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TERPENOIDS—XCIV

SYNTHESIS OF NOVEL LONGIFOLANE DERIVATIVES VIA OXIDATION WITH LEAD TETRAACETATE*

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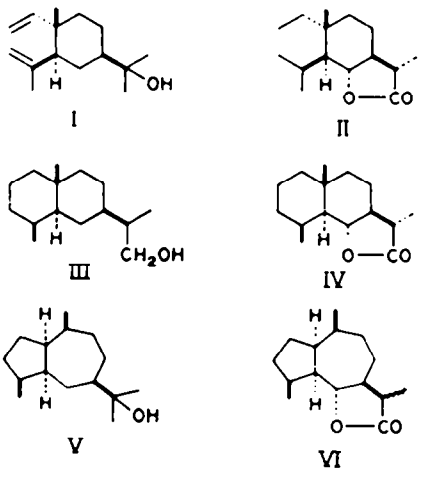
Abstract—Oxidation with lead tetraacetate has been found to be a useful tool for the syntheses of novel type of longifolane derivatives without ring re-arrangement. Isolongifolol (VIII) on treatment with lead tetraacetate in benzene solution is converted to isolongifolanoxide (IX), further oxidation of which with chromic acid yields isolongifolanolide (X). The structure of this lactone is consistent with the spectral data and the Hudson-Klyne lactone rule. The structure has been rigorously confirmed by converting it by a series of reactions to isolongifolane diol (XIII), keto-isolongifolic acid (XIV), keto-isolongifolol (XVI), isolongifolanol (XVII), and isolongifolanone (XVIII). Most of the key compounds are crystalline.

OXIDATION of aliphatic alcohols with lead tetraacetate has been investigated by Micovic *et al.*[1] and its use in the bicyclic bridge systems by Akio Matshura.[2] This oxidation, in the case of terpenic[4,5] and non-terpenic alcohols,[3] lead to the conversion of I, III and V to the lactones II, IV and VI respectively.

CHART-1



* Communication No. 926 from the National Chemical Laboratory, Poona-8, India.

[1] V. M. Micovic, R. I. Mamuzic, D. Jeremic and M. Mihailovic, *Tetrahedron* **20**, 2279 (1964); G. Cainelli, B. Kamber, J. Keller, M. Lj. Mihalovic, D. Arigoni and O. Jeger, *Helv. Chim. Acta* **44**, 518 (1961); A. Bowers, E. Denot, L. C. Ibanez, M. E. Cabezas and H. J. Ringold, *J. Org. Chem.* **27**, 1862 (1962).

[2] K. Kitahanaki and A. Matsuura, *Tetrahedron Letters* No. 33, 2263 (1964).

[3] S. G. Patnekar, H. H. Mathur and S. C. Bhattacharyya, *Indian. J. Chem.* in press.

[4] A. D. Wagh, S. K. Paknikar and S. C. Bhattacharyya, *Tetrahedron* **20**, 2647 (1964).

[5] M. V. Kadival, M. S. R. Nair, unpublished data to be communicated.

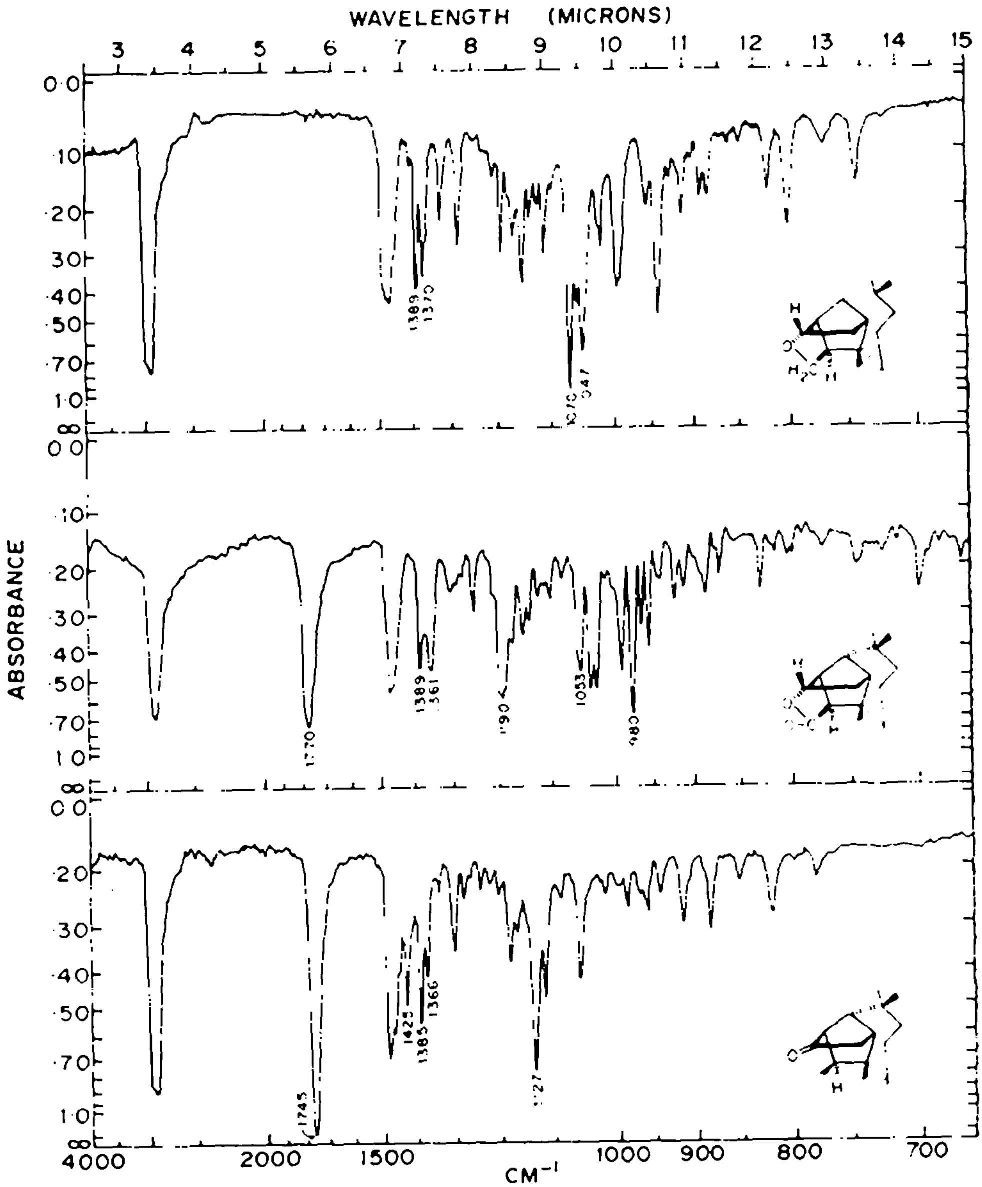

WAVELENGTH (MICRONS)
3 4 5 6 7 8 9 10 11 12 13 14 15
ABSORBANCE
0·0 ·10 ·20 ·30 ·40 ·50 ·70 1·0 ∞
1389
1370
1010
947
1389
1361
1904
1053
980
1770
1425
1385
1366
1127
1745
4000 2000 1500 1000 900 800 700
CM⁻¹

FIG. 1

This reaction is convenient for introducing a reactive function into an inaccessible part of an otherwise stable, saturated molecule. We have, therefore, extended it to saturated compounds of the longifolene series and the results are communicated in this paper. Most of the reactions of longifolene (VII), many similar to those of camphene, which have been investigated[6,7] involve rearrangement of the molecule.

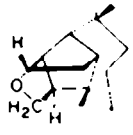
Our object was to prepare longifolene derivatives without rearrangement via oxidation with lead tetraacetate and to study their subsequent reactions. The stable crystalline alcohol, isolongifolol (VIII) was used as the starting material.[8]

Longifolene was oxidized according to the method of Dev *et al.*[9] The pure methyl ester, m.p. 53–54°, on reduction with LAH yielded pure isolongifolol (VIII), m.p. 111–112°, $[\alpha]_D^{25}$ −49·9°. On refluxing with lead tetraacetate in benzene solution for 24 hr; the alcohol afforded in 30% yield, an oxide, isolongifolanoxide (IX), which on the basis of GLC–TLC analyses was a single compound. On oxidation with chromic acid in acetic acid, it is converted into a crystalline γ-lactone, isolongifolanolide (X; 1770 cm^{-1}; Fig. 1) in about 60% yield. There are three possible structures (X, XI, XII) for the lactone and similarly for the corresponding oxide, depending on whether the oxide formation involves C_8, C_{13} or C_4. The possibility of attachment to C_{13} is ruled out from the NMR spectra of the oxide and the lactone (Fig. 2), which clearly

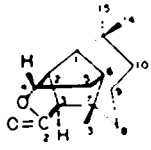
CHART - 2

VII

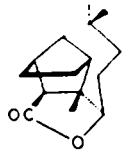
VIII



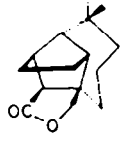
IX



X



XI



XII

[6] P. Naffa and G. Ourisson, *Bull. Soc. Chim. Fr.* 1115 (1954); J. Lhomme and G. Ourisson, *Ibid.* 1888 (1964).

[7] E. J. Corey, M. Ohno, R. B. Mitra and P. A. Vatakencherry, *J. Amer. Chem. Soc.* **86**, 478 (1964); J. R. Prahlad, R. Ranganathan, U. R. Nayak, T. S. Santhanakrishnan and Sukh Dev, *Tetrahedron Letters* 417 (1964).

[8] H. H. Zeiss and M. Arakawa, *J. Amer. Chem. Soc.* **76**, 1653 (1954).

[9] U. R. Nayak and Sukh Dev, *Tetrahedron* **19**, 2293 (1963).

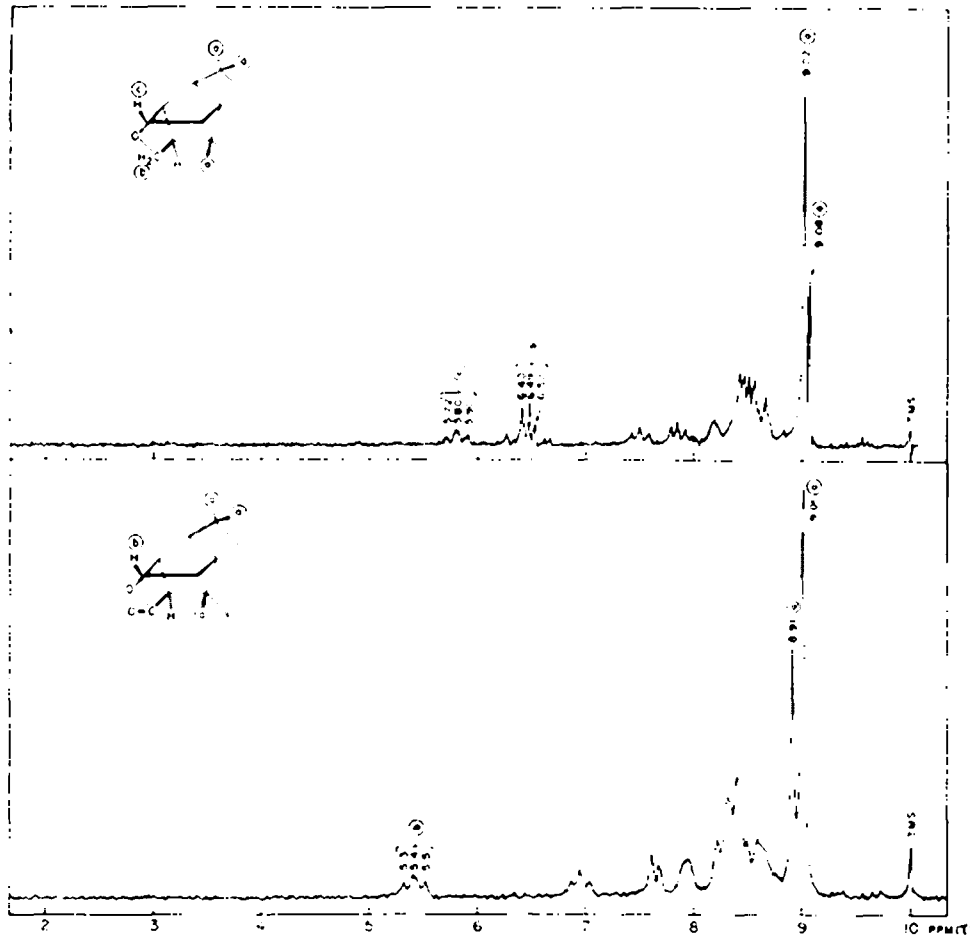


FIG. 2

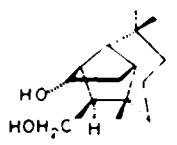
show the presence of all three methyl groups, originally present in the molecule of the parent alcohol, isolongifolol.

The triplet at 5·39 τ for the proton at C_4 does not give sufficient support for the structure X and, therefore, unambiguous chemical evidence was desirable. On reduction with LAH the lactone gave a crystalline diol, isolongifolane diol (XIII), which on oxidation with Jones' reagent[10] was converted into a keto-carboxylic acid, keto-isolongifolic acid (XIV), the methyl ester of which on reduction with LAH via its ketal (XV) and hydrolysis, was converted into the keto-alcohol, keto-isolongifolol (XVI), showing clear IR absorption at 1740 cm^{-1} for the cyclopentanone derivative. The alternative structure XI would have lead to the formation of a cycloheptanone derivative (1700 cm^{-1}). Finally, controlled LAH reduction of the lactone X, followed by Huang-Minlon reduction of the resulting product, according to the procedure previously used,[11] gave a crystalline secondary alcohol, isolongifolanol (XVII), which

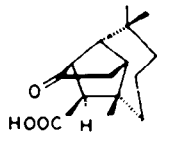
[10] A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, *J. Chem. Soc.* 2555 (1953).
[11] A. M. Shaligram, A. S. Rao and S. C. Bhattacharayya, *Tetrahedron* **18**, 969 (1962).

on further oxidation was converted to a pure cyclopentanone derivative, isolongifolanone (XVIII) with characteristic IR band at 1745 cm^{-1} (Fig. 1). In this type of ring closure the *trans*-formation is always favoured. This is supported by the NMR data and further confirmed by the application of the Hudson-Klyne lactone[12] rule. The molecular rotation difference between the lactone (X) and the diol (XIII) is +145·73, which is in agreement with the expected values.

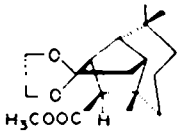
CHART - 3



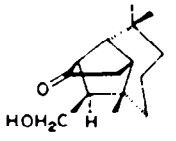
XIII



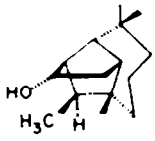
XIV



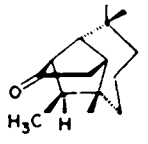
XV



XVI



XVII



XVIII

EXPERIMENTAL

All m.ps and b.ps are uncorrected. Rotations: chf solns unless otherwise stated. IR spectra: solids in nujol and liquids as liquid films were recorded on the Perkin-Elmer Infracord spectrophotometer, Model 137 E by Miss Shitole.

NMR spectra: CCl_4 solns using TMS as internal reference by Dr. P. M. Nair *et al.* Microanalyses: Mr. Pansare *et al.* GLC analyses; Dr. Ghatge *et al.* on a Griffin and George apparatus (MKII-A model), on polyester columns, using H as the carrier gas.

Oxidation of longifolene (VII) *with chromic acid.* A soln of chromic acid (1 kg) in water (600 ml, and conc. H_2SO_4 (40 ml) was added dropwise to a stirred soln of VII (500 g) in glacial AcOH (2 l.)) the temp being maintained at 45°. After addition (2 hr), the contents was heated on a water-bath for 1 hr, diluted with water (5 l.), extracted with benzene (300 ml × 5) and finally twice with ether. The combined extracts were washed with 10% NaOHaq (200 ml × 3) to separate the acidic portion. The alkaline extract on acidification gave the crude epimeric acid mixture (180 g).

A mixture of the crude acid (180 g), MeOH (360 ml), benzene (600 ml) and conc. H_2SO_4 (50 ml) was refluxed azeotropically for 72 hr. The reaction product was vac. distilled, b.p. 140–155°/0·1 mm n_D^{30} 1·4930. The distillate (200 g) was chilled in a deep freeze after adding pet. ether (50 ml). The solid ester, methyl isolongifolate (50 g) was filtered and crystallized from pet. ether to give the pure (GLC/TLC) ester, m.p. 53–54°; $[\alpha]_D$ −11·9° (*c*, 2·52); ν_{max} 2959; 1724 (ester CO); 1453, 1429; 1372 and 1351 (*gem*-dimethyl); 1302, 1282, 1258, 1241, 1224, 1189, 1168, 1112, 1063, 1031, 1011, 996, 981, 971, 952, 927, 901, 885, 870, 848, 817, 806 and 766 cm^{-1}. (Found: C, 77·11; H, 10·60. $C_{16}H_{26}O_2$ requires: C, 76·8; H, 10·4%.)

[12] W. Klyne, *Chem. and Ind.* 1198 (1954).

LAH reduction of methyl isolongifolate. A soln of methyl isolongifolate (50 g) in ether (150 ml) was added dropwise during 1 hr to a stirred soln of LAH (10 g) in dry ether (150 ml) under ice cold conditions. The reaction mixture was refluxed for 6 hr and finally yielded VIII (45 g), which was crystallized from pet. ether to give the pure isolongifolol as needle-shaped crystals, m.p. 111–112°; $[\alpha]_D^{25}$ −49·9° (*c*, 2·81); ν_{max} 3145, 2899, 1471, 1389, 1370, 1307, 1282, 1227, 1183, 1163, 1124, 1081, 1059, 1037, 1015, 1001, 986, 949 and 885 cm^{-1}. (Found: C, 81·23; H, 11·9. $C_{15}H_{26}O$ requires: C, 81·02; H, 11·79%.)

Lead tetraacetate oxidation of isolongifolol (VIII). A mixture of isolongifolol (50 g), freshly prepared lead tetraacetate (110 g) and benzene (300 ml) was refluxed on a water-bath for 24 hr under N atmosphere and mechanical stirring. The lead salt was filtered off and the benzene layer washed free of acid. The reaction product (50 g), after removal of benzene, was saponified with KOH (25 g) in MeOH (200 ml), for 2 hr, diluted with water, acidified and extracted with ether. The ether layer was washed free of acid and dried over Na_2SO_4. Removal of ether gave the product (45 g), which was found to be a mixture of IX and VIII. This was chromatographed over alumina grade II (1 kg) and eluted with pet. ether (2 l.) to isolate IX (14 g) and finally with MeOH to recover the unreacted alcohol (26 g). The oxide on vacuum distillation gave the pure (GLC/TLC) oxide, b.p. 120° (bath)/0·2 mm, n_D^{26} 1·5100; $[\phi]_D^{25}$ −32·37° (*c*, 2·4); ν_{max} 2941, 1471, 1408; 1389 and 1370 (*gem* dimethyl); 1325, 1282, 1193, 1163, 1149, 1136, 1124; 1105 and 1070 (tertahydrofuran moiety); 1047, 1020, 999, 952, 943, 912, 892, 882, 821, 801, 770 and 745 cm^{-1} (Fig. 1). NMR signals: a triplet at 5·8 τ due to a proton α- to the oxygen function ('c' in Fig. 2); a triplet at 6·49 τ due to two protons at α'-position ('b' in Fig. 2) and signals at 9·02 and 9·08 τ due to three methyl groups ('a' in Fig. 2). (Found: C, 82·08; H, 11·04. $C_{15}H_{24}O$ requires: C, 81·76; H, 10·98%.)

Chromic acid oxidation of the oxide to the lactone isolongifolanolide (X). To a soln of the oxide (5 g) in glacial AcOH (100 ml) a soln of chromic acid (5 g) in AcOH (90%; 100 ml) was added slowly and the mixture heated on a water bath for ½ hr. Water (200 ml) was added and the mixture extracted with ether. The ether layer was washed free of acid and dried over Na_2SO_4. Removal of ether gave the mixture of the unreacted oxide and the lactone. This mixture (5 g) was saponified by refluxing with KOH (4 g) in MeOH (10 ml) for 3 hr. The mixture was diluted with water and extracted with ether thrice to remove the unreacted oxide (1·82 g). The aqueous portion after acidification with dil HCl, was warmed on a water bath for 10 min and then extracted with ether. The ether layer was washed free of acid with 10% Na_2CO_3aq and dried over Na_2SO_4. Removal of ether gave a solid (2·77 g), which on crystallization gave the pure (TLC) crystalline lactone, X, m.p. 60–61°, $[\alpha]_D^{20}$ +37·84° (*c*, 4·18), M_D +88·67°. ν_{max} 2899, 1770 (γ-lactone); 1471, 1389 and 1361 (*gem*-dimethyl); 1307, 1252, 1190, 1176, 1152, 1143, 1124, 1111, 1099, 1083, 1053, 1037, 1028, 995, 980, 967, 957, 943, 922, 912, 888, 870, 830, 817, 806, 800, 772, 746, and 699 cm^{-1} (Fig. 1).

NMR signals: a triplet at 5·4 τ due to a proton α- to oxygen atom ('b' in Fig. 2); and signals at 9·02 and 8·91 τ due to three methyl groups (9H; 'a' in Fig. 2). (Found: C, 76·65; H, 9·54. $C_{15}H_{22}O_2$ requires: C, 76·88; H, 9·46%.)

LAH reduction of the lactone to isolongifolanediol (XIII). The lactone X (3 g) in ether (25 ml) was added dropwise to a soln of LAH (2·5 g) in ether (25 ml) under stirring, and then refluxed for 6 hr. The reaction product was crystallized from pet. ether to give XIII (2·5 g), m.p. 88–89°; $[\alpha]_D^{24}$ −23·94° (*c*, 5·01), M_D −57·06 ν_{max} 3268 (two hydroxyls); 2941, 2874, 1471, 1462; 1383 and 1370 (*gem*-dimethyls); 1355, 1311, 1282, 1276, 1241, 1214, 1190, 1176, 1157, 1134, 1099, 1071, 1042, 1016, 1000, 961, 943, 882, 850, 841 and 817 cm^{-1}. (Found C, 75·50; H, 11·2. $C_{15}H_{26}O_2$ requires: C, 75·58; H, 11·00%.)

Chromic acid oxidation of the longifolane diol (XIII). The diol (1 g) was dissolved in acetone (20 ml) and Jones' reagent was added dropwise during 5 min till brown colour persisted. It was kept at the room temp for 1 hr and gave the keto acid, XIV (0·8 g), which was further purified by crystallization from pet. ether–ether; m.p. 185–186° $[\alpha]_D^{25}$ +60·56° (*c*, 2·84, pyridine).

ν_{max} 3268 (hydroxyl of acid), 2941, 2899, 1739 (>CO of cyclopentanone merged with acid >CO); 1471, 1389, 1370, 1333, 1299, 1274, 1258, 1230, 1212, 1198, 1183, 1167, 1143, 1117, 1105, 1058, 1026, 995, 968, 948, 930, 910, 892, 818, 858, 850, 827, 818, 780 and 730 cm^{-1}. (Found: C, 71·81; H, 9·11. $C_{15}H_{24}O_3$ requires: C, 71·97; H, 8·86%); semicarbazone m.p. 223–224°. (Found: N, 12·99. $C_{16}H_{27}N_3O_3$ requires: N, 13·6%.)

This keto acid (XIV, 1 g) was esterified with diazomethane to give the keto ester (0·75 g). m.p. 68–69°; $[\alpha]_D^{24}$ +102·4° (*c*, 4·87).

ν_{max} 2857; 1748 (ester carbonyl and >CO of cyclopentanone); 1460, 1449, 1379, 1344, 1307, 1277, 1263, 1229, 1208, 1183, 1163, 1134, 1107, 1042, 1020, 1005, 995, 935, 909, 893, 829, 800, 767 and 746 cm^{-1}. (Found: C, 73·24; H, 9·32. $C_{16}H_{24}O_3$ requires: C, 72·69; H, 9·15%.)

Preparation of the ketal-ester (XV). A mixture of the keto ester (0·7 g), ethylene glycol (15 ml), *p*-toluenesulphonic acid (0·5 g), and benzene (300 ml) was refluxed azetropically on a water bath for 50 hr with mechanical stirring. Benzene was removed and the product, a crude mixture (0·7 g) was chromatographed over alumina grade I (5 g). The pet. ether benzene and benzene fractions gave the pure (TLC) XV (0·51 g), b.p. 170° (bath)/0·2 mm; $[\alpha]_D^{25}$ −72·90° (*c*, 7·13); ν_{max} 2941; 1754 (ester CO); 1488, 1460, 1418, 1399, 1379, 1339, 1316, 1282, 1258, 1235, 1212, 1205, 1190, 1176, 1143, 1111, 1093, 1064, 1032, 990, 979, 960, 938, 925, 903, 870, 858, 819, 806, 782 and 709 cm^{-1}. (Found; C, 70·60; H, 9·16. $C_{18}H_{28}O_4$ requires: C, 70·12; H, 9·15%.)

LAH reduction of the ketal-ester XV *and its conversion to the keto alcohol* (XVI). The ketal-ester XV (0·3 g) was reduced with excess of LAH (0·5 g) in dry ether (25 ml) to give the crude ketal alcohol (0·3 g). This, in acetone (10 ml) was refluxed on a water bath, after adding 20% H_2SO_4 (10 ml) for 4 hr. Water was added and the mixture extracted with ether. The ether layer was washed free of acid and dried over Na_2SO_4. Removal of ether gave a crude keto alcohol, which was passed on alumina grade II (5 g) and eluted with benzene to give the pure XVI (0·050 g) b.p. 170° (bath)/0·1 mm. ν_{max} 3448 (hydroxyl); 2941, 2899, 1742 (>CO in cyclopentanone); 1466; 1381 and 1370(*gem*-dimethyl); 1319, 1305, 1285, 1225, 1199, 1182, 1163, 1134, 1116, 1101, 1046, 1036, 1014, 985, 961, 932, 922, 894, 840 and 804 cm^{-1}. (Found: C, 75·5; H, 11·20; $C_{16}H_{26}O_3$ requires: C, 75·63; H, 10·92%.)

Controlled LAH reduction of isolongifolanolide (X) *and Huang-Minlon reduction of the reaction product*. The lactone X (1·5 g) was reduced by gradual addition of an ethereal solution of LAH (15 ml; 1 g of 65% purity in 100 ml) under cooling (−4°). The reaction mixture was stirred for 3 hr at 0° and for another 3 hr at the room temp. It was then worked up as usual after decomposing with water. The reaction product (1·5 g) was immediately reduced.

A mixture of the product (1·5 g), diethylene glycol (25 ml), KOH (4 g) and hydrazine hydrate (10 ml; 100%) were kept at 170° for 5 hr under N_2-atmosphere. After diluting with water, the resulting mixture of monol and diol was chromatographed over alumina grade II (20 g) and eluted with benzene (200 ml) to give the TLC pure XVII, which on crystallization from pet. ether gave shining flakes (0·8 g); m.p. 166–167°; $[\alpha]_D^{25}$ −33·56° (*c*, 2·98); ν_{max} 3236 (hydroxyl); 2933, 1471, 1389, 1351, 1333, 1318, 1299, 1282, 1250, 1235, 1220, 1183, 1156, 1130, 1111, 1095, 1081, 1042, 992, 988, 960, 932, 910, 890, 871, 850, 825, 804 and 785 cm^{-1}. (Found: C, 81·08; H, 11·92. $C_{15}H_{26}O$ requires: C, 81·02; H, 11·79%.)

Chromic acid oxidation of the monol (XVII) *to the ketone isolongifolanone* (XVIII). Monol (0·184 g) was dissolved in acetone (10 ml) and Jones' reagent was added dropwise to it till the brown colour persisted. The mixture was allowed to stand at the room temp for 1 hr and then after diluting with water (20 ml) gave pure (GLC) XVIII (0·150 g), b.p. 125° (bath)/0·03 mm; n_D^{25} 1·4590; $[\alpha]_D^{25}$ 0°; ν_{max} 2941; 1745 (CO in cyclopentanone); 1471, 1456, 1441; 1425 (—CH_2—CO); 1383 and 1363 (*gem*-dimethyl); 1337, 1299, 1276, 1256, 1238, 1214, 1196, 1172, 1157, 1127, 1109, 1083, 1060, 1012, 997, 978, 961, 952, 931, 909, 877, 846, 814 and 773 cm^{-1} (Fig. 1). (Found: C, 81·66, H, 10·72. $C_{15}H_{24}O$ requires: C, 81·76; H, 10·98%.) Semicarbazone, m.p. 237–238° (dec). (Found: N, 14·88; $C_{16}H_{27}N_3O$ requires: N, 15·15%.)