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SYNTHESES IN THE TERPENE FIELD—XIII[1]

A NEW ROUTE TO A KEY INTERMEDIATE IN THE TOTAL SYNTHESIS OF α-ONOCERIN

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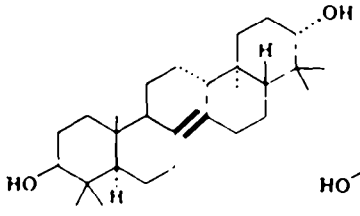
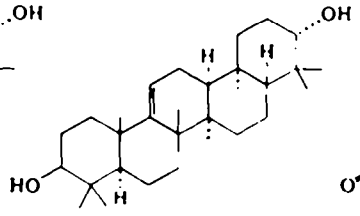
Abstract—6β-Hydroxy-2-keto-5,5,9-trimethyl-*trans*-decal-1β-ylacetic acid (XIIa) is an important intermediate in the synthesis of α-onocerin (I) by Stork *et al.* A new and convenient synthesis of XIIa is described proceeding in 8 steps from 1β-hydroxy-5,5,9-trimethyl-Δ⁴-octal-6-one benzoate (IVa). The key reactions are the selenium dioxide oxidation of the αβ-unsaturated ester Xb to the αβ-unsaturated γ-lactone XI, and the direct conversion of XI to XIIa with sodium hydroxide.

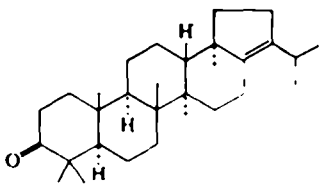
THE symmetrical tetracyclic triterpene α-onocerin (I) has been synthesized by Stork *et al.*[2] This triterpene had been converted to γ-onocerin (II)[3] and hence to hopenone-I (III),[4] a dehydration product of the natural pentacyclic triterpene hydroxyhopanone.[5]



I



II



III

The synthesis of α-onocerin therefore leads further to these pentacyclic triterpene systems.

The racemic hydroxy-keto acid XIIa is a key intermediate in Stork's synthesis of α-onocerin, and can be converted to the natural triterpene by successive resolution, electrolytic coupling, and transformation of the carbonyl to methylene groupings.[2] Stork *et al.* prepared the racemic acid XIIa by a 17-step sequence from β-naphthol methyl ether.[2,6] We now report the details of a completely different synthesis of racemic XIIa,[7] which involves 15 steps from resorcinol. A synthesis of racemic XIIa has also been carried out by Church *et al.*[8] (utilizing the same intermediate IVa[9]

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[1] For Part XII, see E. Ghera and F. Sondheimer, *Tetrahedron Letters* 3887 (1964).

[2] G. Stork, J. E. Davies and A. Meisels, *J. Amer. Chem. Soc.* **81**, 5516 (1959); G. Stork, A. Meisels and J. E. Davies, *Ibid.* **85**, 3419 (1963).

[3] D. H. R. Barton and K. H. Overton, *J. Chem. Soc.* 2639 (1955).

[4] K. Schaffner, L. Caglioti, D. Arigoni and O. Jeger, *Helv. Chim. Acta* **41**, 152 (1958).

[5] H. Fazakerley, T. G. Halsall and E. R. H. Jones, *J. Chem. Soc.* 1877 (1959).

[6] G. Stork, *J. Amer. Chem. Soc.* **69**, 576 (1947).

[7] For a preliminary communication, see N. Danieli, Y. Mazur and F. Sondheimer, *Tetrahedron Letters* 310 (1961).

[8] R. F. Church, R. E. Ireland and J. A. Marshall, *Tetrahedron Letters* 34 (1961); *J. Org. Chem.* **27**, 1118 (1962).

[9] F. Sondheimer and D. Elad, *J. Amer. Chem. Soc.* **79**, 5542 (1957).

employed by us), but the route was considerably less direct than either of the others.

Our starting material was the unsaturated keto-benzoate IVa (obtainable in 7 steps from resorcinol),[9,10] which was saponified to the corresponding hydroxy-ketone IVb.[11,12] It has been shown previously that the catalytic hydrogenation of IVb in alcohol over a Pd–C catalyst leads mainly to the saturated hydroxy-ketone VIIa.[12] We have now found that when this reaction is carried out in acetic acid over Pt, the saturated diol V(m.p. 180–182°) is formed in 85% yield. Partial oxidation of this substance with ca. 1·1 equivalents of chromium trioxide in pyridine at room temperature gave the required hydroxy-ketone VIa[12,13] (m.p. 72–74°) in 44% yield (based on unrecovered diol V), in addition to 38% of the ketol VIIa[12] (m.p. 63–65°), a small amount of the diketone VIII (m.p. 80–82°), and unchanged diol V. The unwanted oxidation products VIIa and VIII could be reconverted to the diol V in high yield by reduction with LAH, and the yield of VIa based on unrecovered V was thereby brought to ca. 80%. The present three-step method for transforming IVa to VIa is considerably simpler than the previously described one,[12] proceeding via the ketol VIIa.

The next objective was the preparation of the $\alpha\beta$-unsaturated ester Xb. This substance [m.p. 85–86° and 99–100°, polymorphic forms; UV max at 221 mμ (ε 13,400)] was obtained readily in 54% yield from VIa by reaction with lithium ethoxyacetylide to give the ethoxyacetylenic carbinol IX, rearrangement with 5% sulphuric acid in aqueous methanol at room temperature,[14] and acetylation. The stereochemistry of Xb was not determined, although the double bond in this substance most likely possesses the configuration with the hydrogen substituent on the side of the angular methyl group.

The necessary additional oxygen function at C-2 was now introduced simply by allylic oxidation of Xb with selenium dioxide in boiling acetic acid, whereby the $\alpha\beta$-unsaturated γ-lactone XI (m.p. 129–130°) was obtained in 76% yield. The spectral properties of this substance [UV max at 215 mμ (ε 11,900);[15] IR band at 1757 cm^{-1} ($\alpha\beta$-unsatd γ-lactone)[16]] are in accord with the assigned structure. The stereochemistry at C-2 was not definitely established, but the α-configuration for the 2-oxygen group is assumed since the introduction of oxygen with selenium dioxide appears to occur from the less hindered side.[17]

Finally, the lactone XI could be converted directly to the required keto acid XIIa in 55% yield by means of 20% sodium hydroxide in boiling aqueous ethylene glycol. The resulting XIIa (m.p. 185–186°) was identified by direct comparison with an authentic sample, prepared by Stork *et al.*[2] Similarly, the methyl ester XIIb (m.p.

[10] S. Swaminathan and M. S. Newman, *Tetrahedron* **2**, 88 (1958).

[11] J. D. Cocker and T. G. Halsall, *J. Chem. Soc*, 3441 (1957).

[12] F. Sondheimer and D. Elad, *J. Amer. Chem. Soc.* **80**, 1967 (1958).

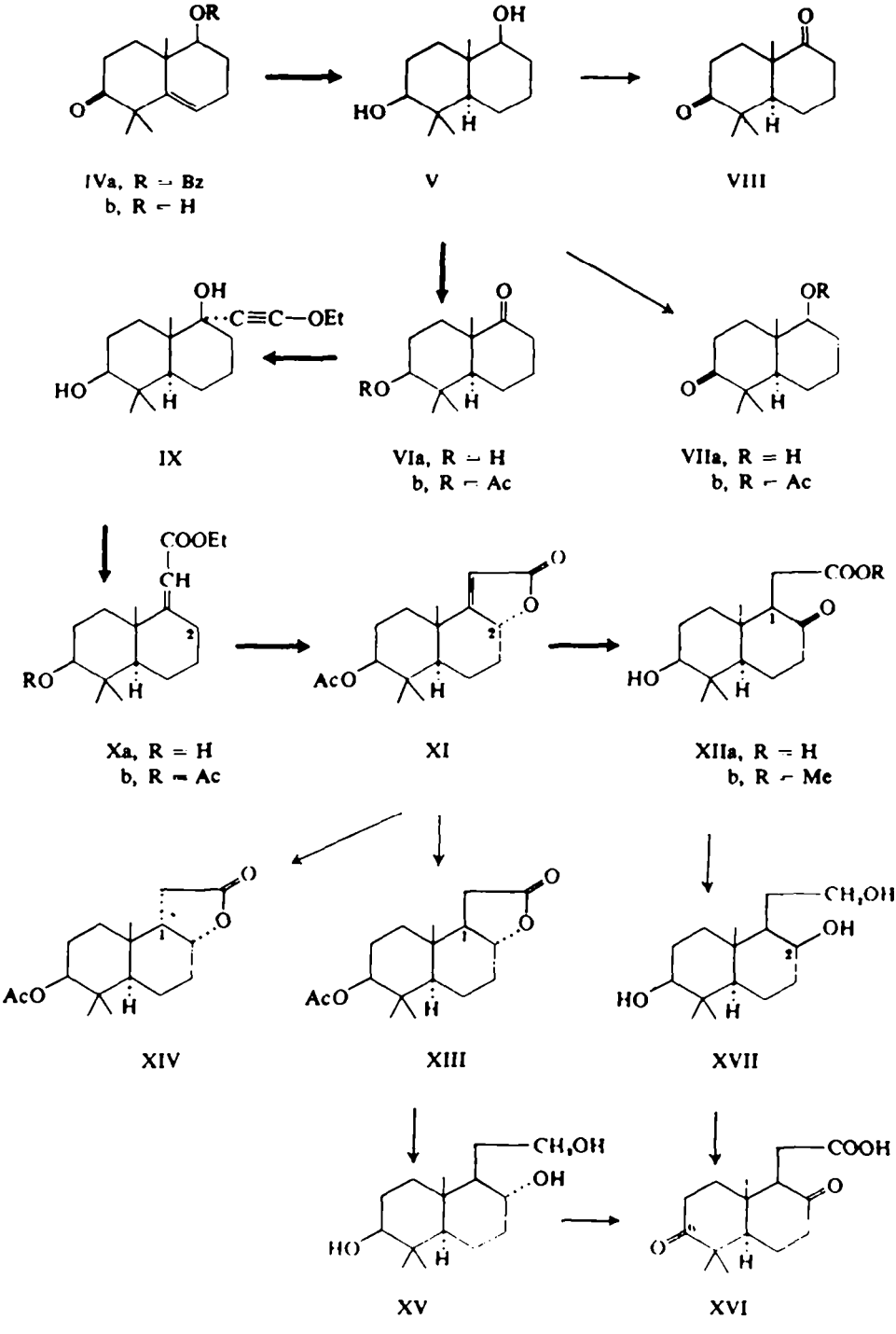
[13] J. Kalvoda and H. Loeffel, *Helv. Chim. Acta* **40**, 2340 (1957); B. Gaspert, T. G. Halsall and D. Willis, *J. Chem. Soc.* 624 (1958); N. B. Haynes and C. J. Timmons, *Proc. Chem. Soc.* 345 (1958).

[14] See J. F. Arens, *Advances in Organic Chemistry, Methods and Results* (Edited by R. A. Raphael E. C. Taylor and H. Wynberg) Vol. II; pp. 159–160 and Refs. cited there. Interscience, New York (1960).

[15] *E.g.*, loliolide, containing the same chromophore as XI, shows UV max at 215 mμ (ε 14,800); R. Hodges and A. L. Porte, *Tetrahedron* **20**, 1463 (1964).

[16] See L. J. Bellamy, *The Infrared Spectra of Complex Molecules* (2nd Edition) pp. 186–187. Wiley, New York (1958).

[17] See the 17α-hydroxylation of cardenolides with selenium dioxide; N. Danieli, Y. Mazur and F. Sondheimer, *Tetrahedron Letters* 1281 (1962); *Tetrahedron* in press.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OR
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VIa, R = H
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VIIa, R = H
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XV
XVI

110–111°), obtained by treatment with diazomethane, proved to be identical with an authentic specimen.[2]

Before the discovery that XI could be converted directly to XIIa, we investigated the possibility of carrying out this transformation by first reducing the double bond of XI. Catalytic hydrogenation of XI in acetic acid over Pt resulted in two isomeric saturated lactones. The one obtained in larger amount (m.p. 164–165°; isolated in 66% yield) was considered to be the 1β-isomer XIII, since addition of hydrogen was expected to take place mainly from the less hindered α-side. This assignment was confirmed subsequently (see below). The minor product (m.p. 119–120°; 8% isolated) is therefore the 1α-isomer XIV.

LAH reduction of XIII led to the triol XV (m.p. 181–182°), which on oxidation with chromium trioxide in acetic acid gave the diketo acid XVI (m.p. 176–177°). It was necessary preferentially to reduce the 6-keto group in this substance to the 6β-ol in order to obtain XIIa, but this reaction was not investigated when it was found that XIIa could be obtained directly from XI.

Reduction of the keto ester XIIb with LAH yielded a triol (m.p. 200–201°), which differed from XV, and is therefore assigned the 2β-hydroxy structure XVII. Chromium trioxide oxidation of this triol then led to the same diketo acid XVI as obtained previously. This interconversion indicates that the saturated lactone with m.p. 164–165° (major component) is represented by structure XIII, possessing the same 1β-configuration as the keto ester XIIb. It is unlikely that this saturated lactone is actually the 1α-isomer XIV, and that inversion to the more stable 1β-configuration has occurred during the oxidation step, since this type of isomerization has been found not to occur on oxidation of similar systems with chromium trioxide in acetic acid.[18]

EXPERIMENTAL

M.ps are uncorrected. UV spectra: in 95% EtOH soln on a Cary model 14 recording spectrophotometer; IR spectra: as KBr discs (unless specified otherwise) on a Perkin–Elmer Infracord recording spectrophotometer; Chromatograms: with Merck acid-washed Al_2O_3; Analyses: under the direction of Mr. Erich Meier in our microanalytical laboratory.

Diol V. Saponification of IVa[9] with KOH in EtOH, as described previously,[18] yielded crude IVb (m.p. 86–90°) in quantitative yield. This substance (10 g) in glacial AcOH (200 ml) was shaken in H_2 with PtO_2 (500 mg) in a "Parr" hydrogenation apparatus at room temp for 24 hr (initial H_2 press, 21 psi). The catalyst was removed and washed with EtOAc. Evaporation of the solvents, and crystallization of the residue from ether–hexane yielded V (8·65 g; 85%) m.p. 179–181°. The analytical sample showed m.p. 180–182°; no IR bands in carbonyl region. (Found: C, 73·33; H, 11·26. $C_{13}H_{24}O_2$ requires: C, 73·53; H, 11·39%.) There was no depression in m.p. on admixture with the corresponding Δ^6-diol (m.p. 184–186°)[18], but the IR spectra were markedly different.

Oxidation of V *to* VIa, VIIa *and* VIII. A soln of V (6·0 g; 28·3 mmoles) in pyridine (60 ml) was cooled to 0°, and added dropwise to a mixture of CrO_3 (2·1 g; 21 mmoles) and pyridine (20 ml) at 0°. The mixture was allowed to stand at room temp for 65 hr, and MeOH (20 ml) was then added. After a further 30 min, the mixture was evaporated to dryness under red. press, and the residue extracted twice with EtOAc and twice with chf. The combined extracts were evaporated and the semi-crystalline residue was extracted twice with pet. ether. The insoluble residue (3·85 g; 64%), m.p. 178–180°, consisted of unchanged diol. V The pet. ether extract on evaporation led to an oil (2·15 g), which was chromatographed on Al_2O_3 (200 g).

Elution with benzene–ether (9:1) gave VIII (225 mg; 4%), m.p. 79–82°. Crystallization from ether–pet. ether led to a pure sample, m.p. 82–83°; IR band at 1707 cm^{-1} (ketone), no OH bands. (Found: C, 74·76; H, 9·55. $C_{13}H_{20}O_2$ requires: C, 74·96; H, 9·68%.)

[18] See Y. Mazur, N. Danieli and F. Sondheimer, *J. Amer. Chem. Soc.* **82**, 5889 (1960).

Elution with benzene–ether (4:1) gave VIa (820 mg; 14%; 44% based on unrecovered V), m.p. 72–74° from pentane. Identity with an authentic sample (m.p. 73–75°)[13] was established by mixture m.p. determination and IR comparison. Acetylation (Ac_2O pyridine, room temp for 16 hr) led to VIb, m.p. 96–97° from pet. ether. Identification with an authentic specimen was carried out as before.

Elution with benzene–ether (4:1 to 2:1) provided VIIa (710 mg; 12%; 38% based on unrecovered V) as an oil, which slowly crystallized. Crystallization from ether–hexane led to a pure sample, m.p. 63–65°; IR spectrum identical to that of an authentic specimen (previously reported as an oil).[13] Acetylation as above led to VIIb, m.p. 75–76° from pet. ether, IR bands at 1724 and 1250 cm^{-1} (acetate), 1697 (ketone). (Found: C, 71·24; H, 9·54. $C_{14}H_{24}O_3$ requires: C, 71·39; H, 9·59%.)

Finally, elution with ether gave unchanged diol V (270 mg; 4·5%; total, 69%), m.p. 177–180°.

Reduction of VII with excess LAH in ether (3 hr boiling) led to V in 86% yield. Similar reduction of VIIa gave V in 88% yield. The actual yield of VIa based on unrecovered V was therefore ca. 80%.

Unsaturated ester Xb. Ethoxyacetylene (3·5 g; 50 mmoles; Pfister Chemical Works Inc., Ridgefield, N.J.; freshly distilled before use) in ether (20 ml) was added dropwise during 20 min to an ethereal soln of 1·25 N MeLi (32 ml; 40 mmoles; prepared from Li and MeI). The addition was carried out at 0° under N_2 with vigorous stirring, which was continued at room temp for 30 min. The soln was then cooled to −18°, and VIa (840 mg; 4 mmoles) in ether (25 ml) was added dropwise during 15 min. Stirring was continued at −10° under N_2 for 1 hr, and at room temp for 16 hr. Finally the mixture was boiled under reflux for 2 hr, cooled, and poured into ice-water. The product was extracted with ether, washed with NaClaq, dried and evaporated under red. press.

The resulting crude IX (strong acetylene IR band at 2270 cm^{-1}, in chf) was dissolved in MeOH (24 ml), 5N H_2SO_4 (6 ml) was added, and the solution was allowed to stand at room temp for 1 hr. Extraction with ether led to crude Xa, which no longer showed the acetylene IR band. Acetylation (Ac_2O, pyridine, 16 hr at room temp) and isolation with ether in the usual way led to 1·25 g of product, which was chromatographed on Al_2O_3 (100 g). Pentane–benzene (1:1) eluted Xb (690 mg; 54%), m.p. 84–85°. Crystallization from ether–pentane led to the analytical sample, m.p. 85–86°; UV λ_{max}^{EtOH} 221 mμ (ε 13,400); IR bands at 1739 cm^{-1} (acetate), 1718 (αβ-unsatd ester) and 1640 (double bond). (Found: C, 70·74; H, 9·37; $C_{16}H_{26}O_4$ requires: C, 70·77; H, 9·38%.) In one experiment, a different polymorphic form, m.p. 99–100°, was obtained; the IR spectrum (chf) was identical in every respect with that of the lower melting form. Elution with benzene–ether (9:1 to 4:1) yielded unchanged VIb (220 mg), m.p. 94–96°. Very similar results were obtained when the ethoxyacetylene reaction was carried out with VIb instead of VIa.

Unsaturated lactone XI. A soln of Xb (400 mg) and SeO_2 (175 mg; freshly sublimed) in glacial AcOH (15 ml) was boiled under reflux for 3 hr. The mixture was cooled, diluted with ether, and the pptd Se was removed. The filtrate was washed twice with $NaHCO_3$aq and twice with NaClaq, and was then dried and evaporated. The crystalline residue (335 mg) was chromatographed on Al_2O_3 (30 g). Elution with benzene led to unchanged Xb (37 mg), m.p. 82–84°. Elution with benzene–ether (9:1) afforded XI (277 mg; 76%), m.p. 125–128°. Crystallization from ether–pentane gave a pure sample, m.p. 129–130°; UV λ_{max}^{EtOH} 215 mμ (ε 11,900); IR bands at 1757 cm^{-1} (αβ-unsatd γ-lactone),[14] 1736 (acetate) and 1640 (double bond). (Found: C, 69·67; H, 8·12. $C_{17}H_{24}O_4$ requires: C, 69·83; H, 8·27%.)

Acid XIIa *and methyl ester* XIIb. NaOH (8 g) in H_2O (8 ml) was added to a soln of XI (240 mg) in ethylene glycol (32 ml), and the soln was boiled under reflux for 2 hr. The mixture was cooled, diluted with H_2O and washed with EtOAc (this organic extract on evaporation yielded 14 mg of neutral material). The aqueous layer was then acidified with 10% HClaq, and extracted twice with EtOAc. The organic extract was shaken twice with 10% Na_2CO_3aq (evaporation of the EtOAc soln gave no significant amount of lactonic material), and the aqueous basic layer was acidified with 10% HClaq. Extraction with EtOAc, drying and evaporation then yielded acidic material (166 mg), which was crystallized from acetone–ether. The resulting XIIa (122 mg; 55%) showed m.p. 178–181°, raised by further crystallization to m.p. 185–186°. The m.p. was undepressed on admixture with an authentic sample (m.p. 186–187°)[3], and the IR spectra were identical in every respect.

Treatment of XIIa with diazomethane in CH_2Cl_2 and ether (2 hr at 0°) led to XIIb, m.p. 110–111° after crystallization from acetone–hexane. (Found: C, 67·71; H, 9·24. $C_{16}H_{26}O_4$ requires: C, 68·05; H, 9·28%.) Identity with an authentic specimen (m.p. 110–111°)[3] was established by mixture m.p. determination and IR comparison.

Hydrogenation of XI *to* XIII *and* XIV. A soln of XI (165 mg) in glacial AcOH (10 ml) was shaken

in H_2 with a pre-reduced PtO_2 catalyst (ca. 20 mg) for 3 hr at room temp and atm. press. The catalyst was removed, the filtrate was evaporated to dryness, and the residue was crystallized repeatedly from ether–pentane. The resulting XIII (110 mg; 66%) showed m.p. 164–165°; UV end absorption only; IR bands at 1776 cm^{-1} (satd γ-lactone) and 1725 (acetate). (Found: C, 69·47; H, 8·80. $C_{17}H_{26}O_4$ requires: C, 69·36; H, 8·90%.)

Crystallization of the mother liquors from ether–pentane led to XIV (13 mg; 8%), m.p. 119–120°; UV end absorption only; IR similar to that of XIII (bands at 1776 and 1721 cm^{-1}), but distinctly different in fingerprint region.

Triol XV. A soln of XIII (50 mg) in ether (10 ml) and THF (10 ml) was boiled under reflux with LAH (150 mg) for 1 hr. The mixture was cooled, the excess reagent was destroyed by dropwise addition of EtOAc, and ice-water was then added. Acidification with H_2SO_4, extraction with EtOAc, and crystallization of the resulting product from ether gave XV (38 mg; 87%), m.p. 181–182°; no IR bands in carbonyl region. (Found: C, 70·20; H, 10·97. $C_{16}H_{30}O_5$ requires: C, 70·27; H, 11·01%.)

Triol XVII. Substance XIIb (50 mg) was reduced with LAH exactly as described above for the preparation of XV. Crytallization from ether gave XVII (34 mg; 78%), m.p. 200–201°; IR spectrum (no bands in carbonyl region) distinctly different from that of XV. (Found: C, 70·23; H, 10·88. $C_{16}H_{30}O_5$ requires: C, 70·27; H, 11·01%.)

Diketo acid XVI

(a) *From triol* XV. The triol XV (25 mg) was oxidized with CrO_3 (20 mg) in glacial AcOH (10 ml) for 16 hr at room temp. Addition of water, extraction with ether, and crystallization from acetone–ether led to XVI (16 mg; 62%), m.p. 176–177°; IR bands at 1725 cm^{-1} (acid) and 1703 (ketone). (Found: C, 67·37; H, 8·07. $C_{16}H_{26}O_4$ requires: C, 67·64; H, 8·33%.)

(b) *From triol* XVII. The triol XVII (20 mg) was oxidized with CrO_3 (16 mg) in glacial AcOH (8 ml) exactly as described under (a). Crystallization of the product from acetone–ether yielded XVI (13 mg; 63%), m.p. 174–176°. The m.p. was undepressed on admixture with the above-described sample, and the IR spectra were identical in every respect.

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