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The Total Synthesis of Hydroxyisochamaecynone and Its Stereochemical Assignment[1]

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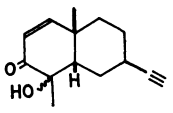
The structure of an acetylenic nor-sesquiterpene, hydroxyisochamaecynone, was determined to be 4α-hydroxy-5β*H*-13-noreudesm-1-en-11-yn-3-one (Ib) by means of the stereoselective total syntheses of two possible stereoisomers, Ib and 4β-hydroxy-5β*H*-13-noreudesm-1-en-11-yn-3-one.

The acetylenic nor-sesquiterpene alcohol named "hydroxyisochamaecynone" has been isolated from the essential oil of the Benihi tree (*Chamaecyparis formosensis* Matsum., Cupressaceae) as an extremely minor component,[2] together with the related acetylenic compounds.[2,3] The structure of this compound has been inferred to be as is shown in I, except for the stereochemistry at C_4 by only the spectral evidence. This paper will give details of the total syntheses of 4β-hydroxy-5β*H*-13-noreudesm-1-en-11-yn-3-one (Ia) and its C_4-epimer, 4α-hydroxy-5β*H*-13-noreudesm-1-en-11-yn-3-one (Ib), in optically active forms in the regio- and stereo-selective manners, with the object of establishing the structure of "hydroxyisochamaecynone."



(I)

Fig. 1.

We chose an acetylenic ketone (**1**) as the starting material mainly for the following three reasons: 1) The ketone **1** can easily be obtained from *l*-α-santonin by means of the previously reported method,[4] 2) the ketone **1** is conveniently functionalized as the starting material of both of Ia and Ib, and 3) although acetylenic ketone, **1**, and its related compounds are conformationally mobile and their reaction mode is rather complex, their stereochemical behavior has been well documented and their stereochemical reaction course is predictable.[4]

The starting point of the synthesis is the enol acetylation of **1**. The treatment of **1** with isopropenyl acetate in the presence of *p*-TsOH gave mainly the thermodynamically more stable trisubstituted enol acetate (**2**). The amount of undesired $\Delta^{2,3}$-enol acetate (**16**) formed under these conditions was negligible, judging from the NMR spectrum of the crude product. In Compound **2** there are two possible conformers, the non-steroid conformation (**A**) and the steroid conformation (**B**), as is shown in Fig. 2. Judging from the results of the equilibrium reaction between **1** and its C_4-epimer (**17**),[5] which was reported in the previous paper of this series,[4] Compound **2** is presumed to exist as an equilibrium mixture of the **A** and **B** conformers in solution. Actually, the NMR spectrum of **2** showed

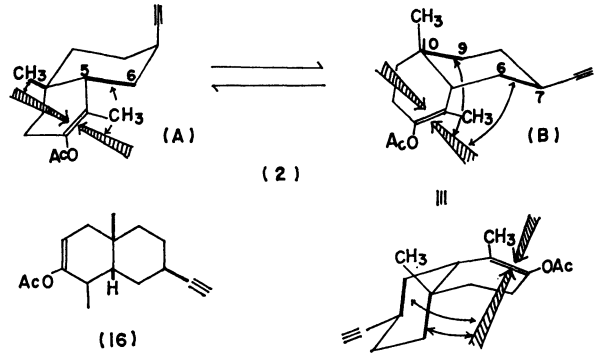


Fig. 2.

two pairs of methyl groups, possibly corresponding to **A** and **B**.

The treatment of **2** with monoperoxyphthalic acid gave an epoxide (**3**) as a single product. The high stereoselectivity of this reaction was explained as follows (Fig. 2). In the non-steroid conformation (**A**) the β-side approach of the incoming reagent is hindered by the angular methyl group, while its α-side approach is hindered by the C_5–C_6 bond. On the contrary, in the steroid conformation (**B**) there is no significant hindrance in the convexed β-side, although the α-side is strongly hindered by the C_6–C_7 and C_9–C_{10} bonds. Thus, in the epoxidation of the equilibrium mixture of the **A** and **B** conformers the reagent attacks the least hindered β-side of **B** to give β-epoxide (**3**) stereoselectively. This stereochemical assignment was confirmed by the epoxidation of the enol acetate (**12**) with a rigid conformation. A detailed discussion of this will appear below.

The hydrolysis of **3** gave a hydroxy ketone (**4**). The hydroxyl group of **4**, which was introduced newly at C_4, was assigned a β-configuration the same as that of the epoxide ring of **3**. Although we expected the preferential formation of α-bromo ketone (**6**) in the bromination of **4** in the presence of HBr,[4,6] **4** gave a mixture of a tribromide (**5**) and the desired α-bromo ketone (**6**) under those reaction conditions. Probably the C_2 position of the enol form of **4** is sterically hindered, and the addition rate of Br_2 to the terminal triple bond and the enol double bond is comparable. In agreement with the **6** structure, IR ($CHCl_3$) showed carbonyl absorption at 1727 cm^{-1} and NMR (CCl_4) showed C_2–H at δ 5.05 (1H, q, J=7.0 and 13.0 Hz).

The dehydrobromination of **6** with LiBr–Li_2CO_3 in DMF produced 4β-hydroxy-5β*H*-13-noreudesm-1-en-11-yn-3-one (Ia), which exhibited completely different IR

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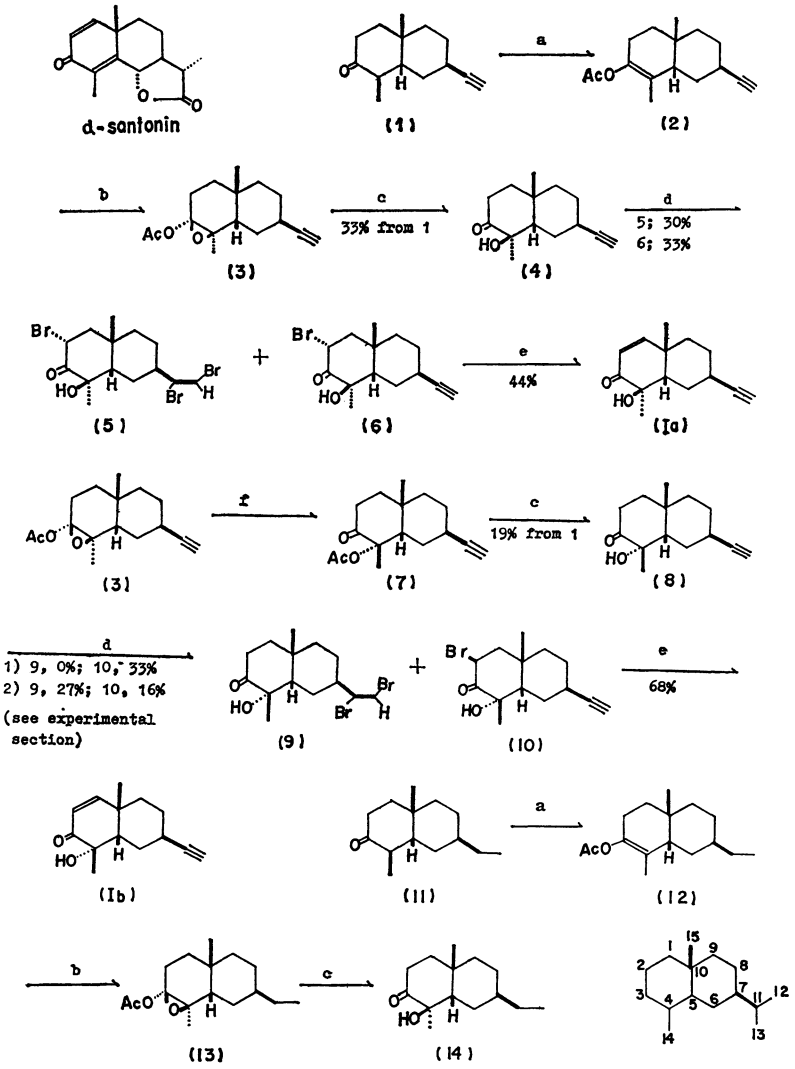


a: >-OAc, *p*-TsOH; b: monoperoxyphthalic acid, $CHCl_3$; c: 10% KOH aq soln, EtOH; d: 48% HBr, Br_2, AcOH; e: LiBr, Li_2CO_3, DMF; f: Δ (170—178 °C), 15 min.

Scheme 1.

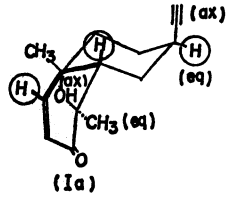


Fig. 3.

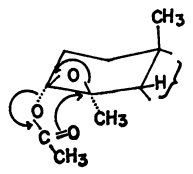


Fig. 4.

($CHCl_3$), NMR ($CDCl_3$), ORD (MeOH), and mass (70 eV) spectra from those of naturally occurring "hydroxyisochamaecynone." In accordance with the Ia structure with its non-steroid conformation, as is shown in Fig. 3, the NMR (CCl_4, 100 MHz) spectrum showed a long-range coupling (J=1.5 Hz) between C_1–H and C_5–H. The half-band width of C_7–H was *ca.* 14 Hz, which agreed with the expected value of α-(*eq*) C_7–H. The IR spectrum of Ia in CCl_4 showed absorption bands at 3580 (w) and 3500 (s) cm^{-1}, which suggested the existence of β(*ax*)-OH,[7,8] in accordance with the Ia structure with its non-steroid conformation.

Our next target was the synthesis of 4α-hydroxy-5βH-13-noreudesm-1-en-11-yn-3-one (Ib), the C_4-epimer of Ia. The thermal rearrangement of **3** gave a keto acetate (**7**). From the consideration of the reaction mechanism[9] depicted in Fig. 4, the stereochemistry of the newly introduced acetoxyl group was deduced to be the α-orientation. The hydrolysis of **7** gave a hydroxy ketone (**8**), which was the C_4-epimer of **4**. The bromination of **8** gave a mixture of an addition product (**9**) and the desired α-bromo ketone (**10**). The ratio of **9** to **10** depended upon the reaction conditions. Judging from the carbonyl absorption (1727 cm^{-1}) in IR (KBr) and the coupling pattern of C_2–H [δ 5.53 (q, J=7.0 and

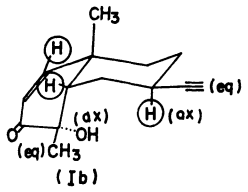


Fig. 5

13.0 Hz)] in NMR (CCl_4), the bromine atom at C_2 of **10** is situated in the $\beta(eq)$-configuration. The dehydrobromination of **10** with LiBr–Li_2CO_3 in DMF produced 4α-hydroxy-5β*H*-13-noreudesm-1-en-11-yn-3-one (Ib), which was identical with naturally occurring "hydroxyisochamaecynone" in its IR (KBr), NMR ($CDCl_3$), ORD (MeOH), and mass (70 eV) spectra and which showed no depression in its melting point when admixed with an authentic specimen. In accordance with the stereo-structure Ib with the steroid conformation, shown in Fig. 5, the NMR (100 MHz) did not show a long-range coupling between C_1–H and C_5–H. The half-band width of C_7–H was *ca.* 24 Hz, which agreed with the expected value of $\alpha(ax)$ C_7–H. The IR spectrum (CCl_4) of Ib showed two absorption bands, at 3590 (w) and 3500 (s) cm^{-1}, which agreed with the stereo-structure of a steroid conformation possessing an $\alpha(ax)$–OH bond.[7,8] From the stereoselective syntheses mentioned above and the spectroscopic evidence concerning Ia and Ib, the structure of naturally occurring "hydroxyisochamaecynone" was concluded to be 4α-hydroxy-5β*H*-13-noreudesm-1-en-11-yn-3-one (Ib) with the steroid conformation, as is depicted in Fig. 5.

In the above-mentioned syntheses, we employed the epoxidation of a conformationally mobile enol acetate (**2**) as a key step and concluded by an examination of the Dreiding molecular models that the reagent should approach from the β-side. Since there is no similar example in the literature, we decided to confirm the above conclusion by the following chemical correlation. Hexahydroisochamaecynone (**11**) was employed as the starting material. The enol acetylation of **11** gave an enol acetate (**12**). Since this compound has a bulky ethyl group at C_7, the conformation was considered to be fixed in the steroid conformation, as is shown in Fig. 6. In this case, the epoxidation of **12** occurred, apparently from the convexed β-side,[10] giving a β-epoxide (**13**). The hydrolysis of **13** gave a hydroxy ketone (**14**), which was identical with the tetrahydro derivative obtained by the catalytic hydrogenation of **4**, in accordance with the above-mentioned conclusion.

The ORD Studies of the Synthetic Intermediates of Ia and Ib. In the *cis*-decalone derivatives with a mobile conformation, the studies of the ORD curves are a convenient method for predicting their conformations. For the application of this method to Ia, Ib, and their synthetic intermediates, we need to know the degree of the contribution of the axial hydroxyl group at the α-position of the carbonyl group. The ORD data of **4** and Ia and the corresponding deoxy derivatives (**17** and **18**) are summarized in Table 1. This table shows that the contribution of the $\beta(ax)$-hydroxyl group to the Cotton effect of **4** and Ia is negative, as predicted by the octant rule.

On the other hand, the ORD data of **15**, **8**, **10**, and Ib and the corresponding deoxy derivatives (**19**, **1**, **20**, and **21**), summarized in Table 2, show that the

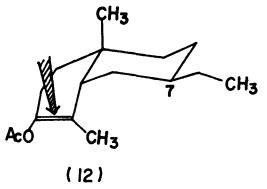


Fig. 6.

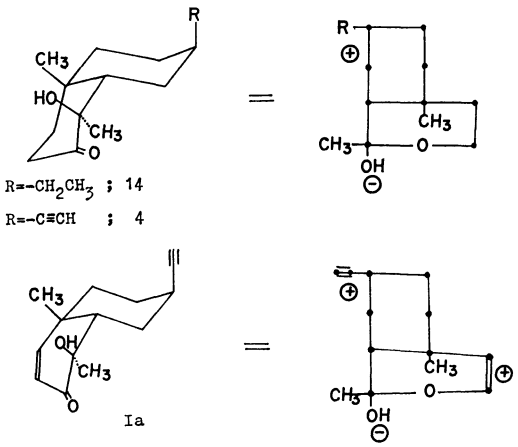


Fig. 7.

Table 1. The ORD spectral data of **14**, **4**, and Ia, and their reference deoxy derivatives, **17** and chamaecynone (**18**) in MeOH

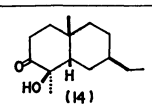
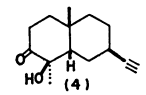
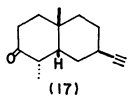
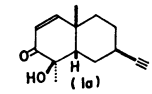
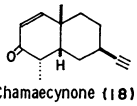
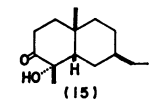
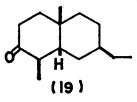
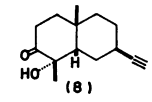
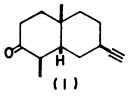
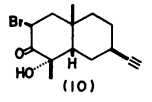
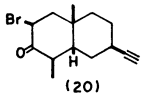
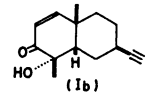
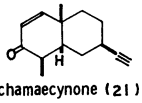
Compound	ORD	Corresponding deoxy derivative	ORD	Contribution of OH (ΔA)
 (14)	$[\phi]_{315}=-1100$ $[\phi]_{245}=+2610$ $A=-37$			
 (4)	$[\phi]_{310}=-1490$ $[\phi]_{260}=+2000$ $A=-35$	 (17)	$[\phi]_{304}=+900$ $[\phi]_{205}=-1790$ $A=+27$	−62
 (Ia)	$[\phi]_{360}=-560$ $[\phi]_{310}=+220$ $A=-7.8$	 Chamaecynone (18)	$[\phi]_{352}=+600$ $[\phi]_{310}=-4000$ $A=+46$	−53.8

Table 2. The ORD spectral data of **15**, **8**, **10**, and Ib and their reference deoxy derivatives, **19**, **1**, **20**, and isochamaecynone (**21**) in MeOH

Compound	ORD	Corresponding deoxy derivative	ORD	Contribution of OH (ΔA)
 (15)	$[\phi]_{325}=+160$ $[\phi]_{260}=+1000$ $A=-8.4$	 (19)	$[\phi]_{302}=-660$ $[\phi]_{260}=+1960$ $A=-26.2$	+17.8
 (8)	$[\phi]_{325}=-520$ $[\phi]_{300}=0$ $A=-5.2$	 (1)	$[\phi]_{340}=-900$ $[\phi]_{265}=+1790$ $A=-26.9$	+21.7
 (10)	$[\phi]_{310}=-990$ $[\phi]_{270}=0$ $A=-9.9$	 (20)	$[\phi]_{310}=-470$ $[\phi]_{260}=+600$ $A=-10.7$	+0.8
 (Ib)	$[\phi]_{340}=-1010$ $[\phi]_{285}=+1450$ $A=-24.6$	 Isochamaecynone (21)	$[\phi]_{345}=-870$ $[\phi]_{270}=+2120$ $A=-29.9$	+5.3

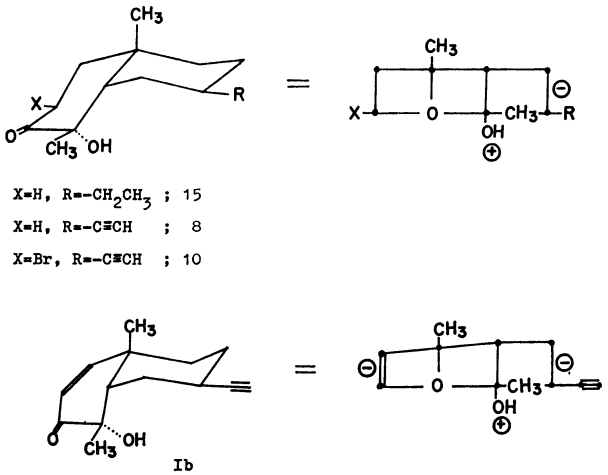


Fig. 8

contribution of the α(*ax*)-hydroxyl group of **15**, **8**, **10**, and Ib to the Cotton effect is positive, as predicted by the octant rule, though the magnitude of the ΔA value is irregular.

In conclusion, although the axial hydroxyl substituent at the α-position of the carbonyl group contributes to the Cotton effect, as predicted by the octant rule, it is difficult to estimate the conformation of the flexible hydroxy ketones on the basis of the ORD data only, because the magnitude of the contribution of the hydroxyl group to the Cotton effect is not constant.

Experimental

All the melting points are uncorected. The IR spectra were recorded on Shimadzu IR-27, Hitachi EPI-S2, and Hitachi EPI-G28 spectrophotometers. The NMR spectra were recorded on Varian A-60, Nichiden-Varian T-60, and Varian HA-100 spectrometers, employing tetramethylsilane as the internal reference. The ORD and CD spectra were recorded on a Nihonbunko ORD/UV-5 spectrophotometer.

3-Acetoxy-5βH-13-noreudesm-3-en-11-yne (2). A solution of 4α*H*,5β*H*-13-noreudesm-11-yn-3-one (**1**) (600 mg, 2.94 mmol) in isopropenyl acetate (6 ml) containing *p*-toluenesulfonic acid (60 mg) was heated under N_2 at the boiling point and then concentrated in 30 min to give a brown, oily residue, which was subsequently dissolved in ether (100 ml). The ether solution was washed with a saturated aq soln of NaCl (50 ml×2), dried ($MgSO_4$), and concentrated to give 600 mg of an oily material, which was a mixture of two conformers of **2**. IR (neat): 3300, 2160, and 1755 cm^{-1}. NMR (CCl_4): δ 1.02 (s, C_{10}–Me of the major component), 1.05 (s, C_{10}–Me of the minor component), 1.50 (m, C_4–Me of the major component), 1.56 (m, C_4–Me of the minor component), 1.90 (1H, d, J=3.0 Hz), and 2.03 (3H, s, –C(=O)–C<u>H</u>$_3$) ppm.

3α-Acetoxy-3β,4β-epoxy-5βH-13-noreudesm-11-yne (3). To a solution of **2** (600 mg, 2.44 mmol) in $CHCl_3$ (15 ml) we added a solution of monoperoxyphthalic acid (500 mg, 2.75 mmol) in ether (15 ml). The mixture was allowed to stand at room temperature for 7 days and then filtered to remove the phthalic acid. The filtrate was poured into an aq soln of KI and stirred for a few min. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (20 ml×2). The combined extracts were washed successively with a 0.2 M aq soln of $Na_2S_2O_3$, a saturated aq soln of $NaHCO_3$, and a saturated aq soln of NaCl, dried ($MgSO_4$), and concentrated to give 668 mg of an oily material, which was employed for the next reaction. This crude oil (445 mg) was chromatographed over silica gel (40 g, Merck, <230 mesh) and eluted with CCl_4–$CHCl_3$ (1: 1) to give 103 mg of spectroscopically pure **3** (mp 48—50 °C), which was then recrystallized from pentane to give a crystalline material; mp 68—69 °C. IR ($CHCl_3$): 3289, 2123, and 1748 cm^{-1}. NMR (CCl_4): δ 1.13 (3H, s), 1.25 (3H, s), 2.02 (3H, s, –C(=O)–C<u>H</u>$_3$), 1.92 (1H, d, J=2.5 Hz, C_{12}–H), and 2.80 (1H, m, $W_{h/2}$=*ca.* 10 Hz, C_7–H) ppm. Found: C, 73.38; H, 8.45%. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45%.

4β-Hydroxy-5βH-13-noreudesm-11-yn-3-one (4). Into a solution of **3** (610 mg) [prepared from **1** (600 mg, 2.94 mmol) without any purification at any step] in ethanol (30 ml) we added a 10% aq soln of KOH (9 ml). The mixture was allowed to stand at room temperature overnight, poured into a saturated aq soln of NaCl (100 ml), and extracted with ether (30 ml×3). The combined ether layers were washed with a saturated aq soln of NaCl, dried ($MgSO_4$), and evaporated to give an oily material, which was then chromatographed over silica gel (25 g, Merck, <230 mesh) and eluted with CCl_4–$CHCl_3$ (1: 1) to give spectroscopically pure **4** (214 mg, 33% overall yield from **1**); mp 89 °C. This was recrystallized from pentane to give the analytical sample;

mp 95 °C. IR (KBr): 3480, 3300, 2130, and 1712 cm^{-1}. NMR (CCl_4): δ 1.27 (3H, s), 1.45 (3H, s), and 1.90 (1H, d, J=2.5 Hz, C_{12}–H) ppm. ORD (MeOH): $[\phi]_{310}$=−1490, $[\phi]_{260}$=+2000; A=−35. Found: C, 76.51; H, 8.96%. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15%.

Bromination of **4**. *Formation of 2α,11,12-Tribromo-4β-hydroxy-5βH-13-noreudesm-11-en-3-one* (**5**) *and 2α-Bromo-4β-hydroxy-5βH-13-noreudesm-11-yn-3-one* (**6**). To a solution of **4** (170 mg, 0.77 mmol) in AcOH (5 ml) we added a 48% aq soln of HBr (0.1 ml) and Br_2 (140 mg, 0.88 mmol). The mixture was stirred for 1 h at room temperature, poured into a saturated aq soln of NaCl, and extracted with ether (20 ml ×3). The combined extracts were washed with a saturated aq soln of NaCl, dried ($MgSO_4$), and concentrated to give an oily product (250 mg), which was then chromatographed over silica gel (18 g, Merck, <230 mesh) and eluted with CCl_4–$CHCl_3$ (1: 1). The first fraction gave **5** (105 mg, 30%) as a crystalline material. IR (KBr): 3521, 3106, and 1730 cm^{-1}. NMR (CCl_4): δ 1.12 (3H, s), 1.47 (3H, s), 5.47 (1H, q, J=6.5 and 13.0 Hz, C_2–H), and 6.37 (1H, s, C_{12}–H) ppm. The second fraction gave **6** (77 mg, 33%) as a crystalline material. IR ($CHCl_3$): 3546, 3333, 2119, and 1727 cm^{-1}. NMR (CCl_4): δ 1.42 (3H, s), 1.59 (3H, s), 1.93 (1H, d, J=2.0 Hz, C_{12}–H), and 5.05 (1H, q, J=7.0 and 13.0 Hz, C_2–H) ppm.

4β-Hydroxy-5βH-13-noreudesm-1-en-11-yn-3-one (4β-Hydroxychamaecynone Ia). A mixture of **6** (22 mg, 0.10 mmol), Li_2CO_3 (22 mg, 0.30 mmol), and LiBr (22 mg, 0.25 mmol) in anhydrous DMF (4 ml) was stirred at 140—150 °C for 6.5 h under N_2, cooled, poured into a saturated aq soln of NaCl (30 ml), and extracted with ether (10 ml×3). The combined extracts were washed successively with 2 M HCl (10 ml) and a saturated aq soln of NaCl, dried ($MgSO_4$), and concentrated to give 17 mg of an oily material, which was then chromatographed over silica gel (2 g, Merck, <230 mesh) and eluted with CCl_4–$CHCl_3$ (1: 1) to give 7 mg (44%) of Ia as a crystalline material; mp 71 °C, IR ($CHCl_3$): 3521, 3322, 2114, and 1672 cm^{-1}. NMR (CCl_4, 100 MHz): δ 1.34 (3H, s), 1.44 (3H, s), 1.93 (1H, d, J=2.5 Hz, C_{12}–H), 2.83 (1H, m, $W_{h/2}$=*ca.* 14 Hz, C_{17}–H), 5.88 (1H, d, J=10.0 Hz, C_2–H), and 6.43 (1H, dd, J=1.5 and 10.0 Hz, C_1–H) ppm. UV (MeOH): λ_{max}=228 nm (ε=7400). ORD (MeOH): $[\phi]_{360}$=−560, $[\phi]_{310}$=+220, A=−7.8. CD (MeOH): $[\theta]_{340}$=−560.

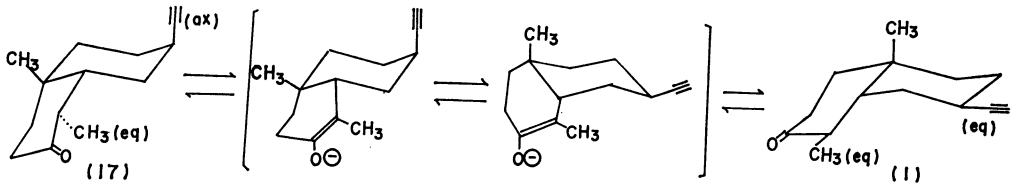
4α-Hydroxy-5βH-13-noreudesm-11-yn-3-one (**8**). The crude epoxide (**3**, 860 mg) [prepared from **1** (800 mg, 3.92 mmol)] was heated at 170—178 °C under N_2 to give 4α-acetoxy-5β*H*-13-noreudesm-11-yn-3-one (**7**) as an oily material. IR (neat): 3279, 1730, and 1721 cm^{-1}. This crude material was dissolved in a mixture of EtOH (24 ml) and a 10% aq soln of KOH (8 ml). The mixture was allowed to stand at room temperature for 100 min, poured into a saturated aq soln of NaCl (100 ml), and extracted with petroleum ether (20 ml×4). The combined extracts were washed with a saturated aq soln of NaCl, dried ($MgSO_4$), and concentrated to give 463 mg of an oily material, which was then chromatographed over silica gel (25 g, Merck, <230 mesh) and eluted with a mixture of CCl_4–$CHCl_3$ (1: 1). The first fraction gave **4** (58 mg, 7% overall yield from **1**). The second fraction gave 163 mg (19% overall yield from **1**) of **8**, which was recrystallized from pentane to give colorless prisms; mp 103 °C. IR (KBr): 3436, 3268, 2119, and 1712 cm^{-1}. NMR (CCl_4): δ 1.22 (3H, s), 1.25 (3H, s), and 1.92 (1H, d, J=2.5 Hz, C_{12}–H) ppm. ORD (MeOH): $[\phi]_{325}$=−520, $[\phi]_{300}$=0, A=−5.2. CD (MeOH): $[\theta]_{312}$=−274. Found: C, 76.35; H, 9.09%. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15%.

Bromination of **8**. *Formation of 11,12-Dibromo-4α-hydroxy-5βH-13-noreudesm-3-one* (**9**) *and 2β-Bromo-4α-hydroxy-5βH-13-noreudesm-11-yn-3-one* (**10**). A solution of **8** (122 mg, 0.55 mmol) in AcOH (5 ml) was stirred in the presence of a 48% aq soln of HBr (0.1 ml) for 10 min at room temperature. Into the mixture we then added a solution of Br_2 (108 mg, 0.68 mmol) in AcOH (1 ml). The mixture was stirred for 40 min at room temperature, poured into a saturated aq soln of NaCl (50 ml), and extracted with petroleum ether (20 ml ×4). The combined extracts were washed successively with a 10% aq soln of Na_2CO_3 and a saturated aq soln of NaCl, dried ($MgSO_4$), and concentrated to give 172 mg of an oily material, which was then chromatographed over silica gel (10 g, Merck, <230 mesh) and eluted with $CHCl_3$–CCl_4 (1: 1) to give spectroscopically pure **10** (54 mg, 33%) as a semisolid compound. This was subsequently recrystallized from petroleum ether–ether to give prisms; mp 140.5 °C. IR (KBr): 3497, 3300, 2105, and 1727 cm^{-1}. NMR (CCl_4): δ 1.30 (3H, s), 1.50 (3H, s), 1.93 (1H, d, J=2.0 Hz), and 5.53 (1H, q, J=7.0 and 13.0 Hz, C_2–H) ppm. ORD (MeOH): $[\phi]_{310}$=−990, $[\phi]_{270}$=0, A=−9.9. Found: C, 57.34; H, 5.81%. Calcd for $C_{14}H_{19}O_2Br$: C, 56.23; H, 6.41%. In another experiment, to a solution of **8** (130 mg, 0.59 mmol) in AcOH (5 ml) we added a 48% aq soln of HBr (0.1 ml) and Br_2 (110 mg, 0.69 mmol) successively. The mixture was stirred for 40 min at room temperature, poured into a saturated aq soln of NaCl (50 ml), and extracted with petroleum ether (20 ml×4). The combined extracts were washed successively with a 10% aq soln of Na_2CO_3 and a saturated aq soln of NaCl, dried ($MgSO_4$), and concentrated to give 207 mg of an oily material, which was chromatographed over silica gel (10 g, Merck, <230 mesh) and eluted with CCl_4–$CHCl_3$ (1: 1). The first fraction gave spectroscopically pure **9** (61 mg, 27%) as a crystalline material; this was subsequently recrystallized from pentane to give microcrystals; mp 90 °C. IR (KBr): 3521, 3086, and 1706 cm^{-1}. NMR (CCl_4): δ 1.11 (3H, s), 1.46 (3H, s), and 6.35 (1H, s) ppm. Found: C, 44.25; H, 5.26%. Calcd for $C_{14}H_{20}O_2Br_2$: C, 44.21; H, 5.30%. The second fraction gave **10** (29 mg, 16%).

4α-Hydroxy-5βH-13-noreudesm-1-en-11-yn-3-one (4α-Hydroxyisochamaecynone, Ib). A mixture of **10** (83 mg, 0.28 mmol), LiBr (88 mg, 1.01 mmol), and Li_2CO_3 (88 mg, 1.19 mmol) in anhydrous DMF (10 ml) was stirred at 150—155 °C for 5 h under N_2, cooled, poured into a saturated aq soln of NaCl (50 ml), and extracted with ether (15 ml×3). The combined extracts were washed successively with 2 M HCl (15 ml) and a saturated aq soln of NaCl, dried ($MgSO_4$), and concentrated to give 75 mg of a crystalline material, which was subsequently chromatographed over silica gel (5 g, <230 mesh) and eluted with CCl_4–$CHCl_3$ (1: 1) to give spectroscopically pure Ib (41 mg, 68%) as a crystalline material, which was then recrystallized from pentane to give colorless prisms; mp 160 °C. This material showed no depression in its melting point when admixed with an authentic sample of natural "hydroxyisochamaecynone" and was identical in all respects with this specimen in IR (KBr), NMR ($CDCl_3$), ORD (MeOH), and MS (70 eV).

Synthesis of 4β-Hydroxy-5βH-13-noreudesm-3-one (**14**) *from 4αH,5βH-13-Noreudesman-3-one (Hexahydroisochamaecynone,* **11**). A solution of **11** (760 mg, 3.65 mmol) in isopropenylacetate (8 ml) containing *p*-toluenesulfonic acid (80 mg) was heated under N_2 at the boiling point and then concentrated for 30 min to give a brown, oily residue, which was subsequently dissolved in ether (100 ml). The ether solution was washed with a saturated aq soln of NaCl (50 ml×2), dried ($MgSO_4$), and concentrated to give 780 mg of crude 3-acetoxy-5β*H*-noreudesm-3-ene (**12**).

To a solution of this crude material (780 mg) in $CHCl_3$



non-steroid conformation | non-steroid conformation | steroid conformation | steroid conformation

Fig. 9.

Table 3.

Compound	Absorptions of -OH (cm^{-1})		Absorptions of C=O (cm^{-1})
	Weak band	Strong band	
1			1716
Ia	3580	3500	1708 (sh), 1684
4	3590	3490	1715
14	3595	3475	1713
Ib	3590	3500	1710 (sh), 1685
8	3600	3490	1718
15	3597	3480	1716

These IR spectra were recorded by a Hitachi-EPI-G28 instrument in a 0.2 M CCl_4 solution.

(16 ml) we added a solution of monoperoxyphthalic acid (728 mg, 4.00 mmol) in ether (16 ml). The mixture was allowed to stand at room temperature for 5 days and then filtered to remove any phthalic acid. The filtrate was poured into an aq soln of KI and stirred for a few min. The organic layer was then separated, and the aqueous layer was extracted with $CHCl_3$ (30 ml×2). The combined extracts were washed successively with a 0.2 M aq soln of $Na_2S_2O_3$, a saturated aq soln of $NaHCO_3$, and a saturated aq soln of NaCl, dried ($MgSO_4$) and concentrated to give 850 mg of crude 3α-acetoxy-3β,4β-epoxy-5β*H*-13-noreudesmane (**13**). which was almost pure, judging from the TLC analysis and the spectroscopic evidence. IR (neat): 1739 cm^{-1}. NMR (CCl_4): δ 0.96 (3H, s), 1.38 (3H, s), and 2.03 (3H, s) ppm.

Into a solution of this crude material (850 mg) in EtOH (30 ml) we added a 10% aq soln of KOH (10 ml). The mixture was allowed to stand at room temperature for 2 h, poured into a saturated aq soln of NaCl (100 ml), and extracted with ether (30 ml×3). The combined ether layers were washed with a saturated aq soln of NaCl, dried ($MgSO_4$), and evaporated to give a crystalline material, which was subsequently chromatographed over silica gel (10 g, Merck, <230 mesh) and eluted with CCl_4–$CHCl_3$ (1: 1) to give spectroscopically pure **14** (143 mg, 17% overall yield from **11**). This was recrystallized from pentane to give needles; mp 91.5 °C. IR (KBr): 3484 and 1715 cm^{-1}. NMR (CCl_4): δ 1.12 (3H, s) and 1.35 (3H, s) ppm. ORD (MeOH): $[\phi]_{315}=-1100$, $[\phi]_{245}=+2610$, $A=-37$. Found: C, 75.08; H, 10.49%. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78%.

Catalytic Hydrogenation of **4**. *Formation of* **14**: A mixture of **4** (50 mg), EtOH (3 ml), and 5% Pd/C was shaken under an atmosphere of H_2 for 2 h and then filtered. The filtrate was concentrated to give **14** (50 mg) as a crystalline material.

Catalytic Hydrogenation of **8**. *Formation of 4α-Hydroxy-5β*H*-13-noreudesm-3-one (**15**)*: A mixture of **8** (40 mg), EtOH (3 ml), and 5% Pd/C was shaken under an atmosphere of H_2 for 2 h and then filtered. The filtrate was concentrated to give **15** (30 mg) as an oily material. IR (neat): 3472 and 1715 cm^{-1}. NMR (CCl_4): δ 1.05 (3H, s) and 1.32 (3H, s) ppm. ORD (MeOH): $[\phi]_{325}=+160$, $[\phi]_{260}=+1000$, $A=-8.4$. CD (MeOH): $[\theta]_{295}=-372$.

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