Synthesis of Coleon U 12-Methyl Ether

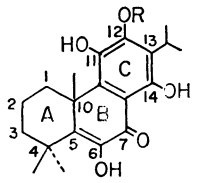
Takashi MATSUMOTO* and Shoji TAKEDA

Department of Chemistry, Faculty of Science, Hiroshima University, Higashisenda-machi, Hiroshima 730

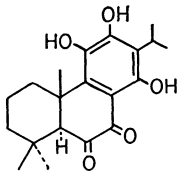
(Received January 16, 1979)

Reduction of 11-benzoyloxy-12-methoxyabieta-8,11,13-trien-7-one with sodium borohydride, followed by dehydration of the resulting alcohols with *p*-toluenesulfonic acid, afforded the corresponding 6,8,11,13-tetraene derivative. This was converted into 11-benzoyloxy-12-methoxyabieta-8,11,13-trien-6-one (**8**) *via* an epoxide. The 6-oxo compound (**8**) was reduced with lithium aluminium hydride. Subsequent oxidation of the resulting alcohol with *m*-chloroperbenzoic acid afforded 6*β*-hydroxy-12-methoxyabieta-8,12-diene-11,14-dione. This compound was further transformed into 11,14-diacetoxy-12-methoxyabieta-8,11,13-trien-6-one (**13**) by a series of reactions: Jones oxidation, reduction with a mixture of zinc powder and hydrochloric acid, and acetylation. The diacetate (**13**) was then oxidized with Jones reagent and the 6,7-dioxo product was immediately converted into 11-acetoxy-6,14-dihydroxy-12-methoxyabieta-5,8,11,13-tetraene (**15**) by repeated column chromatography on silica gel. The tetraene (**15**) was finally hydrolyzed with hydrobromic acid to give coleon U 12-methyl ether.

The isolation and structural elucidation have been reported for many naturally-occurring highly-oxygenated tricyclic diterpenes with a fully substituted aromatic C ring. Some of these also possess the oxygen functions at both the C-6 and C-7 positions in ring B, as depicted in coleon U (**1**) and coleon V (**2**), which were isolated as pigments from leaf-glands of *Plectranthus myrianthus* Briq. (*Labiatae*) by Eugster *et al.*[1] As a part of our synthetic studies on the naturally-occurring diterpenes we attempted to devise an efficient synthetic route for these highly-oxygenated tricyclic diterpenes. This paper will describe a successful synthesis of coleon U 12-methyl ether (**3**), starting from the optically active 11-benzoyloxy-12-methoxyabieta-8,11,13-trien-7-one (**4**) which was previously synthesized[2] from (+)-ferruginol (**5**). Since the total synthesis of (+)-**5** has recently been accomplished in our laboratory,[3] the present work can be regarded as a total synthesis of **3**.

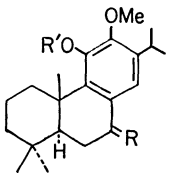


1 R=H
3 R=Me

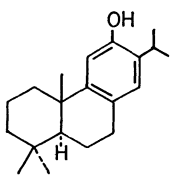


2

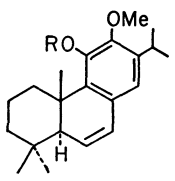
Reduction of the carbonyl group in **4** with sodium borohydride in methanol afforded a mixture of the corresponding epimeric alcohols (**6**), which was immediately dehydrated with *p*-toluenesulfonic acid in refluxing toluene to give 11-benzoyloxy-12-methoxyabieta-6,8,11,13-tetraene (**7**) in nearly quantitative yield. The tetraene (**7**) was then subjected to epoxidation at 0—5 °C with *m*-chloroperbenzoic acid in dichloromethane. The resulting epoxide, without purification, was refluxed with hydrochloric acid in ethanol to produce 11-benzoyloxy-12-methoxyabieta-8,11,13-trien-6-one (**8**), whose IR spectrum showed an absorption band of a newly formed carbonyl group at 1718 cm^{-1}. Treatment of **8** with lithium aluminium hydride in refluxing ether afforded an alcohol (**9**). The *β*-configuration of the hydroxyl group at the C-6 position was supported by its NMR spectrum, which showed a signal at δ 4.51 ppm with a half-height width of 9 Hz, suggesting the presence of an equatorial α hydrogen. To introduce an oxygen function at the C-14 position, **9** was oxidized at room temperature with *m*-chloroperbenzoic acid in dichloromethane; the desired 6*β*-



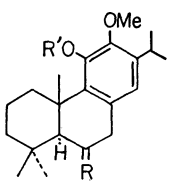
4 R=O, R'=COPh
6 R=H,OH; R'=COPh



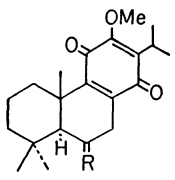
5



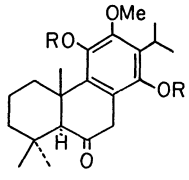
7 R=COPh



8 R=O, R'=COPh
9 R=α-H,β-OH; R'=H

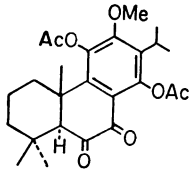


10 R=α-H, β-OH
11 R=O

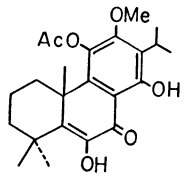


12 R=H
13 R=Ac

hydroxy-12-methoxyabieta-8,12-diene-11,14-dione (**10**) was obtained in 55% yield. The C-14 aromatic proton singlet (δ 6.32 ppm) in **9** disappeared in the NMR spectrum of **10**, while its IR spectrum showed *p*-quinone bands at 1655, 1640, and 1605 cm^{-1}. Oxidation of **10** with Jones reagent at 0—5 °C gave 12-methoxyabieta-8,12-diene-6,11,14-trione (**11**) which, without purification, was used in the next reaction. For the protection of the unstable C ring, the trione (**11**) was reduced with a mixture of zinc powder and dilute hydrochloric acid in refluxing benzene. The resulting crude phenol (**12**) was further acetylated at 75—80 °C with acetic anhydride in pyridine to give 11,14-diacetoxy-12-methoxyabieta-8,11,13-trien-6-one (**13**: 53% yield from **10**). Subsequently, oxidation of the C-7 position in **13** was carried out with Jones reagent at room temperature. The resulting crude 6,7-dioxo compound (**14**) was immediately subjected to repeated column chromatography on silica gel to afford a diosphenol derivative, 11-acetoxy-6,14-dihydroxy-12-methoxyabieta-5,8,11,13-tetraen-7-one (**15**), whose NMR spectrum showed signals due to an acetoxyl group at δ 2.35 ppm, a C-6 hydroxyl group at δ 6.92 ppm, and a hydrogen-bonded C-14 hydroxyl group at δ 13.00 ppm. The acetate (**15**) was finally hydrolyzed at 95—100 °C with hydrobromic acid in acetic acid under a nitrogen atmosphere to afford a phenol (**3**), mp 174—176 °C, $[\alpha]_D$ −12.4° ($CHCl_3$), which was shown to be identical with the authentic coleon U 12-methyl ether by mixed melting point determination and by IR and NMR spectral comparisons.



14



15

Experimental

All melting points are uncorrected. The IR spectra were taken in chloroform, and the NMR spectra in carbon tetrachloride at 60 MHz, with tetramethylsilane as an internal standard, unless otherwise stated. The chemical shifts are presented in terms of δ values; s: singlet, bs: broad singlet, d: doublet, bd: broad doublet, dd: double doublet, m, multiplet. The optical rotations were measured in chloroform using a Yanaco OR-50D. Column chromatography was performed using Merck silica gel (0.063 mm).

11-Benzoyloxy-12-methoxyabieta-6,8,11,13-tetraene (7). Sodium borohydride (650 mg) was added at 15—20 °C to a stirred solution of 11-benzoyloxy-12-methoxyabieta-8,11,13-trien-7-one (**4**)[2] (1.870 g) in methanol (250 ml). The mixture was stirred at this temperature for 4 h, acidified with dilute hydrochloric acid, and concentrated *in vacuo*. The residue was extracted with ether and the ether extract was washed with brine, dried over sodium sulfate, and then evaporated to afford a mixture of the corresponding 7α- and 7β-alcohol (**6**) which, without purification, was used in the next reaction.

The above mixture (**6**) was refluxed for 2 h with *p*-toluenesulfonic acid (250 mg) in dry toluene (12 ml), cooled, and then diluted with ether. The ether solution was washed with aqueous sodium hydrogencarbonate and water, dried over sodium sulfate, and evaporated *in vacuo*. The crude product was purified by column chromatography on silica gel (100 g) using benzene as the eluent to give a tetraene (**7**) (1.760 g: 97.7%), which was recrystallized from acetone-methanol; mp 151.5—152.5 °C, $[\alpha]_D$ −67.8°; IR: 1734 cm^{-1}; NMR: 0.97 and 1.02 (each 3H and s, $-\dot{C}(CH_3)_2$), 1.14 and 1.20 (each 3H, d, and J=6.5 Hz, $-CH(C\underline{H}_3)_2$), 1.30 (3H, s, C_{10}–CH_3), 3.60 (3H, s, $-OCH_3$), 5.87 (1H, dd, J=3 and 9.5 Hz, C_6–H), 6.43 (1H, dd, J=3 and 9.5 Hz, C_7–H), 6.73 (1H, s, C_{14}–H), 7.3—7.7 (3H, m) and 8.0—8.3 (2H, m) (aromatic protons). Found: C, 80.48; H, 8.16%. Calcd for $C_{28}H_{34}O_3$: C, 80.34; H, 8.19%.

11-Benzoyloxy-12-methoxyabieta-8,11,13-trien-6-one (8). A solution of **7** (1.760 g) and *m*-chloroperbenzoic acid (70%: 1.14 g) in dichloromethane (20 ml) was allowed to stand at 0—5 °C for 45 min. The solution was diluted with ether and then washed successively with aqueous potassium iodide, aqueous sodium thiosulfate, aqueous sodium hydrogencarbonate, and water. After drying over sodium sulfate, the solution was evaporated *in vacuo* to give a crude epoxide which was immediately subjected to the next reaction.

A solution of the above epoxide and concentrated hydrochloric acid (2.0 ml) in ethanol (40 ml) was refluxed for 1.5 h. After the solution had been concentrated *in vacuo*, the residue was extracted with ether. The ether extract was washed with aqueous sodium hydrogencarbonate and brine, dried over sodium sulfate, and then evaporated *in vacuo*. The crude product was recrystallized from ethanol to give a ketone (**8**) (580 mg: 31.8%); mp 182—184 °C; $[\alpha]_D$ +105°; IR: 1735; 1718 cm^{-1}; NMR: 1.05 and 1.31 (each 3H and s, $-\dot{C}(CH_3)_2$), 1.25 (6H, bd, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.31 (3H, bs, C_{10}–CH_3), 2.50 and 2.68 (each *ca.* 0.5H and bs, C_5–H),[4] 3.57 and 3.65 (each *ca.* 2.5H and bs, $-COCH_2-$ and $-OCH_3$),[4] 6.79 (1H, s, C_{14}–H), 7.45—7.7 (3H, m) and 8.05—8.35 (2H, m) (aromatic protons). Found: C, 77.29; H, 7.87%. Calcd for $C_{28}H_{34}O_4$: C, 77.39; H, 7.89%.

The mother liquor of the above crystallization was evaporated *in vacuo* and the residue was chromatographed on silica gel (80 g) using ether–benzene (1 : 99) as the eluent to give additional **8** (485 mg: 26.6%).

12-Methoxyabieta-8,11,13,-triene-6β,11-diol (9). A mixture of **8** (1.460 g), lithium aluminium hydride (380 mg), and dry ether (50 ml) was refluxed for 1.5 h. The mixture was poured into a mixture of ice and aqueous ammonium chloride, and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (20 g), using ether–benzene (3:97) as the eluent, to give an alcohol (**9**) (908 mg: 80.8%), which was recrystallized from hexane; mp 157.5—158.5 °C; $[\alpha]_D$ +34.8°; IR: 3520, 3410 cm^{-1}; NMR: 1.03 and 1.27 (each 3H and s, $-\dot{C}(CH_3)_2$), 1.19 and 1.21 (each 3H, d, and J=7 Hz, $-CH-(C\underline{H}_3)_2$), 1.65 (3H, s, C_{10}–CH_3), 3.72 (3H, s, $-OCH_3$), 4.51 (1H, m, $W_{1/2}$=9 Hz, C_6–H), 5.92 (1H, s, C_{11}–OH), 6.32 (1H, s, C_{14}–H). Found: C, 75.84; H, 9.73%. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70%.

6β-Hydroxy-12-methoxyabieta-8,12-diene-11,14-dione (10). A solution of **9** (386 mg) and *m*-chloroperbenzoic acid (80%: 429 mg) in dichloromethane (10 ml) was allowed to stand at room temperature for 30 h, and then diluted with ether. The solution was washed successively with aqueous potassium iodide, aqueous sodium thiosulfate, aqueous sodium hydrogencarbonate, and brine. After drying over

sodium sulfate, the solution was evaporated *in vacuo* and the crude product was purified by column chromatography on silica gel (40 g), using ether–benzene (2:98) as the eluent, to give the recovered **9** (64 mg: 16.6%) and a quinone compound (**10**) (222 mg: 55.2%) which was recrystallized from methanol; mp 212—214 °C; $[\alpha]_D$ −51.9°; IR 3625, 3525, 1655, 1640, 1605 cm^{-1}; NMR ($CDCl_3$): 1.02 and 1.26 (each 3H and s, $-\dot{C}(CH_3)_2$), 1.21 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.69 (3H, s, $C_{10}-CH_3$), 3.90 (3H, s, $-OCH_3$), 4.67 (1H, m, $W_{1/2}$=9 Hz, C_6–H). Found: C, 72.81; H, 8.75%. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73%.

*11,14-Diacetoxy-12-methoxyabieta-8,11,13-trien-6-one (**13**).* A solution of **10** (495 mg) in acetone (20 ml) was oxidized with Jones reagent (2.67 mol dm^{-3}: 0.75 ml) at 0—5 °C for 5 min and then diluted with ether. The solution was washed with brine, dried over sodium sulfate, and evaporated *in vacuo* to give a crude 6-oxo compound (**11**); IR: 1720, 1655, 1640, 1605 cm^{-1}.

The above crude compound (**11**) was dissolved in benzene (12 ml) and the solution was stirred and refluxed for 10 min with a mixture of zinc powder (1.2 g) and dilute hydrochloric acid (10%: 12 ml). After cooling, the mixture was extracted with ether and the extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo* to give a crude phenol (**12**).

The crude phenol (**12**) was immediately acetylated at 75—80 °C for 1.5 h with acetic anhydride (1.0 ml) and pyridine (2.0 ml). After the usual work-up, the product was purified by column chromatography on silica gel (30 g), using ether–benzene (5:95) as the eluent, to give a diacetate (**13**) (327 mg: 53%) which was recrystallized from methanol; mp 183.5—185 °C; $[\alpha]_D$ +130°; IR: 1765, 1720 cm^{-1}; NMR ($CDCl_3$): 1.02 and 1.22 (each 3H and s, $-\dot{C}(CH_3)_2$), 1.29 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.36 (3H, s, $C_{10}-CH_3$), 2.34 (6H, s, 2-$OCOCH_3$), 2.65 (1H, bs, C_5–H), 3.25(2H, bs, $-COCH_2-$), 3.74 (3H, s, $-OCH_3$). Found: C, 69.79; H, 8.06%. Calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96%.

*11-Acetoxy-6,14-dihydroxy-12-methoxyabieta-5,8,11,13-tetraen-7-one (**15**).* A solution of **13** (372 mg) in acetone (6.0 ml) was oxidized with Jones reagent (2.67 mol dm^{-3}: 0.6 ml) at room temperature for 2 h. After the same work-up as described for the preparation of **11**, the crude 6,7-dioxo compound (**14**) was purified by repeated column chromatography (3 times) on silica gel, using hexane–chloroform (3:7) as the eluent, to give a diosphenol derivative (**15**) (129 mg: 37.2%) which was recrystallized from methanol; mp 145—146 °C; $[\alpha]_D$ +17.9°; IR: 3410, 3160, 1765, 1640, 1615, 1595 cm^{-1}; NMR ($CDCl_3$): 1.44 (9H, s, $-\dot{C}(CH_3)_2$ and $C_{10}-CH_3$), 1.38 (6H, bd, J=7 Hz, $-CH(C\underline{H}_3)_2$), 2.35 (3H, s, $-OCOCH_3$), 3.73 (3H, s, $-OCH_3$), 6.92 (1H, s, C_6–OH), 13.00 (1H, s, C_{14}–OH). Found: C, 68.66; H, 7.61%. Calcd for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51%. Further elution gave the recovered **13** (176 mg: 47.4%).

*Coleon U 12-Methyl Ether (6,11,14-Trihydroxy-12-methoxyabieta-5,8,11,13-tetraen-7-one) (**3**).* A mixture of **15** (157 mg), 47% hydrobromic acid (0.5 ml), and acetic acid (4.0 ml) was heated at 95—100 °C for 1 h in a stream of nitrogen. The reaction mixture was cooled, diluted with ether, and then washed successively with water, aqueous sodium hydrogencarbonate, and brine. The dried solution was evaporated *in vacuo* and the residue was purified by column chromatography on silica gel (15 g) using hexane–chloroform (1 : 1) to give coleon U 12-methyl ether (**3**) (40 mg: 28.3%), which was recrystallized from hexane; mp 174—176 °C dec; $[\alpha]_D$ −12.4°; IR: 3520, 3410, 1642, 1617, 1598 cm^{-1}; NMR ($CDCl_3$); 1.40 and 1.42 (each 3H, d, and J=7 Hz, $-CH(C\underline{H}_3)_2$) 1.44 (6H, s, $-\dot{C}(CH_3)_2$), 1.65 (3H, s, $C_{10}-CH_3$), 3.79 (3H, s, $-OCH_3$), 5.74 (1H, s, C_{11}–OH), 6.93 (1H, s, C_6–OH), 12.57 (1H, s, C_{14}–OH). Found: C, 70.04; H, 7.94%. Calcd for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83%. The identity of the synthetic sample (**3**) with natural coleon U 12-methyl ether was confirmed by mixed melting point determination and by IR and NMR spectral comparisons.

Further elution gave the recovered **15** (62 mg: 39.4%).

The authors are grateful to Arakawa Chemical Co. Ltd. for a generous gift of rosin. Thanks are also due to Professor C. H. Eugster for kindly supplying the natural sample.

References

1) T. Miyase, P. Ruedi, and C. H. Eugster, *Helv. Chim. Acta*, **60**, 2770 (1977).

2) T. Matsumoto and S. Harada, *Chem. Lett.*, **1976**, 1311, *Bull. Chem. Soc. Jpn.*, **52**, 1459 (1979).

3) T. Matsumoto and S. Usui, *Bull. Chem. Soc. Jpn.*, **52**, 212 (1979).

4) These signals arose from rotational isomers due to a methoxyl group, whose free rotation was restricted by two bulky ortho substituents: benzoyloxyl and isopropyl groups.