Synthetic Studies of Sesquiterpenes with a Cis-Fused Decalin System, 5. A Synthetic Approach to the Study of Structure-Activity Relationships of the Termiticidal Norsesquiterpenoids, Chamaecynone and Related Compounds

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SYNTHETIC STUDIES OF SESQUITERPENES WITH A CIS-FUSED DECALIN SYSTEM, 5.[1] A SYNTHETIC APPROACH TO THE STUDY OF STRUCTURE-ACTIVITY RELATIONSHIPS OF THE TERMITICIDAL NORSESQUITERPENOIDS, CHAMAECYNONE AND RELATED COMPOUNDS

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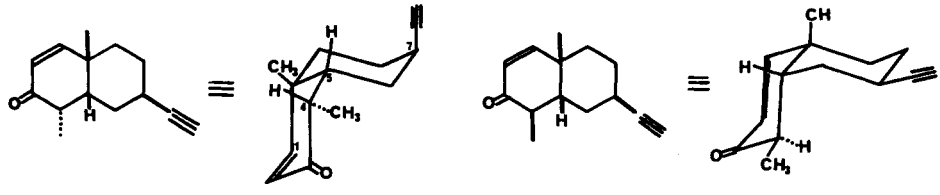
ABSTRACT.—Various analogues of chamaecynone [**1**] were prepared from α-santonin, and the termiticidal activity of these compounds was examined. All compounds possessing a 5βH-13-noreudesmane skeleton with a ethynyl group at C-7 showed significant termiticidal activity. Changes in the structure of the A-ring of these compounds also influenced the potency of their termiticidal activity.

In 1966 Nozoe *et al.* (2) re-examined the components of the essential oil of Benihi wood (*Chamaecyparis formosensis* Matsum.) and reported the isolation and structure determination of the acetylenic norsesquiterpenoids chamaecynone [**1**] and isochamaecynone [**2**] (Figure 1).

In 1971 Kondo *et al.* (3) examined the role of essential oils in the resistance of coniferous woods to termites and found that those of the genus *Chamaecyparis* such as Sawara wood (*Chamaecyparis pisifera* D. Don), Hinoki wood (*Chamaecyparis obtusa* Endl), Benihi wood (*Chamaecyparis formosensis* Matsum.), and Taiwan-Hinoki wood (*Chamaecyparis taiwanesis* Matsum.), which showed high resistance to termite attack, contained termiticidal fractions. In 1973 they isolated the termiticidal principles of the essential oil of Sawara wood and identified them as chamaecynone [**1**] and isochamaecynone [**2**] (4). We are interested in the termiticidal activity of these compounds and decided to undertake a more extensive study of structure-termiticidal activity relationships in order to delineate further the structural requirements for biological activity.

RESULTS AND DISCUSSION

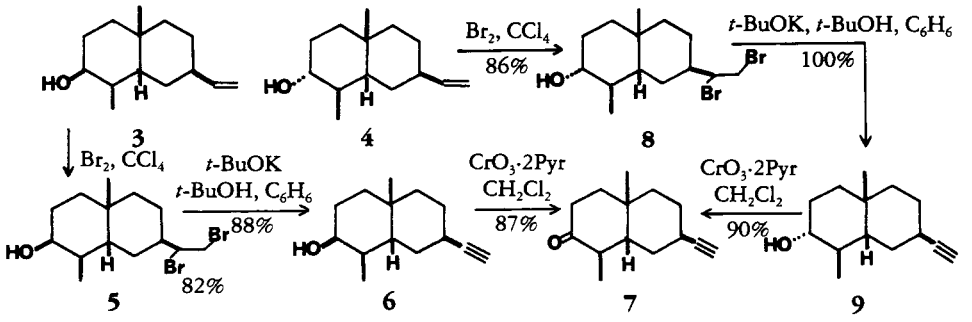
Prior to the preparation of substrates to test their termiticidal activity, our attention was focused on the modification of three portions of the molecule of chamaecynone [**1**]:



1 Chamaecynone | Non-Steroid Conformation | **2** Isochamaecynone | Steroid Conformation

FIGURE 1

[1]For Part 4 in this series, see Ando *et al.* (1).



SCHEME 1

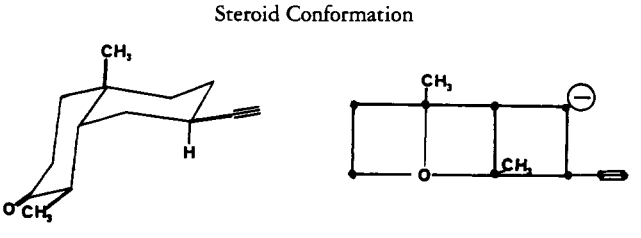
(a) the enone part of the A-ring; (b) the terminal acetylenic bond at C-7; and (c) the conformational change between the non-steroid form and the steroid form resulting from the change of C-4 stereochemistry.

Because it is difficult to obtain large enough quantities of chamaecynone [**1**] by isolation from natural sources, we decided to prepare substrates for the bioassay of the termiticidal activity by modifications of the method of our former synthetic scheme of chamaecynone [**1**] (5).

The synthesis began with the epimeric alcohols **3** and **4**, prepared as previously described from α-santonin (5) (Scheme 1). Bromination of the 3β-alcohol **3** gave the dibromide **5** as a diastereomeric mixture at C-11. Dehydrobromination of **5** with *t*-BuOK in a mixture of *t*-BuOH and C_6H_6 gave the acetylenic 3β-alcohol **6**, which was subsequently oxidized with CrO_3·2pyr complex to give the desired acetylenic ketone [**7**].

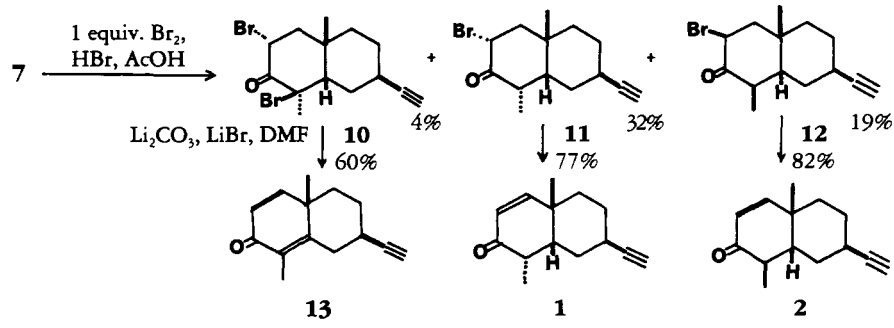
By analogy, bromination of the 3α-alcohol **4** gave the corresponding dibromide **8**. Dehydrobromination of **8** gave the acetylenic 3α-alcohol **9**, which was subsequently oxidized with CrO_3·2pyr complex to give **7**. The ord curve of **7** showed a negative Cotton effect, which was in accordance with the expected sign for **7** with a steroid conformation bearing the β(eq)-Me group at C-4 (Figure 2).

Bromination of **7** with 1 molar equivalent of Br_2 in AcOH in the presence of HBr gave the dibromoketone **10**, the 2α-bromoketone **11**, and the 2β-bromoketone **12** in 4%, 32%, and 19% yields, respectively (Scheme 2). Analysis of the ^{1}H-nmr spectrum of **10** showed that this compound possessed a non-steroid conformation with 2α(eq)- and 4β(ax)-Br atoms, and 4α(eq)-Me and 7β(ax)-ethynyl groups (Figure 3). The deshielding effect of the 4β(ax)-Br atom caused the downfield shift of the signals of the 10-Me group (δ 1.69) and 2β(ax)-H (δ 5.77). The observed long-range coupling between 1β(eq)-H and 5β-H (J=2.0 Hz), the coupling constants between 5β-H and 6-H_2 (J=13.0 and 4.5 Hz), and the half band-width of 7α(eq)-H ($W_{h/2}$=12.0 Hz) indicated that **10** possessed a non-steroid conformation with a 7β(ax)-ethynyl group. The α(eq)-configu-



7 Octant Projection of **7**

FIGURE 2

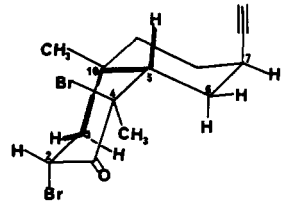


SCHEME 2

ration of the Br atom at C-2 was proved by the observed coupling constants of 2β(ax)-H (J=13.6 and 6.2 Hz).

The stereochemistry of **11** with a non-steroid conformation bearing a 2α(eq)-Br atom and 4α(eq)-Me and 7β(ax)-ethynyl groups was proved from an analysis of the ^{1}H-nmr spectrum (Figure 4). The half band-width of H-7 ($W_{h/2}$=11.0 Hz) showed that **11**

Non-Steroid Conformation

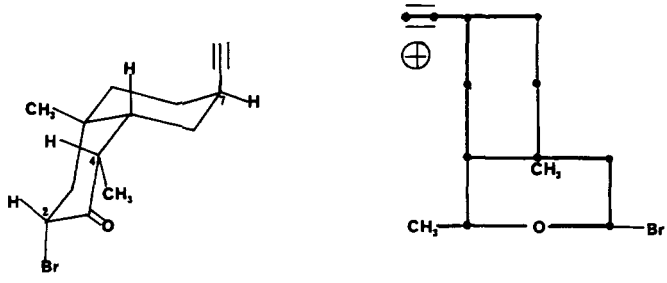


10

FIGURE 3

possessed a non-steroid conformation bearing a 7β(ax)-ethynyl group. The α(eq)-configuration of the Br atom at C-2 was confirmed by the coupling constants of 2β(ax)-H (J=13.5 and 6.7 Hz). The ord curve of this compound showed a positive Cotton effect in accordance with the expected sign for **11**, with a non-steroid conformation bearing the α(eq)-Br atom at C-2 and an α(eq)-Me group at C-4.

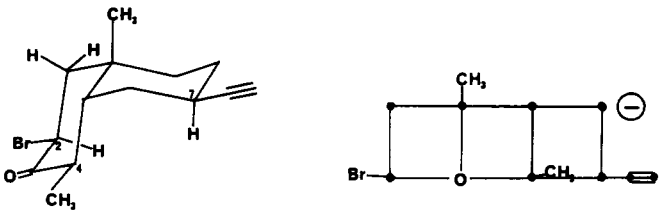
Non-Steroid Conformation



11 Octant Projection of **11**

FIGURE 4

Steroid Conformation



12 Octant Projection of **12**

FIGURE 5

In contrast, the half band-width of H-7 of **12** ($W_{h/2}$=24.0 Hz) showed that **12** possessed the steroid conformation bearing the 7β(eq)-ethynyl group (Figure 5). The β(eq)-configuration of the Br atom at C-2 was inferred from the coupling constants of 2α(ax)-H (J=13.5 and 6.0 Hz). The ord curve of this compound showed a negative Cotton effect in accordance with the expected sign for **12** with the steroid conformation bearing the β(eq)-Br atom at C-2 and the β(eq)-Me group at C-4.

Dehydrobromination of **10**, **11**, and **12** with a mixture of LiBr and Li_2CO_3 in DMF gave dehydrochamaecynone [**13**], chamaecynone [**1**], and isochamaecynone [**2**] in 60%, 77%, and 82% yields, respectively. The dienone structure of **13** in the A ring with a 7β(eq)-ethynyl group at C-7 was supported by the ir and ^{1}H-nmr spectral data shown in the Experimental.

The stereostructure of **1** with a non-steroid conformation bearing 4α(eq)-Me and 7β(ax)-ethynyl groups (see Figure 1) was indicated by the following analysis of the ^{1}H-nmr spectrum. The coupling constant between H-1 and H-5 (J=2.3 Hz) based on the W long-range coupling and the coupling constant between H-4 and H-5 (J=4.1 Hz), as well as the half band-width ($W_{h/2}$=12.0 Hz) of H-7, were in good agreement with the stereostructure of **1** with a non-steroid conformation. The ord curve of **1** showed a positive Cotton effect in accordance with the sign for **1** with a non-steroid conformation bearing the α(eq)-Me group at C-4.

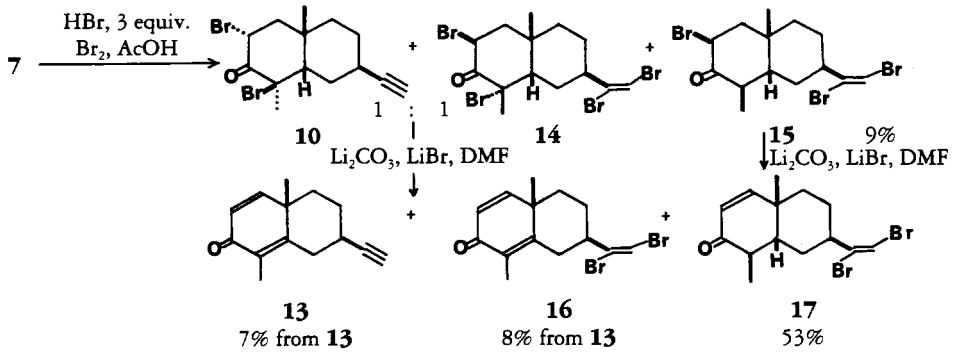
The stereostructure of **2** (see Figure 1) was also revealed from interpretation of its ^{1}H-nmr spectral data. Long-range coupling between H-1 and H-5 was not observed in **2**. The coupling constant between H-4 and H-5 (J=13.4 Hz) as well as the half band-width of H-7 ($W_{h/2}$=24.0 Hz) showed that **2** possessed the steroid conformation with 4β(eq)-Me and 7β(eq)-ethynyl groups. The ord curve of **2** showed a negative Cotton effect in accordance with the steroid conformation bearing the β(eq)-Me group at C-4.

Bromination of **7** with 3 molar equivalents of Br_2 in AcOH in the presence of HBr gave the acetylenic dibromoketone **10**, the tetrabromide **14**, and the tribromide **15** (Scheme 3). Successive dehydrobromination of **10**, **14**, and **15** with a mixture of LiBr and Li_2CO_3 in DMF gave dehydrochamaecynone [**13**], dibromodehydrochamaecynone [**16**], and dibromoisochamaecynone [**17**], in 7%, 8%, and 5% overall yields from **7**, respectively.

The structure of **16** was fully supported by the ^{1}H- and ^{13}C-nmr spectral data shown in the Experimental.

The stereostructure of **17** was also revealed by the analysis of ^{1}H-nmr spectral data. The long-range coupling between H-1 and H-5 was not observed. The coupling constant between H-4 and H-5 (J=13.0 Hz) and the half band-width of H-7 ($W_{h/2}$=28.0 Hz) showed that **17** possessed the steroid conformation with 4β(eq)-Me and 7β(eq)-dibromovinyl groups.

The acetylenic ketone **7** was treated with a 2% EtOH solution of KOH and then



SCHEME 3

quenched by aqueous AcOH to give a 1:1.6 mixture of **7** and **18**, which gave **18** after separation by Si gel chromatography (Figure 6). The structure of **18** with a non-steroid conformation bearing 4α(eq)-Me and 7β(ax)-ethynyl groups was fully supported by the ord curve, which showed a positive Cotton effect, as well as by analysis of ^{1}H-nmr spectral data (Figure 7).

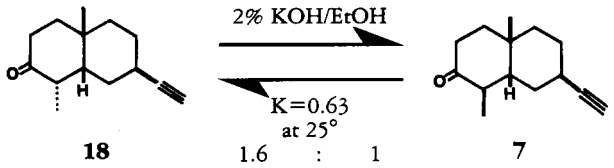


FIGURE 6

The termiticidal activity of chamaecynone [**1**] and ten related compounds that were synthesized by the above-mentioned methods was examined (Tables 1 and 2). All compounds possessing an ethynyl group at C-7 (**1**, **2**, **6**, **7**, **9**, **13**, **18**) showed significant termiticidal activity. A terminal acetylene (ethynyl group) at C-7 seems to be essential for the activity of these compounds.

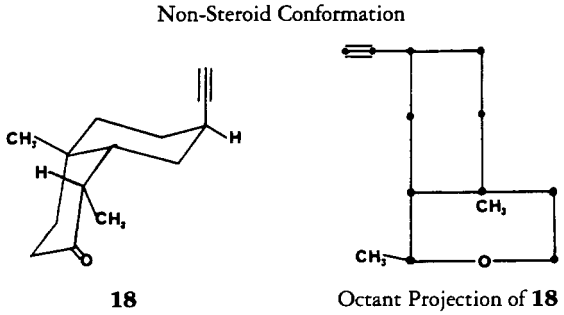


FIGURE 7

The potency of the termiticidal activity was also influenced by changes in the structure of the A-ring of the compounds, with the compounds being ranked in the following order of decreasing potency: dienone **13**>enone **1**>enone **2**=ketone **18**=ketone **7**≧alcohol **9**>alcohol **6**. These results show that the dienone and enone groups in the A-ring enhance the activity of compounds.

TABLE 1. The List of Compounds for Bioassay of Termiticidal Activity.

Compound	Functional groups and stereochemistry of substrates			
	Functional group in A ring	Substituent at C-7	C-4 stereochemistry	Conformation
1	1-en-3-one	ethynyl	α-Me	non-steroid
2	1-en-3-one	ethynyl	β-Me	steroid
3	3β-ol	vinyl	β-Me	steroid
4	3α-ol	vinyl	β-Me	steroid
6	3β-ol	ethynyl	β-Me	steroid
7	3-one	ethynyl	β-Me	steroid
9	3α-ol	ethynyl	β-Me	steroid
13	1,4-dien-3-one	ethynyl	—	—
16	1,4-dien-3-one	1,2-dibromovinyl	—	—
17	1-en-3-one	1,2-dibromovinyl	β-Me	steroid
18	3-one	ethynyl	α-Me	non-steroid

Concerning the C-4 stereochemistry, chamaecynone [**1**] with a non-steroid conformation bearing an α-Me group at C-4, showed stronger activity than isochamaecynone [**2**], with the steroid conformation bearing a β-Me group at C-4. The activities of the corresponding saturated ketones **18** and **7** were approximately the same. It is interesting to note that compounds **3** and **4** bearing a vinyl group at C-7 and compound **16** bearing an 1,2-dibromovinyl group at C-7 showed significant activity after 5 days.

In conclusion, the most effective termiticidal compound was dehydrochamaecynone **13**, and the order of termiticidal activity in the test samples was: **13>1>2=18=7≧9>6>16>3>4>17**.

TABLE 2. Termiticidal Activities of Norsesquiterpenoids Against *C. formocencis* by Filter Paper Contact Method.

Compound	Concentration (ppm)	Mortality (%) (days)		
		1	2	5
1	100	0	10	
	1000	100	100	
2	100	0	10	
	1000	30	100	
3	100	0	0	0
	1000	20	30	100
4	100	0	0	0
	1000	0	0	80
6	100	0	0	
	1000	0	70	
7	100	0	0	
	1000	20	100	
9	100	0	0	
	1000	0	100	
13	100	0	50	
	1000	100	100	
16	100	0	10	90
	1000	0	0	90
17	100	10	10	10
	1000	10	10	20
18	100	0	0	
	1000	30	100	

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—All mps are uncorrected. ^{1}H-Nmr spectra were recorded at 200 MHz in $CDCl_3$ unless otherwise stated. Coupling constants are in Hz. ^{13}C-Nmr spectra were recorded at 50.3 MHz in $CDCl_3$. The ord spectra were recorded on a Nihonbunko ORD/UV-5 spectrophotometer. Hreims were recorded on a JEOL-HX110 instrument. Reactions were run under an atmosphere of N_2. $CHCl_3$ and CCl_4 dried over $CaCl_2$ and distilled. Pyridine was distilled from CaH_2, C_6H_6 and ether were dried over Na wire, and *t*-BuOH was dried by refluxing with K and distilled. Hplc was monitored with a refractive index (ri) detector. To describe hplc conditions, the column, solvent, flow rate (ml/min), and retention time (*R*, in min) are designated in order. The column codes are as follows: A, 250×4 mm i.d. stainless steel column packed with 10 μm Si gel; B, 250×8 mm i.d. stainless steel column packed with 10 μm Si gel.

TEST COMPOUNDS.—Compounds **3** and **4** were prepared by previous methodology (5).

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

BIOASSAYS.—A 1-ml quantity of an Me_2CO 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° for 5 days. The number of dead termites was counted to calculate the percent mortality at 1, 2, and 5 days after treatment.

4αH,5βH-13-NOREUDESM-11-EN-3β-OL [**3**].—Needles: mp 53°; ir ν max ($CHCl_3$) 3632, 3484, 3088, 1640, 1000, 916 cm^{-1}; ^{1}H nmr δ 0.97 (3H, d, *J*=7.3 Hz, CH_3-4), 0.99 (3H, s, CH_3-10), 2.02 (1H, m, $W_{h/2}$=25.0 Hz, H-7), 3.80 (1H, br s, $W_{h/2}$=6.5 Hz, H-3), 4.89 (1H, ddd, *J*=10.6, 1.8, and 1.1 Hz, H-12), 4.96 (1H, ddd, *J*=17.2, 1.8, and 1.6 Hz, H-12), 5.76 (1H, ddd, *J*=17.2, 10.6, and 6.4 Hz, H-11); ^{13}C nmr δ 16.72 (q, CH_3-10), 27.78 (q, CH_3-4), 28.02 (t), 28.58 (t), 28.78 (t), 29.76 (t), 32.43 (s, C-10), 33.38 (d), 34.35 (t), 34.86 (d), 40.77 (d), 72.47 (d, C-3), 111.77 (t, C-12), 144.79 (d, C-11); $[\alpha]^{25}$D +33.7° (*c*=1.13, $CHCl_3$); hreims *m/z* 208.1835 ($C_{14}H_{24}O$ requires 208.1827). *Anal.* calcd for $C_{14}H_{24}O$, C 80.71, H 11.61; found C 80.85, H 11.29.

4αH,5βH-13-NOREUDESM-11-EN-3α-OL [**4**].—Oil: ir ν max ($CHCl_3$) 3620, 3480, 3088, 1642, 1002, 916 cm^{-1}; ^{1}H nmr δ 0.95 (3H, s, CH_3-10), 1.00 (3H, d, *J*=6.4 Hz, CH_3-4), 3.13 (1H, ddd, *J*=10.5, 10.5, and 4.6 Hz, H-3), 4.89 (1H, ddd, *J*=10.6, 1.8, and 1.1 Hz, H-12), 4.96 (1H, ddd, *J*=17.2, 1.8, and 1.6 Hz, H-12), 5.75 (1H, ddd, *J*=17.2, 10.6, and 6.4 Hz, H-11); ^{13}C nmr δ 15.26 (q, CH_3-10), 27.73 (q, CH_3-4), 28.12 (t), 28.87 (t), 30.31 (t), 30.86 (t), 32.42 (s, C-10), 35.01 (d), 37.60 (d), 39.06 (t), 46.69 (d, C-7), 76.51 (d, C-3), 111.83 (t, C-12), 114.64 (d, C-11); $[\alpha]^{25}$D +4.6° (*c*=1.24, $CHCl_3$); hreims 208.1830 ($C_{14}H_{24}O$ requires 208.1827). *Anal.* calcd for $C_{14}H_{24}O$, C 80.71, H 11.61; found C 80.34, H 11.15.

11,12-DIBROMO-4αH,5βH-13-NOREUDESMAN-3β-OL [**5**].—Into a stirred solution of **3** (450 mg, 2.16 mmol) in CCl_4 (10 ml) was added a solution of Br_2 (410 mg, 2.59 mmol) in CCl_4 (3 ml). The mixture was stirred for 15 min at 0° and for 2 h at room temperature. The mixture was then washed successively with 2 M aqueous Na_2CO_3 (3×20 ml) and saturated aqueous NaCl, dried (Na_2SO_4), and concentrated to give a crude oil, which was then chromatographed over Si gel (50 g) and eluted with EtOAc-hexane (1:9) to give **5** (649 mg, 82%) as a colorless oil; ir ν max ($CHCl_3$) 3620, 3480 cm^{-1}; ^{1}H nmr δ 1.00 (3H, s, CH_3-10), 1.04 (3H, d, *J*=7.4 Hz, CH_3-4), 3.70–3.90 (3H, m, H-3, H-12), 4.18 (1H, ddd, *J*=13.2, 8.8, and 4.4 Hz, H-11); $[\alpha]^{25}$D +32.7° (*c*=1.48, $CHCl_3$); hreims *m/z* 366.0350 ($C_{14}H_{24}OBr_2$ requires 366.0194).

4αH,5βH-13-NOREUDESMAN-11-YN-3β-OL [**6**].—A mixture of **5** (600 mg, 1.63 mmol), C_6H_6 (12 ml), and 1 M *t*-BuOK in *t*-BuOH (25 ml) was refluxed for 6.5 h (bath temperature 90°). After the removal of half of the volume of the solvent *in vacuo*, the residue was poured into saturated aqueous NaCl and extracted with Et_2O (30 ml, 2×20 ml). The combined extracts were washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated to give a crude oil; which was then chromatographed over Si gel (18 g) and eluted with EtOAc-hexane (1:9) to give **6** (296 mg, 88%) as colorless crystals: mp 88°; ir ν max ($CHCl_3$) 3632, 3488, 3316, 2116, 1008 cm^{-1}; ^{1}H nmr δ 0.99 (3H, d, *J*=6.8 Hz, CH_3-4), 1.03 (3H, s, CH_3-10), 2.03 (1H, d, *J*=2.3 Hz, H-12), 2.30 (1H, m, $W_{h/2}$=24.0 Hz, H-7), 3.80 (1H, $W_{h/2}$=6.0 Hz, H-3); ^{13}C nmr δ 16.64 (q, CH_3-10), 23.05 (d, C-7), 27.62 (q, CH_3-4), 28.53 (t), 28.65 (t), 29.12 (t), 29.47 (t), 32.11 (s, C-10), 33.07 (d), 34.17 (t), 40.46 (d), 67.46 (d, C-12), 72.16 (d, C-3), 89.30 (s, C-11); $[\alpha]^{25}$D +19.1° (*c*=1.09, $CHCl_3$); hreims *m/z* 206.1678 ($C_{14}H_{22}O$ requires 206.1671).

PREPARATION OF 4αH,5βH-13-NOREUDESM-11-YN-3-ONE [**7**] FROM **6**.—Chromic anhydride (1.485 g, 14.8 mmol) was added into a mixture of CH_2Cl_2 (12 ml) and pyridine (2.4 ml, 29.7 mmol) at 0° and stirred for 1 h. Then **6** (205 mg, 0.99 mmol) dissolved in CH_2Cl_2 (6.0 ml) was added over a 5 min period, and the

mixture was stirred at 0° for 3 h, stored in a refrigerator overnight, and filtered through Celite under reduced pressure. The filtrate was washed successively with saturated aqueous $NaHCO_3$, 2 M HCl, and saturated aqueous NaCl, dried (Na_2SO_4) and concentrated to give **7** (176 mg, 87%): Colorless prisms, mp 95°; ir ν max ($CHCl_3$) 3316, 2120, 1712 cm^{-1}; ^1H nmr δ 1.03 (3H, d, J=6.5 Hz, CH_3-4), 1.07 (3H, s, CH_3-10), 2.06 (1H, d, J= 2.2 Hz, H-12), 2.25 (1H, ddd, J=13.5, 4.5, and 3.2 Hz, H-6_{eq}), 2.18–2.60 (3H, m, H-4, H-5, H-7); ord (MeOH) $[\phi]_{304}=-896$, $[\phi]_{265}=+1790$, A=−26.9; $[\alpha]^{25}D$ +19.3° (c=2.27, $CHCl_3$); hreims m/z 204.1511 ($C_{14}H_{20}O$ requires 204.1514).

11,12-DIBROMO-4αH,5βH-13-NOREUDESMAN-3α-OL [**8**].—Compound **8** was prepared from **4** in 86% yield by an analogous method to that employed in the preparation of **5** from **3**. **8**: Colorless needles: mp 127°; ir ν max ($CHCl_3$) 3628, 3484 cm^{-1}; ^1H nmr δ 0.97 (3H, s, CH_3-10), 1.02, 1.06 (3H, d, J=7.0 Hz, CH_3-4), 3.14 (1H, ddd, J=10.0, 10.0, and 4.4 Hz, H-3), 3.69–3.90 (2H, m, H_2-12), 4.13–4.25 (1H, m, H-11); $[\alpha]^{25}D$ +34.1° (c=2.09, $CHCl_3$); hreims m/z 366.0193 ($C_{14}H_{24}OBr_2$ requires 366.0194). *Anal.* calcd for $C_{14}H_{24}OBr_2$, C 45.65, H 6.57; found C 45.81, H 6.69.

4αH,5βH-13-NOREUDESMAN-11-YN-3α-OL [**9**].—Compound **9** was prepared from **8** in 100% yield by an analogous method to that employed in the preparation of **6** from **5**. **9**: Colorless oil; ir ν max ($CHCl_3$) 3624, 3492, 3316, 2116, 1008 cm^{-1}; ^1H nmr δ 0.99 (3H, s, CH_3-10), 1.01 (3H, d, J=7.5 Hz, CH_3-4), 2.04 (1H, d, J=2.4 Hz, H-12), 2.32 (1H, m, $W_{h/2}$=25.0 Hz, H-7), 3.12 (1H, ddd, J=10.0, 10.0, and 4.3 Hz, H-3); $[\alpha]^{25}D$ −5.8° (c=1.08, $CHCl_3$); hreims m/z 206.1670 ($C_{14}H_{22}O$ requires 206.1671).

PREPARATION OF **7** FROM **9**.—Compound **7** was prepared from **9** in 90% yield by an analogous method to that employed in the preparation of **7** from **6**.

2α,4β-DIBROMO-5βH-13-NOREUDESM-11-YN-3-ONE [**10**], 2α-BROMO-4,5βH-13-NOREUDESM-11-YN-3-ONE [**11**], AND 2β-BROMO-4αH,5βH-13-NOREUDESM-11-YN-3-ONE [**12**].—To a solution of **7** (50 mg, 0.245 mmol) in AcOH (10 ml) were successively added 48% HBr (50 μl) and a solution of Br_2 (39 mg, 0.25 mmol) in AcOH (1 ml). The mixture was stirred for 1.5 h at room temperature, poured into saturated aqueous NaCl (30 ml), and extracted with Et_2O (3×20 ml). The combined extracts were washed successively with 2 M aqueous Na_2CO_3 (3×20 ml) and saturated aqueous NaCl (2×30 ml), dried (Na_2SO_4), and concentrated to give an oily crude product (80 mg), which was chromatographed over Si gel [5g, EtOAc-hexane (5:95)]. The eluent was further purified by hplc [A, EtOAc-hexane (5:95), 3.0 ml/min].

The first peak (R_t 2.2 min) afforded **10** (3 mg, 4%) as colorless crystals: mp 58°; ir ν max ($CHCl_3$) 3316, 2116, 1734 cm^{-1}; ^1H nmr δ 1.69 (3H, s, CH_3-10), 1.91 (3H, s, CH_3-4), 2.13 (1H, d, J=2.4 Hz, H-12), 2.55 (1H, dd, J=13.6 and 13.6 Hz, H-1_{ax}), 2.62 (1H, ddd, J=13.0, 4.5, and 2.0 Hz, H-5), 2.91 (1H, m, $W_{h/2}$=12.0 Hz, H-7), 5.77 (1H, dd, J=13.6 and 6.2 Hz, H-2).

The second peak (R_t 3.2 min) afforded **11** (22 mg, 32%) as colorless crystals: mp 112°; ir ν max ($CHCl_3$) 3316, 2116, 1734 cm^{-1}; ^1H nmr δ 1.05 (3H, d, J=6.6 Hz, CH_3-4) 1.38 (3H, s, CH_3-10), 2.06 (1H, d, J=2.5 Hz, H-12), 2.56 (1H, dd, J=13.5 and 13.5 Hz, H-1_{ax}), 2.89 (1H, m, $W_{h/2}$=11.0 Hz, H-7), 3.12 (1H, qdd, J=6.6, 6.4, and 1.2 Hz, H-4), 4.88 (1H, ddd, J=13.5, 6.7, and 1.2 Hz, H-2); ^{13}C nmr δ 11.99 (q, CH_3-4), 25.35 (t), 26.44 (d), 27.01 (t), 27.63 (q, CH_3-10), 34.33 (t), 36.44 (s, C-10), 43.11 (d), 44.44 (t), 46.37 (d), 54.29 (d), 69.99 (d, C-12), 86.23 (s, C-11), 202.83 (s, C-3); ord (MeOH) $[\phi]_{310}=+396$, $[\phi]_{270}=-1200$, A=+16; hreims m/z 282.0601 ($C_{14}H_{19}OBr$ requires 282.0619). *Anal.* calcd for $C_{14}H_{19}OBr$, C 59.41, H 6.77; found C 58.53, H 6.89.

The third peak (R_t 4.0) afforded **12** (13 mg, 19%) as colorless crystals: mp 113°; ir ν max ($CHCl_3$) 3316, 2120, 1734 cm^{-1}; ^1H nmr δ 1.11 (3H, s, CH_3-10), 1.12 (3H, d, J=6.5 Hz, CH_3-4), 2.07 (1H, d, J=2.2 Hz, H-12), 2.37 (1H, dd, J=13.5 and 6.0 Hz, H-1_{eq}), 2.39 (1H, m, $W_{h/2}$=24.0 Hz, H-7), 2.65 (1H, dqd, J=12.0, 6.5, and 1.0 Hz, H-4), 4.83 (1H, ddd, J=13.5, 6.0, and 1.0 Hz, H-2); ^{13}C nmr δ 12.29 (q, CH_3-4), 22.68 (t), 26.20 (d), 28.13 (t), 30.09 (q, CH_3-10), 30.27 (t), 35.62 (s, C-10), 42.63 (d), 49.61 (t), 53.36 (2C, d), 68.38 (d, C-12), 87.54 (s, C-11), 203.45 (s, C-3); ord (MeOH) $[\phi]_{310}=-470$, $[\phi]_{260}=+604$, A=−10.7. *Anal.* calcd for $C_{14}H_{19}OBr$, C 59.41, H 6.77; found C 59.62, H 6.85.

PREPARATION OF 13-NOREUDESM-1,4-DIEN-11-YN-3-ONE [**13**] FROM **10**.—A mixture of **10** (3 mg, 0.008 mmol), Li_2CO_3 (2.5 mg, 0.033 mmol) and LiBr (2.5 mg, 0.029 mmol) in DMF (1 ml) was heated at 155° for 5.5 h and worked up as usual to give an oily crude material (2.9 mg), which was purified by hplc [A, EtOAc-hexane (1:9), 3.0 ml/min]. The major peak (R_t 6.8 min) afforded **13** (1 mg, 60%) as colorless crystals: mp 84°; ir ν max ($CHCl_3$) 3316, 2120, 1662, 1630, 1612 cm^{-1}; ^1H nmr δ 1.26 (3H, s, CH_3-10), 1.93 (3H, s, CH_3-4), 2.18 (1H, d, J=1.9 Hz, H-12), 2.24–2.36 (2H, m, H-6_{ax}, H-7), 3.08 (1H, dd, J=10.5 and 1.6 Hz, H-6_{eq}), 6.24 (1H, d, J=9.9 Hz, H-2), 6.74 (1H, d, J=9.9 Hz, H-1); hreims m/z 200.1203 ($C_{14}H_{16}O$ requires 200.1201).

CHAMAECYNONE [**1**] FROM **11**.—A mixture of **11** (20 mg, 0.07 mmol), Li_2CO_3 (21 mg, 0.28 mmol), LiBr (21 mg, 0.24 mmol) in DMF (2 ml) was heated at 155° for 5.5 h and worked up as usual to give an oily

crude product (15 mg), which was purified by Si gel cc [5 g, EtOAc-hexane (5:95)] to give **1** (11 mg, 77%) as colorless crystals: mp 88°; ir ν max ($CHCl_3$) 3316, 2112, 1676 cm^{-1}; ^1H nmr δ 1.09 (3H, d, J=6.9 Hz, CH_3-4), 1.30 (3H, s, CH_3-10), 2.09 (1H, d, J=2.6 Hz, H-12), 2.86 (1H, m, $W_{h/2}$=12.0 Hz, H-7), 3.01 (1H, qd, J=6.9 and 4.1 Hz, H-4), 5.91 (1H, d, J=10.0 Hz, H-2), 6.45 (1H, dd, J=10.0 and 2.3 Hz, H-1); $[\alpha]^{25}D$ −101.3° (c=1.35, $CHCl_3$); ord (MeOH) $[\phi]_{352}$=+600; hreims m/z 202.1359 ($C_{14}H_{18}O$ requires 202.1358).

ISOCHAMAECYNONE [**2**] FROM **12**.—A mixture of **12** (12 mg, 0.042 mmol), Li_2CO_3 (13 mg, 0.17 mmol), and LiBr (13 mg, 0.15 mmol) was treated as mentioned above to give **2** (7 mg, 82%) as colorless crystals: mp 95°; ir ν max ($CHCl_3$) 3316, 2120, 1678 cm^{-1}; ^1H nmr δ 1.16 (3H, d, J=6.7 Hz, CH_3-4), 1.23 (3H, s, CH_3-10), 2.08 (1H, d, J=2.3 Hz, H-12), 2.38 (1H, m, $W_{h/2}$=24.0 Hz, H-7), 2.45 (1H, dq, J=13.4 and 6.7 Hz, H-4), 5.88 (1H, d, J=10.0 Hz, H-2), 6.56 (1H, d, J=10.0 Hz, H-1); $[\alpha]^{25}D$ +1.8° (c=1.09, $CHCl_3$); ord (MeOH) $[\phi]_{340}$=−870°; hreims m/z 202.1357 ($C_{14}H_{18}O$ requires 202.1358).

4,5βH-13-NOREUDESM-11-YN-3-ONE [**18**].—A solution of **7** (370 mg, 1.81 mmol) in 2% KOH/EtOH (25 ml) was allowed to stand at room temperature for 14 h and poured into saturated aqueous NaCl (100 ml). The mixture was treated in the usual manner to give a mixture of **7** and **18** (1:1.6), which was separated by Si gel cc. The first run gave **18** (111 mg), which was then recrystallized from pentane to give colorless prisms: mp 105°; ir ν max (KBr) 3279, 2120, 1701 cm^{-1}; $[\alpha]^{25}D$ −16.1° (c=0.87, $CHCl_3$); ^1H nmr δ 0.95 (3H, d, J=7.0 Hz, CH_3-4), 1.32 (3H, s, CH_3-10), 2.05 (1H, d, J=2.5 Hz, H-12), 2.87 (1H, m, $W_{h/2}$=12.0 Hz, H-7); ^{13}C nmr δ 11.53, 25.50, 26.74, 27.12, 27.42, 31.10, 33.62, 34.74, 37.89, 43.24, 46.39, 69.60, 86.81, 213.56; ord (MeOH) $[\phi]_{304}$=+897, $[\phi]_{265}$=−1790, A=+26.9. *Anal.* calcd for $C_{14}H_{20}O$, C 82.30, H 9.87; found C 81.77, H, 9.71.

REACTION OF **7** WITH THREE MOLAR EQUIVALENTS OF Br_2. THE FORMATION OF **10**, A TETRABROMIDE **14**, AND A TRIBROMIDE **15**.—A mixture of **7** (30 mg, 0.15 mmol) and 48% HBr (0.15 mmol) in AcOH (2 ml) was stirred for 30 min at room temperature. Then, Br_2 (72 mg, 0.45 mmol) was added into the mixture and stirred for 2 h and worked up as usual to give an oily crude product (62 mg), which was passed through a Si gel column [5 g, EtOAc-hexane (5:95)] and then further purified by hplc [A, EtOAc-hexane (5:95), 3.0 ml/min].

The first peak (R_t 2.0 min) afforded a 1:1 mixture of **10** and **14** (15 mg): ^1H nmr of **14**, δ 1.14 (3H, s, CH_3-10), 1.96 (3H, s, CH_3-4), 5.79 (1H, dd, J=14.3 and 5.4 Hz, H-2), 6.48 (1H, s, H-12).

The second peak (R_t 2.4 min) gave **15** (6 mg, 9%) as a colorless crystalline material: ^1H nmr δ 1.13 (3H, s, CH_3-10), 1.16 (3H, d, J=6.4 Hz, CH_3-4), 2.40 (1H, dd, J=13.3 and 6.1 Hz, H-1_{eq}), 2.81 (1H, qd, J=6.4 and 6.4 Hz, H-4), 3.08 (1H, dddd, J=12.0, 12.0, 3.7, and 3.7 Hz, H-7), 4.89 (1H, dd, J=14.3 and 6.1 Hz, H-2), 6.41 (1H, s, H-12).

FORMATION OF **13** AND **16** FROM A 1:1 MIXTURE OF **10** AND **14**.—A 1:1 mixture of **10** and **14** (15 mg), Li_2CO_3 (12 mg), and LiBr (12 mg) in DMF (2 ml) was heated at 155° for 5 h and worked up as usual to give an oily crude product (11 mg), which was purified by hplc [A, EtOAc-hexane (1:9), 3.0 ml/min].

The first peak (R_t 4.6 min) gave **16** (4 mg, 8%) as a crystalline material: ^1H nmr δ 1.29 (3H, s, CH_3-10), 1.45 (1H, ddd, J=13.0, 13.0, and 4.0 Hz, H-9_{ax}), 1.64 (1H, dddd, J=13.0, 4.0, 2.0, and 1.7 Hz, H-8_{eq}), 1.87 (1H, ddd, J=13.0, 4.0, and 2.0 Hz, H-9_{eq}), 1.94 (3H, d, J=1.1 Hz, CH_3-4), 2.04 (1H, dddd, J=13.0, 13.0, 13.0, and 4.0 Hz, H-8_{ax}), 2.47 (1H, ddd, J=13.0, 13.0, and 1.1 Hz, H-6_{ax}), 2.72 (1H, ddd, J=13.0, 4.0, and 1.7 Hz, H-6_{eq}), 2.94 (1H, dddd, J=13.0, 13.0, 4.0, and 4.0 Hz, H-7), 6.26 (1H, d, J=9.9 Hz, H-2), 6.49 (1H, s, H-12), 6.76 (1H, d, J=9.9 Hz, H-1); ^{13}C nmr δ 10.57 (q, CH_3-4), 23.41 (q, CH_3-10), 24.80 (t, C-8), 31.51 (t, C-6), 36.44 (t, C-9), 39.78 (s, C-10), 43.63 (d, C-7), 102.23 (d, C-12), 126.38 (d, C-2), 130.43 (s), 130.72 (s), 156.11 (d, C-1), 156.90 (s, C-11), 186.04 (s, C-3); hreims m/z 357.9568 ($C_{14}H_{16}OBr_2$ requires 357.9568).

The second peak (R_t 5.8 min) afforded **13** (2 mg, 7% from **13**).

11,12-DIBROMO-4αH,5βH-13-NOREUDESM-1,11-DIEN-3-ONE [**17**].—A mixture of **15** (6 mg, 0.014 mmol), Li_2CO_3 (4 mg, 0.05 mmol), LiBr (4 mg, 0.05 mmol) in DMF (2 ml) was heated at 155° for 5.5 h and worked up as usual to give an oily crude product, which was purified by hplc [A, EtOAc-hexane (1:9), 3.0 ml/min].

The major peak (R_t 2.4 min) gave **17** as a colorless crystalline material (2.6 mg, 53%): ^1H nmr δ 1.19 (3H, d, J=6.7 Hz, CH_3-4), 1.25 (3H, s, CH_3-10), 2.64 (1H, dq, J=13.0 and 6.7 Hz, H-4), 3.05 (1H, m, $W_{h/2}$=28 Hz, H-7), 5.90 (1H, d, J=10.0 Hz, H-2), 6.41 (1H, s, H-12), 6.57 (1H, d, J=10.0 Hz, H-1); hreims m/z 359.9700 ($C_{14}H_{18}OBr_2$ requires 359.9724).

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