-Cl]^+$ (96, 100), 337, 335, 333 $[MH-BrBzOH]^+$ (25, 100, 58).

X-Ray structure analysis. Laucapyranoid B (**2**) crystallized from CH_2Cl_2–*n*-hexane as prisms in the space group $P2_12_12_1$, $Z = 4$, with unit cell dimensions $a = 8.024$ (4), $b = 8.773(3)$, c

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* CD Spectra were obtained in MeCN rather than in MeOH to avoid potential ester exchange during measurements [26]. The concentrations of the CD samples were determined from the UV spectra using the ε value of 21 300 for the mono-*p*-bromobenzoate chromophore [22].

$= 24.608(13)$ Å. The calculated density was 1.65 g/cm^3. A total of 864 unique reflections, 746 with $I > 3\sigma$ (I) treated as observed, were measured. Final $R = 0.076$ with anisotropic heteroatoms, isotropic carbons and fixed isotropic contribution for H's. The absolute configuration was established as compound **2** by using 19 Bijvoet pairs with $10. < F_o < 60.$, $F_o > 15\sigma(F_o)$ and $0.20 < \sin\theta/\lambda < 0.45$. The averaged Bijvoet differences are 5.7 for the right enantiomer vs 6.9 for the wrong one. Fig. 1 shows an ORTEP plot of the molecule.

Compound **8** crystallized from *n*-hexane as plates in the monoclinic system, space group $P2_1$, $a = 7.980(8)$, $b = 10.262(8)$, $c = 11.048(12)$ Å, $\beta = 110.4$ (1)°, $V = 874$ Å^3, $Z = 2$, calculated density 1.44 g/cm^3. A total of 536 unique reflections were measured as described above. After corrections for Lorentz and polarization factors, all of them were treated as observed with $I > 3\sigma$ (I). The structure was solved in the same way as stated above. Final refinement with anisotropic halogen, isotropic carbon and oxygen atoms and fixed isotropic contribution by hydrogens, converged to residual of $R = 0.061$. The absolute configuration, shown in Fig. 2, was established by using 15 more significant Bijvoet pairs in the range $F_o > 10\sigma(F_o)$, $15. \leqslant F_o \leqslant 60.$ and $0.20 \leqslant \sin\theta/\lambda \leqslant 0.58$. The averaged Bijovet differences are 0.31 for the right enantiomer vs 3.43 for the wrong one.

Compound **10** crystallized from *n*-hexane in the orthorhombic system, space group $P2_12_12_1$, $a = 5.918(1)$, $b = 27.364(14)$, $c = 11.573(1)$ Å, $V = 1874$ Å^3, $Z = 4$, calculated density 1.45 g/cm^3. A total of 1152 independent reflections were measured under the same conditions described above; after corrections for Lorentz and polarization factors, 1122 were judged as observed with $I > 3\sigma$ (I). The structure was solved as for the preceding compounds. Final refinement with anisotropic halogen atoms, isotropic oxygen and carbon atoms, and fixed isotropic contribution for hydrogen atoms converged to a residual of $R = 0.040$. The absolute configuration was established by comparison of 50 Bijvoet pairs, with $F_o > 5\sigma$ (F_o), which are in the range $10. \leqslant F_0 \leqslant 50$ and $0.20 \leqslant \sin\theta/\lambda \leqslant 0.60$. The averaged Bijvoet differences are 0.36 for the right enantiomer (shown in Fig. 3) *vs* 4.06 for the wrong one. For these two later compounds tables in the supplementary material give atom coordinates, anisotropic temperature factors, bond lengths, bond angles, and hydrogen coordinates.

6-Hydroxycaespitol (**4**) crystallized from CH_2Cl_2–*n*-hexane as plates in the space group $P2_12_12_1$, $Z = 4$, with unit cell dimensions $a = 6.987(4)$, $b = 11.256(2)$, $c = 22.778(3)$ Å. The calculated density was found to be 1.66 gcm^{-3}. A total of 1082 unique reflections, 1028 with $I > 3\sigma$ (I) treated as observed, were measured on an automated four-circle diffractometer using monochromatic copper radiation. The structure was solved by direct methods (MULTAN 80) and Fourier synthesis (X Ray 76). Final refinement with anisotropic halogen and oxygen atoms, isotropic carbon and fixed isotropic contribution for hydrogen one, converged to a conventional crystallographic residual of $R = 0.037$. The absolute configuration was determined by comparison of the more significant 49 Bijvoet pairs with $F_o > 15\sigma$ (F_o). The averaged Bijvoet differences are 0.97 for the right enatiomer *vs* 3.93 for the wrong one. Fig. 4 shows an ORTEP plot of the molecule and tables in the supplementary material section give atom coordinates, anisotropic temperature factors, bond lengths and bond angles.

X-Ray crystallographic data of compounds **2**, **8**, **10** and **4** have been submitted to the Cambridge X-Ray Crystallographic Centre.

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