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The Total Syntheses of Chamaecynone, Isochamaecynone, and Dihydroisochamaecynone[1)]

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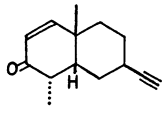
A novel acetylenic nor-sesquiterpene, chamaecynone, and its related natural products, isochamaecynone and dihydroisochamaecynone, have been synthesized starting from α-santonin. In the base-induced equilibration of three pairs of compounds, chamaecynone and isochamaecynone, 4β*H*,5β-13-noreudesm-11-yn-3-one and 4α*H*, 5β-13-noreudesm-11-yn-3-one, and 4β*H*,5β-13-noreudesm-11-en-3-one and 4α*H*,5β-13-noreudesm-11-en-3-one, the ΔH values were determined to be +1.47 kcal/mol, +0.77 kcal/mol, and −2.28 kcal/mol respectively.

Chamaecynone (**1**), one of the nor-sesquiterpenes originally isolated from the essential oil of the Benihi tree (*Chamaecyparis formosensis* Matsum., Cupressaceae), has been shown to have a novel non-steroid *cis*-decalin conformation and to be one of the first examples of a natural acetylenic compound of terpenoid origin.[5)] Recently this compound has become of particular interest because of its efficient termiticidal activity without any significant toxicity on humans or domestic animals.[6,7)]



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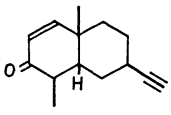

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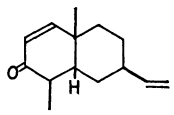

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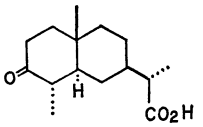
This paper will detail the total syntheses of chamaecynone and the related natural products, isochamaecynone (**2**) and dihydroisochamaecynone (**3**), in optically active forms.

Syntheses

We chose α-santonin (**4**) as the starting material of these syntheses mainly for the following four reasons: 1) Pure α-santonin is commercially available in large quantities, and its total synthesis has already been completed.[8)] 2) α-Santonin is conveniently functionalized as the starting material of the syntheses of chamaecynone and its related compounds, including the absolute configuration. 3) Since the *cis*-decalin intermediates in these syntheses are expected to be conformationally mobile, the optically active starting material is convenient for following the stereochemistry of intermediates by the analyses of CD or ORD curves. 4) Since chamaecynone is a bioactive compound, we want to get enough of chamaecynone and its related compounds in optically active forms for their bioassay.

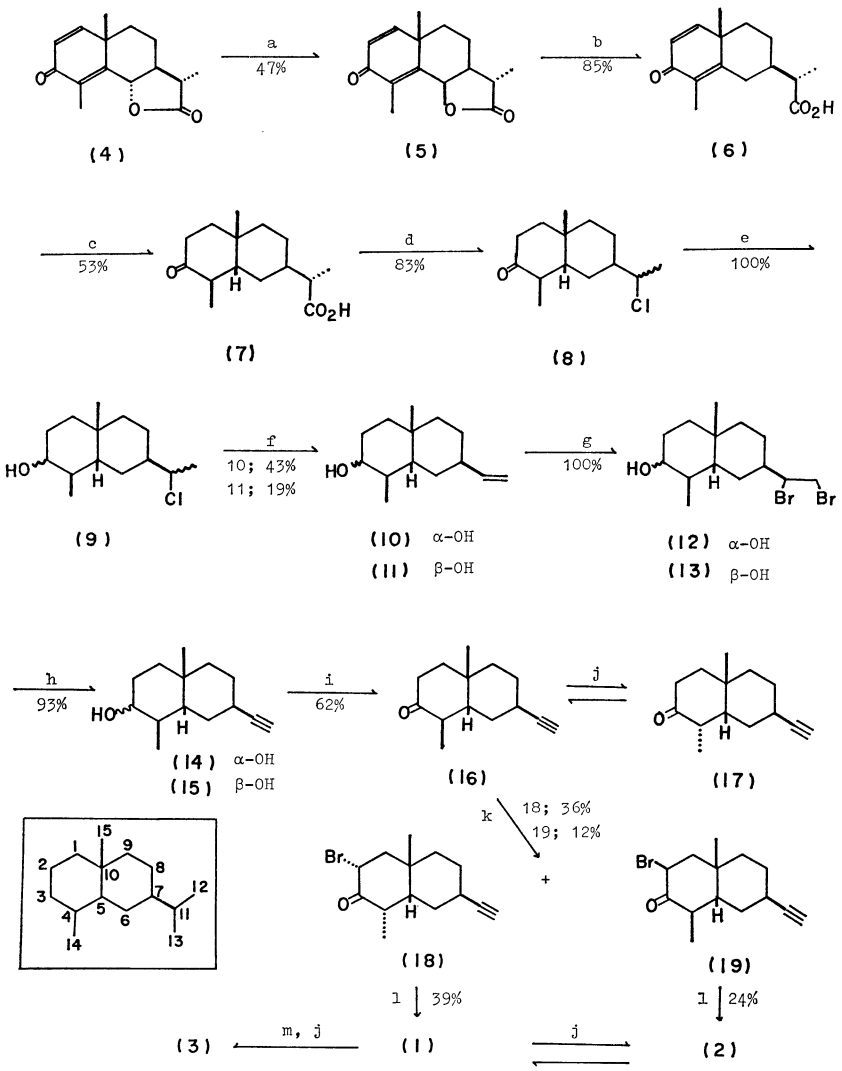
In the syntheses of chamaecynone and its related compounds, there are three problems to overcome: 1) how to introduce the AB *cis*-ring junction, 2) how to introduce the terminal double bond (in dihydroisochamaecynone) or the terminal triple bond (in chamaecynone and isochamaecynone), and 3) how to introduce the α,β-unsaturated carbonyl moiety with an α-oriented methyl group (in chamaecynone) or a β-oriented methyl group (isochamaecynone and dihydroisochamaecynone) at the C_4-position. Keeping these problems in mind, we planned and carried out the syntheses according to the accompanying flow chart.

The first target was the preparation of the *cis*-decalone derivative (**7**). According to the method reported by Ishikawa,[9)] α-santonin was transformed into 6-episantonin (**5**), which was then easily reduced by zinc and acetic acid in methanol to give dienone carboxylic acid (**6**), although α-santonin had been recovered under the same conditions.[10)] Since the stereochemical course of the hydrogenation of α,β-unsaturated ketones is generally influenced by the presence of an acid or base, and by the solvent and catalyst employed,[11)] we examined the conditions of the catalytic hydrogenation of **6**; the best results will be presented below. The catalytic hydrogenation of **6** in ethanol containing potassium hydroxide (1.8 equiv) in the presence of 5% Pd/C gave a *ca.* 3:1 mixture of *cis*-**7** and *trans*-**20**. Fortunately, **7** was easily separated from the mixture by recrystallization. In agreement with the structure, the ORD curve of **7** exhibited a negative Cotton effect; on the contrary, the ORD curve of **20** showed positive Cotton effect.[15)]



(20)

The next problem is the replacement of the carboxyl group of **7** with halogen. For this purpose, the Hunsdiecker reaction is well knwon. The silver salt of **7** was treated with bromine or iodine in carbon tetrachloride, but the results were disappointing. Probably the free halogen employed in this reaction attacked not only the silver salt of carboxyl group, but also the α-position of the carbonyl group to give a complex mixture. The application of Kochi's chlorodecarboxylation reaction[12)] to **7** gave an excellent result. Compound (**7**) was treated with lithium chloride (7 equiv) and lead tetraacetate (8 equiv) in refluxing benzene to give a desired chloro ketone (**8**) as a single stereoisomer, although the stereochemistry at C_{11} was not determined. When the ratio of lithium chloride to lead tetraacetate was increased, the chlorination of the α-position of the carbonyl group occurred, along with chlorodecarboxylation. When lithium bromide or lithium iodide was employed instead of lithium chloride, the reaction gave a complex mixture.

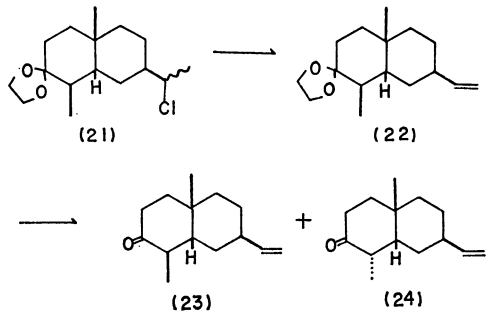


a: HCl gas, DMF; b: Zn, AcOH, MeOH; c: H_2, 5% Pd/C, KOH/EtOH; d: LiCl, $Pb(OAc)_4$, C_6H_6; e: $NaBH_4$, MeOH, ether; f: 1 M *t*-BuOK/*t*-BuOH; g: Br_2, CCl_4; h: 1 M *t*-BuOK/*t*-BuOH, C_6H_6; i: $CrO_3 \cdot 2Py$, Py; j: OH^- or H_3O^+; k: 48% HBr, Br_2, AcOH; l: LiBr, Li_2CO_3, DMF; m: H_2, Lindlar catalyst.

Scheme 1.

In the next step we envisioned the regioselective introduction of a double bond at the terminal position by the dehydrochlorination of **8** or an analogous method. Compound (**8**) was treated with lithium chloride and lithium carbonate in *N*,*N*-dimethylformamide to give a complex mixture of the double-bond isomers. Compound (**8**) was inert toward dehydrochlorination with such amines as *N*,*N*-dimethylaniline and collidines or toward substitution reactions with dimethylamine, bromide ions, and iodide ions. Since attempted dehydrochlorination of **8** with potassium *t*-butoxide gave unidentified acidic products by the air oxidation of the enolate anion of **8**,[13] we decided to try the same reaction after the protection of the carbonyl group.

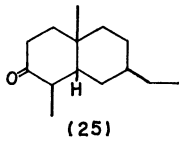
The acetalization of **8** under standard conditions gave chloro acetal (**21**). The treatment of **21** with potassium *t*-butoxide gave the desired olefinic acetal (**22**). The deacetalization of **22** with dil. hydrochloric acid in ethanol gave a 2:1 mixture of **23** and **24**. The



stereochemistry of **23** and **24** will be discussed below.

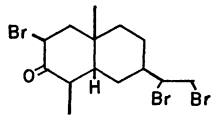
The dehydrochlorination of **8** was achieved by an alternate route. The reduction of **8** with sodium borohydride gave an oily mixture of epimeric alcohols (**9**). The dehydrochlorination of **9** with potassium *t*-butoxide gave a mixture of olefinic alcohols, which then afforded a 3α-alcohol (**10**) and 3β-alcohol (**11**) in 43% and 19% yields respectively after separation,

The oxidation of **10** and **11** gave the same ketone (**23**), while the catalytic hydrogenation of **23** afforded hexahydroisochamaecynone (**25**), which was identical with an authentic sample in its IR and NMR spectra.[5]



(25)

In the following steps we envisioned an approach to isochamaecynone which consisted of the bromination of **23** and the successive dehydrobromination of the resulting tribromide (**26**). The bromination of **23** with bromine (2 equiv) in carbon tetrachloride gave a tribromide (**26**). The dehydrobromination of **26** with potassium *t*-butoxide gave a complex mixture whose IR spectrum showed a strong absorption of the terminal triple bond at 3280 cm^{-1} but no absorption of an α,β-unsaturated carbonyl group. The treatment of **26** with lithium bromide and lithium carbonate in *N,N*-dimethylformamide or with such amines as *N,N*-dimethylaniline, collidines, and dimethylamine gave a mixture whose IR showed an absorption of an α,β-unsaturated carbonyl group, but no absorption of a triple bond. An attempted synthesis of dihydroisochamaecynone by the dehydrohalogenation of the bromo chloro ketone (**27**), which had been prepared



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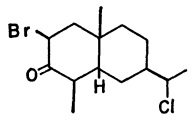
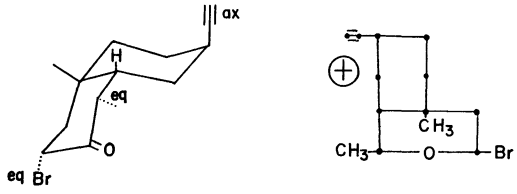


(27)

from **8**, gave analogous negative results. Since these results suggested that the reaction conditions of the formation of an α,β-unsaturated carbonyl moiety and a terminal triple bond were quite different, we decided to introduce these functional groups step by step.

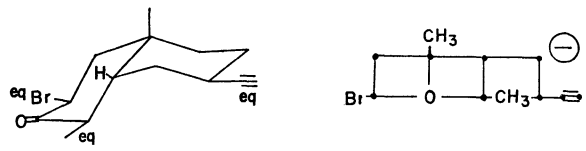
The bromination of **10** gave a dibromide (**12**) as a diastereomeric mixture at C_{11}. The dehydrobromination of **12** with potassium *t*-butoxide gave an acetylenic alcohol (**14**), which was subsequently oxidized with the chromium trioxide–pyridine complex gave the desired acetylenic ketone (**16**). For practical purposes, **16** was prepared from **8** in a 32% overall yield without any separation or purification of the intermediates. The equatorial configuration of the C_4–Me group of **16** was suggested from the solvent effect in the NMR spectrum on passing from CCl_4 to benzene.[14] The ORD curve showed a negative Cotton effect, which was in accordance with the expected sign for **16**, with the steroid conformation bearing a $\beta(eq)$-methyl group at C_4.[15]

The bromination of **16** with bromine in acetic acid in the presence of hydrobromic acid afforded two kinds of unstable monobromides (**18** and **19**) after separation by column chromatography. The NMR spectrum of **18** in CCl_4 exhibited peaks at δ 0.98 (d, J=6.5 Hz, C_4–Me), 1.33 (s, C_{10}–Me), 1.85 (d, J=2.5 Hz, –C≡CH), and 4.57 (q, J=7.5 and 13.0 Hz, C_2–H). In particular, the bromine atom at C_2 was shown to be situated in an equatorial position by the magnitude of the coupling constans of C_2–H. This assignment was also supported by the IR absorption of the carbonyl group, which appeared a frequency higher by 20 cm^{-1} than that of **16**.[16] Judging from the reaction conditions, the C_4–Me group of **18** was deduced to be thermodynamically the more stable equatorial configuration. In addition, the $\alpha(eq)$-configuration of the C_4–Me group was confirmed by the transformation of **18** to chamaecynone, as will be shown later. The ORD curve of this compound showed a positive Cotton effect, which was in accordance with the expected sign for **18**, with the non-steroid conformation bearing an $\alpha(eq)$-bromine atom at C_2 and an $\alpha(eq)$-methyl group at C_4.



(18) Non-Steroid conformation

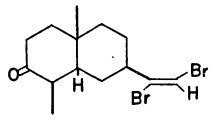
On the other hand, the NMR spectrum of **19** in carbon tetrachloride showed peaks at δ 1.09 (d, J=6.0 Hz, C_4–Me), 1.12 (s, C_{10}–Me), 1.90 (d, J=2.0 Hz, –C≡CH), and 4.75 (q, J=7.0 and 12.5 Hz, C_2–H). The coupling pattern and constant of the signal at δ 4.75 showed that the bromine atom at C_2 was equatorial. This assignment was also supported by the IR spectrum. The C_4–Me group of **19** was deduced to be thermodynamically the more stable equatorial configuration, considering the reaction conditions. In addition, the $\beta(eq)$-configuration of the C_4–Me group was confirmed by the transformation of **19** to isochamaecynone, as will be shown later. The ORD curve of this compound showed a negative Cotton effect, which was explained by the structure **19** in the steroid conformation bearing a $\beta(eq)$-bromine atom at C_2 and a $\beta(eq)$-Me group at C_4.



(19) Steroid conformation

The formation of the bromides **18** and **19** starting from **16** can reasonably be explained as follows. The ketone (**16**) was epimerized at C_4 in the presence of hydrobromic acid to give an equilibrium mixture of **16** and its C_4-epimer, **17**. The bromination of **16** and **17** in the reaction mixture at the C_2-position gave **19** and **18** respectively. The isolation of **17** and a detailed discussion of the stereochemistry will appear in a later section. The preferential formation of α-bromo ketones from **16** under those reaction conditions can also be reasonably explained by the reaction-rate difference between the bromination on an enol double bond and that on a termianl triple bond.[17] On the contrary, when **16** was brominated in acetic

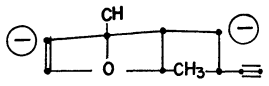
acid in the presence of sodium acetate, **16** absorbed bromine slowly, giving a dibromide (**28**) as the sole product.



(28)

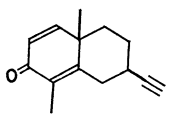
The dehydrobromination of **18** with lithium bromide and lithium carbonate in *N,N*-dimethylformamide produced chamaecynone, which was identical with natural material in its mixed melting point, thin-layer and gas-chromatographic behavior, and IR, NMR, and Mass spectra, and ORD curve.

The dehydrobromination of **19** with lithium bromide and lithium carbonate in *N,N*-dimethylformamide gave isochamaecynone (**2**). Although isochamaecynone was not isolated in a pure state from the natural surce,[5] these NMR absorptions were in accordance with those corresponding to isochamaecynone in the equilibrium mixture of chamaecynone and isochamaecynone, which was easily obtained by the base treatment of chamaecynone. In agreement with the structure **2** the product exhibited the absorption of a terminal triple bond at 3300 and 2123 cm^{-1} and the absorption of an α,β-unsaturated carbonyl group at 1672 cm^{-1} in its IR spectrum (KBr). The ORD curve (n-π^*) showed a negative Cotton effect which agreed with the sign expected from isochamaecynone, with the steroid conformation bearing a $\beta(eq)$-methyl group at C_4.[15,18]



Octant Projection of **2**

Since the isolated yields of the bromides **18** and **19** were poor, probably because of their chromatographic unstability, we tried to prepare chamaecynone and isochamaecynone employing a crude mixture of bromides. In this case, *ca.* a 1:1 mixture of chamaecynone and isochamaecynone was obtained in a 65% yield, based on **16**, accompanied by a 10% yield of dehydrochamaecynone (**29**).



(29)

Since naturally occurring chamaecynone has already been converted to dihydroisochamaecynone, the total synthesis of **3** has also been completed formally.[5]

The Stereochemical Studies

In the course of the structural determination of chamaecynone, it was observed that hexahydrochamaecynone (**30**) was quantitatively isomerized to hexahydroisochamaecynone by base treatment. On the other hand, dihydrochamaecynone (**31**) gave an equilibrium mixture consisting of 10% of dihydrochamaecynone and 90% of dihydroisochamaecynone, whereas chamaecynone afforded an equilibrium mixture of 70% of chamaecynone and 30% of isochamaecynone.[5] These results strongly suggested that the relative stability of normal-series compounds (chamaecynone, dihydrochamaecynone, and hexahydrochamaecynone) to iso-series compounds (isochamaecynone, dihydroisochamaecynone, and hexahydroisochamaecynone) depended upon the bulkiness of the β-substituent at the C_7-position.

In this section we want to deal with the analyses of the energy difference between three pairs of normal- and iso-series compounds, chamaecynone and isochamaecynone, **17** and **16**, and **24** and **23**. The values for ΔH and ΔS of the equilibrium reaction were calculated using the values found for the equilibrium constant, K, and fitting a straight line to Eq. 1:

$$\ln K = -\left(\frac{1}{T}\right)\left(\frac{\Delta H}{R}\right) + \frac{\Delta S}{R} \quad (1)$$

Equilibration of Chamaecynone and Isochamaecynone. Chamaecynone was treated with a 2% potassium hydroxide solution of ethanol for 6 h and then quenched by the use of aqueous acetic acid solution. The ratio of chamaecynone and isochamaecynone was determined by gas-chromatographic analyses. A plot of ln K *vs.* $1/T$ was made and was found to be linear. From the slope and intercept of the line, the thermodynamic constants of the equilibrium reaction were determined.

ΔH and ΔS were determined to be +1.47 kcal/mol and +2.69 e.u. respectively. Although no equilibration data starting from isochamaecynone were obtained because of its limited aomunt, isochamaecynone gave the same composition mixture as chamaecynone at 25 °C in a 2% potassium hydroxide solution of ethanol.

*Equilibration of **17** and **16**.* The equilibration data for the **17**⇌**16** reaction, starting from **16** were determined to be as shown in Table 2 by the procedures mentioned above.

The C_4-epimer (**17**) was isolated from the equilibrium mixture by column chromatography. The small downfield shift [$\delta_{(CCl_4)} - \delta_{(C_6H_6)}$] of the C_4-methyl

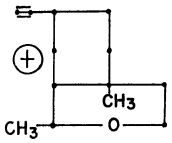
Table 1. Equilibration data for the chamaecynone (**1**) ⇌ isochamaecynone (**2**) reaction, starting from **1**

Temp/°C	K (**2**/**1**)	ΔG/kcal mol^{-1}
25	0.321	0.67
52	0.397	0.60
80	0.472	0.53

Table 2. Equilibration data for the **17** ⇌ **16** reaction, starting from **16**

Temp/°C	K (**16**/**17**)	ΔG/kcal mol^{-1}
25	0.637	0.27
40	0.671	0.25
60	0.714	0.22
80	0.775	0.18

resonance in the NMR spectrum of **17** on passing from carbon tetrachloride to benzene suggested the equatorial configuration of the C_4-methyl group.[14] The ORD curve of **17** showed a positive Cotton effect ($[\phi]_{304}=+897$, $[\phi]_{265}=-1790$, $A=+26.9$), which could reasonably be explained by **17** with a non-steroid conformation bearing a $\beta(ax)$-ethynyl group at C_7 and an $\alpha(eq)$-methyl group at C_4.[14]



Octant Projection of **17**

The equilibration data for the **17**⇌**16** reaction, starting from **17** were also determined to be as shown in Table 3 by the same procedure. The results were in accordance with the results shown in Table 2. A plot of ln K *vs.* $1/T$ was made and found to be linear. From the slope and intercept of the line, ΔH and ΔS were determined to be $+0.77$ kcal/mol and $+1.68$ e. u. respectively.

Equilibration of ***24*** *and* ***23***. The equilibration data for the **24**⇌**23** reaction, were determined to be as shown in Table 4 by the procedure used in the cases of the equilibration of chamaecynone and iso-chamaecynone.

The plot of ln K *vs.* $1/T$ became linear, and from the slope and the intercept of the line ΔH and ΔS were calculated to be -2.28 kcal/mol and -3.87 e. u. respectively.

Consideration of the Results. The examination of Dreiding models showed there to be two Me–H and two R–H 1,3-diaxial interactions and two inner H–H interactions, as depicted by the arrows in the normal-series compounds. On the other hand, in the iso-series compounds there are two Me–H 1,3-diaxial interactions and three inner H–H interactions, as depicted by the arrows. Since two Me–H 1,3-diaxial interactions and two inner H–H interactions exist in both series of compounds, the observed ΔH values should reflect the difference between the two R–H 1,3-diaxial interactions in normal-series compounds and one inner H–H interaction in the iso-series compounds. Actually, the observed ΔH values reflect well the bulkiness of R at C_7. When R is the ethynyl group, **17** with non-steroid conformation bearing an axial ethynyl group is the favored isomer and ΔH is $+0.77$ kcal/mol. In this case, the R group is a linear ethynyl group and the magnitudes of the 1,3-diaxial interactions of this group and of two hydrogen atoms at C_5 and C_9 are the smallest of the three normal-series compounds. On the contrary, when R is a vinyl group, **24**, with a non-steroid conformation, is not the favored isomer and the observed ΔH is -2.28 kcal/mol. In this case, the vinyl group is planar and the magnitudes of the 1,3-diaxial interactions of this group and of the two hydrogen atoms at C_5 and C_9 are larger than that of the linear ethynyl group. When R is a three-dimensional ethyl group, the 1,3-diaxial interactions of R and the two hydrogen atoms at C_5 and C_9 may be expected to be far larger than that of the vinyl group. Actually, hexahydrochamaecynone (**30**) was completely isomerized to hexahydroisochamaecynone (**25**) by base treatment.

The equilibrium reaction of chamaecynone (**1**) and isochamaecynone (**2**) gave a tendency similar with that of the equilibrium reaction of **17** and **16**. The ΔH value is $+1.47$ kcal/mol, larger than the latter case, because in chamaecynone one Me–H interaction and two inner H–H interactions are eliminated compared with **17** by the introduction of a double bond at C_1, whereas in isochamaecynone one inner H–H interaction is eliminated compared with **16**.

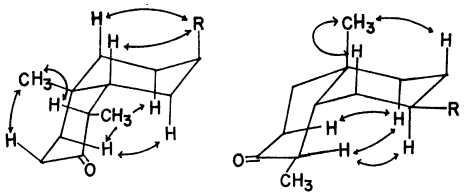
Table 3. Equilibration data for the **17** ⇌ **16** reaction, starting from **17**

Temp/°C	K (**16**/**17**)	ΔG/kcal mol^{-1}
25	0.629	0.27
40	0.676	0.24
60	0.714	0.22
80	0.781	0.17

Table 4. Equilibration data for the **24** ⇌ **23** reaction, starting from **23**

Temp/°C	K (**23**/**24**)	ΔG/kcal mol^{-1}
25	6.30	−1.09
40	5.73	−1.08
62	4.59	−1.01
80	3.62	−0.90

Normal Series Compounds (Non-Steroid Conformation) Iso Series Compounds (Steroid Conformation)

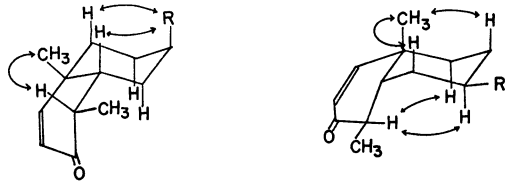


R= -C≡CH (17) ⟷ (16)

R= -CH=CH$_2$ (24) ⟵ (23)

R= -CH$_2$-CH$_3$ (30) ⟶ (25)

Normal Series Compounds (Non-Steroid Conformation) Iso Series Compounds (Steroid Conformation)



R= -C≡CH (1) ⟷ (2)

R= -CH=CH$_2$ (31) ⟵ (3)

Experimental

All the melting points are uncorrected. The IR spectra were determined on Shimadzu IR-27 and Hitachi EPI-S2 spectrophotometers. The NMR spectra were recorded on Varian A-60 and HA-100 spectrometers, employing tetramethylsilane as the internal reference. Gas-liquid partion chromatography (GLPC) analyses were performed on a Hitachi-Perkin Elmer F-6 apparatus. The ORD spectra were recorded on a Nihonbunko ORD/UV-5 spectrophotometer.

*3-Oxo-6α*H,*11β*H-*eudesma-1,4-dieno-13,6-lactone (5).* Compound **5** was prepared in a 47% yield as colorless plates by the method reported by Ishikawa;[9] mp 105 °C. IR (KBr): 1786, 1664, 1634, and 831 cm^{-1}. NMR ($CDCl_3$): δ 1.29 (3H, s, C_{10}–Me), 1.38 (3H, d, J=7.5 Hz, C_{11}–Me), 2.06 (3H, s, C_4–Me), 5.57 (1H, d, J=5.5 Hz, C_6–H), 6.25 (1H, d, J=10.0 Hz, C_2–H), and 6.78 (1H, d, J=10.0 Hz, C_1–H) ppm.

(11S)-3-Oxo-eudesma-1,4-dien-13-oic Acid (6). Compound **6** was prepared in an 85% yield as colorless columns by the method reported by Miki;[10] mp 102 °C. IR (KBr): 3200, 1739, 1650, 1616, 1595, and 836 cm^{-1}. NMR ($CDCl_3$): δ 1.21 (3H, s, C_{10}–Me), 1.23 (3H, d, J=6.5 Hz, C_{11}–Me), 1.83 (3H, s, C_4–Me), 6.17 (1H, d, J=10.0 Hz, C_2–H), and 6.71 (1H, d, J=10.0 Hz, C_1–H) ppm. Found: C, 72.70; H, 8.30; O, 19.31%. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12; O, 19.33%.

*(11S)-3-Oxo-4α*H,*5β-eudesman-13-oic Acid (7).* A mixture of **6** (7.41 g, 29 mmol), an ethanol solution (300 ml) of KOH (3 g, 54 mmol), and 5% Pd/C (3 g) was shaken under an atmosphere of hydrogen until the gas absorption had been completed. In 2 h, 1440 ml (1330 ml for one mole equiv) of hydrogen was consumed. After the filtration of the catalyst, the filtrate was poured into water, acidified with 6 M HCl (20 ml), and extracted with ether (200 ml×5). The combined extracts were washed with a satd. NaCl aq solution, dried ($MgSO_4$), and concentrated to give 7.0 g of a semisolid, which was then recrystallized from benzene–cyclohexane (1:2) to give 4.06 g (54%) of **7** as colorless prisms; mp 129 °C. IR (KBr): 1733 and 1675 (this band shifted to 1700 cm^{-1} in $CHCl_3$ or CS_2) cm^{-1}. NMR (CCl_4): δ 0.93 (3H, d, J=6.5 Hz, C_4–Me), 1.03 (3H, s, C_{10}–Me), 1.18 (3H, d, J=7.0 Hz, C_{11}–Me) ppm. ORD (MeOH): $[\phi]_{303}$=−760, $[\phi]_{260}$=+2580, A=−33.4.[19] Found: C, 71.12; H, 9.74%. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59%. The concentration of the mother liquor gave 3.35 g of a viscous oil, which was then dissolved in ether and methylated with a slight excess of CH_2N_2 in ether. The crude product was chromatographed over neutral alumina (170 g, activity grade 1) and eluted with benzene to give the oily methyl ester of (11*S*)-3-oxo-4*βH*,5α-eudesman-13-oic acid (**20**) (1.14 g, the faster running) and the oily methyl ester of **7** (0.75 g, the slower running). The methyl ester of **20** was hydrolyzed with 2 M KOH aq in EtOH to give 1.03 g of a crude crystalline compound, which was then recrystallized from benzene–cyclohexane (1:2, 5 ml) to give 0.45 g of **20** as colorless prisms; mp 109 °C. IR (KBr): 1727 and 1681 cm^{-1}. NMR (CCl_4): δ 0.91 (3H, d, J=6.5 Hz, C_4–Me), 1.06 (3H, s, C_{10}–Me), and 1.15 (3H, d, J=6.5 Hz, C_{11}–Me) ppm. ORD (MeOH): $[\phi]_{306}$=+1010. Found: C, 71.58; H, 9.78%. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59%.

*11-Chloro-4α*H,*5β-13-noreudesman-3-one (8).* A mixture of **7** (1 g, 4 mmol) dissolved in anhydrous benzene (50 ml), $Pb(OAc)_4$ (14.2 g, 32 mmol), and LiCl (1.2 g, 28 mmol) were placed in a round-bottomed flask equipped with a condenser and cooled in a dry ice–acetone bath to freeze the solvent. After the solvent had frozen, the system was evacuated and filled with N_2. The mixture was refluxed under vigorous stirring for 30 min, cooled to room temperature, and filtered. The filtrate was washed with 3 M HCl aq until it became colorless, and then 2 M Na_2CO_3 aq (10 ml×3), which had been acidified with a 6 M HCl aq solution; it was then extracted with ether, dried ($MgSO_4$), and concentrated to give 50 mg (5%) of the recovered **7**. The benzene layer was washed with a satd. NaCl aq solution, dried ($MgSO_4$), and concentrated to give 0.91 g of an oil, which was then chromatographed over silica gel (Merck, <230 mesh) and eluted with $CHCl_3$ to give 800 mg (83%) of **8** as a colorless oil. IR (neat): 1709 cm^{-1}. NMR (CCl_4): δ 0.93 (3H, d, J=7.0 Hz, C_4–Me), 1.04 (3H, s, C_{10}–Me), 1.49 (3H, d, J=6.5 Hz, C_{11}–Me), and 3.87 (1H, m, C_{11}–H) ppm. ORD (MeOH): $[\phi]_{303}$=−870, $[\phi]_{260}$=+2470, A=−33.4. Found: C, 68.86; H, 9.45%. Calcd for $C_{14}H_{23}OCl$: C, 69.19; H, 9.54%.

*11-Chloro-4α*H,*5β-13-noreudesman-3-ol (9).* To a solution of **8** (2.05 g, 8.4 mmol) in a mixture of ether (50 ml) and MeOH (34 ml), we added $NaBH_4$ (0.85 g, 22.5 mmol). The mixture was allowed to stand at room temperature for 2 h and then poured into a satd. NaCl aq solution (100 ml). The ether layer was separated after shaking, and the aqueous layer was further extracted with ether (50 ml×2). The combined extracts were washed with a satd. NaCl aq solution, dried ($MgSO_4$), and concentrated to give 2.03 g of **9** as an oil, which was then employed in the next step without any further purification.

A part of the product (152 mg) was chromatographed over silica gel (Merck, <230 mesh) and eluted with $CHCl_3$–CCl_4 (1:1) to give 127 mg of an oil. IR (neat): 3360 cm^{-1}. Found: C, 68.48; H, 9.90%. Calcd for $C_{14}H_{25}OCl$: C, 68.63; H, 10.29%.

*4α*H,*5β-13-Noreudesm-11-en-3α-ol (10) and 4α*H,*5β-13-Noreudesm-11-en-3β-ol (11).* A mixture of **9** (1.45 g, 5.92 mmol) and a 1 M *t*-BuOK/*t*-BuOH soln (60 ml) was refluxed for 44 h under N_2 and then concentrated *in vacuo*. The residue was poured into a satd. NaCl aq solution and extracted with ether (50 ml×3). The combined extracts were washed with a satd. NaCl aq solution, dried ($MgSO_4$), and concentrated to give 1.20 g of an oily crude product, which was then chromatographed over silica gel (Merck, <230 mesh) and eluted with CCl_4–$CHCl_3$ (2:1). The first running gave **11** (234 mg, 19%); mp 49—51 °C. IR (KBr): 3436, 3096, 1639, 993, and 900 cm^{-1}. NMR (CCl_4): 0.93 (3H, d, J=6.5 Hz, C_4–Me), 0.98 (3H, s, C_{10}–Me), 3.70 (1H, m, $W_{h/2}$=5.0 Hz, C_3–H), and 4.65—6.00 (3H, m, ABX pattern olefinic protons) ppm. Found: C, 80.85; H, 11.29%. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61%. The second running gave **10** (527 mg, 43%) as an oily material. IR (neat): 3378, 3115, 1642, 1000, and 909 cm^{-1}. NMR (CCl_4): δ 0.95 (3H, s, C_{10}–Me), 0.97 (3H, d, J=6.0 Hz, C_4–Me), 2.96 (1H, ddd, J=5.0, 9.0, and 9.0 Hz, C_3–H), and 4.65—6.00 (3H, m, ABX pattern olefinic protons) ppm. Found: C, 80.34; H, 11.15%. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61%.

*11,12-Dibromo-4α*H,*5β-13-noreudesman-3α-ol (12).* Into a stirred solution of **10** (0.798 g, 3.83 mmol) in CCl_4 (10 ml), we added a solution of Br_2 (0.70 g, 4.38 mmol) in CCl_4 (5 ml) at 0 °C. The mixture was stirred at 0 °C for 2 h, washed with a 10% Na_2CO_3 aq solution, dried ($MgSO_4$), and concentrated to give **12** (1.44 g, 100%) as a crystalline material, which was then employed in the next step without further purification. A part of this material was recrystallized from CCl_4 to give colorless needles; mp 127—128 °C. IR

(KBr): 3310 cm^{-1}. NMR (CCl_4); δ 0.97 (3H, s, C_{10}–Me), 0.98 (1H, d, J=5.5 Hz, C_4–Me of the minor isomer), 1.01 (2H, d, J=5.5 Hz, C_4–Me of the major isomer), 2.7—3.3 (1H, m, C_3–H), and 3.60—4.35 (3H, m, C_{11}–H, and C_{12}–H) ppm. Found: C, 45.81; H, 6.69%. Calcd for $C_{14}H_{24}OBr_2$: C, 45.65; H, 6.57%.

*4α*H,*5β-13-Noreudesm-11-yn-3α-ol (**14**).* A mixture of **12** (1.44 g, 3.91 mmol), dry benzene (30 ml), and a 1 M *t*-BuOK/*t*-BuOH solution (60 ml) was refluxed for 6.5 h under N_2. After the removal of a half of the volume of the solvent *in vacuo*, the mixture was poured into a satd. NaCl aq solution and extracted with ether (50 ml×3). The combined extracts were washed with a satd. NaCl aq solution, dried ($MgSO_4$) and concentrated to give **14** (754 mg, 93%) as an oily material, which was then employed in the next step without further purification. IR (neat): 3322 and 2123 cm^{-1}.

*4α*H,*5β-13-Noreudesm-11-yn-3-one (**16**).* A solution of **14** (282 mg, 1.37 mmol) in pyridine (2 ml) was added to a CrO_3–Py complex formed from CrO_3 (411 mg, 4.11 mmol) and anhydrous pyridine (6 ml), after which the mixture was allowed to stand at room temperature overnight. Petroleum ether (50 ml) was then added to the mixture, and the precipitate was filtered. The filtrate was washed successively with a satd. NaCl aq solution (50 ml×2), a 2 M HCl aq solution (50 ml×2), and a satd. NaCl aq solution (50 ml), dried ($MgSO_4$), and concentrated to give 251 mg of a crystalline material, which was then chromatographed over silica gel (Merck, <230 mesh, 12 g) and eluted with CCl_4–$CHCl_3$ (1:1) to give spectroscopically pure **16** (172 mg, 62%), mp 71—80 °C. This was recrystallized from pentane to give colorless prisms; mp 89—94 °C.[20] IR (KBr): 3279, 2119, and 1701 cm^{-1}. NMR (CCl_4): δ 0.98 (3H, d, J=6.2 Hz, C_4–Me), 1.08 (3H, s, C_{10}–Me), and 1.90 (1H, d, J=2.0 Hz, C_{12}–H) ppm. NMR (C_6H_6): δ 0.66 (3H, s, C_{10}–Me), 0.91 (3H, d, J=6.2 Hz, C_4–Me), and 1.90 (1H, d, J=2.0 Hz, C_{12}–H) ppm. ORD (MeOH): $[\phi]_{304}=-896$, $[\phi]_{265}=+1790$, $A=-26.9$.[19] MS (70 eV) *m/e*: 204 (M^+). Found: C, 82.20; H, 10.14%. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87%.

*Preparation of **16** from **8** without Purification in Each Step.* To a solution of **8** (637 mg, 2.60 mmol) in a mixture of ether and MeOH (10 ml and 16 ml each), we added $NaBH_4$ (300 mg, 7.93 mmol). The mixture was allowed to stand at room temperature for 2 h, poured into a satd. NaCl aq solution, and extracted with ether. The extract was washed with a satd. NaCl aq solution, dried, and concentrated to give **9** (580 mg, oil).

A mixture of **9** (580 mg) and 1 M *t*-BuOK/*t*-BuOH solution (30 ml) was refluxed for 45 h under N_2, concentrated *in vacuo*, and poured into a satd. NaCl aq solution. The mixture was extracted with ether, and the extract was washed with a satd. NaCl aq solution, dried ($MgSO_4$), and concentrated to give a mixture of **10** and its C_3-epimer (**11**) (370 mg, oil).

To a stirred solution of the resultant mixture of **10** and **11** (370 mg) in CCl_4 (5 ml), we added a solution of Br_2 (320 mg, 2.0 mmol) in CCl_4 (2.5 ml) at 0 °C. The mixture was stirred at room temperature for 2 h, washed with a 10% Na_2CO_3 aq solution, dried ($MgSO_4$), and concentrated to give a crystalline mixture of bromides (**12** and **13**) (658 mg).

A mixture of the resultant bromides (658 mg), anhydrous benzene (10 ml), and 1 M *t*-BuOK/*t*-BuOH solution (10 ml) was refluxed for 6.5 h under N_2. After the removal of a half of the volume of the solvent *in vacuo*, the mixture was diluted with a satd. NaCl aq solution and extracted with ether. The combined extracts were washed with satd. NaCl aq solution, dried ($MgSO_4$), and concentrated to give a mixture of oily alcohols (**14** and **15**) (270 mg).

A solution of the resultant alcohols (270 mg) in anhydrous pyridine (2 ml) was added to the CrO_3–Py complex formed from CrO_3 (411 mg, 4.11 mmol) and anhydrous pyridine (6 ml), after which the mixture was allowed to stand at room temperature overnight. Petroleum ether (50 ml) was then added to the mixture, and the precipitate was filtered. The filtrate was washed successively with a satd. NaCl aq solution, a 2 M HCl aq solution and a satd. NaCl aq solution, dried ($MgSO_4$), and concentrated to give a crude crystalline product (200 mg), which was then chromatographed over silica gel (10 g, Merck, <230 mesh) and eluted with $CHCl_3$–CCl_4 (1:1) to give **16** (171 mg, 32% overall yield from **8**).

*2α-Bromo-4β*H,*5β-13-noreudesm-11-yn-3-one (**18**) and 2β-Bromo-4α*H,*5β-13-noreudesm-11-yn-3-one (**19**).* To a solution of **16** (360 mg, 1.76 mmol) in AcOH (10 ml), we added 48% HBr (0.3 ml) and a solution of Br_2 (281 mg, 1.76 mmol) in AcOH (4 ml) successively. The mixture was stirred for 1 h at room temperature, poured into a satd. NaCl aq solution (100 ml), and extracted with ether (30 ml×3). The combined extracts were washed successively with a 10% Na_2CO_3 aq solution (20 ml×2) and a satd. NaCl aq solution (30 ml), dried ($MgSO_4$), and concentrated to give 467 mg of an oily product, which was then chromatographed over silica gel (30 g, Merck, <230 mesh) and eluted with CCl_4–$CHCl_3$ (4:1). The first running gave an unidentified oily mixture (58 mg). The second running gave 180 mg (36%) of **18** as a crystalline material. IR ($CHCl_3$): 3344, 2123, and 1724 cm^{-1}. NMR (CCl_4): δ 0.98 (3H, d, J=6.5 Hz, C_4–Me), 1.33 (3H, s, C_{10}–Me), 1.85 (1H, d, J=2.5 Hz, C_{12}–H), 4.57 (1H, q, J=7.5 and 13.0 Hz, C_2–H) ppm. ORD (MeOH): $[\phi]_{310}=+396$, $[\phi]_{270}=-1200$, $A=+16$. Found: C, 58.53, H, 6.89%. Calcd for $C_{14}H_{19}OBr$: C, 59.41; H, 6.77%. The third running gave 68 mg (14%) of **19** as a crystalline material.[21] IR ($CHCl_3$): 3344, 2132, and 1727 cm^{-1}. NMR (CCl_4): δ 1.09 (3H, d, J=6.0 Hz, C_4–Me), 1.12 (3H, s, C_{10}–Me), 1.90 (1H, d, J=2.0 Hz, C_{12}–H), and 4.75 (1H, q, J=7.0 and 12.5 Hz, C_2–H) ppm. ORD (MeOH): $[\phi]_{310}=-470$, $[\phi]_{260}=+604$, $A=-10.7$. Found: C, 59.62; H, 6.85%. Calcd for $C_{14}H_{19}OBr$: C, 59.41; H, 6.77%. The fourth running gave a complex mixture.

*Chamaecynone (**1**).* A mixture of **18** (105 mg, 0.37 mmol), Li_2CO_3 (90 mg, 1.22 mmol), and LiBr (90 mg, 1.04 mmol) in anhydrous DMF (18 ml) was stirred at 140—165 °C for 2 h under N_2, cooled, poured into a satd. NaCl aq solution (100 ml), and extracted with ether (30 ml×3). The combined extracts were washed successively with a 2 M HCl aq solution (30 ml) and a satd. NaCl aq solution, dried ($MgSO_4$), and concentrated to give 70 mg of an oily material, which was then chromatographed over silica gel (10 g, Merck, <230 mesh) and eluted with CCl_4–$CHCl_3$ (4:1) to give 29 mg (39%) of chamaecynone as a crystalline material, which was subsequently recrystallized from pentane to give colorless prisms; mp 88 °C. This material showed no depression in its melting point when admixed with an authentic specimen and was identical in all respects with the corresponding specimen in IR (KBr), NMR (CCl_4), ORD (MeOH), GLPC (SE 30), and MS (70 eV).

*Isochamaecynone (**2**).* A mixture of **19** (23 mg, 0.08 mmol), Li_2CO_3 (22 mg, 0.3 mmol), and LiBr (22 mg, 0.25 mmol) in anhydrous DMF (6 ml) was stirred at 140—165 °C for 6.5 h under N_2, cooled, poured into a satd. NaCl aq solution (20 ml), and extracted with ether (10 ml×3). The combined extracts were washed successively with a 2 M HCl aq solution (10 ml) and a satd. NaCl aq solution, dried ($MgSO_4$), and concentrated to give 18 mg of a crystalline

material, which was then chromatographed over silica gel (3 g, Merck, <230 mesh) and eluted with CCl_4–$CHCl_3$ (4:1) to give 4 mg (24%) of isochamaecynone; mp 79 °C. IR (KBr): 3300, 2123, 1672, and 834 cm^{-1}. NMR (CCl_4): δ 1.12 (3H, d, J=6.5 Hz, C_4–Me), 1.22 (3H, s, C_{10}–Me), 1.90 (1H, d, J=2.0 Hz, C_{12}–H), *ca.* 2.3 (1H, m, $W_{h/2}$= 24.0 Hz, C_7–H), 5.77 (1H, d, J=10.0 Hz, C_2–H), and 6.43 (1H, d, J=10.0 Hz, C_1–H) ppm. NMR (C_6H_6): δ 1.04 (1H, d, J=6.0 Hz, C_4–Me) and 0.71 (3H, s, C_{10}–Me) ppm. MS (70 eV) *m/e*: 202 (M^+). ORD (MeOH): $[\phi]_{340}=-870$.

Conversion of ***16*** *to Chamaecynone (****1****), Isochamaecynone (****2****), and Dehydrochamaecynone (13-Noreudesma-1,4-dien-11-yn-3-one,* ***29****) without the Isolation and Purification of the Corresponding Bromides.* A mixture of **16** (358 mg, 1.75 mmol), AcOH (30 ml), and a 48% HBr aq solution (0.5 ml) was stirred for 2 h at room temperature. To the mixture we then added a solution of Br_2 (290 mg, 1.80 mmol) in AcOH (2 ml). The mixture was stirred for 30 min at room temperature, poured into a satd. NaCl aq solution (100 ml), and extracted with ether (30 ml×3). The combined extracts were washed successively with a 10% Na_2CO_3 aq solution (20 ml×2) and a satd. NaCl aq solution (30 ml), dried ($MgSO_4$), and concentrated to give 494 mg of an oily product, which was then employed for the next reaction.

A mixture of the crude bromide (494 mg), Li_2CO_3 (420 mg, 5.68 mmol), and LiBr (420 mg, 4.83 mmol) in anhydrous DMF (80 ml) was stirred for 5 h at the refluxing temperature under N_2, cooled, poured into a satd. NaCl aq solution (300 ml), and extracted with ether (50 ml×4). The combined extracts were washed successively with a 2 M HCl aq solution (50 ml) and a satd. NaCl aq solution, dried ($MgSO_4$), and concentrated to give 320 mg of an oily material, which was then chromatographed over silica gel (50 g, Merck, <230 mesh) and eluted with CCl_4–$CHCl_3$ (4:1). The first running gave chamaecynone (99 mg). The second running gave a 1:1 mixture of chamaecynone and isochamaecynone (62 mg). The third running gave isochamaecynone (69 mg). The total yield of chamaecynone and isochamaecynone was 230 mg (65%), based on the **16**. The fourth running gave **29** (35 mg, 10%). NMR (CCl_4): δ 1.27 (3H, s, C_{10}–Me), 1.87 (3H, s, C_4–Me), 2.08 (1H, d, J=1.0 Hz, C_{12}–H), 6.09 (1H, d, J=9.8 Hz, C_2–H), and 6.66 (1H, d, J=9.8 Hz, C_1–H) ppm.

*11,12-Dibromo-4α*H*,5β-13-noreudesm-11-en-3-one (****28****).* To a mixture of **16** (113 mg, 0.55 mmol) and AcONa (100 mg, 1.22 mmol) in AcOH (100 ml), we added under mechanical stirring, a solution of Br_2 (90 mg, 0.56 mmol) in AcOH (5 ml). After stirring had continued for 4 h at room temperature, the mixture was poured into a satd. NaCl aq solution (100 ml) and extracted with ether (30 ml×3). The combined extracts were washed successively with 10% Na_2CO_3 (20 ml×2) and a satd. NaCl aq (30 ml) solution, dried ($MgSO_4$), and concentrated to give 195 mg of an oily material, which was then chromatographed over silica gel (15 g, Merck, <230 mesh) and eluted with a mixture of $CHCl_3$–CCl_4 (1:1) to give **28** (75 mg, 37%), which was subsequently recrystallized from hexane to give colorless prisms; mp 119 °C. IR (KBr): 3077, 1712, and 833 cm^{-1}. NMR (CCl_4): δ 1.01 (3H, d, J=6.5 Hz, C_4–Me), 1.10 (3H, s, C_{10}–Me), and 6.33 (1H, s, C_{12}–H) ppm. Found: C, 46.66; H, 5.57%. Calcd for $C_{14}H_{20}OBr$: C, 46.15; H, 5.53%.

*11-Chloro-3,3-ethylenedioxy-4α*H*,5β-13-noreudesmane (****21****).* A mixture of **8** (1.61 g, 6.63 mmol), ethylene glycol (24 ml), and *p*-toluenesulfonic acid (0.28 g) in dry C_6H_6 (60 ml) was refluxed in a flask equipped with a Dean-Stark column packed with anhydrous $MgSO_4$ for 2 h under N_2. The mixture was then cooled and diluted with a satd. NaCl aq solution (100 ml), and the benzene layer was drawn off. The aqueous layer was further extracted with C_6H_6 (30 ml×3). The combined extracts were washed with a NaCl aq solution, dried ($MgSO_4$), and concentrated to give 1.93 g (100%) of **21**, which was then recrystallized from pentane to give a crystalline material; mp 74 °C. NMR (CCl_4): δ 0.78 (3H, d, J=6.5 Hz, C_4–Me), 0.95 (3H, s, C_{10}–Me), 1.47 (3H, d, J=6.5 Hz, C_{11}–Me), and 3.83 (4H, s, ) ppm. Found: C, 67.16; H, 9.39%. Calcd for $C_{16}H_{27}O_2Cl$: C, 66.95; H, 9.48%.

*3,3-Ethylenedioxy-4α*H*,5β-13-noreudesm-11-ene (****22****).* A mixture of **21** (1.93 g, 6.72 mmol) and a 1 M *t*-BuOK/*t*-BuOH solution (70 ml) was refluxed for 31 h under N_2, concentrated *in vacuo*, and diluted with a satd. NaCl aq solution. The mixture was then extracted with benzene (50 ml×3). The combined extracts were washed with a NaCl aq solution, dried ($MgSO_4$), and concentrated to give 1.58 g (94%) of **22**, which was then employed in the next step. IR (neat): 3110, 1642, 1000, and 918 cm^{-1}. NMR (CCl_4): δ 0.77 (3H, d, J=6.5 Hz, C_4–Me), 0.96 (3H, s, C_{10}–Me), 3.83 (4H, s, ), 4.89 (1H, dd, J=3.5 and 18.0 Hz, C_{12}–H_a), 4.83 (1H, dd, J=3.5 and 10.0 Hz, C_{12}–H_b), and 5.70 (1H, ddd, J=6.0, 10,0, and 18.0 Hz, C_{11}–H) ppm.

Deacetalization of ***22****. The formation of a Mixture of 4α*H*, 5β-13-noreudesm-11-en-3-one (****23****) and 4β*H*,5β-13-noreudesm-11-en-3-one (****24****).* A mixture of **22** (1.58 g, 6.31 mmol) and a 2 M HCl aq solution (10 ml) in MeOH (50 ml) was refluxed for 4 h, concentrated to a half of the volume, poured into a satd. NaCl aq solution, and extracted with benzene (30 ml×3). The combined extracts were then washed with a satd. NaCl aq solution, dried ($MgSO_4$), and concentrated to give 1.23 g of an oily material, which was subsequently established by NMR and GLPC (SE 30) analyses to be a *ca* 1:2 mixture of **24** and **23**. The NMR (CCl_4) of **24** in the mixture of **24** and **23**: δ 0.88 (3H, d, J=6.5 Hz, C_4–Me), 1.08 (3H, s, C_{10}–Me), and 4.7–6.1 (3H, m, C_{11}– and C_{12}–H) ppm.

*4α*H*,5β-13-Noreudesm-11-en-3-one (****23****).* To the CrO_3–Py complex formed from CrO_3 (115 mg, 1.15 mmol) and anhydrous pyridine (2 ml), we added **10** (100 mg, 0.48 mmol) in anhydrous pyridine (4 ml). The mixture was then allowed to stand at room temperature overnight, diluted with petroleum ether (20 ml), and filtered. The filtrate was washed with a 2 M HCl aq solution (20 ml×2) and a satd. NaCl aq solution (30 ml), dried, and concentrated to give 90 mg (91%) of **23** as an oily material, which was then purified by pipe-to-pipe distillation. IR (neat): 3106, 1715, 1637, 995, and 908 cm^{-1}. NMR (CCl_4): δ 0.96 (3H, d, J=6.5 Hz, C_4–Me), 1.04 (3H, s, C_{10}–Me), and 4.7—6.1 (3H, m, C_{11}– and C_{12}–H) ppm. CD (MeOH): $[\theta]_{290}=-1875$. Found: C, 81.22; H, 10.92%. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75%. **11** also gave **23** in 87% in the same procedure.

*Hexahydroisochamaecynone (4α*H*,5β-13-Noreudesman-3-one,* ***25****).* A mixture of **23** (20 mg) and 5% Pd/C (20 mg) in MeOH (2 ml) was shaken under H_2 until the hydrogen uptake ceased. The oily crude product (22 mg) was chromatographed over silica gel (1 g, Merck, <230 mesh) and eluted with $CHCl_3$–CCl_4 (1:1) to give **25** (19 mg).

*2β,11,12-tribromo-4α*H*,5β-13-noreudesman-3-one (****26****).* To a CCl_4 solution (5 ml) of a mixture of **24** and **23** (1:2) (60 mg, 0.29 mmol) which had been formed by the deacetalization of **22**, we added Br_2 (96 mg, 0.60 mmol) in CCl_4 (2 ml). The mixture was stirred for 1 h at 0 °C, poured into a satd. NaCl aq solution (50 ml), and extracted with

benzene (10 ml×3). The combined extracts were washed successively with a 10% Na_2CO_3 aq solution (10 ml) and a satd. NaCl aq solution (20 ml), dried ($MgSO_4$), and concentrated to give 110 mg of an oily material, which was then chromatographed over silica gel (6 g, Merck, <230 mesh) and eluted with $CHCl_3$–CCl_4 (3:7) to give **26** (52 mg, 40%). NMR (CCl_4): δ 1.09 (3H, s, C_{10}–Me), 1.13 (3H, d, J=5.5 Hz, C_4–Me), 3.73 (1H, d, J=11.0 Hz, C_{12}–H_a), 3.80 (1H, d, J=4.5 Hz, C_{12}–H_b), 4.0—4.4 (1H, m, C_{11}–H), and 4.72 (1H, q, J=7.0 and 12.0 Hz, C_2–H) ppm.

*2β-Bromo-11-chloro-4αH,5β-13-noreudesman-3-one (**27**).* To a stirred solution of **8** (400 mg, 1.65 mmol) at 0 °C we added Br_2 (320 mg, 2.00 mmol) in CCl_4 (5 ml). The mixture was stirred for 1 h at 0 °C, poured into a satd. NaCl aq solution (100 ml), and extracted with ether (30 ml×3). The combined extracts were washed successively with a 10% Na_2CO_3 aq solution (30 ml) and a satd. NaCl aq solution (50 ml), dried ($MgSO_4$), and concentrated to give 640 mg of a crude, oily material, which was then chromatographed over silica gel (30 g, Merck, <230 mesh) and eluted with $CHCl_3$–CCl_4 (1:1) to give **27** (226 mg, 43%). NMR (CCl_4): δ 1.04 (3H, d, J=6.0, C_4–Me), 1.05 (3H, s, C_{10}–Me), 1.48 (3H, d, J=6.0 Hz, C_{11}–Me), 3.87 (1H, m, C_{11}–H), and 4.68 (1H, q, J=7.0 and 13.0 Hz, C_2–H) ppm.

*4βH,5β-13-Noreudesm-11-yn-3-one (**17**).* A solution of **16** (370 mg, 1.81 mmol) in 2% KOH–EtOH (25 ml) was allowed to stand at room temperature for 14 h and was then poured into a satd. NaCl aq solution (100 ml). The mixture was extracted with ether (30 ml×3). The combined extracts were washed with a satd. NaCl aq solution (50 ml), dried ($MgSO_4$), and concentrated to give a mixture of **16** and **17** (1:1.2), as ascertained by GLPC analysis (column: PEG 6000 on Diasolid M; oven temperature: 170 °C; N_2 flow rate: 30 ml/min; **16**: retention time, 16 min; **17**: retention time, 14 min). The mixture (mp 43—65 °C) was chromatographed over silica gel and eluted with CCl_4. The first running gave 111 mg of **17**, which was then recrystallized from pentane to give colorless prisms: mp 103—105 °C. IR (KBr): 3279, 2120, and 1701 cm^{-1}. NMR (CCl_4): δ 0.88 (3H, d, J=6.5 Hz, C_4–Me), 1.30 (3H, s, C_{10}–Me), and 1.91 (1H, d, J=2.5 Hz, C_{12}–H) ppm. NMR (C_6H_6): δ 0.92 (3H, d, J=6.0 Hz, C_4–Me), 0.98 (3H, s, C_{10}–Me) ppm. ORD (MeOH): $[\phi]_{304}$=+897, $[\phi]_{265}$=−1790, A=+26.9. MS (70 eV) *m/e*: 204 (M^+). Found: C, 81.77; H, 9.71%. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87%. The following running gave a mixture of **16** and **17**.

*The Temperature Dependence of the Equilibrium in **16** and **17**.* Four portions of **16** and **17** (20 mg each) were dissolved separately in 2% KOH–EtOH (10 ml) in 100-ml Erlenmeyer flasks. The flasks were stoppered and kept in water baths thermostated at 25 °C, 40 °C, 60 °C, and 80 °C for 6 h. Each solution was then vigorously stirred into a mixture of AcOH (0.2 ml), ether (20 ml), and a satd.NaCl aq solution (60 ml). The ether layer was thus separated, and the aqueous layer was further extracted with ether (20 ml×3). The combined extracts were washed with a satd. NaCl aq solution (50 ml), dried (Na_2SO_4), and concentrated to give a mixture of **16** and **17** as a crystalline meterial. The ratio of **16** and **17** was determined by GLPC (3 mmϕ×1 m column containing 10% carbowax 20 M on diasolid M; oven temperature, 140 °C; N_2 flow rate, 40 ml/min). The retention times of **16** and **17** were 21 min and 18 min respectively.

The Temperature Dependence of the Equilibrium in Chamaecynone and Isochamaecynone. Three portions of chamaecynone (10 mg) were dissolved separately in 2% KOH–EtOH (10 ml) in 100-ml Erlenmeyer flasks. The flasks were stoppered and kept in water baths thermostated at 25 °C, 52 °C, and 80 °C for 6 h. Each solution was treated as has been described above to give a mixture of chamaecynone and isochamaecynone as a crystalline material. The ratio of chamaecynone and isochamaecynone was determined by GLPC (3 mmϕ×1 m containing 10% carbowax 20 M on diasolid M; oven temperature, 140 °C; N_2 flow rate, 40 ml/min). The retention times of chamaecynone and isochamaecynone were 19 min and 25.5 min respectively.

Isomerization of Isochamaecynone. A solution of isochamaecynone (7 mg) in 2% KOH–EtOH (1 ml) was allowed to stand at 25 °C and was then treated in the usual manner to give a mixture of chamaecynone and isochamaecynone (3:1), as determined by GLPC analysis (column: PEG 6000 on diasolid M; oven temperature, 170 °C; N_2 flow rate, 30 ml/min).

*The Temperature Dependence of the Equiliblium in **23** and **24**.* Four portions of **23** (20 mg) were dissolved separately in 2% KOH–EtOH (10 ml) in 100-ml Erlenmeyer flasks. The flasks were then stoppered and kept in water baths thermostated at 25 °C, 40 °C, 60 °C, and 80 °C for 6 h. Each solution was then treated in the manner described above to give a mixture of **23** and **24** as an oily material. The ratio of **23** and **24** was determined by GLPC (3 mmϕ×1 m column containing 10% carbowax 20 M on diasolid M; oven temperature 140 °C; N_2 flow rate, 40 ml/min). The retention times of **23** and **24** were 54.5 min and 60 min respectively.

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19) In the preliminary report, we reported incorrect maximum and minimum values of the ORD curves of **7** and **16** because of having made careless mistakes. The values reported there are not $[\phi]$ but $[\alpha]$ values.
20) The melting point of this compound was carelessly and erroneously reported to be 49 °C in the preliminary report.
21) Compound **19** was not identical with the crystalline compound with mp of 129 °C reported in the preliminary report.