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ACID-CATALYZED REARRANGEMENT OF *ENT*-ATIS-13,16-DIENES

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ABSTRACT.—The rearrangement in acid medium of the *ent*-atis-13,16-diene system has been studied. One reaction course involved rearrangement to the corresponding *ent*-atis-13,15-diene, which undergoes a retro-Diels-Alder reaction to form a 1,3-disubstituted benzene. If a free hydroxyl group is present at C-11, a typical retro-Prins reaction occurs. The structures of the products have been established by the normal spectroscopic means.

Nonnitrogenous *ent*-atis-13-ene systems are uncommon in nature, and only three of them have been isolated from Spanish *Sideritis: ent*-1β,16α,17-trihydroxyatis-13-ene (sideritol [**1**]) (1), *ent*-7α,16α,17-trihydroxyatis-13-ene)(isosideritol (2), and *ent*-11β,16α,17-trihydroxyatis-13-ene (atisideritol [**2**]) (3), all having the 16,17 dihydroxy group. These probably arise from the biogenetic evolution of an *ent*-12α,17-dihydroxybeyer-15-ene (1).

The *ent*-atis-13,16-dienes have been obtained in our laboratory by desulfuration of the 16,17-thiocarbonyldioxyatis-13-enes and 12,17-thiocarbonyldioxybeyer-15-enes with trimethylphosphite (TMP) (4).

In this work, this and an alternative method have been used to obtain *ent*-atis-13,16-dienes. The presence of the two double bonds and, on one occasion, a hydroxyl group at C-11, leads to interesting reactions in these polycyclic systems.

RESULTS AND DISCUSSION

The oxidation of *ent*-16β,17-dihydroxyatis-13-ene (serradiol) [**3**] (5) with $NaIO_4$ yielded the 17-nor-17-keto-derivative **4**, which yielded two tertiary alcohols epimeric at C-16 on treatment with methylmagnesium iodide (**5**, 61% and **6**, 39%). The configuration at C-16 in **5** and **6** was assigned according to literature data for the ^{13}C-nmr chemical shift of the methyl group at C-16 (6).

Treatment of alcohols **5** or **6** with mesyl chloride (MsCl), led to the diene **7** which had both the C-13, C-14 double bond and an exocyclic methylene group (^{1}H, ^{13}C nmr, ir) with signals characteristic of an atis-13,16-diene (4). Product **7** has also been obtained through its thiocarbonate derivative **8** and further treatment with TMP (4), and also from ketone **4** by a Wittig reaction (7). Thus, diene **7** can be obtained by three different routes from *ent*-16α,17-dihydroxyatis-13-ene [**3**].

Similar reactions were carried out using *ent*-1β-acetoxy-12α,17-dihydroxybeyer-15-ene [**10**] and *ent*-1β-acetoxy-16α,17-dihydroxyatis-13-ene [**11**] to yield *ent*-1β-acetoxyatis-13,16-diene [**14**] (4). The use of the *ent*-beyerene **10** as a starting material was expedient in view of its relative abundance in nature.

Treatment of **14** in acidic media (pyridinium-*p*-toluensulfonate) (PyTs) gave *ent*-1β-acetoxyatis-13,15-diene [**19**] (15%) and a product **20** (26%) due to an extensive rearrangement.

Diene **19** showed in its ^{1}H-nmr spectrum an ABX system due to the proton at C-12 and those on the C-13 and C-14 double bond, as well as a new olefinic methine at δ 5.60 (1H, m, $W\frac{1}{2} = 8$ Hz) and an allylic methyl group at δ 1.75 (3H, d, $J = 2$ Hz). The ^{13}C-nmr spectrum of **19** also confirmed the presence of these double bonds with three signals for olefinic methynes at δ 134.67, 134.91, and 136.41 and a quaternary olefinic carbon at δ 145.00.

Product **20** had an interesting structure, deduced as follows: Its mass spectrum indicated a molecular weight of 328 daltons, the same as the starting diene **14** and the

4 R=H
16 R=OAc
5 R=H
17 R=OAc
6 R=H
18 R=OAc
9 R=H
15 R=H
7 R=H
14 R=OAc
19 R=OAc
20 R=OAc
1 OH H H
3 H H H
8 H -O-C-O- S
11 OAc H H
13 OAc -O-C-O- S
10 R1=OAc, R2=R3=H
12 R1=OAc, R2,R3= -O-C-O- S

cyclic *endo* diene **19**. In its ^{13}C-nmr spectrum, the presence of five methyl groups at δ 11.92, 21.16, 21.41, 21.99, and 33.06 can be seen, one of them due to a methyl of an acetoxyl group (confirmed by a signal at δ 170.48 from its carbonyl carbon and one at δ 2.00 in its ^{1}H nmr). In addition, eight sp^2 carbon resonances were observed (2 quaternaries at δ 140.77 and 146.07; 5 methines at δ 128.3, 129.61, 131.31, 132.14, and 150.30; and a methylene at δ 116.80).

In its ^{1}H-nmr spectrum an olefinic ABX system with its X signal at 5.65 (1H, dd, $J_{AX}+J_{BX}=30$ Hz) and the AB signals as an apparent double doublet between δ 5.0 and 5.25 (2H) was observed, as well as four aromatic protons between δ 6.90 and 7.30, possibly from a 1,3-disubstituted benzene system. This supposition was supported by its ir spectrum which showed bands at 900, 790, and 700 cm^{-1} for 1,3-disubstituted benzenes.

The product thus had an acetate group, a vinyl group, a 1,3-disubstituted benzene, and, from its DEPT-^{13}C-nmr spectrum, four methylenes, one methyne, and the four methyl groups mentioned above. The geminal proton of the acetoxyl group had an appearance similar to that located at C-1 in compounds **14** and **19**, but a little more deshielded (δ 4.75, 1H, dd, $J_1=11$, $J_2=8$ Hz). This product appears to have ring A intact but to have undergone extensive rearrangement in rings C and D. The spectroscopic data suggested that product **20** had the structure *ent*-1β-acetoxy-(8,9),(11,12)-disecoatis-8(14),9(11),12,15-tetraene, resulting from a retro-Diels-Alder reaction (RDA) (8).

Although both dienes **14** and **19** can undergo an RDA reaction, only in the case of **19** is the benzene system obtained directly. We thus suggest that diene **14** is converted to **20** via the intermediate **19**. Temperatures of about 200° are normally required for processes of this type (9), but in this case reaction takes place at 110°.

To check the possible influence of the functional groups present in the rings which suffer rearrangement, we have synthesized a diene similar to **14** but with a functional group at C-11. Atisideritol [**2**] (3) was treated with *N*-*N*′-thiocarbonyldiimidazole and thereafter with TMP as described above, yielding *ent*-11β-hydroxyatis-13,16-diene [**21**]. Rearrangement of **21** under the same conditions as for **14** gave only product **22** (50%), with different spectroscopic properties from those of **19** and **20**. Its ms indicated it to be a rearrangement product. Its ir, ^{13}C-nmr, and ^{1}H-nmr spectra showed the presence of an aldehyde group with one vicinal proton (doublet at δ 9.50). When no aromatic signals were present, three olefinic protons, giving an ABX system between δ 5.5 and 6.0, appeared clearly. The ^{13}C-nmr spectrum revealed the presence of three olefinic methines (δ 128.99, 124.80, and 120.41) and a quaternary olefinic carbon (δ 137.40). Its ^{1}H-nmr spectrum also indicated the presence of four methyl groups (one of them allylic at δ 1.59 and the others at δ 1.18, 0.85, and 0.82) confirmed in the DEPT spectrum by signals at δ 33.45, 23.13, 21.75, and 18.64. Double resonance experiments showed that the δ 9.50 aldehyde proton was coupled with a doublet signal at δ 1.31 (1H, $J=7.5$ Hz) which must be H-9.

These data suggest that the rearrangement product **22** is the result of a retro-Prins reaction. When the reaction was carried out in the presence of deuterated pyridinium *p*-toluene sulfonate, a deuterium atom was located at C-17 of the product **23**. This result is readily predicted on the basis of a normal retro-Prins mechanism.

Protection of the 11-hydroxyl group as an acetate prevented the retro-Prins process. Treatment of the acetate **24** under the usual acid conditions afforded **25** (10%) a product of simple double band migration, and the retro-Diels-Alder product **26** (21%) with a *Z*-enol acetate system (δ 6.91, 1H, d, $J=7.5$ Hz), in accordance with the published data for this type of system (10).

22 R=H
23 R=D
21
24
25
26
27
28
2

EXPERIMENTAL

Mp's were determined in a Kofler apparatus and are uncorrected. ^{1}H-nmr spectra were measured at 80 MHz and 300 MHz ($CDCl_3$ solution with TMS as internal standard). ^{13}C-nmr spectra were determined at 20.13 MHz (Bruker WP 80 SY) and 75.74 MHz (Bruker AM 300) in $CDCl_3$ (which also provides the lock signal) with TMS added as internal reference. Assignments were made with the aid of distortionless enhancement by polarization transfer (DEPT) using a "flip angle" of 135°. NOe-difference experiments were carried out at 300 MHz with an irradiation time for nOe generation of 4 sec and a relaxation delay of 8 sec.

Ir spectra were recorded in a Perkin-Elmer 983-G Spectrophotometer. Optical rotations were measured on a Perkin-Elmer 240 polarimeter. Mass spectra were carried out on a Hewlett-Packard 5988-A. Elemental analyses were performed on a Perkin-Elmer 240C Elemental Analyzer.

Si-gel Merck 7729 (≤ 0.08 mm) and Scharlau 60 were used for flash chromatography. The eluents used were CH_2Cl_2 and CH_2Cl_2 containing increasing amounts of Me_2CO, and C_6H_{14} with different amounts of Et_2O.

GENERAL THIOCARBONATION AND DESTHIOCARBONATION PROCEDURE.—Formation of thiocarbonates and desthiocarbonation were carried out according to the procedure of Corey and Winter (11).

OXIDATION OF 1,2-DIOLS WITH $NaIO_4$.—To a flask containing 100 mg of $NaIO_4$ dissolved in 3 ml of H_2O (in an ice bath with magnetic stirring), 100 mg of the product dissolved in MeOH/H_2O, and then, if necessary, 40 mg of $NaHCO_3$ to destroy the HCOOH formed, were added. A white precipitate of the nonsoluble product appears immediately.

WITTIG REACTION.—Methyl-triphenyl-phosphonium bromide (4.2 g, 0.01 mol) was placed in a flask, and 35 ml of anhydrous THF was added. The mixture was shaken, and 7 ml (115 mmol) of *n*-butyllithium in hexane was added dropwise. Reaction mixture was stirred for 30 min at room temperature, developing a strong brown-reddish color. The flask was then cooled to −7°, and 0.01 mol of ketone, dissolved in 5 ml of dry THF, added in 5 min, and the mixture was stirred for 1 h (during this time the color changes to pale-brown). H_2O (20 ml) was then added and the two layers separated. The aqueous layer was extracted with CH_2Cl_2, and the combined extracts dried under vacuum.

GRIGNARD REACTION.—Freshly prepared magnesium strips (30 mg) were poured into a flask fitted with a condenser and an addition funnel, and 1.1 mmol of the alkyl halide, dissolved in 3 ml of dry Et_2O, was added and stirred until dissolution of magnesium. Then, a solution of 1 mmol of the carbonyl compound in 3 ml of dry Et_2O was dropped through the addition funnel and stirred for 5 min, and 15 ml of H_2O was added. The two layers were separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts dried under vacuum.

TREATMENT OF DIENES WITH PyTs.—A very small amount (ca. 5 mg) of PyTs was added to a solution of 220 mg of diene in 5 ml of toluene, and the mixture was refluxed for 3 days.

OXIDATION OF *ent*-16β,17-DIHYDROXYATIS-13-ENE [**3**] WITH $NaIO_4$ TO YIELD NORKETONE **4**.—Oxidation of **3** (120 mg) with $NaIO_4$, as described above, gave the 17-nor-16-ketoderivative **4** (115 mg). Mp 80–82°; $[\alpha]^{20}D$ +151.8° ($CHCl_3$, c = 1); ir (KBr) ν max cm^{-1} 2470, 2432, 1737, 1461, 1443, 1394, 1387, 1210, 1111, 1087, 943, 692; ^{1}H nmr (300 MHz, $CDCl_3$) δ between 6.20 and 6.00 (2H, AB part of an ABX system), 305 (1H, m, W½ = 16 Hz, H-12, X part of the ABX system), 0.90, 0.82, and 0.67 (3H each, s, 18-Me, 19-Me, 20-Me); ms *m/z* (rel. int.) $[M]^+$ 272 (7), 231 (20), 230 (95), 149 (17), 137 (76), 124 (25), 123 (30), 109 (21), 106 (100), 105 (23), 104 (28), 95 (36), 94 (23), 92 (57), 91 (74), 81 (41), 69 (39). *Anal.* calcd for $C_{19}H_{28}O$, C 83.82; H 10.29, O 5.89; found C 83.41, H 10.53, O 6.06.

ADDITION OF MeMgI TO KETODERIVATIVE **4**.—Reaction of MeMgI with product **4** (60 mg), as described above, gave alcohols **5** (36 mg, 61%) and **6** (24 mg, 39%).

ent-16α-HYDROXYATIS-13-ENE [**5**].—Mp 97–99°; $[\alpha]^{20}D$ +24.7° ($CHCl_3$, c = 1); ir (KBr) ν max cm^{-1} 3408, 2940, 2860, 1463, 1382, 1206, 1123, 924, 732; ^{1}H nmr (80 MHz, $CDCl_3$) δ between 6.10 and 5.70 (2H, AB part of an ABX system, H-13 and H-14); 2.30 (1H, m, W½ = 12 Hz, H-12, X part of the ABX system); 1.12 (3H, s, 17-Me); 0.88, 0.80, and 0.67 (3H each, s, 18-Me, 19-Me, 20-Me); ^{13}C nmr see Table 1; ms *m/z* (rel. int.) $[M]^+$ 288 (1), 231 (19), 230 (100), 176 (3), 145 (7), 137 (80), 106 (93), 92 (48), 91 (58), 69 (25). *Anal.* calcd for $C_{20}H_{32}O$, C 83.33, H 11.11, O 5.55; found C 82.96, H 10.74, O 6.30.

ent-16β-HYDROXYATIS-13-ENE [**6**].—Mp 80.82°; $[\alpha]^{20}D$ +67.6° ($CHCl_3$, c = 1); ir (KBr) ν max cm^{-1}; 3429, 2930, 2870, 1732, 1468, 1372, 1246, 1125, 942, 725; ^{1}H nmr (80 MHz, $CDCl_3$) δ between 6.20 and 6.00 (2H, H-13 and H-14); 2.40 (1H, m, W½ = 12 Hz, H-12); 1.30 (3H, s, C-17 Me

TABLE 1. ^{13}C-nmr Chemical Shifts.

Carbon	Compound														
	6	**7**	**8**	**10**	**15**	**18**	**19**	**20**	**22**	**26**	**28**	**29**	**21**	**23**	**27**
1	39.06	38.80	38.43	39.60	83.08	83.15	82.92	82.64	39.16	40.15	41.96	39.01	78.35	40.53	40.19
2	18.17	16.15	17.45	18.32	24.85	24.72	24.87	24.81	18.32	18.39	19.54	16.06	24.04	18.50[a]	18.64
3	42.46	42.23	41.52	42.33	39.67	39.65	39.63	39.74	42.21	42.05	42.12	42.13	39.07	41.69	41.96
4	33.07	32.06	32.32	33.25	32.96	32.96	32.94	32.96	33.10	33.28	33.30	32.62	34.13	37.47[b]	34.99
5	55.69	57.75	55.08	56.51	54.80	54.80	54.86	54.23	55.54	56.44	56.25	46.70	52.58	55.65	53.57
6	27.03	24.77	18.74	18.92	18.96	24.74	26.26	18.98	19.43	19.24	19.91	27.70	29.48	18.14[a]	31.18
7	37.07	37.16	36.40	39.50	37.19	37.20	37.29	35.18	36.87	34.12	37.14	72.74	39.48	40.01	39.77
8	37.99	37.96	—	33.55	39.20	39.74	39.91	29.80	39.65	—	40.62	43.82	142.46	—	143.46
9	52.89	52.90	53.56	52.89	52.80	51.70	51.64	54.90	63.80	58.53	61.03	49.04	147.38	72.38	—
10	39.62	39.80	—	37.81	43.10	41.95	41.95	42.26	37.72	39.14	39.52	38.36	46.46	37.60[b]	40.95
11	19.47	19.36	29.01	28.88	31.21	19.00	18.88	28.39	70.63	75.27	76.10	28.26	113.69	207.15	132.09
12	44.22	44.34	41.23	36.72	42.10	44.22	44.40	43.32	50.52	48.68	52.08	42.13	126.51	120.40	126.50
13	131.23	130.03	129.56	28.85	131.35	132.18	130.98	134.67	126.87	131.38	127.47	131.07	128.20	124.80	128.30
14	136.57	138.73	136.10	27.51	136.50	135.82	137.84	136.41	131.23	140.15	141.90	135.16	125.28	128.99	125.31
15	54.23	56.72	44.61	48.40	45.40	54.41	56.62	134.91	45.09	138.15	45.77	29.85	129.06	44.71	129.12
16	74.21	74.40	150.00	152.30	150.50	73.75	73.74	145.20	139.02	141.93	146.80	170.72	137.75	137.40	137.92
17	31.51	27.56	102.61	104.43	103.30	31.39	27.81	19.35	109.06	19.51	106.23	103.47	21.41	23.13	21.43
18	33.78	33.37	33.11	33.89	33.05	33.29	33.28	33.30	33.65	33.28	34.21	33.54	33.06	33.45	33.87
19	22.01	21.95	21.25	21.82	21.88	21.88	21.82	21.93	22.02	22.02	22.32	21.90	21.16	21.75	20.40
20	15.55	15.53	14.90	14.12	11.63	11.71	11.70	11.87	17.65	16.68	20.05	15.50	11.92	18.64	14.20
CH_3-COO					21.88	21.96	21.93	21.79		21.88			21.99		22.37
CH_3-*C*OO					170.67	170.67	170.67	170.67		170.73			170.48		167.73

[a,b]Values with the same superscript may be interchanged.

group); 0.85, 0.77, and 0.62 (3H each, s, 18-Me, 19-Me, 20-Me); ^{13}C nmr see Table 1; ms *m/z* (rel. int.) $[M]^+$ 288 (3), 231 (15), 230 (81), 215 (8), 172 (4), 145 (8), 137 (71), 106 (100), 104 (28), 92 (56), 91 (74), 82 (33), 69 (30). *Anal.* calcd for $C_{20}H_{32}O$, C 83.33, H 11.11, O 5.55, found C 83.10, H 10.86, O 6.04.

DEHYDRATION OF *ent*-16α-HYDROXYATIS-13-ENE [**5**] WITH MsCl/PYRIDINE.—Compound **5** (30 mg) was dissolved in 2 ml of pyridine; MsCl (0.01 ml) was then added and the mixture refluxed for 15 min. After this time, the reaction products were dropped in a solution of 50 ml of $KHSO_4$ (10%), extracted with 50 ml of CH_2Cl_2, and dried over $NaSO_4$, and the solvent was evaporated at reduced pressure. After cc, 10 mg (33%) of *ent*-atis-13,16-diene [**7**] was isolated.

ent-ATIS-13,16-DIENE [**7**].—Mp 55–57°; $[\alpha]^{20}D$ +113.4° ($CHCl_3$, *c* = 1); ir (KBr) ν max cm^{-1} 3080, 3060, 2950, 2940, 1740, 1650, 890, 720; ^{1}H nmr (80 MHz, $CDCl_3$) δ between 6.15 and 5.70 (2H, H-13 and H-14), 4.55 (1H, dd, $J_1 = 2, J_2 = 4$ Hz), 4.32 (1H, dd, $J_1 = 2, J_2 = 3.5$ Hz, 2H-17), 2.80 (1H, m, W½ = 18 Hz, H-12); 0.70, 0.62, and 0.40 (3H each, s, 18-Me, 19-Me, 20-Me); ^{13}C nmr see Table 1; ms *m/z* (rel. int.) $[M]^+$ 270 (19), 255 (15), 175 (13), 163 (17), 161 (13), 149 (100), 147 (44), 145 (28), 137 (30), 135 (50), 123 (33), 121 (29), 109 (45), 107 (36), 105 (52). *Anal.* calcd for $C_{20}H_{30}$, C 88.88, H 11.11, found C 88.53, H 10.96.

DEHYDRATION OF *ent*-16β-HYDROXYATIS-13-ENE[**6**] WITH MsCl/PYRIDINE.—Compound **6** (22 mg) was treated with 0.01 ml of MsCl and 2 ml of pyridine as described for **5** to give after cc 9 mg (41%) of **7**.

WITTIG REACTION OF *ent*-16-OXO-17-NORATIS-13-ENE [**4**].—Compound **4** (50 mg) was treated with methyl-triphenyl-phosphonium bromide as previously described in general procedure to give product **7** (17 mg, 32%).

TREATMENT OF *ent*-16β,17-DIHYDROXYATIS-13-ENE [**3**] WITH *N,N'*-THIOCARBONYLDIIMIDAZOLE TO GIVE *ent*-16α,17-THIOCARBONYLDIOXYATIS-13-ENE [**8**].—Compound **3** (150 mg) dissolved in 20 ml of toluene was treated with 120 mg of *N,N'*-thiocarbonyldimidazole as in Corey and Winter (11) to give 142 mg (83%) of *ent*-16α,17-thiocarbonyldioxyatis-13-ene [**8**]: mp 191–193°; $[\alpha]^{20}D$ −7.6° ($CHCl_3$, *c* = 1); ir (KBr) ν max cm^{-1} 2980, 2920, 1340, 1280, 1200, 1162, 980, 740; ^{1}H nmr (300 MHz, $CDCl_3$) δ between 6.30 and 5.80 (2H, H-13 and H-14); 4.22 and 3.78 (1H each, dd, AB system, *J* = 12 Hz, 2H-17); 2.72 (1H, m, W½ = 16 Hz, H-12); 0.87, 0.79, and 0.55 (3H each, 18-Me, 19-Me, 20-Me); ms *m/z* (rel. int.) $[M]^+$ 346 (10), 303 (10), 287 (4), 286 (3), 240 (7), 146 (12), 138 (15), 132 (18), 118 (24), 105 (30), 91 (74), 69 (59), 42 (100). *Anal.* calcd for $C_{21}H_{30}O_2S$, C 72.83, H 8.67, O 9.26, S 9.24, found C 72.41, H 8.78, O 9.64, S 9.17.

TREATMENT OF *ent*-16α,17-THIOCARBONYLDIOXYATIS-13-ENE [**8**] WITH TMP.—Compound **8** (140 mg) dissolved in 40 ml of TMP was treated as in Corey and Winter (11) to give 88 mg (81%) of diene **7**.

HYDROGENATION OF *ent*-ATIS-13,16-DIENE [**7**].—Hydrogenation of 20 mg of **7** dissolved in 2 ml of EtOH, using Pd (5%)/$BaSO_4$ as catalyst, was carried out at room temperature and normal pressure for 2 h; after cc (Si gel + $AgNO_3$ 10%), 7 mg (35%) of *ent*-atisirene [**9**] was isolated (12).

OXIDATION OF *ent*-1β-ACETOXYATIS-13,16-DIENE [**14**].—Diene **14** (270 mg) was obtained from *ent*-1β-acetoxy-12α,17-dihydroxybeyer-15-ene [**10**] and from *ent*-1β-acetoxy-16α,17-dihydroxyatis-13-ene [**11**] via their thiocarbonates **12** and **13** as described by García-Granados and Parra (4). Oxidation of **11** with $NaIO_4$, as previously described above, gave *ent*-1β-acetoxy-17-noratis-13-en-16-one [**16**] (140 mg).

*ent*1β-ACETOXY-17-NORATIS-13-EN-16-ONE [**16**].—Mp 170° (sublimes); $[\alpha]^{20}D$ +209° ($CHCl_3$, *c* = 1); ir (KBr) ν max cm^{-1} 3040, 1722, 1614, 1458, 1391, 1240; ^{1}H nmr (80 MHz, $CDCl_3$) δ between 6.10 and 5.90 (2H, H-13 and H-14), 4.45 (1H, dd, $J_1 = 11, J_2 = 4$ Hz, H-1), 2.90 (1H, m, W½ = 12 Hz, H-12), 1.85 (3H, s, AcO), 0.78, 0.72, and 0.68 (3H each, 18-Me, 19-Me, 20-Me). *Anal.* calcd for $C_{21}H_{30}O_3$, C 76.36, H 9.09, O 14.55, found C 76.31, H 10.14.

Treatment of **16** with methyl-triphenyl-phosphonium bromide (Wittig) as described above gave *ent*-1β-acetoxyatis-13,16-diene [**14**] (4).

Alternatively, treatment of 75 mg of **16** with MeMgI as described previously above gave the two epimeric alcohols in C-16, *ent*-1β-acetoxy-16α-hydroxyatis-13-ene [**17**] (18 mg, 24%), and *ent*-1β-acetoxy-16β-hydroxyatis-13-ene [**18**] (34.8 mg, 46.4%).

ent-1β-ACETOXY-16α-HYDROXYATIS-13-ENE [**17**].—Colorless gum; $[\alpha]^{20}D$ +22° ($CHCl_3$, *c* = 1); ir (neat) ν max cm^{-1} 3440, 2943, 2870, 1724, 1454, 1376, 1248, 1206, 1028, 980, 924, 728; ^{1}H

nmr (300 MHz, $CDCl_3$) δ between 6.20 and 5.75 (2H, H-13 and H-14), 4.55 (1H, dd, $J_1 = 11, J_2 = 7$ Hz, H-1), 2.23 (1H, m, W½ = 15 Hz, H-12), 1.97 (3H, s, AcO), 1.10 (3H, s, 17-Me), 0.88, 0.81, and 0.76 (3H each, s, 18-Me, 19-Me, 20-Me); ^{13}C nmr see Table 1; ms *m/z* (rel. int.) $[M - AcO]^+$ 288 (8), 228 (29), 214 (11), 172 (22), 157 (29), 124 (100), 109 (56), 91 (63), 81 (38), 79 (15). *Anal.* calcd for $C_{22}H_{34}O_3$, C 76.30, H 9.82, O13.87, found C 75.91, H 9.92.

ent-1β-ACETOXY-16β-HYDROXYATIS-13-ENE [**18**].—Mp 165° (dec); $[\alpha]^{20}D$ +31.6° ($CHCl_3$, *c* = 1); ir (KBr) ν max cm^{-1} 3439, 2983, 2863, 1730, 1450, 1352, 1245, 1118, 1036, 1028, 980, 924, 728; ^1H nmr (300 MHz, $CDCl_3$) δ between 6.25 and 6.00 (2H, H-13 and H-14), 4.53 (1H, dd, $J_1 = 11$, $J_2 = 7$ Hz, H-1), 2.40 (1H, m, W½ = 15 Hz, H-12), 2.05 (3H, s, AcO), 1.30 (3H, s, 17-Me), 0.88, 0.82, and 0.75 (3 each, s, 18-Me, 19-Me, 20-Me); ^{13}C nmr see Table 1; ms *m/z* (rel. int.) $[M - AcO]^+$ 288 (10), 255 (3), 228 (33), 172 (24), 157 (26), 124 (100), 109 (52), 104 (28), 91 (46), 81 (33). *Anal.* calcd for $C_{22}H_{34}O_3$, C 76.30, H 9.82, O 13.8, found C 75.98, H 10.04.

Treatment of 15 mg of **17** with MsCl as indicated for **5** and **6** gave the same diene **14** (6 mg, 37%). Compound **18** (30 mg) also gave **14** (13 mg, 44%).

ACID TREATMENT OF DIENE **14**.—Diene **14** (220 mg) was treated with PyTs as described in general procedures; after cc, *ent*-1β-acetoxyatis-13,15-diene [**19**] (36.8 mg, 17%) and *ent*-1β-acetoxy-(8,9),(11,12)-disecoatis-8(14),9(11),12,15-tetraene [**20**] (65.2 mg 30%) were isolated.

ent-1β-ACETOXYATIS-13,15-DIENE [**19**].—Colorless gum; $[\alpha]^{20}D$ +40° ($CHCl_3$, *c* = 1); ir (neat) ν max cm^{-1} 2928, 2856, 1730, 1460, 1447, 1390, 1356, 1245, 1132, 1011, 880, 725; ^1H nmr (80 MHz, $CDCl_3$) δ between 6.70 and 6.00 (2H, H-13 and H-14); 5.60 (1H, m, W½ = 7 Hz, H-15), 4.50 (1H, dd, $J_1 = 10$, $J_2 = 4$ Hz, H-1), 3.20 (1H, bd, $J = 7$ Hz, H-12); 2.00 (3H, s, AcO), 1.75 (3H, d, $J = 2$ Hz, 17-Me); 0.90, 0.85, and 0.73 (3H each, s, 18-Me, 19-Me, 20-Me); ^{13}C nmr see Table 1; ms *m/z* (rel. int.) $[M]^+$ 328 (35), 268 (50), 253 (31), 239 (16), 225 (14), 215 (11), 212 (14), 198 (20), 183 (20), 171 (22), 163 (24), 158 (38), 144 (48), 131 (53), 117 (52), 105 (80), 95 (56), 91 (100). *Anal.* calcd for $C_{22}H_{32}O_2$, C 80.49, H 9.75, O 9.76, found C 80.17, H 10.11, O 9.72.

ent-1β-ACETOXY-(8,9),(11,12)-DISECOATIS-8(14),9(11),12,15-TETRAENE [**20**].—Colorless gum; $[\alpha]^{20}D$ −34.5° ($CHCl_3$, *c* = 1); ir (neat) ν max cm^{-1} 2950, 2859, 1738, 1638, 1607, 1457, 1242, 1024, 914, 785, 699; ^1H nmr (300 MHz, $CDCl_3$) δ between 7.30 and 6.90 (4H from a disubstituted benzene system), 5.65 (1H, dd, $J_{AX} + J_{BX} = 25$ Hz, H-9, X part of an ABX system); between 5.20 and 5.00 (2H, AB part of the ABX system, 2H-11), 4.75 (1H, dd, $J_1 = 11$, $J_2 = 8$ Hz, H-1); 2.55 (2H, m, W½ = 25 Hz, 2H-7), 2.37 (3H, s, 17-Me), 2.00 (3H, s, AcO), 1.07, 1.02, and 0.96 (3H each, s, 18-Me, 19-Me, 20-Me); ^{13}C nmr see Table 1; ms *m/z* (rel. int.) $[M]^+$ 328 (6), 268 (12), 253 (14), 198 (8), 171 (10), 150 (26), 105 (100), 91 (28), 81 (44), 79 (48), 77 (32). *Anal.* calcd for $C_{22}H_{32}O_2$, C 80.49, H 9.75, O 9.76, found C 80.17, H 10.06.

ent-11β-HYDROXYATIS-13,16-DIENE [**21**].—The natural product atisideritol [**2**] (3) (30 g) was treated with *N,N'*-thiocarbonyldiimidazole and further with TMP, to give a complex mixture of products; after cc 812 mg of *ent*-11β-hydroxyatisa-13,16-diene [**21**] (3%) was isolated. Colorless gum; $[\alpha]^{20}D$ +31.6° ($CHCl_3$, *c* = 1); ir (neat) ν max cm^{-1} 3313, 2999, 2875, 2402, 2310, 1600, 1520, 1481, 1412, 1200, 1125, 870; ^1H nmr (80 MHz, $CDCl_3$) δ between 6.10 and 5.90 (2H, H-13, and H-14), 4.90 (2H, m, W½ = 8 Hz, 2H-17), 3.60 (1H, m, W½ = 18 Hz, H-11), 3.00 (1H, dd, $J_1 = 5$ Hz, $J_2 = 10$ Hz, H-12), 0.85, 0.82, and 0.70 (3H each, s, 18-Me, 19-Me, 20-Me); ^{13}C nmr see Table 1. *Anal.* calcd for $C_{20}H_{30}O$, C 83.91, H 10.49, O 5.60, found C 83.52, H 10.73.

ACID TREATMENT OF DIENE **21**.—Compound **21** (56 mg) was treated as usual with PyTs. After cc, 24 mg of *ent*-(11,12)-secoatis-12(16),13-dien-11-al [**22**] (43%) and 15 mg of **21** (27%) were isolated.

ent(11,12)-SECOATIS-12(16),13-DIEN-11-AL [**22**].—Colorless gum; $[\alpha]^{20}D$ +58.2° ($CHCl_3$, *c* = 1); ir (neat) ν max cm^{-1} 3042, 2912, 1693, 1442, 1389, 1375, 1262, 1127, 1088, 1036, 806, 752; ^1H nmr (300 MHz, $CDCl_3$) δ 9.50 (1H, d, $J = 9$ Hz, H-11), between 6.00 and 5.80 (2H, AB part of ABM system, H-13 and H-14), 5.57 (1H, m, W½ = 8 Hz, M part of the ABM system), 2.15 (1H, bd, $J = 18$ Hz, H-15), 1.75 (1H, ddd, $J_1 = 12$, $J_2 = J_3 = 3$ Hz, H-1eq), between 1.70 and 1.55 [5H (3H of 17-Me at δ 1.60) and the H-1ax, and H-15], 1.37 (1H, ddd, $J_1 = 12$, $J_2 = J_3 = 4.5$ Hz, H-3eq); 1.30 (1H, d, $J = 9$ Hz, H-9); 1.20 (3H, s, 20-Me); 1.03 (1H, ddd, $J_1 = J_2 = 12$ Hz, $J_3 = 4.5$ Hz, H-3ax); 0.85 and 0.82 (3H each, s, 18-Me and 19-Me), 0.75 (1H, m, W½ = 27 Hz, H-5); ^{13}C nmr see Table 1; ms *m/z* (rel. int.) $[M]^+$ 286 (3), 189 (3), 167 (37), 149 (100), 113 (9), 112 (13), 71 (22), 70 (17), 69 (14), 57 (28). *Anal.* calcd for $C_{20}H_{30}O$, C 83.91, H 10.49, O 5.60, found C 83.65, H 10.47.

Treatment of **21** with *p*-TsOD/pyridine under the same conditions described above gave **23** with the same yield as **22**.

ACETYLATION OF **21**.—Acetylation of 700 mg of **21** with 15 ml of Ac_2O and 30 ml of pyridine, under reflux conditions for 48 h, gave acetate **24** (154 mg, 19%) as a colorless gum. ^{1}H nmr (300 MHz, $CDCl_3$) δ between 6.40 and 6.00 (2H, H-13 and H-14), 4.85 (1H, dd, $J_1 = 2, J_2 = 4$ Hz), 4.63 (1H, dd, $J_1 = 2, J_2 = 4$ Hz, 2H-17), 4.25 (1H, dd, $J_1 = 4, J_2 = 9$, H-11), 3.32 (1H, m, W½ = 15 Hz, H-12), 1.00, 0.88, and 0.86 (3H each, s, 18-Me, 19-Me, 20-Me); ms *m/z* (rel. int.) $[M]^+$ 328 (3), 286 (19), 268 (71), 253 (13), 225 (7), 197 (9), 163 (22), 145 (35), 144 (53), 118 (45), 117 (40), 105 (100), 97 (46), 95 (42), 91 (71), 84 (79), 69 (62). *Anal.* calcd for $C_{22}H_{32}O_2$, C 80.49, H 9.75, O 9.76, found C 80.22, H 9.98, O 9.80.

ACID TREATMENT OF DIENE **24**.—Treatment of 150 mg of diene **24** with *p*-TsOH/pyridine in the usual manner gave 32.8 mg of *ent*-11β-acetoxyatis-13,15-diene [**25**] (22%) and *ent*-11β-acetoxy-(8,9),(11,12)-disecoatis-8(14),9(11),12,15-tetraene [**26**] (55.2 mg, 37%).

ent-11β-ACETOXYATIS-13,15-DIENE [**25**].—Colorless gum; $[\alpha]^{20}D$ +35.8° ($CHCl_3$, *c* = 1); ^{1}H nmr (300 MHz, $CDCl_3$) δ between 6.40 and 6.15 (2H, H-13 and H-14), 5.56 (1H, dd, $J_1 = J_2 = 2$ Hz, H-15), 5.20 (1H, dd, $J_1 = 4, J_2 = 11$ Hz, H-11), 3.35 (1H, m, W½ = 18 Hz, H-12), 1.96 (3H, s, AcO), 1.79 (3H, d, $J = 2$ Hz, 17-Me), 0.91, 0.88, and 0.83 (3H each, s, 18-Me, 19-Me, 20-Me); ^{13}C nmr see Table 1; ms *m/z* (rel. int.) $[M]^+$ 268 (60.51), 173 (16), 163 (21), 149 (24), 145 (31), 144 (40), 137 (20), 132 (26), 131 (25), 124 (20), 119 (26), 118 (39), 109 (28), 106 (24), 105 (100), 97 (48), 95 (30), 91 (37), 81 (38), 69 (45). *Anal.* calcd for $C_{22}H_{32}O_2$, C 80.49, H 9.75, O 9.76, found C 80.36, H 10.12, O 9.52.

ent-11β-ACETOXY-(8,9),(11,12)-DISECOATIS-8(14),9(11),12,15-TETRAENE [**26**].—Colorless gum; $[\alpha]^{20}D$ −37.1° ($CHCl_3$, *c* = 1); ir (neat) ν max cm^{-1} 2958, 2928, 1734, 1630, 1443, 1372, 1236, 1134, 1070, 830, 724; ^{1}H nmr (300 MHz, $CDCl_3$) δ between 7.20 and 6.90 (4H, from a disubstituted benzene system), 6.91 (1H, d, $J = 7.5$ Hz, H-11), 4.61 (1H, d, $J = 7.5$ Hz, H-9), 2.60 (2H, dd, $J_1 = J_2 = 9$ Hz, 2H-7), 2.33 (3H, s, 17-Me), 2.10 (3H, s, AcO), 1.20, 1.00, and 0.90 (3H each, s, 18-Me, 19-Me, 20-Me); ^{13}C nmr see Table 1; ms *m/z* (rel. int.) $[M-60]^+$ 268 (56), 253 (6), 225 (6), 173 (12), 163 (16), 144 (30), 118 (32), 105 (100), 97 (37), 94 (21), 84 (62), 69 (27). *Anal.* calcd for $C_{22}H_{32}O_2$, C 80.49, H 9.75, O 9.76, found C 80.31, H 9.91, O 9.78.

ent-11α-HYDROXYATIS-13,16-DIENE [**27**] AND *ent*-7α-HYDROXYATIS-13,16-DIENE [**28**].—A natural extract (500 mg) rich in isosideritol (2) was treated with *N,N'*-thiocarbonyldiimidazole and further with TMP, as described above; after cc, small amounts of **27** (7 mg, 5%) and **28** (20 mg, 15%) were isolated.

ent-11α-HYDROXYATIS-13,16-DIENE [**27**].—Mp 71–73°; $[\alpha]^{20}D$ +55.3° ($CHCl_3$, *c* = 1), ir (KBr) ν max cm^{-1} 3429, 2927, 2864, 1644, 1456, 1440, 1362, 1080, 1052, 885, 712; ^{1}H nmr (80 MHz, $CDCl_3$) δ between 6.50 and 5.90 (2H, H-13 and H-14), 4.85 (1H, dd, $J_1 = 2, J_2 = 4$ Hz), 4.68 (1H, dd, $J_1 = 2, J_2 = 4$ Hz, 2H-17), 3.25 (1H, m, W½ = 18 Hz, H-12), 1.02 (3H, s, 20-Me), 0.82 (6H, s, 18-Me and 19-Me); ^{13}C nmr see Table 1. *Anal.* calcd for $C_{20}H_{30}O$, C 83.91, H 10.49, O 5.60, found C 83.82, H 10.56, O 5.62.

ent-7α-HYDROXYATIS-13,16-DIENE [**28**].—Colorless gum; $[\alpha]^{20}D$ +94.1° ($CHCl_3$, *c* = 1); ir (neat) ν max cm^{-1} 3500, 3090, 3060, 1640, 1070, 1040, 960, 890, 710, 700, 670; ^{1}H nmr (300 MHz, $CDCl_3$) δ between 6.20 and 5.70 (2H, H-13, H-14), 4.72 (1H, dd, $J_1 = 2, J_2 = 4$ Hz), 4.55 (1H, dd, $J_1 = 2, J_2 = 3.5$ Hz, 2H-17), 3.95 (1H, t, $J = 4$ Hz, H-7), 2.98 (1H, m, W½ = 16 Hz, H-12), 0.87, 0.79; and 0.58 (3H each, s, 18-Me, 19-Me, 20-Me); ^{13}C nmr see Table 1. *Anal.* calcd for $C_{20}H_{30}O$, C 83.91, H 10.49, O 5.60, found C 83.62, H 10.74.

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