Synthetic Approach to Exo-Endo Cross-Conjugated Cyclohexadienones and Its Application to the Syntheses of Dehydrobrachylaenolide, Isodehydrochamaecynone, and *trans*-Isodehydrochamaecynone

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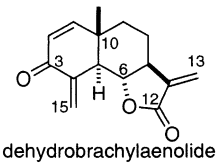
Methodology for synthesis of exo-endo cross-conjugated dienones with *trans*- and *cis*-decalin systems has been reported. Bromination of the silyl enol ether of α′-methyl α,*β*-unsaturated ketones with PTAB and successive dehydrobromination of the resulting α′-bromo-α′-methyl α,*β*-unsaturated ketones under three conditions (DBU/PhH; TBAF/THF; Li_2CO_3, LiBr/DMF) gave the desired exo-endo cross-conjugated dienones in good yield. This method was applied to the syntheses of dehydrobrachylaenolide (**1**), isodehydrochamaecynone (**5c**), and *trans*-isodehydrochamaecynone (**11**) starting from tuberiferine (**7**), chamaecynone (**5a**), and *trans*-chamaecynone (**9**). Eudesmanolides possessing an α-methylene *γ*-lactone moiety, i.e., **1**, **7**, and **13**, exhibited significant inhibitory activity toward the induction of the intercellular adhesion molecule-1 (ICAM-1). Compound **1** showed greater activity than **7** and **13**. All compounds possessing an ethynyl group, **5d**, **9**, **11**, and **14**, showed the same degree of termiticidal activity, and the exo-endo cross-conjugated dienone structure in **11** had no influence on the activity.

A series of eudesmane type natural products possesses an exo-endo cross-conjugated cyclohexadienone structure in the A ring, such as dehydrobrachylaenolide (**1**),[1] gerin,[2]

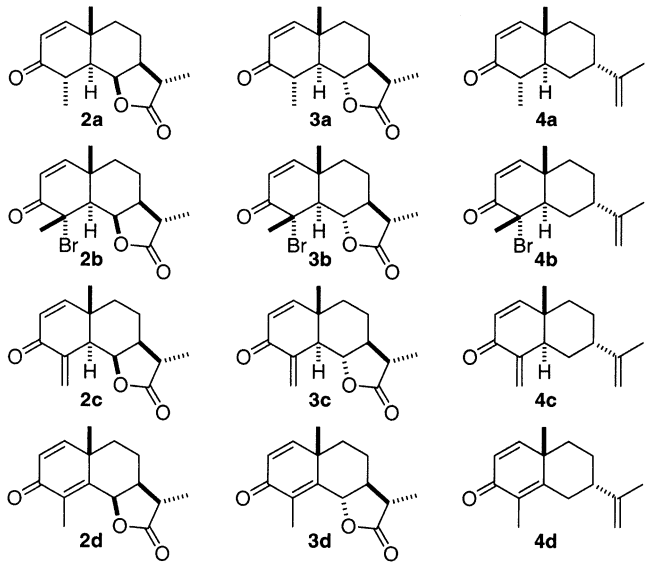


dehydrobrachylaenolide (**1**)

encelin,[3] virginin,[4] and farinosin.[5] Although the biological activities of these compounds have not been reported, they are expected to show some activities because they have a Michael acceptor, the active site in the form of an exo-endo cross-conjugated dienone, in addition to α-methylene *γ*-lactone, α-methylene ester, and α-methyl *γ*-lactone moieties. It is well known that biologically active compounds often express their activities by binding the nucleophilic portion of biomolecules such as the cysteine residues of protein. Exo-endo cross-conjugated dienones are also important as synthetic intermediates in the preparation of biologically active natural products. Thus exo-endo cross-conjugated cyclopentadienones were reported as synthetic intermediates for hirsutic acid and coriolin.[6,7] We have also reported the effective use of isodehydrochamaecynone (**5c**),[8] which possesses an exo-endo cross-conjugated cyclohexadienone moiety, in the synthesis of dehydrochamaecynenol[8] and norsesquibenihiol.[8] The crucial step of this conversion was the efficient preparation of **5c**, and various attempts to improve the yield at that time were unsuccessful.

Results and Discussion

As shown in Figure 1, a general synthetic method for the exo-endo cross-conjugated dienone (structure **c**) from the corresponding α′-methyl α,*β*-unsaturated ketone (structure **a**) in *trans*- and *cis*-decalin derivatives has not been reported in the literature. Because of the interest in the expected biological activities and synthetic use of the compounds possessing structure **c**, we wanted to establish a general synthetic method for this functional group starting from structure **a**. After several unsuccessful attempts,[9] we found that enolsilylation[10] of compounds **2a**, **3a**, and **4a** with trimethylsilyl trifluoromethanesulfonate (TMSOTf) and Et_3N in CH_2Cl_2 and successive treatment of the resulting silyl enol ethers with phenyltrimethylammonium tribromide (PTAB) gave the α′-bromo-α′-methyl α,*β*-unsaturated ketones **2b**, **3b**, and **4b** in 86%, 91%, and 67% yields, respectively. Additional functional groups in



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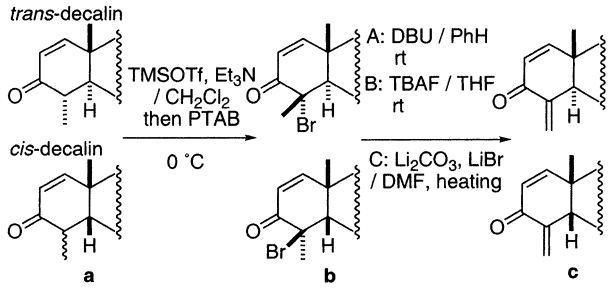
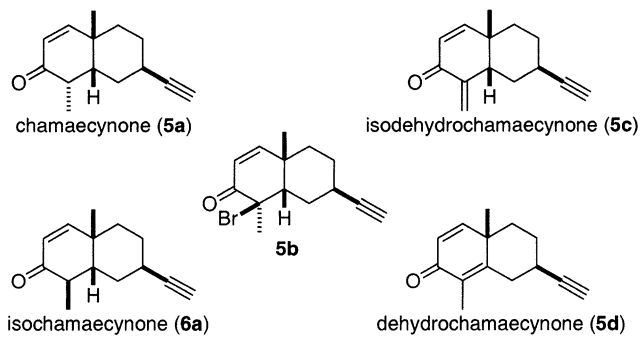


Figure 1. Conversion of α′-methyl α,β-unsaturated ketones **a** with *trans*- and *cis*-decalin systems to exo-endo cross-conjugated dienones **c**.

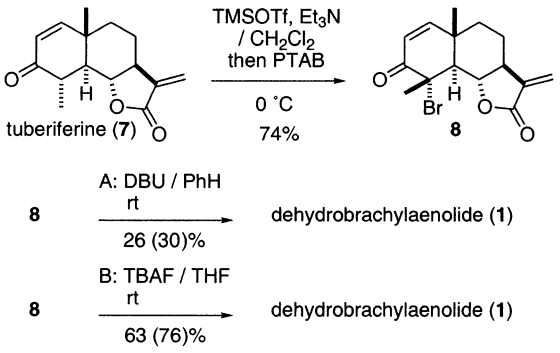
the molecule such as a *cis*-fused γ-lactone, *trans*-fused γ-lactone, or isopropenyl groups did not affect the results. There are three choices for dehydrobromination of α′-bromo-α′-methyl α,β-unsaturated ketone (structure **b**) to the desired exo-endo cross-conjugated dienone (structure **c**): (A) DBU in PhH at room temperature; (B) tetrabutylammonium fluoride (TBAF) in THF at room temperature; (C) Li_2CO_3, LiBr in DMF at 120 °C. The reaction must be controlled by E2 type elimination in order to obtain the desired structure **c**. Since the structure **c** is a good Michael acceptor, the bases employed in the dehydrobromination reactions must be a hard base such as fluoride anion (F^-) or a bulky base such as DBU to avoid 1,4-addition of the base to the product. Since reaction conditions C needed high reaction temperature (120−150 °C) and long reaction time (3−4 h), a part of the desired exo-structure **c** seemed to isomerize gradually to thermodynamically more stable endo-dienone (structure **d**). Dehydrobromination of **2b** by method A gave the desired **2c** in 75% yield and by method B gave a 5:2 mixture of **2c** and **2d**. Dehydrobromination of **3b** and **4b** gave the desired **3c** and **4c** by method B in 56% and 88% yields, respectively.

Then we planned to prepare isodehydrochamaecynone (**5c**) from chamaecynone (**5a**) and isochamaecynone (**6a**) by an analogous method. Enolsilylation of **5a** with TMSOTf and Et_3N in CH_2Cl_2 and successive treatment of the resulting silyl enol ether with PTAB gave α′-bromo-α′-methyl α,β-unsaturated ketone (**5b**)[11] in 60% yield accompanied by dehydrochamaecynone (**5d**) in 35% yield. Analogously, **6a** gave **5b** and **5d** in 57% and 28% yields, respectively. Dehydrobromination of **5b** by method B (TBAF in THF at room temperature) gave the desired **5c** in 30% yield. Dehydrobromination of **5b** by method C (Li_2CO_3, LiBr in DMF at 120 °C) gave the desired **5c** in 40% yield and **5d** in 37% yield. Isodehydrochamaecynone (**5c**) is a synthetic intermediate for dehydrochamaecynenol and norsesquibenihiol, and their overall yields were much improved by the improvement of the yield of **5c**.[8]



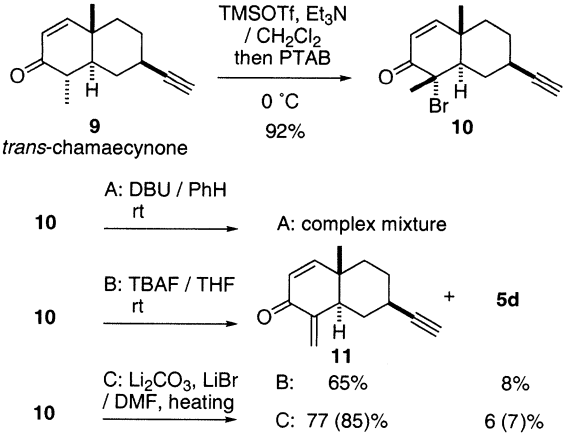
From an interest in the influence of the exo-endo dienone moiety on the biological activities of the compound, we

Scheme 1[a]



[a] The yields in parentheses are based on recovered starting material.

Scheme 2[a]



[a] The yields in parentheses are based on recovered starting material.

wanted to synthesize dehydrobrachylaenolide (**1**) from tuberiferine (**7**)[12] (Scheme 1). Enolsilylation of **7** with TMSOTf and Et_3N in CH_2Cl_2 and successive treatment of the resulting silyl enol ether with PTAB gave bromide **8** in 74% yield. Dehydrobromination of **8** with DBU (method A) gave **1** in only 26% yield. On the contrary, treatment of **8** with TBAF in THF gave **1** in 63% yield. The physical constants and spectral data of **1** were in good agreement with those of natural dehydrobrachylaenolide reported in the literature.[1]

Finally, we wanted to introduce the synthesis of *trans*-isodehydrochamaecynone (**11**) (Scheme 2). Enolsilylation of *trans*-chamaecynone (**9**)[13] with TMSOTf and Et_3N in CH_2Cl_2 and successive treatment of the resulting silyl enol ether with PTAB gave bromide **10** in 92% yield. Treatment of **10** with DBU gave a complex mixture probably because the acetylide anion was formed under the reaction conditions. On the other hand, treatment of **10** with TBAF in THF gave **11** in 65% yield accompanied by **5d** in 8% yield. The yield of **11** was improved to 77% by dehydrobromination of **10** with Li_2CO_3 and LiBr in DMF at 120 °C.

In conclusion, dehydrobrachylaenolide (**1**), isodehydrochamaecynone (**5c**), and *trans*-isodehydrochamaecynone (**11**) have been synthesized by bromination of the silyl enol ether of each substrate with PTAB and successive dehydrobromination with TBAF or Li_2CO_3 and LiBr.

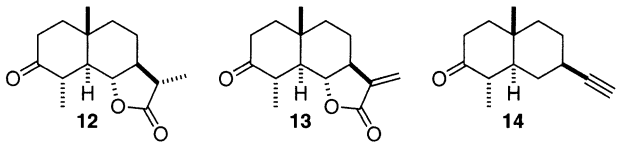
Inhibitory Activity on Expression of Intercellular Adhesion Molecule-1 (ICAM-1) Induced by the Inflammatory Cytokine Interleukin-1 (IL-1). Expression of ICAM-1 is induced by IL-1 on the surface of endothelial cells of blood vessels. ICAM-1 on the activated endothelial cells interacts with lymphocyte function-associated antigen-1 (LFA-1) on leukocytes in the blood stream, and the

Table 1. [12] Inhibitory Activity on Induction of ICAM-1[a]

	12	**13**	**7**	**1**
IC_{50} (μM)	>1000	17	7.4	3.0

[a] A549 cells (3×10^4 cells/well) were pretreated with various concentrations of the compounds for 1 h and then incubated in the presence of IL-1β for 6 h. Absorbance of 415 nm was assayed after treatment of the cells with primary and secondary antibodies and addition of the enzyme substrate as described in the Experimental Section. The experiments were carried out in triplicate cultures. IC_{50} was calculated by using the formula in the Experimental Section.

leukocytes begin rolling, adhere to the surface of endothelium, and finally migrate from the inside of the blood vessel to the inflammatory portion by chemotaxis. The attack of leukocytes occasionally causes serious damage to the inflammatory tissue. Expression of excess ICAM-1 on the surface of endothelial cells of a blood vessel plays an important role in the progress of inflammatory reaction. These facts suggest that inhibitors of induction of ICAM-1 may yield a new type of antiinflammatory agent. With this in mind, we examined **1** and the three related compounds **7**, **12**,[12] and **13**[12] for their inhibitory activity on the



induction of ICAM-1 through bioassay. The compounds were screened for inhibition of induction of ICAM-1 using the human cultured A549 cell line (lung carcinoma, ATCC CCL 185), an in vitro model of human endothelial cells.

All compounds possessing an α-methylene γ-lactone moiety, such as **1**, **7**, and **13**, showed significant inhibitory activity on induction of ICAM-1. Hence, it is inferred that an α-methylene γ-lactone moiety in the molecule must be essential for activity in the case of these compounds. In fact, no inhibitory activity on ICAM-1 expression was observed in compound **12**, which contains no α,β-unsaturated carbonyl residues. However, its structural analogues that contain unsaturated carbonyl residues prevented ICAM-1 expression, greater with increasing number of α,β-unsaturated carbonyl residues (compound **1** > compound **7** > compound **13** > compound **12**) (Table 1). Compound **1** inhibited ICAM-1 expression in a dose-dependent manner ($IC_{50} = 3$ μM) under concentrations that did not decrease cell viability. Toxic activity of compound **1** ($IC_{50} = 55$ μM) required about 20-fold higher concentrations than those required for the inhibition of ICAM-1 expression (Figure 2).

The transcription of the ICAM-1 gene induced by IL-1 is largely dependent on the transcription factor NF-κB. Upon IL-1 stimulation, NF-κB translocates from the cytoplasm into the nucleus and activates a variety of target genes. As reported previously,[14] (11*S*)-2α-bromo-3-oxoeudesmano-12,6α-lactone, devoid of an α-methylene γ-lactone moiety, inhibits the signaling pathway that triggers the nuclear translocation of NF-κB. In our preliminary results,[15] it appears that these compounds possessing an α-methylene γ-lactone moiety control the signaling pathway upstream of the nuclear translocation of NF-κB. Details regarding the mode of action of these compounds will be reported elsewhere.

Termiticidal Activity. The termiticidal activity of **5a** and the corresponding *trans*-fused enone **9** was examined (Table 2). These compounds possessing an ethynyl group

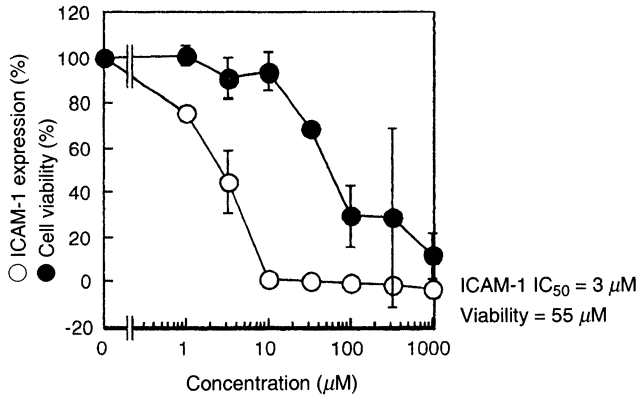


Figure 2. Dehydrobrachylaenolide (**1**) inhibits the induction of ICAM-1 in response to IL-1. A549 cells were pretreated with various concentrations of compound **1** for 1 h and then incubated in the presence of IL-1β for 6 h. Open circles represent the ICAM-1 expression (mean ± SD of triplicate cultures). A549 cells were incubated with various concentrations of compound **1** for 24 h, and cell viability was measured by MTT assay (filled circles). Data points represent mean ±SD of triplicate cultures.

Table 2. Termiticidal Activities of Chamaecynone (**5a**) and *trans*-Chamaecynone (**9**) against *Coptotermes formosanus* by Filter Paper Contact Method

		mortality (%) (days)			
compound	concentration (ppm)	1	2	5	7
5a	100	0	0	27	87
	1000	27	97	100	100
9	100	0	0	43	100
	1000	20	80	100	100

Table 3. Termiticidal Activities of Norsesquiterpenoids with *Trans* Ring Fusion against *Coptotermes formosanus* by Filter Paper Contact Method

		mortality (%) (days)		
compound	concentration (ppm)	1	2	5
14	100	0	0	0
	1000	0	93	100
9	100	0	3	100
	1000	47	80	100
11	100	0	3	17
	1000	33	93	100
5d	100	0	0	7
	1000	13	90	100

at C-7 showed significant termiticidal activity. The difference in the stereochemistry of ring fusion did not influence the potency of the termiticidal activity. We then examined the termiticidal activity of **9** and three related compounds **5d**, **11**, and **14**[13] (Table 3). All compounds possessing an ethynyl group at C-7 showed significant termiticidal activity. The termiticidal activity was increased by introduction of a double bond at the α,β-position of **14**. However, further introduction of an exo- or endo-double bond at the α′,β′-position had no effect.

Experimental Section

General Experimental Procedures. All melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 200 (500) MHz and at 50 (125) MHz, respectively, in $CDCl_3$. ^{1}H NMR assignments were determined by decoupling and H−H COSY experiments. ^{13}C NMR assignments were determined by DEPT, C−H COSY, HMQC, and HMBC experiments. All reactions were run under an atmosphere of N_2. Benzene, CH_2Cl_2, DMF, diisopropylamine, and triethylamine were distilled from CaH_2. MeOH was distilled from $Mg(OMe)_2$. THF was distilled from sodium benzophenone ketyl. The

column codes are as follows: A, 25 × 0.46 cm i.d. stainless steel column packed with 10 μm silica gel; B, 15 × 0.46 cm i.d. stainless steel column packed with 5 μm silica gel. Silica gel (230−400 mesh) was employed for flash chromatography, and 70−230 mesh silica gel was employed for column chromatography.

(11*S*)-4α-Bromo-3-oxoeudesm-1-eno-12,6*β*-lactone (2b). To a stirred solution of **2a** (19.6 mg, 0.0789 mmol) and Et_3N (65.6 μL, 0.473 mmol) in CH_2Cl_2 (0.9 mL) was added TMSOTf (45.8 μL, 0.237 mmol) at 0 °C. After 2.5 h, the mixture was treated with PTAB (89.1 mg, 0.237 mmol) in CH_2Cl_2 (0.5 mL) and stirred at this temperature for 2 h. The reaction was quenched with a mixture of 10% aqueous solution of $Na_2S_2O_3$ and a saturated aqueous solution of $NaHCO_3$, and the mixture was extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4), concentrated, and purified by flash chromatography [2.5 g; 1.2 cm i.d.; EtOAc−hexane (3:7)] to give **2b** (22.1 mg, 86%) as colorless needles ($CHCl_3$−EtOAc): mp (dec) 134 °C; $[\alpha]^{20}_D$ −225.6° (*c* 1.68, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1776, 1684 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 6.73 (1H, d, *J* = 10.0 Hz, H-1), 6.00 (1H, d, *J* = 10.0 Hz, H-2), 5.31 (1H, dd, *J* = 4.3, 2.2 Hz, H-6), 2.59 (1H, d, *J* = 2.2 Hz, H-5), 2.42 (1H, q, *J* = 7.7 Hz, H-11), 2.14 (1H, m, H-7), 2.10 (3H, s, H-15), 1.86 (1H, m, H-8), 1.38 (3H, d, *J* = 7.7 Hz, H-13), 1.32 (3H, s, H-14); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 194.5 (s, C-3), 179.4 (s, C-12), 159.3 (d, C-1), 124.0 (d, C-2), 77.8 (d, C-6), 70.3 (s, C-4), 55.1 (d, C-5), 43.6 (d, C-11), 42.4 (d, C-7), 38.4 (t, C-9), 37.7 (s, C-10), 27.4 (q, C-15), 23.6 (t, C-8), 21.3 (q, C-14), 14.1 (q, C-13); *anal.* C 54.85%, H 5.82%, calcd for $C_{15}H_{19}O_3Br$, C 55.06%, H 5.85%.

(11*S*)-3-Oxoeudesma-1,4(15)-dieno-12,6*β*-lactone (2c): Dehydrobromination of 2b by Method A. A solution of **2b** (38.2 mg, 0.117 mmol) and DBU (52.5 μL, 0.351 mmol) in PhH (1 mL) was stirred at room temperature for 47 h, poured into 1 M HCl (5 mL), and extracted with EtOAc. The combined extracts were washed with a saturated aqueous solution of $NaHCO_3$ and a saturated aqueous solution of NaCl, dried (Na_2SO_4), concentrated (35 mg), and purified by flash chromatography [2.5 g; 1.2 cm i.d.; EtOAc−hexane (3:7)] to give **2c** (21.6 mg, 75%) as colorless plates (EtOAc): mp 134−137 °C; $[\alpha]^{20}_D$ −345.8° (*c* 1.65, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3004, 1774, 1676, 1624 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 6.75 (1H, d, *J* = 9.9 Hz, H-1), 6.32 (1H, dd, *J* = 2.1, 0.8 Hz, H-15), 6.01 (1H, dd, *J* = 9.9, 0.8 Hz, H-2), 5.74 (1H, ddd, *J* = 2.1, 0.8, 0.8 Hz, H-15), 4.91 (1H, dd, *J* = 4.3, 2.6 Hz, H-6), 2.73 (1H, ddd, *J* = 2.6, 2.1, 2.1 Hz, H-5), 2.42 (1H, q, *J* = 7.6 Hz, H-11), 2.13 (1H, ddd, *J* = 11.4, 6.8, 4.3 Hz, H-7), 1.35 (3H, d, *J* = 7.6 Hz, H-13), 1.09 (3H, s, H-14); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 188.6 (s, C-3), 179.6 (s, C-12), 159.9 (d, C-1), 141.3 (s, C-4), 126.7 (d, C-2), 121.7 (t, C-15), 76.4 (d, C-6), 49.0 (d), 43.7 (d), 41.8 (d), 36.9 (s, C-10), 34.9 (t), 23.6 (t), 19.7 (q), 14.1 (q); HREIMS *m/z* 246.1256 (calcd for $C_{15}H_{18}O_3$, 246.1256).

Dehydrobromination of 2b by Method B. A solution of **2b** (45.3 mg, 0.138 mmol) and TBAF (1 M in THF, 276 μL) in THF (2.5 mL) was stirred at room temperature for 9 h. Then additional TBAF (1 M in THF, 276 μL) was added, and stirring was continued for 3.3 h. Since **2b** was still detected in the reaction mixture, TBAF (1 M in THF, 69.0 μL) was further added and stirring was continued for 1.8 h. The reaction mixture was poured into a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4), concentrated, and purified by flash chromatography [3 g; 1.2 cm i.d.; EtOAc−hexane (3:7)] to give a regioisomeric mixture of **2c** and 6*β*-santonin **2d** (18.9 mg, 55%). The ratio (**2c**:**2d** = 5:2) was determined by ^1H NMR integration values.

(11*S*)-4α-Bromo-3-oxoeudesm-1-eno-12,6α-lactone (3b). To a stirred solution of **3a** (56.5 mg, 0.228 mmol) and Et_3N (126 μL, 0.909 mmol) in CH_2Cl_2 (1.8 mL) was added TMSOTf (88.1 μL, 0.456 mmol) at 0 °C. After 3 h, the mixture was treated with PTAB (94.4 mg, 0.251 mmol) in CH_2Cl_2 (0.7 mL) and stirred at this temperature for 15 min. The reaction mixture was poured into 10% aqueous solution of $Na_2S_2O_3$ and extracted with $CHCl_3$. The dried product (180 mg) was purified by flash chromatography [8 g; 1.6 cm i.d.; EtOAc−hexane (3:7)] to give **3b** (67.9 mg, 91%) as colorless prisms ($CHCl_3$−EtOAc): mp (dec) 140 °C; $[\alpha]^{20}_D$ −59.8° (*c* 0.89, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1784, 1692 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 6.81 (1H, d, *J* = 9.9 Hz, H-1), 6.11 (1H, d, *J* = 9.9 Hz, H-2), 4.14 (1H, dd, *J* = 11.5, 10.0 Hz, H-6), 3.09 (1H, d, *J* = 11.5 Hz, H-5), 2.37 (1H, dq, *J* = 12.2, 6.9 Hz, H-11), 2.08 (3H, s, H-15), 1.28 (3H, d, *J* = 6.9 Hz, H-13), 1.12 (3H, s, H-14); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 193.2 (s, C-3), 178.3 (s, C-12), 157.6 (d, C-1), 125.8 (d, C-2), 78.6 (d, C-6), 60.7 (s, C-4), 57.2 (d, C-5), 52.6 (d, C-7), 40.7 (d, C-11), 39.7 (s, C-10), 38.8 (t), 24.2 (q, C-15), 22.9 (t), 22.3 (q, C-14), 12.5 (q, C-13); *anal.* C 54.98%, H 5.85%, calcd for $C_{15}H_{19}O_3Br$, C 55.06%, H 5.85%.

(11*S*)-3-Oxoeudesma-1,4(15)-dieno-12,6α-lactone (3c): Dehydrobromination of 3b by Method B. A solution of **3b** (52.6 mg, 0.161 mmol) and TBAF (1 M in THF, 322 μL) in THF (3 mL) was stirred at room temperature for 16 h. Then the additional TBAF (1 M in THF, 161 μL) was added, and stirring was continued for 7.5 h. Since the starting material **3b** was detected by TLC, TBAF (1 M in THF, 161 μL) was further added. The reaction mixture was stirred again for 2 h, poured into a saturated aqueous solution of NH_4Cl, and extracted with CH_2Cl_2. The dried (Na_2SO_4) and concentrated product was separated by flash chromatography [8 g; 1.6 cm i.d.; EtOAc−hexane (3:7)]. The faster running gave **3c** (22.2 mg, 56%) as colorless prisms (EtOAc−hexane): mp 123−125 °C; $[\alpha]^{20}_D$ −49.2° (*c* 1.65, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1780, 1678, 1624 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 6.80 (1H, d, *J* = 9.9 Hz, H-1), 6.27 (1H, dd, *J* = 2.3, 1.0 Hz, H-15), 6.03 (1H, dd, *J* = 9.9, 0.8 Hz, H-2), 5.67 (1H, ddd, *J* = 2.3, 1.0, 0.8 Hz, H-15), 4.13 (1H, dd, *J* = 10.8, 9.8 Hz, H-6), 2.89 (1H, ddd, *J* = 10.8, 2.3, 2.3 Hz, H-5), 2.38 (1H, dq, *J* = 12.1, 6.8 Hz, H-11), 1.26 (3H, d, *J* = 6.8 Hz, H-13), 1.07 (3H, s, H-14); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 187.8 (s, C-3), 178.7 (s, C-12), 158.6 (d, C-1), 140.7 (s, C-4), 127.4 (d, C-2), 122.0 (t, C-15), 78.9 (d, C-6), 52.2 (d), 52.1 (d), 40.7 (d, C-11), 39.6 (s, C-10), 36.3 (t), 22.7 (t), 19.6 (q, C-14), 12.5 (q, C-13); *anal.* C 72.90%, H 7.40%, calcd for $C_{15}H_{18}O_3$, C 73.15%, H 7.37%. The slower running gave α-santonin (**3d**) (2.2 mg, 6%) as colorless crystals.

4α-Bromo-7*βH*-eudesma-1,11-dien-3-one (4b). To a stirred solution of **4a** (19.0 mg, 0.0870 mmol) and Et_3N (36.2 μL, 0.261 mmol) in CH_2Cl_2 (0.6 mL) was added TMSOTf (25.3 μL, 0.131 mmol) at 0 °C. After 1 h, the mixture was treated with PTAB (36.0 mg, 0.0957 mmol) in CH_2Cl_2 (0.3 mL) and stirred at this temperature for 10 min. The reaction mixture was poured into 10% aqueous solution of $Na_2S_2O_3$ and extracted with CH_2Cl_2. The combined extracts were dried and separated by flash chromatography [2.5 g; 1.2 cm i.d.; EtOAc−hexane (5:95)]. The faster running gave 7*βH*-eudesma-1,4(15),11-trien-3-one (**4c**) (1.0 mg, 5%) as a colorless oil: $[\alpha]^{20}_D$ −34.5° (*c* 0.67, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3096, 1672, 1624 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.77 (1H, d, *J* = 9.8 Hz, H-1), 6.07 (1H, dd, *J* = 2.2, 1.5 Hz, H-15), 5.96 (1H, d, *J* = 9.8 Hz, H-2), 5.19 (1H, br s, $W_{h/2}$ = 3 Hz, H-15), 4.93 (1H, ddd, *J* = 1.5, 1.5, 1.5 Hz, H-12), 4.80 (1H, br s, $W_{h/2}$ = 4 Hz, H-12), 2.69 (1H, dddd, *J* = 12.5, 2.2, 2.2, 2.2 Hz, H-5), 2.49 (1H, br s, $W_{h/2}$ = 12 Hz, H-7), 2.04 (1H, dddd, *J* = 13.9, 2.2, 2.2, 2.2 Hz, H-6), 1.98 (1H, m, H-8), 1.83 (1H, dddd, *J* = 14.1, 14.1, 5.7, 4.0 Hz, H-8), 1.75−1.67 (2H, H-6 and -9), 1.73 (3H, d, *J* = 0.5 Hz, H-13), 1.43 (1H, ddd, *J* = 12.7, 4.0, 3.2 Hz, H-9), 0.98 (3H, s, H-14); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 189.8 (s, C-3), 162.1 (d, C-1), 146.4 (s), 145.9 (s), 126.6 (d, C-2), 117.8 (t, C-15), 111.3 (t, C-12), 42.8 (d, C-5), 38.2 (s, C-10), 37.8 (d, C-7), 32.6 (t, C-9), 25.1 (t, C-6), 23.1 (t, C-8), 22.7 (q, C-13), 17.4 (q, C-14); HREIMS *m/z* 216.1527 (calcd for $C_{15}H_{20}O$, 216.1514). The slower running gave **4b** (17.3 mg, 67%) as colorless crystals: mp 108−111 °C; $[\alpha]^{20}_D$ −56.5° (*c* 0.74, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3100, 1680 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 6.77 (1H, d, *J* = 9.9 Hz, H-1), 5.96 (1H, d, *J* = 9.9 Hz, H-2), 4.95 (2H, br s, $W_{h/2}$ = 6 Hz, Hs-12), 2.67 (1H, dd, *J* = 12.8, 2.2 Hz, H-5), 2.53 (1H, br s, $W_{h/2}$ = 11 Hz, H-7), 2.33 (1H, dddd, *J* = 14.0, 2.2, 2.2, 2.2 Hz, H-6), 1.81 (6H, H-13 and -15), 1.19 (3H, s, H-14); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 195.4 (s, C-3), 161.1 (d, C-1), 145.3 (s, C-11), 124.4 (d, C-2), 111.7 (t, C-12), 70.7 (s, C-4), 49.3 (d), 39.1 (s, C-10), 38.4 (d), 35.9 (q), 25.3 (q), 25.1 (t), 23.3 (q), 22.7 (t), 20.4 (t); HREIMS *m/z* 296.0745 (calcd for $C_{15}H_{21}OBr$, 296.0776).

Dehydrobromination of 4b by Method B. A solution of **4b** (15.7 mg, 0.0528 mmol) and TBAF (1 M in THF, 106 μL) in THF (1 mL) was stirred at room temperature for 16.3 h. Then the mixture was treated with additional TBAF (1 M in THF, 52.8 μL) and stirred for a further 10.3 h. Since **4b** was still detected in the reaction mixture, TBAF (1 M in THF, 52.8 μL) was further added. After 1.3 h, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2. The combined extracts were dried and purified by flash chromatography [2.5 g; 1.2 cm i.d.; EtOAc−hexane (3:97)] to give **4c** (10.1 mg, 88%) as a colorless oil.

***4β*-Bromo-5*βH*-13-noreudesm-1-en-11-yn-3-one (5b): Bromination of Chamaecynone (5a).** To a stirred solution of **5a** (16.7 mg, 0.0826 mmol) and Et_3N (34.4 μL, 0.248 mmol) in CH_2Cl_2 (0.6 mL) was added TMSOTf (24.0 μL, 0.124 mmol) at 0 °C. After 1.5 h, the mixture was treated with PTAB (34.2 mg, 0.0909 mmol) in CH_2Cl_2 (0.3 mL) and stirred at this temperature for 20 min. The reaction mixture was poured into 10% aqueous $Na_2S_2O_3$ and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and separated by flash chromatography [2.5 g; 1.2 cm i.d.; EtOAc−hexane (5:95)]. The faster running gave **5b** (13.9 mg, 60%) as a colorless oil: IR ($CHCl_3$) ν_{max} 3316, 2120, 1682 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 6.54 (1H, d, J = 10.3, 1.5 Hz, H-1), 6.01 (1H, d, J = 10.3 Hz, H-2), 2.84 (1H, br s, $W_{h/2}$ = 13 Hz, H-7), 2.68 (1H, ddd, J = 10.4, 5.2, 1.5 Hz, H-5), 2.15 (1H, d, J = 2.3 Hz, H-12), 1.93 (3H, s, H-15), 1.59 (3H, s, H-14); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 193.2 (s, C-3), 157.5 (d, C-1), 125.0 (d, C-2), 86.0 (s, C-11), 70.4 (d, C-12), 59.8 (s, C-4), 49.1 (d, C-5), 38.2 (s, C-10), 36.8 (t), 31.0 (t), 29.6 (q, C-14), 28.7 (q, C-15), 27.0 (t), 26.6 (d, C-7). The slower running gave dehydrochamaecynone (**5d**) (5.7 mg, 35%) as colorless crystals: mp 84 °C; $[\alpha]^{20}_D$ −181.9° (*c* 0.57, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3316, 2120, 1662, 1630, 1612 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.71 (1H, d, J = 9.8 Hz, H-1), 6.21 (1H, d, J = 9.8 Hz, H-2), 3.05 (1H, ddd, J = 12.8, 2.1, 2.1 Hz, H-6), 2.32 (1H, dd, J = 12.8, 12.7 Hz, H-6), 2.26 (1H, m, H-7), 2.16 (1H, d, J = 2.2 Hz, H-12), 1.96 (1H, m, H-8), 1.90 (3H, s, H-15), 1.86 (1H, m, H-8), 1.78 (1H, ddd, J = 13.4, 3.9, 2.4 Hz, H-9), 1.29 (1H, ddd, J = 13.4, 13.4, 4.4 Hz, H-9), 1.24 (3H, s, H-14); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 186.1 (s, C-3), 156.6 (s, C-5), 156.2 (d, C-1), 130.1 (s, C-4), 126.2 (d, C-2), 86.6 (s, C-11), 69.2 (d, C-12), 39.7 (s, C-10), 36.8 (t, C-9), 33.7 (t, C-6), 30.5 (d, C-7), 27.5 (t, C-8), 23.4 (q, C-14), 10.6 (q, C-15); HREIMS *m/z* 200.1203 (calcd for $C_{14}H_{16}O$, 200.1201).

Isodehydrochamaecynone (5c): Dehydrobromination of 5b by Method B. A solution of **5b** (6.5 mg, 0.0231 mmol) and TBAF (1 M in THF, 46.0 μL) in THF (0.5 mL) was stirred at room temperature for 4.2 h. Since **5b** was still detected in the reaction mixture, TBAF (1 M in THF, 34.2 μL) was further added. The reaction mixture was stirred for a further 26.2 h, poured into a saturated aqueous solution of NH_4Cl, and extracted with CH_2Cl_2. The combined extracts were dried and separated by flash chromatography [2 g; 1.2 cm i.d.; EtOAc−hexane (5:95)]. **5c** was separated as a colorless oil (1.4 mg, 30%): $[\alpha]^{20}_D$ −101° (*c* 0.09, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3316, 2116, 1670, 1624, 1456 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.65 (1H, dd, J = 10.1, 1.9 Hz, H-1), 6.07 (1H, br s, $W_{h/2}$ = 3 Hz, H-15), 6.06 (1H, d, J = 10.1 Hz, H-2), 5.36 (1H, br s, $W_{h/2}$ = 3 Hz, H-15), 2.92 (1H, ddd, J = 12.1, 4.5, 1.9 Hz, H-5), 2.83 (1H, br s, $W_{h/2}$ = 11 Hz, H-7), 2.13 (1H, d, J = 2.4 Hz, H-12), 1.88 (1H, ddd, J = 13.5, 13.5, 3.4 Hz, H-9), 1.80−1.72 (2H, H-6 and -8), 1.65 (1H, m, H-6), 1.61 (1H, m, H-9), 1.50 (1H, dddd, J = 13.5, 13.5, 3.9, 3.7 Hz, H-8), 1.17 (3H, s, H-14); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 187.9 (s, C-3), 158.5 (d, C-1), 145.6 (s, C-4), 128.8 (d, C-2), 122.0 (t, C-15), 86.5 (s, C-11), 70.1 (d, C-12), 46.1 (d, C-5), 38.2 (s, C-10), 34.4 (t, C-9), 34.0 (t, C-6), 29.2 (q, C-14), 27.6 (t, C-8), 26.0 (d, C-7); HREIMS *m/z* 200.1196 (calcd for $C_{14}H_{16}O$, 200.1201).

Dehydrobromination of 5b by Method C. A mixture of **5b** (21.9 mg, 0.0779 mg), Li_2CO_3 (23.1 mg, 0.312 mmol), and LiBr (23.1 mg) in DMF (1.6 mL) was stirred at 120 °C for 2 h, cooled to room temperature, poured into saturated aqueous NaCl, and extracted with EtOAc. The combined extracts were washed with 2 M HCl and saturated aqueous NaCl, dried (Na_2SO_4), and separated by flash chromatography [2.5 g; 1.2 cm i.d.; EtOAc−hexane (5:95)]. The faster running gave **5c** (6.1 mg, 40%) as colorless crystals. The slower running gave **5d** (5.7 mg, 37%) as colorless crystals.

***4β*-Bromo-5*βH*-13-noreudesm-1-en-11-yn-3-one (5b): Bromination of Isochamaecynone (6a).** To a stirred solution of **6a** (16.4 mg, 0.0811 mmol) and Et_3N (33.7 μL, 0.243 mmol) in CH_2Cl_2 (0.6 mL) was added TMSOTf (23.6 μL, 0.122 mmol) at 0 °C. After 1 h, the mixture was treated with PTAB (42.6 mg, 0.113 mmol) in CH_2Cl_2 (0.3 mL) and stirred for 20 min. The reaction mixture was poured into 10% aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$. The combined extracts were washed, dried, and separated by flash chromatography [2.5 g; 1.2 cm i.d.; EtOAc−hexane (5:95)]. The faster running gave **5b** (12.9 mg, 57%) as colorless crystals. The slower running gave **5d** (4.5 mg, 28%) as colorless crystals.

4α-Bromotuberiferine (8). To a stirred solution of **7** (37.1 mg, 0.151 mmol) and Et_3N (104.7 μL, 0.755 mmol) in CH_2Cl_2 (1.1 mL) was added TMSOTf (73.1 μL, 0.378 mmol) at 0 °C. After 2 h, the mixture was treated with PTAB (90.8 mg, 0.242 mmol) in CH_2Cl_2 (0.4 mL) and stirred for 25 min. The reaction mixture was poured into 10% aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$. The combined extracts were washed, dried, and purified by flash chromatography [2.5 g; 1.2 cm i.d.; EtOAc−hexane (3:7)] to give **8** (36.2 mg, 74%) as colorless prisms (EtOAc): mp (dec) 150 °C; $[\alpha]^{20}_D$ −63.6° (*c* 0.50, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1776, 1682, 1624 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 6.84 (1H, d, J = 9.9 Hz, H-1), 6.17 (1H, d, J = 3.2 Hz, H-13), 6.12 (1H, d, J = 9.9 Hz, H-2), 5.50 (1H, d, J = 3.2 Hz, H-13), 4.14 (1H, dd, J = 11.5, 11.5 Hz, H-6), 3.21 (1H, d, J = 11.5 Hz, H-5), 2.67 (1H, m, H-7), 2.09 (3H, s, H-15), 1.12 (3H, s, H-14); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 193.1 (s, C-3), 169.7 (s, C-12), 157.4 (d, C-1), 137.9 (s, C-11), 125.8 (d, C-2), 118.1 (t, C-13), 78.8 (d, C-6), 60.4 (s, C-4), 57.6 (d, C-5), 49.8 (d, C-7), 39.8 (s, C-10), 38.5 (t), 24.3 (q, C-15), 22.3 (q, C-14), 21.2 (t); *anal.* C 55.50%, H 5.27%, calcd for $C_{15}H_{17}O_3Br$, C 55.40%, H 5.27%.

Dehydrobrachylaenolide (1): Dehydrobromination of 8 by Method A. A solution of **8** (25.2 mg, 0.0775 mmol) and DBU (23.2 μL, 0.155 mmol) in PhH (0.5 mL) was stirred at room temperature for 43 h, poured into 1 M HCl, and extracted with EtOAc. The combined extracts were washed, dried (Na_2SO_4), and passed through a short column of silica gel. The eluate was concentrated and separated by HPLC [column B; EtOAc−hexane (3:7); 3.0 mL/min]. The peak (t_R 2.8 min) gave **1** (4.9 mg, 26%) as colorless prisms ($CHCl_3$−EtOAc): mp 222−224 °C; $[\alpha]^{24}_D$ +67.9° (*c* 0.16, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1778, 1678, 1624 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.82 (1H, d, J = 9.8 Hz, H-1), 6.28 (1H, m, H-15), 6.15 (1H, d, J = 3.2 Hz, H-13), 6.04 (1H, d, J = 9.8 Hz, H-2), 5.72 (1H, m, H-15), 5.48 (1H, d, J = 3.2 Hz, H-13), 4.13 (1H, dd, J = 10.7, 10.7 Hz, H-6), 3.03 (1H, ddd, J = 10.7, 2.3, 2.3 Hz, H-5), 2.64 (1H, m, H-7), 2.16 (1H, m, H-8), 1.87 (1H, m, H-9), 1.07 (3H, s, H-14); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 187.7 (s, C-3), 170.0 (s, C-12), 158.4 (d, C-1), 140.4 (s, C-4), 138.1 (s, C-11), 127.5 (d, C-2), 122.3 (t, C-15), 117.7 (t, C-13), 79.1 (d, C-6), 52.6 (d, C-5), 49.4 (d, C-7), 39.7 (s, C-10), 36.0 (t, C-9), 21.1 (t, C-8), 19.6 (q, C-14); HREIMS *m/z* 244.1096 (calcd for $C_{15}H_{16}O_3$, 244.1100). The peak (t_R 3.7 min) gave starting material **8** (3.3 mg, 13%).

Dehydrobromination of 8 by Method B. A solution of **8** (24.0 mg, 0.0738 mmol) and TBAF (1 M in THF, 148 μL) in THF (2.2 mL) was stirred at room temperature for 5 h, poured into saturated aqueous NH_4Cl (5 mL), and extracted with CH_2Cl_2 (5 × 10 mL). The extracts were washed, dried, and separated by flash chromatography [3.4 g; 1.2 cm i.d.; EtOAc−hexane (3:7)]. The eluate was concentrated and further separated by HPLC [column A; EtOAc−hexane (4:6); 3.0 mL/min]. The first peak gave **1** (11.3 mg, 63%) as colorless crystals. The second peak gave starting material **8** (4.1 mg, 17%).

4α-Bromo-13-noreudesm-1-en-11-yn-3-one (10). To a stirred solution of **9** (23.5 mg, 0.116 mmol) and Et_3N (48.2 μL, 0.348 mmol) in CH_2Cl_2 (0.8 mL) was added TMSOTf (33.6 μL, 0.174 mmol) at 0 °C. After 1.6 h, the mixture was treated with PTAB (48.1 mg, 0.128 mmol) in CH_2Cl_2 (0.4 mL) and stirred at this temperature for 20 min. The reaction mixture was poured into 10% aqueous $Na_2S_2O_3$ and extracted with CH_2-

Cl_2. The extracts were dried and purified by flash chromatography [2.5 g; 1.2 cm i.d.; EtOAc−hexane (5:95)] to give **10** (29.9 mg, 92%) as colorless crystals: mp 115−119 °C; $[\alpha]^{20}_D$ −184.1° (*c* 1.32, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3316, 2120, 1682 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.79 (1H, d, J = 9.9 Hz, H-1), 5.99 (1H, dd, J = 9.9, 0.7 Hz, H-2), 2.49 (1H, dd, J = 12.7, 2.2 Hz, H-5), 2.39 (2H, H-6 and -7), 2.15 (1H, dd, J = 2.2, 0.5 Hz, H-12), 1.95 (1H, m, H-8), 1.80 (3H, d, J = 0.7 Hz, H-15), 1.58 (1H, ddd, J = 13.3, 3.3, 3.3 Hz, H-9), 1.45 (1H, ddd, J = 13.3, 13.3, 3.9 Hz, H-9), 1.17 (3H, s, H-14); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 194.8 (s, C-3), 160.0 (d, C-1), 124.7 (d, C-2), 87.2 (s, C-11), 69.2 (s, C-4), 68.7 (d, C-12), 54.3 (d, C-5), 39.4 (t, C-9), 38.0 (s, C-10), 29.8 (t, C-6), 29.4 (d, C-7), 28.0 (t, C-8), 25.1 (q, C-15), 20.4 (q, C-14); HREIMS *m*/*z* 280.0462 (calcd for $C_{14}H_{17}OBr$, 280.0463).

Dehydrobromination of 10 by Method A. A solution of **10** (10.4 mg, 0.0370 mmol) and DBU (11.1 μL, 0.0740 mmol) in PhH (0.3 mL) was stirred at room temperature for 17.5 h. Additional DBU (5.6 μL, 0.0370 mmol) was added. The mixture was stirred for 20.5 h, poured into 1 M HCl, and extracted with EtOAc. The combined extracts were washed, dried, and separated by flash chromatography [2.5 g; 1.2 cm i.d.; EtOAc−hexane (5:95)], yielding a mixture of **10**, **11**, and unknown product (4.9 mg) (1:1:1). The slower running gave **5d** (0.8 mg, 11%) as colorless crystals.

13-Noreudesma-1,4(15)-dien-11-yn-3-one (11): Dehydrobromination of 10 by Method B. A solution of **10** (23.4 mg, 0.0832 mmol) and TBAF (1 M in THF, 166 μL) in THF (1.8 mL) was stirred at room temperature for 14.8 h. The reaction mixture was treated with additional TBAF (1 M in THF, 166 μL) and stirred for 5 h, poured into saturated aqueous NH_4Cl, and extracted with CH_2Cl_2. The combined extracts were dried and separated by flash chromatography [3 g; 1.2 cm i.d.; EtOAc−hexane (1:9)]. The eluate was further separated by HPLC [column A; EtOAc−hexane (1:9); 3.0 mL/min]. The first peak (t_R 2.9 min) gave **11** (10.9 mg, 65%) as colorless prisms (EtOAc−hexane): mp 112−115 °C; $[\alpha]^{20}_D$ −183.6° (*c* 0.81, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3316, 2120, 1674, 1624 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.80 (1H, dd, J = 10.0, 0.5 Hz, H-1), 6.10 (1H, dd, J = 2.2, 1.0 Hz, H-15), 6.00 (1H, dd, J = 10.0, 0.7 Hz, H-2), 5.21 (1H, ddd, J = 2.4, 1.0, 0.7 Hz, H-15), 2.51 (1H, dddd, J = 12.2, 2.4, 2.2, 2.2 Hz, H-5), 2.38 (1H, m, H-7), 2.13 (1H, d, J = 2.4 Hz, H-12), 2.07 (1H, m, H-6), 1.96 (1H, m, H-8), 1.74 (1H, m, H-8), 1.52 (1H, ddd, J = 13.3, 13.3, 3.9 Hz, H-9), 0.97 (3H, d, J = 0.5 Hz, H-14); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 189.0 (s, C-3), 160.9 (d, C-1), 145.1 (s, C-4), 127.0 (d, C-2), 118.5 (t, C-15), 87.6 (s, C-11), 68.4 (d, C-12), 47.4 (d, C-5), 37.2 (s, C-10), 36.3 (t, C-9), 29.9 (t, C-6), 28.9 (d, C-7), 27.9 (t, C-8), 17.7 (q, C-14); *anal.* C 83.93%, H 8.02%, calcd for $C_{14}H_{16}O$, C 83.96%, H 8.05%. The second peak (t_R 4.5 min) gave **5d** (1.3 mg, 8%) as colorless crystals.

Dehydrobromination of 10 by Method C. A mixture of **10** (20.4 mg, 0.0726 mg), Li_2CO_3 (21.6 mg, 0.290 mmol), and LiBr (21.6 mg) in DMF (1.5 mL) was stirred at 120 °C for 30 min and cooled to room temperature. The mixture was extracted with EtOAc, washed with 2 M HCl and aqueous NaCl, dried, and separated by flash chromatography [2.5 g; 1.2 cm i.d.; EtOAc−hexane (5:95)]. After the slower running **5d** (0.9 mg, 6%) was removed, the faster running was further separated by HPLC [column A; EtOAc−hexane (5:95); 3.0 mL/min]. The first peak gave **11** (11.2 mg, 77%) as colorless crystals. The second peak (t_R 5.6 min) gave starting material **10** (1.8 mg, 9%).

Inhibitory Activity on Induction of ICAM-1. Human lung carcinoma cell line A549 cells were maintained in RPMI 1640 medium (Invitrogen, Carlsbad, CA) supplemented with 10% (v/v) fetal calf serum (JRH Bioscience, Lenexa, KS), 50 μM 2-mercaptoethanol, and penicillin−streptomycin−neomycin antibiotic mixture (Invitrogen).

Mouse anti-human ICAM-1 antibody C167 was purchased from Leinco Technologies, Inc. (Ballwin, MO), and peroxidase-conjugated goat anti-mouse IgG antibody was obtained from Jackson ImmunoResearch Laboratories, Inc. (West Grove, PA). Recombinant human IL-1β was a commercial product of Genzyme Diagnostic (Cambridge, MA).

After 1 h of A549 cells with or without test compounds in a microtiter plate at 3×10^4 cells/well in 150 μL, 50 μL of IL-1β was added to the culture at a final concentration of 0.25 ng/mL, and the cells were further incubated for 6 h. The cells were washed once with phosphate-buffered saline (PBS) and fixed by 15 min of incubation with 1% paraformaldehyde-PBS for 15 min and then washed once with PBS. After blocking with 1% bovine serum albumin-PBS overnight, the fixed cells were treated with mouse anti-human ICAM-1 antibody for 60 min at 37 °C. After being washed with 0.02% Tween-PBS, the cells were treated with peroxidase-linked anti-mouse IgG antibody for 60 min at 37 °C. The cells were washed three times with 0.02% Tween-PBS. The cells were incubated with the substrate (0.1% *o*-phenylenediamine dihydrochloride and 0.02% H_2O_2 in 0.2 M sodium citrate buffer, pH 5.3) for 20 min in the dark and assayed for the absorbance at 415 nm by using a microplate reader. Expression of ICAM-1 was calculated as follows.

Expression of ICAM-1 (% of control) =
(absorbance with sample treatment − absorbance without IL-1β treatment)/(absorbance with IL-1β treatment − absorbance without IL-1β treatment) × 100

A549 cells were incubated in the presence or absence of test compounds for 24 h. At the last 4 h of incubation, the cells were pulsed with 500 μg/mL of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) for 4 h. MTT formazan was solubilized with 5% sodium dodecyl sulfate (SDS) overnight. Absorbance at 595 nm was measured. Cell viability (%) was calculated as (experimental absorbance − background absorbance)/(control absorbance − background absorbance) × 100.

Termiticidal Activities. The termites used in this test were the active, healthy workers of *Coptotermes formosanus* Shiraki, a subterranean termite commonly found in Japan.

A 1 mL quantity of an acetone solution of each test compound (1 mg for 1000 ppm and 0.1 mg for 100 ppm test solutions) was applied to a filter paper disk (9 cm diameter) placed in a Petri dish. After air-drying, the filter paper was moistened with 1 mL of distilled H_2O and 10 active worker termites were introduced. Each dish was covered with a lid and kept at 25 ± 1 °C for 5 or 7 days. The number of dead termites was counted to calculate the percent mortality at 1, 2, and 5 days after treatment.

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Supporting Information Available: Synthetic outlines of dehydrochamaecynenol and norsesquibenihiol are shown in Scheme 1.[8] Details of the NMR experiments performed on compounds **1**, **9**, and **11** are summarized in Tables 1−3. The leukocyte-endothelial cell interactions are illustrated graphically in Figure 1, and a possible target of sample is shown in Figure 2. The experimental data of inhibitory activities of **1** on expression of ICAM-1 and cell viability are summarized in Table 4. This material is available free of charge via the Internet at http://pubs.acs.org.

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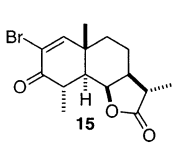
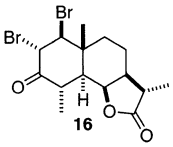
(9) Bromination of **2a** with PTAB in THF at 0 °C was attempted. The purified products were a mixture of undesired monobromide **15** and additional product **16** (97%, **15**:**16** = 78:19), which are probably produced by the following successive reaction: (i) the Michael addition of Br^- of PTAB to the β-position of α,β-unsaturated ketone; (ii) addition of Br^+ to the resulting anion at α-position (formation of **16**); (iii) dehydrobromination of **16** in the reaction conditions.



15



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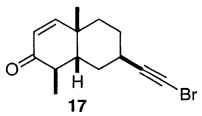

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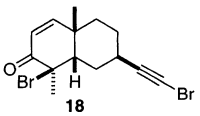

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(12) Compounds **7**, **12**, and **13**, which were used in the bioassay (Table 3), were synthesized by our published method: Ando, M.; Wada, T.; Kusaka, H.; Takase, K.; Hirata, N.; Yanagi, Y. *J. Org. Chem.* **1987**, *52*, 4792−4796.
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