Tetrahedron Vol. 34, pp. 41 to 46. Pergamon Press 1978. Printed in Great Britain

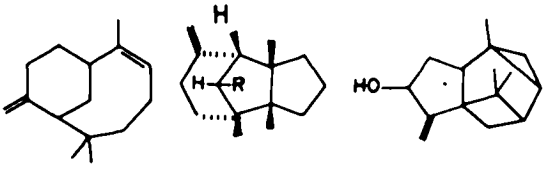
ANASTREPTENE, A COMMONLY ENCOUNTERED SESQUITERPENE OF LIVERWORTS (HEPATICAE)

NIELS H. ANDERSEN,†[1a] YOSHIMOTO OHTA,[1b] ANA MOORE and CHIA-LI W. TSENG
Department of Chemistry, University of Washington, Seattle, WA 98195, U.S.A.

(*Received in the USA* 18 *April* 1977; *Received in the UK for publication* 11 *July* 1977)

Abstract—Anastreptene (9b), a tetracyclic mono-ene of the same skeleton as myliol (10) has been found as a common constituent of essential oils derived from liverworts. The relationship to myliol is established by spectral comparison between the hydroboration products and the related ketones from anstreptene and myliol degradation products. The additional degradative chemistry for anastreptene could not be rationalized based on the original myliol assignment (4), but accord with the recent revision based on X-ray crystallography and provide a confirmation of the stereochemical assignments for myliol and anastreptene.

That the liverworts (Hepaticae) are an unusually rich source of sesquiterpenes has been convincingly demonstrated by recent work from Hüneck,[2] Matsuo *et al.*,[3] Herout's group,[4] and our laboratories.[5] A number of novel skeletons have been found of which those of bazzanene (1),[3a] β-barbatene (2)[5a,b] (and gymnomitrol 3[4]), and myliol (4)[4b] remain unique to the Hepaticae. The barbatenes have been found in virtually every leafy liverwort (20+ taxa of *Jungermanniales* have been examined in our laboratories) studied. The indicated stereochemistry of β-barbatenes, supported by all three published degradative studies,[3c,5b,6] is clearly diastereomeric to the related fungal products, the trichothecanes.[7]



1 2 R=H 3 R=OH 4†

Sesquiterpenes presumed to be derived from 11-membered ring intermediates or germacrenes, when isolated from liverworts have uniformly[8] been strictly enantiomeric to the vascular plant products.[9,10]

We now present a detailed structure elucidation for a novel hydrocarbon ($C_{15}H_{22}$) which has been encountered in numerous oil samples over the last 5 years. It was not until the oil of *Anastrepta orcadensis*[10] was examined that this entity was recongnized. For this reason the crystalline hydrocarbon was designated anastreptene.

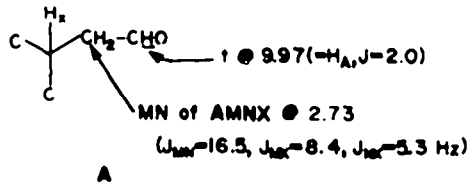
RESULTS AND DISCUSSION

Anastreptene is easily recognized in oil samples by its unique gc retention properties. The relative retention (α-copane as the standard) of anastreptene is radically, for a non-aromatic hydrocarbon, altered on columns of differing polarity, α (phase): 0.840 (Apiezon-L), 1.15 (Carbowax 20 M) and 1.22 (DEGS). When isolated anastreptene can be recognized by its crystallinity[11] (m.p. 91–93°), high degree of unsaturation (MW 202), and unusual spectra: although IR and NMR indicate a nonconjugated olefin the UV spectrum is very intense (190 nm, ϵ 8,700) with substantial absorbance at lower energy (ϵ = 4400 @ 215 nm). The NMR spectrum displayed, besides three singlet Me resonances, a vinyl hydrogen (5.18) a multiplet vinyl Me (1.71), and two allyl protons (integration from 1.9 to 2.8 ppm). In addition a complex multiplet at 0.25–0.70 ppm (integrating for 2–3 H) suggested a cyclopropyl ring system. With these data we were led to consider structures in which the olefin and cyclopropane were conjugated. A number of studies of acid-catalyzed reactions based on this premise were, and remain in retrospect, uninformative.

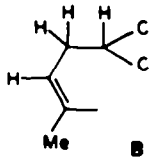
We therefore set about a typical degrative sequence for an endocyclic olefin. Osmylation of anastreptene afforded a single crystalline glycol (m.p. 91–93°) in 90% yield indicating a distinct sideness to the olefinic bond. That only the expected changes had occurred was evident from the NMR spectrum which still displayed cyclopropyl hydrogen signals, three singlet Me's (now coincident at 1.04 ppm) as well as a new Me carbinol singlet at 1.28 ppm. A methine signal appearing at 3.75 ppm, ascribed to the secondary alcohol unit, was an approximate quartet with one coupling due to the OH indicating a neighboring methylene. On reaction with $Pb(OAc)_4$ under mild conditions a keto-aldehyde could be obtained, but not purified due to its rapid decomposition on chromatography or on storage in the presence of catalytic amounts of basic materials. The aldehyde could be separated from polar by-products based on its greater solubility in dry hexane, and when so obtained displayed two CO absorptions (1732; 1718, 2735 cm^{-1}). The NMR clearly showed the aldehyde chain (A) and thus partial structure B for the olefin. The signal of the adjacent methylene collapsed to a simple ABX pattern on irradiation at the $-CH_2O$ resonance. The methyl ketone grouping was not as obvious in the NMR, a multiplet ($w_{h/2}$ = 3 Hz) at 1.71 ppm being the only signal which could be attributed to the acetyl Me. Attempts at an aldol condensation of the keto-aldehyde were not successful.

The keto-aldehyde was not stable to storage giving

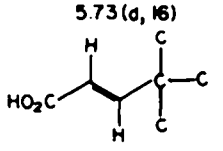
†We illustrate here the structure proposed in 1971[4b] and the only one available to us throughout this work.

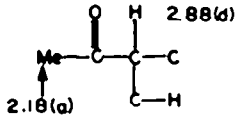


A

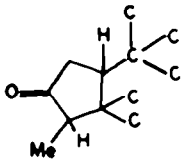


B

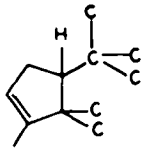




C



D



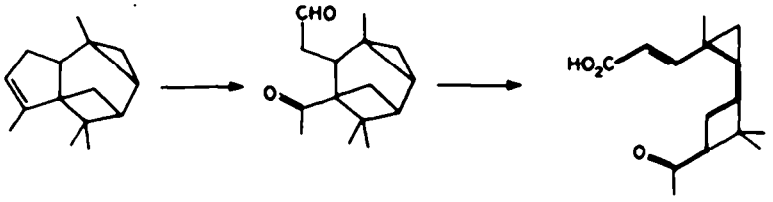
E

among other products, an unsaturated acid. The same acid was obtained (~30% yield) when the $Pb(OAc)_4$ cleavage was run for longer periods. The partial structure (C) of this material follows from the spectroscopic data.

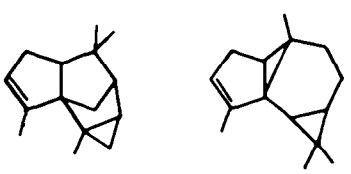
On hydroboration anastreptene afforded two secondary alcohols and oxidation of the mixture afforded a single ketone which was clearly a cyclopentanone ($\nu_{C=O}$ 1742 cm^{-1}). The hydrogen coupling to the doublet-Me could be located in the hydroboration product and decoupling at the Me signal produces a sharp doublet for this resonance indicating no additional neighboring hydrogens. From this partial structure D for the ketone and E for anastreptene could be assigned with complete certainty. At this stage the possible relationship to myliol (4) was recognized. The spectral properties of the ketone were essentially identical to those reported[4b] for a degradation product of myliol. In accord with this, the hydroboration product afforded guaiazulene on dehydrogenation, albeit in low yield. The 100 MHz NMR spectrum of the myliol degradation product[12] proved superimposable with that of the hydroboration-oxidation product obtained from anastreptene.

Our careful reconsideration of the degradative work on myliol[4b] indicated that this work also served to indicate partial structure E together with evidence for a cyclopropane ring bearing at least two, likely three, hydrogens, two additional rings, and three singlet Me's—precisely the indication of our work and in no way a convincing demonstration of the suggested structure (4). Previous experience in the spirovetivane series[13,14] made us chary of accepting either dehydrogenation experiment as a proof of skeleton for anastreptene (or myliol). In fact the osmylation-cleavage sequence on anastreptene was clearly inconsistent with the skeletal assignment which implied structures 5, 6 and 7 for the olefin, aldehyde and acrylate in the sequence.

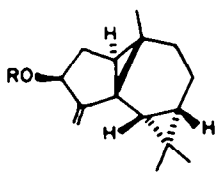
In particular, the methine α to CO of the ketoacid was a sharp doublet (J = 11 Hz), not a triplet. And the major fragment in the ms of the ketoacid was $C_8H_5O_3$, a composition quite difficult to arrive at from formula 7 in which a minimum of nine C atoms separate the oxygens. Two skeletal assignments (8, 9) that overcome these problems and still provide a rational for guaiazulene production are shown below. With the recent report of a



5 6 7



8 9



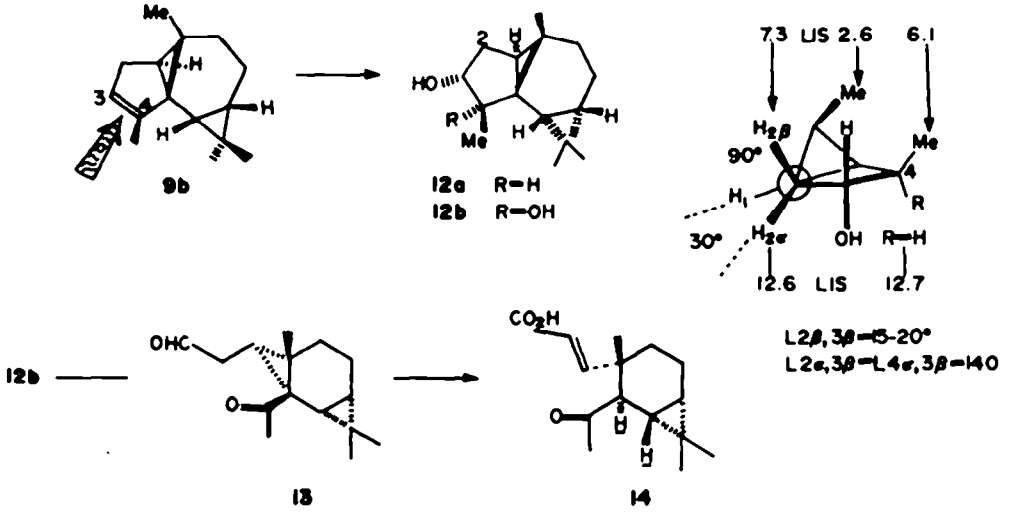
10 R=H
11 R=COC6H4Br

revised structure for myliol (10) via X-ray crystallography of the *p*-bromobenzoate (11),[15] we will leave the discussion of efforts to distinguish between 5, 8 and 9 to their present published form[16] and present only a rationale based on the new myliol structure.

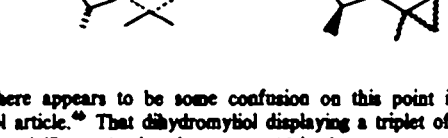
Anastreptene can thus be viewed as 9b with osmylation and hydroboration proceeding predominantly from the α-face affording diastereomers 12. The stereochemistry is confirmed in the coupling constants $J_{3\beta,2\beta} \simeq J_{3\beta,2\alpha} \simeq J_{3\beta,4\alpha} = 7.5$–$8.5$ Hz for both 12a and 12b. Throughout the series of compounds with the full constraints of the tetracyclic system, H-1 appears as a sharp doublet (4–6 Hz) at *ca.* 1.3–1.4 ppm, a feature consistent with the dihedral angles observed in models. In the case of alcohol 12a, Lanthanide Induced Shift (LIS) studies using sequential addition of $Eu(FOD)_3$ revealed that only the C-2 hydrogen *cis* to the hydroxyl couples with H-1.† These stereochemical features are shown in projection. The full LIS assignments appear in the Experimental. The spectral properties of the cleavage product and retro-Michael product accord with expectation for 13 and 14. For the latter a boat conformation produces a 150–160° dihedral for the underlined protons (J = 11 Hz).

Although the LIS-structure correlations cannot provide a proof of structure they do establish that only structure 12a (not any diastereomers of it) fits to the major hydroboration product of anastreptene once the skeleton is assumed. However oxidation of this material afforded a ketone identical to that derived from the "less mobile" dihydromyliol, that hydrogenation product obtained in somewhat lower yield.‡ The "less mobile" dihydromyliol can be assigned structure 16 based on both the tlc data and the expectations concerning the relative ease of hydrogenation from the α- and β-face.§ Thus it was necessary to assume rapid equilibration at C-4 when alcohol 12a is oxidized or upon isolation of the ketone product (18). That such an equilibration would favor 18 (over 17) was resonable based on the interaction of the Me groups at C-4 and C-10 in structure 17.

In order to clarify these questions we reexamined the



†The full set of LIS values for the major hydroboration product distances measured from models of 12a using either $(LIS_{calc})_i = Ar_i^{-m}$ or $(\ln LIS_{calc})_i = \ln A - m(\ln r)_i$ with $\sigma = 0.6$–0.7 ppm comparable to correlations for compounds of well defined rigid structures.[17] However diastereomers *i* and *ii* based on skeletons 5 and 8 respectively gave comparable agreement.[16]



‡There appears to be some confusion on this point in the myliol article.[16] That dihydromyliol displaying a triplet of doublets at 4.47 ppm (assigned structure 16 in the present work) is called the less polar one in this text, but a small R_f is quoted in the Experimental.

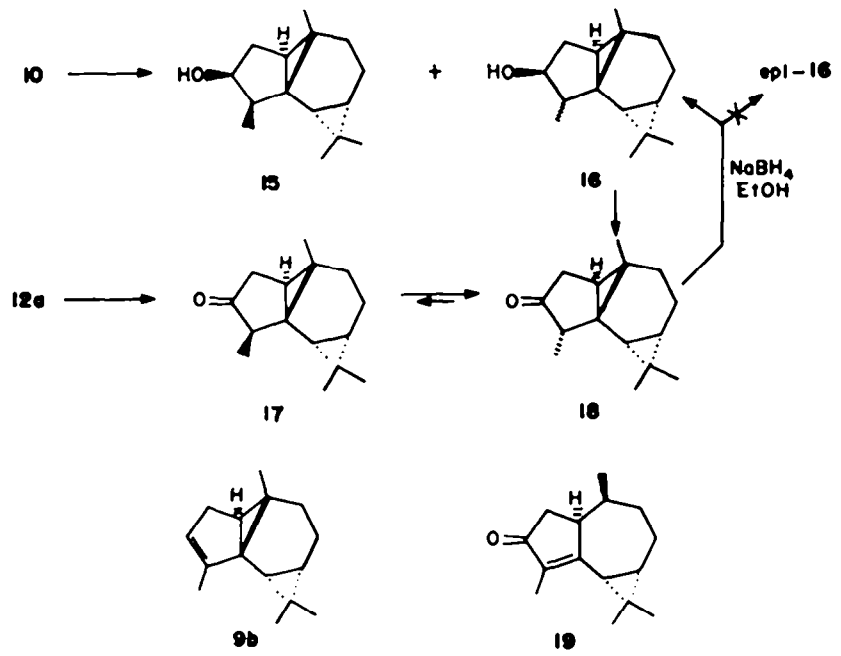
§Note that the C-10-Me interferes with β-approach at C-3 or over C-4,5 to a much greater extent than at the C-4 exocyclic double bond of myliol (10).

¶Although the alcohols and ketones proved to be difficult to analyze by gc we eventually found that an SF-96 column gave acceptable resolution and minimal decomposition (Experimental).

hydroboration of anastreptene in order to isolate alcohol 16 which should be the minor product. Alcohol 16 could be isolated in 26% yield and displayed a 100 MHz NMR superimposable with the marvelously detailed one provided by Benesova and Herout for the myliol hydrogeneration product. The *cis* relationship of the OH and C-10-Me is evident in the 0.24 ppm downfield shift for the Me signal relative to isomer 12a. Oxidation of alcohol 16 afforded the ketone (18) which returned predominantly (75°%) alcohol 16 on borohydride reduction reflecting the hindrance of the C-10-Me.

When the oxidation product of alcohol 12a, using less than one equivalent of H_2CrO_4, is examined by gc¶ prior to chromatographic purification, ketone 17 can be detected as the major product. This material could not be isolated without extensive conversion to its epimer (18). With these results the stereostructure of myliol 10 revealed in the X-ray crystal structure[15] is fully confirmed by degradation and spectroscopic data.

Anastreptene (9b), a very common liverwort constituent, also is in the same skeletal class. There is no apparent rationale for its prevalence in Hepaticae based on co-occurrence, but it should be noted that (+)-cyclocolorenone (19) has been found in a number of Porella species[23] and in *Plagiochila acanthophylla*.[24]



EXPERIMENTAL

General methods. The general methods have been detailed previously.[5d] Additional gc phases employed in this work are: B, silicone SF-96; E, silicone SE-52. All relative retention data for oxygenated sesquiterpenes employed cedrol as the standard (RR = 1.00) either directly or indirectly. NMR spectra at 60 and 100 MHz are for $CDCl_3$ solns unless otherwise stated. High resolution mass spectral data (AEI-MS-9) were obtained by a computer controlled scan of masses for compound and a perfluoro standard. The computer reports masses for non-standard peaks to 0.0001 amu together with the best fitting formula, with error (in mmass) by comparison with five neighboring standard peaks. Therefore our ms data is reported as follows: mass (% of base peak, formula or other designation of peak identity, error in mmass).

Isolation of anastreptene (9b). The isolations from *Anastrepta orcadensis*[5e] and *Diplophyllum albicans*[5d] have already been described. The properties of the material freshly collected by preparative gc and recrystallized from EtOH are: m.p. 91–93;† ms, *m/e* (%) 202.172 (P, $C_{15}H_{22}$, 55), 187 (42), 159 (100), 145 (53), 131 (65) and 105 (47%); $[\alpha]_D = +29°$ (*c* 0.26, CH_3CN); UV-CD (CH_3CN) 190 ($\epsilon = 8{,}700$, $\Delta\epsilon \sim +4.5$), 215 ($\epsilon = 4500$, shoulder; $\Delta\epsilon$ (max) = +5.5), 235 ($\epsilon = 2700$, $\Delta\epsilon = +2.2$); IR (CCl_4) 3060 (vinyl-H), 3045 (cyclopropyl-H), 1640 (C=C), 1456, 1448, 1436, 1375, 1328, 1305, 1170, 1067, 1040, 1025 and 892 cm^{-1}; δ 0.24–0.72 (2–3H, cyclopropyl), 0.76 (3H, Me s), 0.99 (6H, s), 1.33 (1H, d, 6.5 Hz), 1.71 (vinyl-Me, m.) and 5.18 ppm (1H, m).‡

The widespread natural occurrence of anastreptene. The essential oils of *Barbilophozia* species previously reported[5b] to contain a component eluting at $I_A^{190} = 1403$ were reexamined.

Barbilophozia lycopoidiodes No. 1

Peak No.	%	I_A^{190}	I_C^{165}	assignment
1	60	1270	1496.5	?
2	11	1404.5	1582	anastreptene
4	5	1498.3	(1656)	?
6	18	1534	1716	β-barbatene
7	3	1536	1771.5	
8	6	1554		α-alaskene?

Barbilophozia lycopoidiodes No. 2

2	12.6	1410		anastreptene?
4	19	1498	1656	?
6	58	1530	1714	β-barbatene
8	10	1555		α-alaskene?

Barbilophozia attenuata No. 1

1	38	1267	1493	?
2	31	1406	1583	anastreptene
4	6	1419	1617	
6	16	1532	1716	β-barbatene
7	4	1554		α-alaskene?
8	5	1595		

Barbilophozia attenuata No. 2

1	26	1266	1490	?
2	4	1403	1581	anastreptene
4	8	1418	1617	
5	6	1480	1698	
5b	8	1499.5		
6	18	1532	1714	β-barbatene
7	15	1561		

The occurence in *Scapania aspera, aequiloba* and *undulata* has been documented[5e] and more recently anastreptene has been found in oils derived from *Scapania paludosa* and *nemorea*.[16]

Attempted degradation of anastreptene via osmylation followed by lead tetraacetate cleavage. A soln of 9b (186 mg, 0.92 mmol) in 4.5 ml pyridine was added dropwise to a soln of osmium tetroxide (250 mg, 1 mmol) in 3 ml benzene and the mixture was stirred for 48 hr at room temp. To the mixture was added 540 mg $NaHSO_3$, 9 ml water and 6 ml pyridine and the mixture stirred for 2 hr. Extraction with CH_2Cl_2 (3 times) and washing with $CuSO_4$ aq and water gave dark colored soln. Evaporation of solvent gave 250 mg of brownish oil which was chromatographed on neutral silica and 195 mg (0.83 mmol) of crystalline diol was obtained, m.p. 91–93°. Recrystallization from CCl_4 gave 12b (m.p. 90–90.5°) with the following spectral properties: δ 0.2–0.9 (~3H, cyclopropane), 1.04 (9H, s), 1.28 (3H, s), 2.85 (OH, d, ~9), and 3.75 ppm (CH_2OH, q, 8.5 Hz); IR ($CHCl_3$) 3595, 3500 (OH), 3050 (cyclopropane), 1460, 1390 (doublet), 1100, 1075, 1020 and 895 cm^{-1}. Sublimation afforded an analytical sample, m.p. 91–93°: ms 236.1752 (11, $C_{15}H_{24}O_2 - 2.2$), 221.1518 (6, $C_{14}H_{21}O_2 - 2.2$), 218.1646 (23, $C_{15}H_{22}O - 2.4$), 175.1116 (23, $C_{12}H_{15}O - 0.6$), 163.1490 (35, $C_{12}H_{19} + 0.2$), 107.0872 (36%, $C_8H_{11} + 1.2$ mmass), 68.96 amu (100%).

(A) To a stirred soln of 12b (100 mg; 0.424 mmol) in 7 ml

†Crystals of anastreptene have been examined (J. Clardy, Iowa St.), but apparently are disorded even at reduced temperatures.

‡ORD-UV-CD in pentane: $[\alpha]_D = +32°$, $\epsilon_{220\text{-}212} = 4800$, $\Delta\epsilon_{214} = +5.2$ (max).

pyridine was added 250 mg (0.54 mmol) recrystalized $Pb(OAc)_4$ at room temp. The reaction was quenched after 1 hr with addition of ethylene glycol to decompose excess reagent. The organic material was extracted with ether after dilution with large amounts of water and the extract was washed with sat $CuSO_4$ aq and water and dried over Na_2SO_4. Evaporation of solvent yielded 93 mg of heterogeneous oil which gave several more polar spots besides the major one on the tlc plate. Being least polar, the major product was largely separated from the rest by its relatively better solubility in hexane. NMR and IR spectra of the major hexane soluble product indicated 13 (88 mg): δ 0.77, 0.83 and 1.02 (3 Me s), 1.71 (3H, m, $W_{h/2}$ ~3 Hz), 2.73 (MN of AMNX, J_{MN} = 16.5, J_{MX} = 8.4, J_{NX} = 5.3, $J_{AM} = J_{AN}$ = 2.0) and 9.97 ppm (1H, H_A, CHO, t, 2.0 Hz); IR ($CHCl_3$) 1732, 1718 and 2735 cm^{-1}.

A soln of the crude keto-aldehyde (88 mg, impure) in 2 ml MeOH was added to a soln of KOH (290 mg) in 0.5 ml water and 2.8 ml MeOH. The mixture was stirred for 2 hr at about 45° and then was poured into 30 ml brine and extracted with ether. The organic layer was washed with water and dried over $MgSO_4$. Upon evaporation 70 mg of yellowish oil was obtained. The oil was chromatographed on preparative thin layer plates but nothing isolated from the plate was of any significance.

(B) Another batch of diol (135 mg, 0.57 mmol) was also oxidized with $Pb(OAc)_4$ (900 mg, 2 mmol) by the procedure used above except that the reaction was stirred for 1.8 hr and during work-up 1 N HCl was used for washing instead of sat $CuSO_4$ aq. NMR of crude product (95 mg) showed major new peaks in addition to those from keto-aldehyde 13. IR of the crude oil indicated a carboxylic acid. Preparative tlc afforded 41.5 mg (31%) of 14 as the most polar zone: δ 7.9 (CO_2H, broad), 7.31 (1H, d, 16), 5.73 (1H, d, 16), 2.88 (1H, d, 11 Hz), 2.18 (3H, s), 1.09, 1.05 and 0.89 ppm (3 Me s); IR ($CHCl_3$) 2500–3600, 1705, 1655 (C=C–CO_2H), 1390, 1365, ~1120 and 915 cm^{-1}.

Further purification by acid-base extraction followed by sublimation afforded an analytical sample, m.p. 128–132°: ms 250.1580 (5, $C_{15}H_{22}O_3$ + 1.2), 235.1344 (15, $C_{14}H_{19}O$ + 1.0), 177.0578 (15, $C_{10}H_9O_3$ + 2.6), 149.0236 (67, $C_8H_5O_3$ − 0.2), 81.0684 (48, C_6H_9 − 2.0), 43.0542 (57, C_3H_7 − 0.6) and 43.0178 amu (100%, C_2H_3O − 0.6 mmass).

Hydroboration-oxidation of anastreptene

Hydroboration initially at 0°, using excess. Anastreptene, 60 mg in 1 ml dry THF, was treated with 1 ml of 1 M BH_3·THF (3.3 eq.) initially at 0°, then at ambient for 2.5 hr with stirring. At this point the reaction was maintained at *ca.* 30° while adding 100 μl of 3N NaOH and 300 μl of 30% aqueous H_2O_2. After 2 hr the product was isolated with ether with the addition of water, affording 45 mg of oily product. Preparative layer chromatography (SiO_2, 8% EtOAc in ϕH) afforded two products. The polar isomer (12a), 34 mg (52%), displayed: IR (film) 3340 (OH), 3040 (cycloprophy-H), 1470, 1390, 1380, 1045 (C–O), 980, 940 and 895 cm^{-1}; R_f (5% EtOAc/PhH, SiO_2) = 0.21; δ (60 MHz), 1.02, 1.08, 1.16 (Me), 1.30 (1H, d, 6), 2.0–2.6 (2–3H, m) and 3.77 ppm (1H, CHOH, q., 7.7 Hz). A later 100 MHz spectrum established that this material is not identical to myliol degradation product 15[12] which also displays a quartet at 3.77 ppm. Only 6 mg (9%) of the less polar isomer was isolated: R_f (5% EtOAc/PhH, SiO_2) = 0.37; δ 4.5 (CHOH, triplet of doublets J_t = 9.5, J_d = 3 Hz), 2.15–2.95 (2–3H), 0.98–1.30 ppm unresolved Me-signals).

Upon oxidation (25 mg CrO_3 in 15 ml pyridine, 16 hr, 25°) 25 mg of the major alcohol afforded after addition of water, ether extraction, and preparative tlc (benzene, SiO_2), 16 mg (64%) of oily product. The chloroform soln was treated with gaseous H_2S to remove trace metals for spectral comparison: IR (film) 3050, 1743 (C=O), 1461, 1379, 1348, 1230, 1144, 1074, 1023, 970, 913 and 885 cm^{-1}; δ (60 MHz) 0.88, 1.03, 1.10 (3 Me, s), 1.17 (Me, d), 2.1–3.0 ppm (3H, m). At 100 MHz the spectrum was strictly superimposable with that of myliol degradation product 18[12] (see Discussion).

Hydroboration of anastreptene at room temperature. A soln of 1 M BH_3·THF (3 ml, 3 mmole) was added slowly to a soln of anastreptene (80 mg, 0.4 mmole) in anhyd THF and the mixture stirred at room temp. for 3 hr. Excess hydride was cautiously decomposed with water and 3 N NaOH (0.2 ml) added followed by 30% H_2O_2 (0.6 ml). The mixture was stirred at 30–40° for 2.5 hr and then poured into 60 ml of H_2O, extracted with ether, washed with water and dried over Na_2SO_4. Removal of the solvent followed by chromatography of the residue on preparative thin layer plates afforded two epimeric alcohols. The more polar isomer (30 mg, 38%, m.p. 95–96°) proved identical to the material obtained above. A 100 MHz NMR confirmed the previous assignments and a series of $Eu(FOD)_3$ additions provides LIS data:[17] δ 1.025 (6H, s, Me LIS = 1.57 and Me LIS = 2.50), 1.075 (3H, s, Me LIS = 2.56), 1.16 (3H, d, 7.5, LIS = 6.13), 1.30 (1H, d, 6, LIS = 3.75), 2.0–2.6 (2–3H, including a 1H resonance, an A of ABX ● 2.18, J_{AB} = 15.5, J_{AX} = 7.5, LIS = 7.27), and 3.77 ppm (1H, CHOH, q., J = 7.7 Hz, LIS = 17.2 ppm). In addition the LIS studies revealed a quintet (J = 7.5) displaying LIS = 12.75 extrapolating to an initial δ of ~2.03; NMDR indicates coupling to the doublet Me. The B of the previous ABX was also located (δ initial by extraplation, 1.63) and displayed LIS = 12.6 and a 5 line 1:2:2:2:1 pattern when separated from its closely coupled neighbors. The formula for the polar isomer (12a) was confirmed by mass spectrometry, *m/e*: 220.1830 (29, $C_{15}H_{24}O$ + 0.4), 202.174 (30, $C_{15}H_{22}$ − 0.6), 177.1284 (61, $C_{12}H_{17}O$ + 0.6), 159.1176 (100, $C_{12}H_{15}$ + 0.4), 107.0870 amu (62%, C_8H_{11} + 1.0 mmass).

The more mobile zone yielded 21 mg (26%) of 16: δ 1.01, 1.035 and 1.31 (3 Me s), 1.06 (Me, d, 7.7), 1.43 (1H, d, 4), 2.3–2.7 (2H, m), and 4.48 ppm (CHOH, triplet of doublets, J_t = 9.2, J_d = 2.6 Hz). This NMR, and the corresponding IR spectrum, were superimposable on those of myliol degradation product 16[4b,12] (see discussion for assignment).

Gc proved to be the most effective method for analysis. The gc retentions (relative to cedrol) are: RR_A^{190} = 0.89, RR_B^{200} = 1.07, RR_C^{200} = 1.34 and RR_D^{205} = 1.22 (for isomer 16); RR_A^{190} = 0.89, RR_B^{200} = 0.96, RR_C^{200} = 1.28, RR_D^{205} = 1.21 (for the polar isomer, 12a). Gc analysis of the initial hydroboration mixture revealed these isomers in the ratio 34:66.

Oxidation of the alcohol isomers

(a) *The less polar isomer* (16). The soln of 0.5 ml diethyl ether and 11 mg (0.05 mmol) minor hydroboration product was chilled in ice bath for about 30 min. Chromic acid soln[19] (50 μl) was also cooled in an ice bath for 30 min. The chilled chromic acid soln was added to the stirred soln of alcohol dropwise. After addition, vigorous stirring was continued for an additional 5 min. Then the mixture was diluted with Et_2O, washed with $NaHCO_3$ and water and dried (Na_2SO_4). Removal of the solvent followed by chromatography on SiO_2 thin layer plate gave 9.5 mg of clear oil; IR ($CHCl_3$) 1742 cm^{-1}; δ_{CDCl_3} (100 MHz and 60 MHz) although not entirely superimposable with that of myliol degradation product 18,[4a,12] all characterizable bands correspond including singlet Me's at 0.88, 1.03 and 1.095; a doublet (J = 7.5) Me at 1.16; a one proton doublet (H-1) at 1.35; and α-H's at 2.19 (d, 19.5) and 2.67 ppm (dd, 19.5, 6.5 Hz). Gc analysis revealed one major peak (82% 18: RR_B^{200} = 0.98, RR_C^{200} = 1.10) and minor one (18% 17: RR_B^{200} = 1.09). On standing overnight in 9:1 MeOH–H_2O containing solid K_2CO_3, a portion of this product showed the same two gc components in the ratio 69:31.

(B) *The more polar isomer* (12a). Using the procedure above 26.4 mg (0.12 mmole) of major alcohol gave 24 mg of ketone: IR ($CHCl_3$) 3050, 1742, 1472, 1426, 1400, 1390, 1305 and 880 cm^{-1}. The 100 MHz NMR was absolutely superimposable with that of myliol degradation product 18[4b,12] and corresponded to that of the material obtained from the minor hydroboration product. This chromatographed product did not display the characteristic Me-signals and α-H signals reported for the other myliol degradation ketone (presumably 17). Gc analysis revealed the same major product (60%, RR_B^{200} = 0.97, 18) but more of the minor component (27%, RR_B^{200} = 1.08, 17). The ms confirmed the formula: 218.1678 (14, $C_{15}H_{22}O$ + 0.8), 175.1422 (21, $C_{12}H_{19}$ − 6.4), 147.1184 (35, $C_{11}H_{15}$ + 3.0), 138.1008 (5, $C_9H_{14}O$ − 3.6), 105.0696 (55, C_8H_9 − 0.8), 41.0388 amu (100%, C_3H_5 − 0.2 mmass).

The procedure was repeated using 5 mg of major alcohol 12a and only 0.9 equiv chromic acid. The crude ether extract in this case displays by gc largely the other isomer: 39% RR_B^{200} = 0.97 (18), 61% RR_B^{200} = 1.08 (17). When treated with methanolic K_2CO_3 the ratio changed to 6:3. The crude product (39% less

retained isomer 18) was subjected to preparative tlc affording for the major zone (R_f = 0.80 5% EtOAc in benzene) material analyzing as 62% RR_D^{200} = 0.98 and 38% RR_D^{200} = 1.09: epimerization occurs on preparative tlc.

Further transformations of crude ketone 18. The preparative tlc isolated ketone (original derived from the more polar hydroboration product), *ca.* 5 mg, was reduced with ethanolic $NaBH_4$ and the product was analyzed by tlc and gc: tlc (R_f) – 0.21 (very minor), 0.26 (very minor), 0.37 (major); gc (RR_D^{200}) – 0.96 (5%) 1.06–1.07 (70%) and 1.17–1.20 (13%). This indicates that the stable ketone from the more polar hydroboration product (12a) returns (on reduction) largely the less polar hydroboration product (16). Epimerization has occurred at the Me-center during isolation of the ketone and ketone 18 reduces to give largely (75%) the β-OH isomer.

The mixture of alcohols (~3 mg) was dehydrogenated with 130 mg of Se in the presence of 80 μl of hexadecane and 10 μl octadecane at 280° for 30 min† under argon.[20] Workup as previously described[20] followed by chromatography on basic Al_2O_3 (activity II)† afforded blue fractions judged to contain 0.01 mg of S-guaiazulene by UV (λ_{max} = 366, 349, 303, 288, 283 nm).‡ Gc analysis revealed S-guaiazulene—gc std. = cadalene RR_A^{195} = 1.61, RR_D^{200} = 1.76§—together with eudalene (~21%) and cadalene (~36%).

REFERENCES

[1a]Alfred P. Sloan Research Fellow, 1972–74; Dreyfus Teacher-Scholar, 1974–79; NHA acknowledges support via an NIH Career Development Award (GM-00134); [b]Senior post-doctoral associate, 1972–74, supported by NIH grant GM-18143.

[2a]S. Huneck and E. Klein, *Phytochemistry* 6, 383 (1967); [b]S. Huneck, *Z. Naturforschg.* 22b, 462 (1967); [c]S. Huneck, R. Grolle and O. Vevle, *J. Hattori Bot. Lab.* 36, 93 (1972).

[3a]A. Matsuo, *Tetrahedron* 27, 2757 (1971); [b]A. Matsuo, M. Nakayama and S. Hayashi, *Bull. Chem. Soc., Japan* 46, 1010 (1973); [c]A. Matsuo, H. Nozaki, M. Nakayama, Y. Kushi, S. Hayashi and N. Kamijo, *Tetrahedron Letters* 241 (1975); and refs. therein; [d]A. Matsuo, M. Nakayama, S. Sato, T. Nakamoto, S. Uto and S. Hayashi, *Experientia* 30, 321 (1974); [e]A. Matsuo, M. Nakayama and S. Hayashi, *Chemistry Letters* 769 (1973).

[4a]V. Benešová, Z. Samek, V. Herout and F. Sorm, *Coll. Czech. Chem. Commun.* 34, 582 (1969); [b]V. Benešová, P. Sedmera, V. Herout and F. Šorm, *Tetrahedron Letters* 2679 (1971); *ibid.* 30, 1084 (1973); [c]V. Benešová, V. Herout and F. Šorm, *ibid.* 34, 1810 (1969).

[5a]N. H. Andersen and S. Huneck, *Phytochemistry* 12, 1818 (1973); [b]N. H. Andersen, C. R. Costin, C. M. Kramer, Jr., Y. Ohta and S. Huneck, *Ibid.* 12, 2709 (1973); [c]N. H. Andersen, B. Shunk and C. R. Costin, *Experientia* 29, 645 (1973); [d]Y. Ohta, N. H. Andersen and C.-B. Liu, *Tetrahedron* 33, 617 (1977); [e]N. H. Andersen, P. Bissonette, C.-B. Liu, B. Shunk, Y. Ohta, C.-L. W. Tseng, A. Moore and S. Huneck, *Phytochemistry* 16, 0000 (1977); [f]N. H. Andersen, Y. Ohta, C.-B. Liu, C. M. Kramer, K. Allison and S. Huneck, *Ibid.* 16, 0000 (1977).

[6]J. D. Connolly, A. E. Harding and I. M. S. Thornton, *Chem. Commun.* 1320 (1972).

[7]W. O. Godtfredsen and S. Vangedal, *Proc. Chem. Soc.* 188 (1964); B. Bohner, E. Retz, E. Harri, H. P. Sigg, Ch. Stoll and Ch. Tamm, *Helv. Chim. Acta* 48, 1079 (1965); S. Nozoe and Y. Machida, *Tetrahedron Letters* 2671 (1970).

[8]This conclusion can be extended to over 18 species now. The one *apparent* exception is chiloschyphone (whose structure is not absolutely established): A. Matsuo, *Tetrahedron* 28, 1203 (1970).

[9]The stereochemical homogeneity of vascular plants has been noted previously: N. H. Andersen, *Phytochemistry* 9, 145 (1970).

[10]N. H. Andersen, Y. Ohta and D. D. Syrdal, *Bioorganic Chemistry* (Edited by E. E. van Tamelen), Vol. 2, Chap. 1. Academic Press, New York (1977).

[11]Sesquiterpene hydrocarbons typically crystallize only below 0°. The only other exception known to us is isobarbatene,[5a] another liverwort derived material. The structure of isobarbatene is presented in the accompanying article: N. H. Andersen, C.-L. W. Tseng, A. Moore and Y. Ohta, *Tetrahedron* 34, 47 (1978).

[12]These spectra were kindly provided by Drs. Benešová and Herout.

[13]J. A. Marshall, N. H. Andersen and P. C. Johnson, *J. Am. Chem. Soc.* 89, 2748 (1967).

[14]N. H. Andersen, M. S. Falcone and D. D. Syrdal, *Tetrahedron Letters* 1759 (1970).

[15]A. Matsuo, H. Nozaki, M. Nakayama, Y. Kushi, S. Hayashi, N. Kamijo, V. Benešová and V. Herout, *J. Chem. Soc.* Chem. Commun. 1006 (1976).

[16]C.-L. W. Tseng, Ph.D. Thesis, *Studies on Sesquiterpene Constituents of Liverworts*, Part I: University of Washington (1976).

[17]The LIS-structure correlation methodology employed has appeared only in fragmentary forms.[5b,18a] We do not use the $(3\cos^2\theta - 1)$ factor of the equation since this method of LIS determination does not give bound shift values for the 1:1 adduct. Under these conditions primarily the 2:1 adduct is formed.[18b] There is no compelling theoretical or empirical basis for applying the angular factor to LIS data for 2:1 adducts or mixed stoichiometry adducts. A manuscript describing our work is in preparation.

[18a]N. H. Andersen, B. J. Bottino and S. E. Smith, *Chem. Commun.* 1193 (1972); [b]N. H. Andersen, B. J. Bottino, A. Moore and J. R. Shaw, *J. Am. Chem. Soc.* 96, 603 (1974).

[19]H. C. Brown, C. P. Garg and K.-T. Liu, *J. Org. Chem.* 36, 387 (1971).

[20]N. H. Andersen, M. S. Falcone and D. D. Syrdal, *Phytochemistry* 9, 1341 (1970).

[21]B.-P. Suaz, Y.-R. Naves and C. Colland, *Helv. Chim. Acta* 42, 1375 (1959).

[22]T. Nozoe, K. Takase and S. Fukuda, *Bull. Chem. Soc., Japan* 44, 2215 (1971).

[23]Y. Asakawa, M. Toyota, M. Masaharu and T. Aratani, *Phytochemistry* 15, 1929 (1976).

†The extremely mild Se-dehydrogenation conditions and the use of activity-II Al_2O_3 allow isolation of S-guaiazulene rather than Se-guaiazulene. The low yield was as expected.

‡Reported for S-guaiazulene,[21] λ_{max} (log ϵ): 367 (3.59), 349 (3.69), 305 (4.05), 289 (4.63) and 284 (4.64); for Se-guaiazulene:[22] 362 (2.96), 348 (3.77), 308 (4.00), 290 (4.82). The isomers are readily distinguishable particularly in the 330–380 nm region.

§Our original report[20] gives: S-guaiazulene, RR_A^{195} = 1.55, RR_D^{200} = 1.76: Se-guaiazulene, RR_A^{195} = 1.675, RR_D^{200} = 1.91. At the time that the anastreptene related compounds were dehydrogenated we also dehydrogenated guaiol under both conditions,[20] with the following results—S-guaiazulene, RR_A^{195} = 1.59–1.62, RR_D^{200} = 1.70–1.76; Se-guaiazulene, RR_A^{195} = 1.71–1.72, RR_D^{200} = 1.82–1.89. The Se-product contained up to 80% S-guaiazulene when the exposure time was short (30 min) and the work-up either avoided alumina chromatography or used deactivated Al_2O_3. With Act. I Al_2O_3 the azulene ratio changed favoring Se-guaiazulene (70–85%).