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SELECTIVE REDUCTION OF SERRULATENOL AS A ROUTE TO SECO-PSEUDOPTEROSIN ANALOGUES

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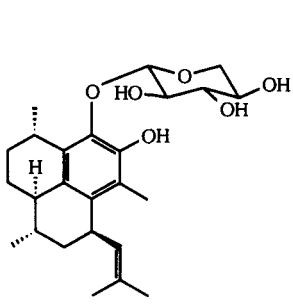
ABSTRACT.—Deoxygenation of serrulatenol [**3**], from *Eremophila rotundifolia*, at C-13 and C-18, gave 5,8-dimethoxyserrulatane [**12**]. Catalytic hydrogenolysis and metal/NH_3 cleavage of the allylic carbon-oxygen bond was followed by deoxygenation at C-18 via the tri-*n*-butylstannane reduction of the C-18 iodo derivative.

Considerable interest has been generated by the recent discovery by Fenical (1,2) of a new group of anti-inflammatory compounds in the marine genus *Pseudopterogorgia*. These compounds, the pseudopterosins and the seco-pseudopterosins which exist as mixtures of the monoacetates of **1** and **2**, respectively, are pentose glycosides of diterpenes and are reported to have significant antimicrobial activity in addition to their potency as anti-inflammatory and analgesic agents. Importantly, the mechanism of their action as anti-inflammatory agents appears to be distinct from that of existing drugs (2,3). The importance of these inaccessible compounds has stimulated interest in the synthesis of both the pseudopterosins (4,5) and the seco-pseudopterosins (6,7).

As an alternative approach we have been investigating the use of the serrulatane diterpenes from *Eremophila* species, which are shrubs indigenous to the arid regions of Australia, as a possible source of isomeric aglycones suitable for glycosylation. We report here the selective reduction of serrulatenol [**3**], a diterpene isolated (8) from *Eremophila rotundifolia*, as a route to compounds related to the seco-pseudopterosins but with different stereochemistry. Serrulatenol is the only serrulatane reported which allows access to the 5,8-dioxygenated substitution pattern in contrast with the 7,8 pattern found in the aglycone of the seco-pseudopterosins. The stereochemistry of serrulatenol has been confirmed by X-ray analysis (8). The present problem, which involves conversion of serrulatenol [**3**] into 5,8-dimethyoxyserrulatane [**12**], essentially requires deoxygenation at C-13 and C-18 without isomerization at C-11.

Serrulatenol [**3**] was methylated with NaH and MeI to prevent oxidation of intermediate quinols during the transformation. Catalytic hydrogenolysis of the ether **4** in the presence of Pd/C was studied with varying amounts of HOAc to promote the desired reaction. However, hydrogenation always predominated to give **5** with only about a 30% yield of the hydrogenolysis product **6** being formed. The hemiacetal **6** was found by 300 MHz ^{1}H nmr spectroscopy to be a mixture of C-18 epimers in a ratio of 2:1. The hemiacetal proton (H-18) appeared at δ 5.23 in the major epimer as a doublet of doublets, coupled to the vicinal proton ($J = 8.9$ Hz) and the hydroxyl proton. The analogous proton (δ 5.59) for the minor epimer showed coupling only to the hydroxyl proton. The possibility that enolization of the aldehyde, from opening of the cyclic hemiacetal, led to epimerization at C-11 was excluded when the mixture of hemiacetals **6**, on reduction with $LiAlH_4$, gave the diol **7**. The diol **7** was homogenous, by 300 MHz ^{1}H nmr spectroscopy, with a pair of doublet of doublets at δ 3.38 and 3.62 corresponding to the AB part of the ABX system of the hydroxymethyl group.

A more efficient method for cleavage of the O-C-18 bond was found with Li/NH_3/EtOH reduction. After the metal/



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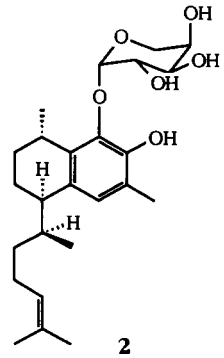

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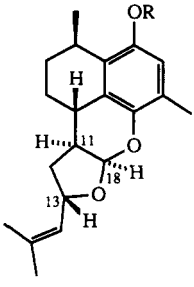
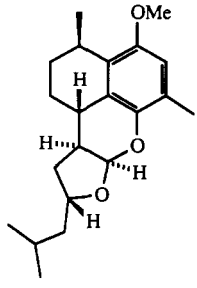


3 R=H
4 R=Me



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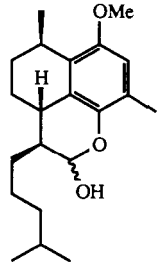

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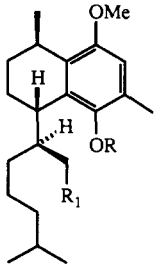
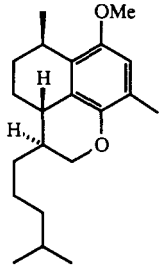


7 R=H, R_1=OH
8 R=Ac, R_1=OAc
9 R=Me, R_1=OH
10 R=Me, R_1=OMs
11 R=Me, R_1=I
12 R=Me, R_1=H



13

NH_3 reaction and hydrogenation to remove the double bond, the diol **7** and its C-11 epimer were obtained in good yield in a ratio of 10:1. Pure **7** could be obtained by recrystallization of the mixture, and chromatographic separation could be achieved with the corresponding acetates. Because the major isomer was identical with the diol **7** from the catalytic hydrogenolysis/$LiAlH_4$ sequence, it can be concluded that the configuration at C-11 is the same as that in the natural product and only a small amount of equilibration of the intermediate aldehyde occurred during the Li/NH_3/EtOH reduction.

Reduction of a C-18 sulfonate ester of the diol **7** was a method considered for the removal of the C-18 oxygen. However, because tosylation of **7** gave the cyclic ether **13**, diol **7** was converted into the dimethoxy alcohol **9**. Mesylation, followed by reaction of the mesylate **10** with NaI in Me_2CO gave the iodide **11** in good yield. Subsequent reduction of **11** with tri-*n*-butylstannane gave the desired product **12**. The spectral data supported the structure of **12**; in particular the new methyl (H-18) appeared as a doublet at δ 0.76.

We plan to prepare **12** on a scale sufficient to enable an analogue of seco-pseudopterosin to be prepared for assay. This will require demethylation of **12** and glycoside formation, which should be possible in a manner analogous to that reported recently in the pseudopterosins (4).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Ir spectra were measured on a Jasco-102 spectrophotometer. ^{1}H nmr (300 MHz) were recorded in $CDCl_3$ on Bruker CXP-300 or ACP-300 spectrometers and 60 MHz on a Varian T60 spectrometer, using TMS as internal standard. Chemical shifts are reported in δ (ppm) values. Eims were obtained with an AEI MS-30 double focusing mass spectrometer operating at 70 eV. Si gel 60 Merck (230–400 mesh) and Merck PF_{254} were used for flash chromatography and chromatography [dry column (9), solvent gradient], respectively. Si gel Merck HF_{254} was used for preparative tlc. All solvents were distilled before use, and dry Et_2O and THF were obtained by distillation from sodium benzophenone ketyl. The serrulatenol used in this study was part of a sample whose structure has been confirmed by X-ray crystallography (8).

METHYLATION OF SERRULATENOL [**3**].—Me_2SO (3.2 ml) was added to a mixture of serrulatenol [**3**] (400 mg, 1.27 mmol) and NaH (64 mg, 2.68 mmol, 50% mineral oil suspension). The mixture was stirred for 15 min, MeI (0.47 ml, 7.62 mmol) was injected, and the mixture was stirred for 48 h. Dilute HCl (15 ml) was added and the mixture extracted with CH_2Cl_2. After drying ($MgSO_4$) and removal of the solvent under reduced pressure, chromatography on Si gel (petroleum ether/CH_2Cl_2 gradient) gave (13*S*,18*R*)-5,18:13,18-diepoxy-8-methoxyserrulat-14-ene [**4**] (300 mg, 72%), mp 108–109° (from MeOH). Found C 76.6, H 8.4; calcd for $C_{21}H_{28}O_3$, C 76.8, H 8.6%. Ir ν max ($CHCl_3$) cm^{-1} 2950, 2925, 2850, 1670, 1600, 1480, 1460, 1440, 1220, 1100, 1060, 970, 840; ^{1}H nmr δ (300 MHz) 1.21 (3H, d, J = 6.9 Hz, H-20), 1.5–2.4 (polymethylene CH_2 and CH), 1.76 (6H, s, H-16, H-17), 2.27 (3H, s, H-19), 2.57 (1H, m, H-4), 3.10 (1H, m, H-1), 3.78 (3H, s, OMe), 5.12–5.25 (2H, m, H-13, H-14), 5.3 (1H, d, J = 5.7 Hz, H-18) 6.54 (1H, s, H-7); eims *m/z* [M]$^+$ 329.

CATALYTIC HYDROGENOLYSIS OF THE METHYL ETHER **4**.—The ether **4** was stirred in EtOAc under H_2 in the presence of varying amounts of HOAc and Pd/C. The best yield of hydrogenolysis product **6** was 30% using **4** (100 mg), 10% Pd/C (100 mg), HOAc (10% in EtOAc). Filtration through Celite, removal of solvent under vacuum, and preparative tlc on Si gel with CH_2Cl_2-petroleum ether (3:2) gave the higher R_f hydrogenation product, (13*R*,18*R*)-5,18:13,18-diepoxy-8-methoxyserrulatane [**5**] as an oil. ^{1}H nmr (60 MHz) δ 0.98 (6H, d, J = 6 Hz, H-16, H-17), 1.17 (3H, d, J = 6 Hz, H-20), 1.3–2.5 (polymethylene CH_2 and CH, H-4), 2.30 (3H, s, H-19), 3.10 (1H, m, H-1), 3.80 (3H, s, OMe), 4.60 (1H, m, H-13), 5.33 (1H, d, J = 5.0 Hz, H-18), 6.57 (1H, s, H-7). The lower R_f hydrogenolysis product was recrystallized from petroleum ether: mp 115–116°; hreims *m/z* [M]$^+$ 332.2364 ($C_{21}H_{32}O_3$ requires 332.2351); ir ν max ($CHCl_3$) cm^{-1} 3575, 2900, 2850, 1600, 1470, 1460, 1360, 1330, 1220, 1100, 1080, 1020; ^{1}H nmr (300 MHz) revealed two isomers in a ratio of 2:1, (18*R*) and (18*S*)-5,18-epoxy-8-methoxyserrulatan-18-ol [**6**]. *Major isomer*: δ 0.88 (6H, d, J = 6.6 Hz, H-16, H-17), 1.23 (3H, d, J = 6.7 Hz, H-20), 1.3–2.1 (polymethylene CH_2 and CH), 2.20 (3H, s, H-19), 2.93 (1H, m, H-4), 2.76 (1H, d, J = 6.6 Hz, D_2O exch., OH), 3.14 (1H, m, H-1), 3.76 (3H, s, OMe), 5.23 (1H, d, J = 6.6, 8.9 Hz, H-18), 6.56 (1H, s, H-7). *Minor isomer*: δ 0.88 (6H, d, J = 6.6 Hz, H-16, H-17), 1.23 (3H, d, J = 6.7 Hz, H-20), 1.3–2.1 (polymethylene CH_2 and CH), 2.20 (3H, s, H-19), 2.52 (1H, m, H-4), 2.69 (1H, d, J = 3.7 Hz, D_2O exch., OH), 3.14 (1H, m, H-1), 3.76 (3H, s, OMe), 5.59 (1H, d, J = 3.7 Hz, H-18), 6.58 (1H, s, H-7); eims *m/z* (%) [M]$^+$ 332 (44), 204 (100).

$LiAlH_4$ REDUCTION OF THE EPIMERIC HEMIACETALS **6**.—A solution of $LiAlH_4$ (14 mg) in THF (5 ml) was added to **6** (60 mg), and the mixture was warmed under N_2 for 3 days. Workup and purification by chromatography on Si gel (petroleum ether/CH_2Cl_2 gradient) gave (11*S*)-8-methoxyserrulatane-5,18-diol [**7**] (50 mg, 83%): mp 134–136° (from petroleum ether); hreims *m/z* [M]$^+$ 334.2513 ($C_{21}H_{34}O_3$ requires 334.2508); ir ν max ($CHCl_3$) cm^{-1} 3600, 3325,

2925, 2850, 1460, 1410, 1360, 1210, 1090; ^{1}H nmr (300 MHz) δ 0.86 (3H, d, J = 6.7, H-16 or H-17), 0.88 (3H, d, J = 6.5 Hz, H-16 or H-17), 1.12 (3H, d, J = 6.8 Hz, H-20), 1.3–2.1 (polymethylene CH_2 and CH), 2.25 (3H, s, H-19), 3.02 (1H, m, H-4), 3.15 (1H, m, H-1), 3.38 (1H, dd, J = 10.9, 2.2 Hz, H-18), 3.62 (1H, dd, J = 10.9, 4.5 Hz, H-18), 3.49 (1H, s, D_2O exch., OH), 3.77 (3H, s, OMe), 6.54 (1H, s, H-7); eims *m/z* (%) $[M]^+$ 334 (24), 205 (100).

Li/NH_3 REDUCTION OF METHYL ETHER **4**.—Methyl ether **4** (1.2 g, 3.66 mmol) in dry THF (20 ml) was added to dry NH_3 (100 ml). Li (1.5 g, 214 mmol) and then EtOH (12 ml) were added and the mixture stirred for 5 min before the excess of Li was destroyed with isoprene. After the NH_3 had evaporated, H_2O (50 ml) was added and the mixture extracted with CH_2Cl_2. After drying (Na_2SO_4), evaporation f the solvent gave a residue which was hydrogenated without purification with PtO_2 (400 mg) in EtOAc (150 ml). Filtration through Celite, removal of solvent under reduced pressure, and purification by flash chromatography on Si gel with EtOAc-CH_2Cl_2 (1:19) gave the epimeric diols (850 mg, 71%) in a ratio of 9:1 by ^{1}H nmr (300 MHz) spectroscopy. Recrystallization from hexane gave pure (11*S*)-8-methoxyserrulatane-5,18-diol [**7**] with physical data identical with those above. The minor (11*R*) isomer has ^{1}H nmr (300 MHz) δ 0.85 (3H, d, J = 6.6 Hz, H-16 or H-17), 0.86 (3H, d, J = 6.9 Hz, H-16 or H-17), 1.12 (3H, d, J = 6.7 Hz, H-20), 1.2–2.1 (polymethylene CH_2 and CH), 2.23 (3H, s, H-19), 3.02 (1H, m, H-4), 3.14 (1H, m, H-1), 3.38 (1H, dd, J = 10.9, 2.0 Hz, H-18), 3.62 (1H, dd, J = 10.9, 4.6 Hz, H-18), 3.77 (3H, s, OMe), 6.51 (1H, s, H-7); eims *m/z* (%) $[M]^+$ 334 (26), 205 (100).

Acetylation of some of the mixture with Ac_2O in Et_3N gave the mixture of acetates which were separated by flash chromatography on Si gel with CH_2Cl_2. Higher R_f component, (11*S*)-18-acetoxy-8-methoxyserrulatan-5-yl acetate [**8**]: ^{1}H nmr (300 MHz) δ 0.81 (6H, d, J = 6.7 Hz, H-16, H-17), 1.12 (3H, d, J = 6.9 Hz, H-20), 1.2–2.4 (polymethylene CH_2 and CH), 1.95 (3H, s, 18-OAc), 2.10 (3H, s, H-19), 2.32 (3H, s, 5-OAc), 2.77 (1H, m, H-4), 3.16 (1H, m, H-1), 3.80 (3H, s, OMe), 3.96 (2H, m, H-18), 6.56 (1H, s, H-7). Lower R_f compound, (11*R*)-18-acetoxy-8-methoxyserrulatan-5-yl acetate: ^{1}H nmr (300 MHz) δ 0.79 (3H, d, J = 6.6 Hz, H-16 or H-17), 0.86 (3H, d, J = 6.5 Hz, H-16 or H-17), 1.14 (3H, d, J = 6.5 Hz, H-20), 1.1–2.7 (polymethylene CH_2 and CH, H-4), 1.89 (3H, s, 18-OAc), 2.06 (3H, s, H-19), 2.33 (3H, s, 5-OAc), 3.15 (1H, m, H-1), 3.79 (3H, s, OMe), 5.17 (2H, m, H-18), 6.54 (1H, s, H-7). $LiAlH_4$ reduction of the (11*S*) isomer **8** gave **7**.

TOSYLATION OF THE DIOL **7**.—The diol **7** (24 mg) was treated with TsCl in pyridine for 2 days. Workup and purification by preparative tlc with CH_2Cl_2-hexane (3:7) gave 5,18-epoxy-8-methoxyserrulatane [**13**] (10 mg, 45%): hreims *m/z* $[M]^+$ 316.2392 ($C_{21}H_{32}O_2$ requires 316.2402); ir ν max ($CHCl_3$) cm^{-1} 2952, 2875, 1466, 1260, 1102; ^{1}H nmr (300 MHz) δ 0.88 (6H, d, J = 6.5 Hz, H-16, H-17), 1.21 (3H, d, J = 6.6 Hz, H-20), 1.3–2.3 (polymethylene CH_2 and CH, H-4), 2.17 (3H, s, H-19), 3.19 (1H, m, H-1), 3.67 (1H, t, J = 10.7, H-18), 4.33 (1H, dd, J = 10.7, 3.5 Hz, H-18), 3.76 (3H, s, OMe), 6.56 (1H, s, H-7); eims *m/z* (%) $[M]^+$ 316 (35), 301 (100).

SELECTIVE METHYLATION OF DIOL **7**.—The diol **7** (205 mg, 0.61 mmol) was methylated as described above with NaH (21 mg, 0.87 mmol, 80% in mineral oil), Me_2SO (7 ml), and MeI (0.23 ml, 3.74 mmol). Isolation and purification by flash chromatography on Si gel with EtOAc-CH_2Cl_2 (1:99) yielded, after crystallization from MeOH-H_2O, 5,8-dimethoxyserrulatan-18-ol [**9**] (102 mg, 48%) as colorless crystals: mp 97–100°; found C 76.3, H 10.3 (calcd for $C_{22}H_{36}O_3$, C 75.8, H 10.4%); ir ν max ($CHCl_3$) cm^{-1} 3460, 3016, 2948, 2869, 1604, 1466, 1402, 1326, 1104; ^{1}H nmr (300 MHz) δ 0.86 (6H, d, J = 6.5 Hz, H-16, H-17), 1.13 (3H, d, J = 6.8 Hz, H-20), 1.3–2.2 (polymethylene CH_2 and CH), 2.28 (3H, s, H-19), 2.86 (1H, m, H-4), 3.11 (2H, m, H-1, H-18), 3.38 (1H, dd, J = 13.2, 5.0 Hz, H-18), 3.40 (1H, brs, D_2O exch., OH), 3.65, 3.78 (each 3H, s, 2 × OMe), 6.52 (1H, s, H-7); eims *m/z* (%) $[M]^+$ 348 (11), 219 (100).

PREPARATION OF THE IODIDE **11** AND ITS REDUCTION WITH TRI-*n*-BUTYLSTANNANE.—The dimethoxy alcohol **9** (80 mg) was mesylated with $MeSO_2Cl$ in pyridine at 0° overnight. Workup and chromatography on Si gel (petroleum ether/EtOAc gradient) gave 5,8-dimethoxyserrulatan-18-yl mesylate [**10**] as an oil: ^{1}H nmr (300 MHz) δ 0.84 (6H, d, J = 6.6 Hz, H-16, H-17), 1.13 (3H, d, J = 6.9 Hz, H-20), 1.2–2.2 (polymethylene CH_2 and CH), 2.26 (3H, s, H-19), 2.81 (3H, s, $MeSO_2$), 3.04 (1H, m, H-4), 3.14 (1H, m, H-1), 3.64, 3.78 (each 3H, s, 2 × OMe), 3.94 (1H, t, J = 9.7 Hz, H-20) and 4.12 (1H, dd, J = 9.7, 6.3 Hz, H-20), AB part of ABX system.

The mesylate **10** (80 mg) was refluxed with NaI (85 mg) in dry Me_2CO (10 ml) for 24 h. After removal of Me_2CO, H_2O was added and the mixture extracted with CH_2Cl_2. After drying (Na_2SO_4) and removal of solvent, purification by chromatography on Si gel (petroleum ether/EtOAc gradient) yielded 18-iodo-5,8-dimethoxyserrulatane [**11**] (73 mg, 85%) as an oil: ir ν max ($CHCl_3$) cm^{-1} 2940, 1604, 1466, 1418, 1380, 1098; ^{1}H nmr (300 MHz) δ 0.82 (6H, d, J = 6.6 Hz, H-16, H-17), 1.13 (3H, d, J = 6.9 Hz, H-20),

1.0–2.1 (polymethylene CH_2 and CH), 2.26 (3H, s, H-19), 2.98 (1H, dd, $J=9.8$, 7.4 Hz, H-18), 3.33 (1H, dd, $J=9.8$, 7.3 Hz, H-18), 3.15 (2H, m, H-1, H-4), 3.66, 3.79 (each 3H, s, 2 × OMe), 6.52 (1H, s, H-7); eims *m/z* (%) $[M]^+$ 458 (4), 219 (100).

AIBN (1 mg) was added to the iodide **11** (73 mg, 0.16 mmol) in dry C_6H_6 (1.5 ml) under N_2. Tri-*n*-butylstannane (0.26 ml, 0.95 mmol) was injected, and the mixture was refluxed for 16 h. After the solvent was removed, the residue was dissolved in Et_2O (5 ml) and treated with dilute KF solution (2 × 5 ml). The organic layer was collected, dried, and concentrated. The tin by-products were removed by flash chromatography on Si gel with hexane and the product eluted with CH_2Cl_2-hexane (1:4). A further purification by flash chromatography gave 5,8-dimethoxyserrulatane [**12**] (20 mg, 38%) as an oil: hreims *m/z* $[M]^+$ 332.2721 ($C_{22}H_{36}O_2$ requires 332.2715); $[\alpha]^{23}D$ −30.9° (*c*=1.3, $CHCl_3$); ir ν max ($CHCl_3$) cm^{-1} 2928, 2864, 1466, 1402, 1206, 1226, 1102, 1008; ^1H nmr (300 MHz) δ 0.76 (3H, d, $J=6.9$ Hz, H-18), 0.83 (6H, d, $J=6.7$ Hz, H-16, H-17), 1.12 (3H, d, $J=6.9$ Hz, H-20), 1.2–2.1 (polymethylene CH_2 and CH), 2.27 (3H, s, H-19), 2.80 (1H, m, H-4), 3.12 (1H, m, H-1), 3.63, 3.78 (each 3H, s, 2 × OMe), 6.50 (1H, s, H-7); eims *m/z* (%) $[M]^+$ 332 (7), 219 (100).

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